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Pratiques parentales coercitives, anxiété et traitement de la peur chez les jeunes en bonne santé: corrélats neuronaux, biologiques, physiologiques et comportementaux

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Résumé

L'adversité tôt dans la vie est associée au développement de symptômes anxieux pouvant perdurer jusqu'à l'âge adulte (Casey et el, 2010, Pine 2003). Des études chez l'adulte suggèrent que ces liens pourraient être associés à des altérations du « circuit de la peur » qui inclut l'amygdale, l'hippocampe antérieur, l'insula et le cortex préfrontal (Marek, 2013, Etkin & Wager, 2007). Ceci a cependant peu été étudié chez les jeunes. L'objectif principal de cette thèse était de définir les corrélats comportementaux, physiologiques, biologiques et neuronaux du traitement de la peur chez les jeunes en bonne santé, en lien ou non avec un historique d'adversité -- sous la forme de pratiques parentales coercitives -- et d'anxiété.

D'abord, puisque nous nous intéressions aux pratiques parentales coercitives *chroniques*, nous avons examiné leur évolution et facteurs de risque, en nous concentrant sur la période de 17 à 72 mois. Un total de 2045 dyades mère-enfant ont été incluses dans une analyse de courbe de croissance latente. Nous avons démontré que la coercition maternelle suit une évolution non linéaire durant cette période et atteint un sommet à 42 mois. Les facteurs de risque relatifs à l'enfant et à la mère, mesurés à 17 mois, permettent de prédire les niveaux de coercition à 42 mois. Finalement, les prédicteurs relatifs à l'enfant et l'efficacité maternelle prédisent l'évolution des pratiques parentales coercitives entre 17 et 72 mois.

Ensuite, afin de définir une méthodologie solide pour étudier le traitement de la peur chez des jeunes, nous avons adapté une tâche développée par Lau et ses collaborateurs (2008), employant des visages féminins comme stimuli. Le sexe des participants et des visages employés comme stimuli pouvant potentiellement moduler le traitement de la peur (Kret & de Gelder, 2012; McClure, 2000), nous avons étudié leurs influences respectives sur les réponses électrodermales et subjectives de peur durant le conditionnement et l'extinction de la peur chez 117 jeunes. Nous avons démontré que les stimuli féminins suscitent des réponses davantage comparables entre les garçons et les filles que les stimuli masculins. De plus, nous avons observé un effet du « même sexe », caractérisé par un conditionnement différentiel uniquement face aux stimuli du même sexe que le participant.

Finalement, nous avons exploré les différences individuelles et conjointes associées aux différents niveaux de pratiques parentales coercitives et d'anxiété en termes de réponses de peur et d'activité cérébrale, durant le conditionnement et l'extinction de la peur chez 84 jeunes. Nous avons démontré que la coercition est spécifiquement associée au fonctionnement du lobe temporal médian et aux interactions entre l'amygdale et l'insula, durant le conditionnement. Durant l'extinction, les niveaux d'anxiété étaient associés à des différences spécifiques d'activation du gyrus cingulaire antérieur (GCA) dorsal. Enfin, les pratiques parentales coercitives et l'anxiété interagissent et viennent moduler la connectivité fonctionnelle amygdale - GCA rostral, l'activation d'une sous-région du GCA dorsal et les réponses subjectives de peur.

Ces résultats ajoutent une pièce au casse-tête des neurosciences développementales et fournissent des pistes intéressantes pour le développement d'interventions futures.

Mots-clés : pratiques parentales, adversité, anxiété, enfance, adolescence, IRMf, amygdale, sexe, conditionnement, extinction

Abstract

Early-life adversity is associated with increased risks of developing anxiety symptoms that can persist throughout the lifespan (Casey et al, 2010 Pine 2003). Adult literature suggests that these links could be mediated by alterations of the "fear circuitry " a neural system that includes the amygdala, anterior hippocampus, insula and prefrontal cortex (Marek, 2013, Etkin & Wager, 2007). This, however, has scarcely been studied in youth. The main objective of the present thesis was to investigate the behavioral, physiological, biological and neural correlates of fear processing in physically and psychiatrically healthy youth, associated or not with a history of early-life adversity -- under the form of maternal harsh parenting -- and anxiety.

First, since we were interested in *chronic* harsh parenting levels, we examined the longitudinal evolution and risk factors of maternal harsh parenting practices between child age 17 months and 6 years in 2045 mother-child dyads. During this period, harsh parenting was found to follow a non-linear trajectory, with a peak at 42 months. Risk factors related to the child (i.e. sex and internalized and externalized behaviors) and the mother (i.e. history of depression and perceived parental self-efficacy) measured at 17 months predicted harsh parenting levels at 42 months. As well, child risk factors and maternal self-efficacy predicted harsh parenting evolution between 17 and 72 months.

Second, in order to establish a robust methodology to investigate fear processing in a pediatric population, we adapted a paradigm developed by Lau and collaborators (2008) employing female faces as conditioned and unconditional stimuli. Since sex of participants and sex of faces used as emotional stimuli may modulate fear processing (Kret & De Gelder; McClure, 2000), we examined their respective influences on objective (skin conductance responses or SCRs) and subjective (fear ratings) fear responses during discrimination fear conditioning and extinction tasks in 117 adolescents. This study demonstrated that female stimuli elicit more constant and comparable fear responses in boys and girls relative to male stimuli. In addition, an “own sex effect” was observed for SCRs, illustrated by discrimination conditioning taking place only in boys viewing male faces and in girls viewing female faces.

Finally, we explored the individual and joint differences associated with maternal harsh parenting practices and anxiety levels in terms of objective, subjective, and brain activity responses during the conditioning and extinction of fear in 84 youths. This study demonstrated that harsh parenting practices are specifically associated with differences in medial temporal lobe function and in amygdala-insula functional connectivity during conditioning. During extinction, anxiety levels were associated with specific activation differences in the dorsal anterior cingulate cortex (ACC). Finally, harsh parenting and anxiety were found to interact and modulated differences in activations in a smaller dorsal ACC cluster, in amygdala-rostral ACC functional connectivity, and in subjective fear responses.

These results add a piece to the puzzle of developmental neurosciences and provide guidelines for the development of future better-targeted interventions.

Keywords : harsh parenting, adversity, anxiety, youth, fear conditioning, extinction, fMRI, amygdala, sex, gender.

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ACC: Anterior cingulate cortex

BOLD: Blood oxygen level dependent

CPF: Cortex préfrontal

CPFvm: Cortex préfrontal ventro-médian

CS: Conditioned stimulus

CFI: Comparative Fit index

dACC: Dorsal anterior cingulate cortex

FIML: Full information maximum likelihood

fMRI: Functional magnetic resonance imaging

GCA: Gyrus cingulaire antérieur

GCAd: Gyrus cingulaire antérieur dorsal

GCAr: Gyrus cingulaire antérieur rostral

GCAsg: Gyrus cingulaire antérieur subgénual

GLM: General linear model

HA: High anxiety

HH: High harsh parenting

IRMf: Imagerie par résonance magnétique fonctionnelle

LA: Low anxiety

LGCM: Latent growth curve model

LH: Low harsh parenting

ML: Maximum Likelihood

MLR: Maximum Likelihood with Robust standard errors

PFC: Prefrontal cortex

PPI: Psychophysiological interaction

PTSD: Post-traumatic stress disorder

rACC: Rostral anterior cingulate cortex

RÉD: Réponse électrodermale

RMSEA: Root Mean Square Error of Approximation

ROI: Region of interest

SC: Stimulus conditionné

SI: Stimulus inconditionnel

US: Unconditional stimulus

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Chapitre 1

Introduction

1.1 Mise en contexte

L'enfance et l'adolescence sont des périodes charnières du développement humain, durant lesquelles de nombreux changements ont lieu aux plans physique, cognitif et psychosocial. Parallèlement, au plan neuronal, une évolution constante, non linéaire et hétérogène à travers les différentes structures est observée de la petite enfance au début de l'âge adulte dans diverses régions corticales et sous-corticales (Dennison et al., 2013; Gogtay et al., 2004; Uematsu et al., 2012). Des conditions de vie aversives subies de façon chronique durant ces périodes particulièrement sensibles peuvent ainsi altérer le développement de certaines régions cérébrales, en particulier celles qui sont impliquées dans le traitement émotionnel (Hart & Rubia, 2012; E. McCrory, De Brito, & Viding, 2011; Tottenham & Sheridan, 2009). Les individus exposés à des conditions de vie aversives et/ou traumatiques tôt lors du développement sont ainsi davantage vulnérables au développement de symptômes d'anxiété et de dépression au cours de l'adolescence, qui peuvent perdurer jusqu'à l'âge adulte (Casey et al., 2010; Charney, 2004; Pine, 2003). Par ailleurs, la plupart des troubles psychiatriques surviennent à l'adolescence ou au début de l'âge adulte (Casey et al., 2010), ce qui soulève l'importance de mieux comprendre les mécanismes qui sous-tendent leur apparition au cours de cette période critique du développement.

Les résultats d'études précédentes effectuées chez les adultes et chez les jeunes suggèrent que l'adversité vécue tôt dans la vie est associée à des altérations du développement émotionnel reflétées, entre autres, par une augmentation de l'attention portée aux stimuli menaçants. Au plan neuronal, un ensemble d'études effectuées chez l'adulte, rapporte des altérations au niveau de la structure et du fonctionnement des diverses structures constituant le « circuit neuronal de la peur » (Hart & Rubia, 2012; E. McCrory et al., 2011; McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015; Tottenham & Sheridan, 2009), soit le lobe temporal médian, l'insula et le cortex préfrontal (CPF) (Etkin & Wager, 2007; Marek, Strobel, Bredy, & Sah, 2013), en lien avec un historique d'adversité dans l'enfance. Par ailleurs, bien que plusieurs travaux aient étudié les liens entre l'anxiété, l'adversité et le fonctionnement du circuit neuronal de la peur chez l'adulte, peu d'études ont examiné ces liens chez les jeunes. En effet, parmi les rares études effectuées chez les enfants et les adolescents, aucune n'a examiné

les influences individuelles de l'adversité chronique et de l'anxiété sur le fonctionnement du circuit de la peur, ainsi que leurs possibles interactions. Or, comprendre ces liens alors que les individus sont encore jeunes est crucial afin de mieux saisir la neurobiologie des troubles anxieux pédiatriques et de rapidement mettre en action des méthodes d'intervention pouvant freiner l'émergence des symptômes anxieux, avant que ceux-ci ne deviennent chroniques. Ainsi, l'objectif principal de la présente thèse est de mettre en lumière le fonctionnement du circuit neuronal de la peur chez les jeunes, en lien avec l'anxiété et l'adversité chroniques.

Dans un premier temps, nous nous intéresserons aux conditions d'émergence et à l'évolution des pratiques parentales coercitives à travers le temps. Nous explorerons leur développement de façon longitudinale durant l'enfance, ainsi que les facteurs de risque qui y sont associés.

Ensuite, nous explorerons influences potentielles du sexe des participants et du sexe des acteurs/actrices utilisés dans la constitution des stimuli émotionnels (visages), sur le traitement de la peur chez des adolescents en bonne santé psychologique. Ces aspects seront étudiés puisque la tâche employée dans le cadre de cette thèse était initialement constituée uniquement de visages féminins et que nous nous intéresserons au traitement de la peur tant chez les garçons que chez les filles, alors que des études précédentes ont démontré que ces facteurs peuvent moduler le traitement émotionnel chez les individus sains (Kret & De Gelder, 2012; McClure, 2000; Navarrete et al., 2009).

Nous explorerons ensuite les corrélats individuels liés à (1) l'adversité, prenant ici la forme de pratiques parentales coercitives, et (2) à l'anxiété, sous la forme de manifestations comportementales anxieuses et de traits de personnalité anxieux élevés, ainsi que (3) les interactions potentielles entre ces variables, en termes de fonctionnement du circuit neuronal de la peur, toujours chez des jeunes en bonne santé.

1.2 Les pratiques parentales coercitives : une forme non-négligeable d'adversité

1.2.1 Définition et prévalence

Les pratiques parentales jouent un rôle clé dans le développement socio-affectif au cours de l'enfance et de l'adolescence. La sensibilité et la réceptivité parentales face aux besoins et aux demandes de l'enfant sont associées au développement de relations d'attachement parent/enfant sécurisantes, qui à leur tour créent un contexte favorable au développement des compétences émotionnelles et sociales de l'enfant (Gervai, 2009). En revanche, l'adoption de pratiques hostiles et punitives est liée à des relations d'attachement dites « insécurisantes », ainsi qu'à des risques accrus de difficultés psychologiques et comportementales (Boivin et al., 2005; McKee et al., 2007).

La majorité des études précédentes se sont intéressées aux pratiques parentales hautement aversives telles que l'abus physique et sexuel et la négligence émotionnelle sévère. Toutefois, les pratiques parentales coercitives, soit une forme plus bénigne et socialement acceptée d'adversité, définie par des comportements d'agression mineure qui ne sont pas suffisamment sévères pour être rapportés aux autorités (p. ex., taper sur les fesses ou le bras de l'enfant, crier après l'enfant ou le secouer), sont aussi associées à des difficultés socio-émotionnelles. Ainsi, les enfants ayant vécu cette forme d'adversité présentent des risques accrus de développer une faible estime de soi et des difficultés de régulation émotionnelle, de même que des troubles anxieux, dépressifs et comportementaux pouvant perdurer à l'âge adulte (Gershoff, 2002; Hart & Rubia, 2012; MacMillan et al., 1999; Marchand, 2002; McKee et al., 2007; McLeod, Wood, & Weisz, 2007; Solomon & Serres, 1999; Straus & Stewart, 1999; Wood, McLeod, Sigman, Hwang, & Chu, 2003; Woods et al., 2003).

En dépit des nombreuses conséquences négatives qui y sont associées, les pratiques parentales coercitives sont relativement communes au sein des familles québécoises. Ainsi, un récent rapport de l'Institut de la Statistique du Québec révèle que 35% des parents d'enfants âgés entre 0 et 17 ans rapportent avoir employé des méthodes de discipline physique telles que secouer leur enfant ou le frapper sur les fesses, les mains, les bras ou la jambe, au moins une

fois au cours de l'année, alors que 11% auraient adopté ce genre de pratique trois fois ou plus dans l'année (Clément, Bernèche, Fontaine, & Chamberland, 2012). Selon cette même étude, 49 % des parents auraient employé l'agression psychologique envers leurs enfants trois fois ou plus au cours de l'année, définie ici par le fait de crier, insulter ou menacer l'enfant de recevoir une punition corporelle (Clément et al., 2012). Finalement, 29% des parents ont rapporté avoir employé à la fois l'agression psychologique et une forme de punition corporelle au cours de l'année (Clément et al., 2012).

1.3 Pratiques parentales coercitives : évolution et facteurs de risque

1.3.1 Évolution des pratiques parentales coercitives de la petite enfance à l'adolescence

De la naissance de l'enfant jusqu'à son entrée dans l'âge adulte, la fréquence et la sévérité des pratiques parentales coercitives évolue. De 0 à 3 ans, une augmentation générale a été observée malgré des niveaux initiaux variables, dans différents échantillons de dyades mère-enfant représentatifs de la population générale ou vivant sous des conditions d'adversité psychosociale (Kim, Pears, Fisher, Connelly, & Landsverk, 2010; T. Pierce et al., 2010; Windham et al., 2004). Chez les enfants d'âge scolaire (6-9 ans), ainsi que chez les adolescents (10-15 ans), des patrons d'évolution similaires entre les mères sont encore une fois rapportés, malgré des niveaux initiaux variables (Lansford et al., 2009). Ainsi, environ la moitié des mères des enfants d'âge scolaire (48%) et deux tiers (66%) des mères d'adolescents ont maintenu des niveaux stables à travers le temps, alors que l'autre moitié de la plus jeune cohorte (52%) et le tiers (33%) de la seconde cohorte ont vu leurs niveaux de pratiques parentales coercitives diminuer avec le temps (Lansford et al., 2009).

Ainsi, l'usage de pratiques parentales coercitives tend à augmenter de la naissance à l'âge de 3 ans, alors que des niveaux stables ou des diminutions sont observées à partir de

l'âge de 6 ans. Étrangement, peu d'études ont investigué l'évolution des pratiques parentales coercitives entre l'âge de 3 et 6 ans, à l'exception d'une étude de prévalence examinant exclusivement l'usage de la fessée (« spanking ») chez des parents d'enfants âgés de 3 et 5 ans et employant une échelle dichotomique (présence ou absence de punition corporelle dans l'année) (MacKenzie, Nicklas, Waldfogel, & Brooks-Gunn, 2013). Cette étude a rapporté une légère diminution de l'usage de punition corporelle (la fréquence passant de 57 à 52% entre 3 et 5 ans) (MacKenzie et al., 2013). Or, la période de 3 à 6 ans est une période qui se caractérise par de nombreux changements et défis au plan cognitif, physique et psychosocial et, parallèlement, au sein des diverses régions cérébrales associées au développement cognitif et socioaffectif, incluant l'amygdale et l'hippocampe (Uematsu et al., 2012). L'exposition à des pratiques parentales coercitives durant cette période particulièrement sensible peut donc altérer la structure et le fonctionnement de ces régions cérébrales, augmentant ainsi les risques de difficultés émotionnelles et cognitives (Tottenham & Sheridan, 2009). Il est donc important de mieux caractériser l'évolution de la coercition maternelle durant cette période charnière du développement.

1.3.2 Facteurs de risque associés aux pratiques parentales coercitives et à leur évolution longitudinale

Il est également important de déterminer les facteurs permettant de prédire le niveau de pratiques parentales coercitives et surtout leur évolution à travers le temps. Trois principales catégories de facteurs de risque sont typiquement relevées dans la littérature : les facteurs de risque relatifs à l'enfant, à la mère et au contexte familial.

1.3.2.1 Facteurs de risque associés à des niveaux élevés de pratiques parentales coercitives

En ce qui concerne les caractéristiques relatives à l'enfant, des niveaux élevés de comportements extériorisés (i.e. l'agressivité, l'hyperactivité et l'opposition) ont été associés à un usage accru de pratiques punitives physiques et psychologiques (p. ex., Bor & Sanders,

2004; Lansford et al., 2009). La manifestation de comportements intériorisés (anxiété, comportements dépressifs) chez l'enfant a aussi été associée à une augmentation des pratiques parentales coercitives (Rubin & Mills, 1990), possiblement en lien avec augmentation des pensées négatives à l'égard de l'enfant (e.g. « mon enfant ne me respecte pas »), qui en retour sont associées à des pratiques hostiles (Laskey & Cartwright-Hatton, 2009). Finalement, le sexe de l'enfant semble aussi constituer un facteur de risque des pratiques parentales aversives, les garçons en étant plus souvent la cible selon diverses études, malgré l'absence de consensus à ce sujet (Gershoff, 2002; Windham et al., 2004).

La perception l'efficacité parentale, soit la capacité de subvenir aux besoins et aux demandes de l'enfant, est un des facteurs maternels ayant précédemment été associés aux pratiques parentales coercitives. Ainsi, les mères qui se perçoivent comme étant plus efficaces répondent avec davantage de chaleur et de sensibilité aux besoins de leur enfant, alors que les mères se percevant comme moins efficaces ont plutôt tendance à agir de manière hostile et punitive (Boivin et al., 2005; Bugental, Lewis, Lin, Lyon, & Kopeikin, 1999). Ces relations tendent par ailleurs à diminuer de la naissance à l'âge de trois ans (Pierce et al., 2010). La dépression maternelle a elle aussi été associée à des risques accrus de pratiques parentales coercitives, les mères souffrant de dépression étant davantage irritables et moins émotionnellement disponibles, ce qui peut en retour mener à des réactions hostiles face aux demandes et à l'agitation croissantes de l'enfant (Boivin et al., 2005; Lovejoy, Graczyk, O'Hare, & Neuman, 2000; Shay & Knutson, 2008; Windham et al., 2004).

Finalement, un faible revenu, ainsi que l'insatisfaction maritale, ont aussi été associés a une utilisation accrue de comportements hostiles et de punitions corporelles, probablement en raison des niveaux de stress élevés qui y sont associés (Atzaba-Poria & Pike, 2008; Gershoff, 2002; Gracia, 1995; Krishnakumar & Buehler, 2000; Lansford et al., 2009).

1.3.2.2 Facteurs de risque associés à l'évolution longitudinale des pratiques parentales coercitives

Les facteurs de risque psychologiques relatifs à l'enfant, soit les comportements intériorisés et extériorisés, connaissent une évolution substantielle de la petite enfance à l'âge préscolaire (Cote et al., 2009; Tremblay et al., 2005). De fait, des études effectuées au sein de

la cohorte de l'Étude Longitudinale du Développement des Enfants du Québec (ELDÉQ) ont identifié différentes trajectoires développementales pour ces facteurs et rapportent que les enfants présentant les niveaux initiaux les plus élevés sur les deux variables présentent aussi l'augmentation subséquente la plus prononcée et les niveaux les plus élevés à l'âge de 42 mois (Cote et al., 2009; Tremblay et al., 2005). De façon similaire, les différences sexuelles au plan comportemental deviennent plus évidentes au fur et à mesure que l'enfant grandit et se développe. En raison de leur évolution croissante et de l'accentuation avec le temps des différences sexuelles et au plan des comportements intériorisés et extériorisés, ces variables pourraient être spécifiquement associées à l'évolution longitudinale des pratiques parentales coercitives de la petite enfance à l'âge préscolaire.

1.3.3 Évolution et facteurs de risque des pratiques parentales coercitives : résumé

La majorité des études précédentes se sont penchées sur l'évolution des pratiques parentales coercitives durant la petite enfance (0-3 ans), et de l'âge scolaire à l'adolescence. Alors qu'une augmentation générale est observée entre 0 et 3 ans, des niveaux stables et/ou un déclin sont observés à partir de l'âge de 6 ans. De plus, diverses caractéristiques de l'enfant, de la mère, et du contexte familial, ont été identifiées comme constituant des facteurs de risque des pratiques parentales coercitives chez les enfants de divers âges. Par ailleurs, très peu d'études se sont penchées sur la période allant de la petite enfance à l'âge d'entrée à l'école, et aucune d'entre elles n'a examiné les facteurs de risque permettant de prédire l'évolution longitudinale des pratiques parentales coercitives durant cette période. Le troisième objectif de la présente thèse vise donc l'examen des patrons d'évolution et des facteurs de risque des pratiques parentales coercitives durant cette période importante du développement.

1.4 Adversité durant l'enfant et traitement émotionnel : une sensibilité accrue aux menaces

Bien qu'ils ne concernent pas les pratiques parentales coercitives spécifiquement, les résultats d'études précédentes suggèrent que l'adversité vécue tôt dans la vie affecte le développement émotionnel de l'enfant en altérant la façon dont l'information à connotation émotionnelle est traitée, particulièrement en ce qui concerne les stimuli menaçants. Ces altérations seraient en retour associées au développement de troubles anxieux et dépressifs. De fait, une sensibilité exagérée aux menaces potentielles représente l'une des caractéristiques fondamentales des troubles anxieux (Hofmann, Ellard, & Siegle, 2012). Alors, que les jeunes enfants ayant vécu de la maltraitance éprouvent des difficultés à reconnaitre différentes expressions émotionnelles, particulièrement la peur et la colère, (Fries & Pollak, 2004; Masten et al., 2008; Pears & Fisher, 2005; Pollak, Cicchetti, Hornung, & Reed, 2000; Pollak & Sinha, 2002; Pollak & Tolley-Schell, 2003; Vorria et al., 2006; pour revue voir Hart et Rubia, 2012), les enfants plus âgés sont quant à eux plus prompts à réagir face à ces émotions (Pine et al., 2005; Pollak & Sinha, 2002; Pollak & Tolley-Schell, 2003) et les identifient de manière plus efficace (Maheu et al., 2010; Pollak & Sinha, 2002; Pollak & Tolley-Schell, 2003). Cette sensibilité accrue aux menaces potentielles pourrait être liée à des altérations du circuit neuronal de la peur.

1.5 Adversité durant l'enfance et circuit neuronal de la peur

1.5.1 Définition du circuit neuronal de la peur

Le circuit de la peur est un système neuronal responsable du traitement de la peur, qui est particulièrement sensible à l'adversité survenant tôt dans la vie (Hart & Rubia, 2012; E. McCrory et al., 2011; Tottenham & Sheridan, 2009). Ce système inclut principalement des

structures du lobe temporal médian, soit l'amygdale et l'hippocampe antérieur, qui sont responsables de l'apprentissage et de l'expression de la peur (Etkin & Wager, 2007; Marek et al., 2013), ainsi que le CPF. Alors que les aires latérales du CPF sont typiquement associées au contrôle exécutif (Barbas, 2009), les régions ventrales et médianes, incluant le gyrus cingulaire antérieur (GCA), font partie du système limbique, et sont impliquées dans le traitement des stimuli menaçants (Barbas, 2009; Davidson, 2004). Le cortex préfrontal ventromédian (CPFvm), principalement au niveau du gyrus cingulaire antérieur subgénual (GCAsg), est associé à la régulation de la peur et à la régulation émotionnelle de façon générale (Buchel & Dolan, 2000; Buchel, Morris, Dolan, & Friston, 1998; Etkin & Wager, 2007; LeDoux, 2000; Marek et al., 2013; Milad & Quirk, 2012; Milad, Rauch, Pitman, & Quirk, 2006; Ohman, 2005). Le GCA dorsal (GCAd) joue quant à lui un rôle dans les réactions émotionnelles conscientes face aux menaces potentielles, telles que l'évaluation de la menace et la communication de la peur à autrui, ainsi que l'activation physiologique et les affects négatifs qui y sont associés (Barbas, 2009; Shackman et al., 2011). L'insula est également incluse dans le circuit neuronal de la peur (Etkin & Wager, 2007; Fullana et al., 2015; Sehlmeyer et al., 2009). Cette dernière est impliquée dans la perception des changements intéroceptifs et viscéraux face aux menaces (Craig, 2009; Jones, Ward, & Critchley, 2010; W. K. Simmons et al., 2013), ainsi que dans l'intégration de l'information intéroceptive à l'information externe et aux représentations cognitives de haut niveau (Craig, 2009; Jones et al., 2010; W. K. Simmons et al., 2013).

1.5.2 Adversité dans l'enfance, anxiété et fonctionnement du lobe temporal médian

En plus des anomalies structurelles observées par différentes équipes chez les adultes et les enfants ayant été victimes d'abus durant l'enfance (Carrion, Weems, & Reiss, 2007; De Bellis et al., 1999; De Bellis et al., 2002; Hart & Rubia, 2012; Keding & Herringa, 2014; P. A. Kelly et al., 2013; Kitayama, Quinn, & Bremner, 2006; E. McCrory et al., 2011; McLaughlin, Sheridan, et al., 2015; Mehta et al., 2009; Stein, Koverola, Hanna, Torchia, & McClarty, 1997; Tottenham & Sheridan, 2009), des changements au plan fonctionnel ont été relevés au sein des

structures du lobe temporal médian. Ainsi, une activité accrue de l'amygdale lors du traitement de stimuli menaçants a été observée chez des adultes ayant vécu de l'adversité dans l'enfance (Bremner et al., 2005; E. McCrory et al., 2011; Teicher & Samson, 2013), tout comme il a fréquemment été rapporté chez les jeunes et les adultes atteints d'un trouble anxieux (Britton, Lissek, Grillon, Norcross, & Pine, 2011; Etkin, 2012; Hofmann et al., 2012; Ipser, Singh, & Stein, 2013). De façon similaire, de récentes études rapportent des activations accrues dans l'amygdale et l'hippocampe antérieur chez les jeunes ayant vécu de l'adversité tôt dans la vie (e.g. de la maltraitance, être témoins de violence familiale ou un placement en institution) (Maheu et al., 2010; E. J. McCrory et al., 2013; E. J. McCrory et al., 2011; McLaughlin, Peverill, et al., 2015; Tottenham et al., 2011), même si la plupart d'entre eux présentaient des niveaux normaux d'anxiété.

1.5.3 Adversité dans l'enfance, anxiété et fonctionnement de l'insula

Similairement à ce qui a été observé dans le lobe temporal médian, une augmentation de l'activité insulaire a été observée chez les individus anxieux (Hofmann et al., 2012; Holzschneider & Mulert, 2011; Ipser et al., 2013), ainsi que chez les individus ayant un historique d'adversité dans l'enfance (E. J. McCrory et al., 2013; E. J. McCrory et al., 2011; McLaughlin, Peverill, et al., 2015), durant le traitement de stimuli menaçants ou stressants.

1.5.4 Adversité dans l'enfance, anxiété et fonctionnement du cortex préfrontal

En raison de son développement tardif, le cortex préfrontal est l'une des régions les plus touchées par l'adversité vécue tôt dans la vie (Hart & Rubia, 2012). Tout comme pour les structures du lobe temporal médian, des changements au plan structurel ont été observés dans cette région en lien avec un historique d'adversité, tant chez les sujets jeunes que chez les adultes (voir Hart & Rubia, 2012 pour une revue de la littérature). Au plan fonctionnel, des

activations réduites du GCA et du cortex orbito-frontal ont été relevées chez des adultes ayant été victimes d'abus durant l'enfance et souffrant d'un trouble de stress post-traumatique (TSPT) durant l'exécution de tâches émotionnelles, par rapport au groupe contrôle (Bremner et al., 2005). Des résultats similaires ont été rapportés dans d'autres échantillons d'adultes souffrant d'anxiété (Erhardt & Spoormaker, 2013; Indovina, Robbins, Nunez-Elizalde, Dunn, & Bishop, 2011; Lissek, 2012; Milad, Rauch, et al., 2006; Sehlmeyer et al., 2011). Chez les jeunes atteints d'un TSPT lié à de la maltraitance, en revanche, des augmentations de l'activité du GCA ont été observées durant une tâche d'inhibition comportementale de nature non émotionnelle (Carrion, Garrett, Menon, Weems, & Reiss, 2008). De plus, similairement à ce qui a été observé chez les individus à haut risque d'anxiété en raison de traits de personnalité anxieux (Barrett & Armony, 2009; Hardee et al., 2013; Telzer et al., 2008), de récentes études suggèrent plutôt une augmentation de l'activité du GCAsg chez les adultes et les jeunes psychiatriquement sains, mais ayant été exposés à des situations traumatiques dans l'enfance, durant l'exécution de tâches cognitives et/ou évocatrices de stress (Banihashemi, Sheu, Midei, & Gianaros, 2015; Elsey et al., 2015; Mueller et al., 2010). Enfin, bien que peu d'études se soient intéressées aux régions plus postérieures du CPF, des activations accrues dans le GCA dorsal ont été rapportées chez les personnes atteintes de phobie spécifique, reflétant probablement une augmentation des réponses de peur de nature cognitive face aux stimuli menaçants (Etkin & Wager, 2007). Chez les individus atteints d'un TSPT, en revanche, des hypoactivations du GCAd par rapport aux contrôles ont précédemment été observées, ce qui pourrait être tributaire d'un émoussement émotionnel (Etkin & Wager, 2007).

1.5.5 Adversité dans l'enfance, anxiété et liens entre les diverses structures du circuit neuronal de la peur

De récentes études ont rapporté des réductions de la connectivité fonctionnelle entre l'amygdale et le CPFvm chez des adultes présentant soit un historique d'adversité dans l'enfance (Fan et al., 2014; Herringa et al., 2013), un trouble anxieux (Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010; Hahn et al., 2011; Pannekoek et al., 2013), ou les deux (Birn, Patriat, Phillips, Germain, & Herringa, 2014). Des résultats similaires ont tout récemment été

rapportés chez des jeunes souffrant de maltraitance, qui présentaient également des niveaux plus élevés d'anxiété par rapport aux jeunes du groupe contrôle (Thomason et al., 2015). D'un autre côté, une connectivité amygdale-CPF accrue a été observée chez des adultes et des jeunes en bonne santé psychologique, mais présentant de hauts risques de trouble anxieux (Hardee et al., 2013; Tzschoppe et al., 2014). Une augmentation de l'activité du CPFvm, et une connectivité fonctionnelle plus forte entre l'amygdale et le CPFvm ont en retour été associées à une réduction des symptômes d'anxiété chez les individus anxieux et/ou ayant un historique d'adversité dans l'enfance (Birn et al., 2014; Fan et al., 2014; Gee et al., 2013; Herringa et al., 2013; Monk et al., 2006; Thomason et al., 2015). Ceci suggère l'existence d'influences inhibitrices compensatoires du CPFvm sur l'amygdale, qui permettraient aux personnes à risque d'anxiété de réguler efficacement les réponses initiales aux stimuli inducteurs d'anxiété, pour ainsi aider à réduire la sévérité des symptômes (Monk et al., 2006).

Des changements en termes de connectivité fonctionnelle entre l'insula et l'amygdale ont aussi été rapportés, bien que les résultats divergent d'une étude à l'autre. Ainsi, certains auteurs rapportent des augmentations de connectivité (Rabinak et al., 2011; Roy et al., 2013; Thomason et al., 2015), alors que d'autres rapportent plutôt des réductions de la communication amygdale-insula chez les personnes anxieuses et/ou ayant un historique d'adversité dans l'enfance (Etkin, Prater, Schatzberg, Menon, & Greicius, 2009; Fonzo et al., 2013; Fonzo et al., 2010; A. N. Simmons et al., 2008; van der Werff et al., 2013).

1.5.6 Adversité dans l'enfance, anxiété circuit neuronal de la peur : résumé

En résumé, alors que des activations accrues dans les structures du lobe temporal médian, l'insula et le GCAd semblent refléter une sensibilité et une réactivité accrues face aux menaces potentielles chez les individus ayant un historique d'adversité dans l'enfance et/ou souffrant d'un trouble anxieux, des hypoactivations du CPFvm semblent plutôt témoigner d'une pauvre régulation émotionnelle, résultant de l'inefficacité du CPF à exercer un contrôle inhibiteur suffisant sur les structures temporales et les régions plus postérieures du GCA. En

revanche, une activité accrue du CPFvm et une connectivité accrue entre cette structure et l'amygdale pourraient refléter un facteur de protection contre le développement d'un trouble anxieux.

1.6 Conditionnement et extinction de la peur et circuit neuronal de la peur

1.6.1 Tâches de conditionnement et d'extinction de la peur

Les tâches de conditionnement et d'extinction de la peur sont parmi les paradigmes les plus fréquemment employés pour étudier le traitement de la peur et le fonctionnement du circuit neuronal de la peur chez l'animal et chez l'adulte sain, ainsi que chez les individus atteints de troubles anxieux (Lissek et al., 2005; Milad & Quirk, 2012; Pine, Helfinstein, Bar-Haim, Nelson, & Fox, 2009; Sehlmeyer et al., 2009).

Le conditionnement de la peur est un processus par lequel un stimulus conditionné (SC), un visage neutre par exemple, suscite une réponse conditionnée de peur suite à l'appariement répété avec un stimulus inconditionnel (SI) aversif tel que des électrochocs. Cette réponse conditionnée de peur peut être sujette à l'extinction en présentant de manière répétée le SC sans le SI. Chez les participants jeunes, des contraintes éthiques compliquent l'usage de ce paradigme en proscrivant, par exemple, l'emploi d'électrochocs comme stimuli aversifs (Lau et al., 2008; Pine et al., 2009). Les tâches de conditionnement de la peur utilisées chez les enfants doivent de ce fait employer des SIs suscitant une réponse de peur suffisamment importante, tout en étant moins aversifs que les électrochocs. Les tâches utilisées dans cette thèse ont été développées en fonction de ces exigences. Ainsi, les SIs qui seront employés dans le cadre de la présente thèse seront constitués de visages exprimant la peur qui seront accompagnés de cris de peur. Deux études précédentes employant cette tâche chez des jeunes anxieux et en bonne santé ont révélé que ce type de SI provoquait des réponses de peur suffisamment puissantes, tout en étant moins aversif que les chocs électriques, permettant ainsi d'entrainer un conditionnement de la peur sécuritaire et acceptable

sur le plan éthique pour être employé avec une population pédiatrique (Lau et al., 2011; Lau et al., 2008).

Une variante des tâches classiques de conditionnement de la peur est le conditionnement différentiel de la peur, dans lequel deux SC sont employés au lieu d'un seul: le SC+ (jumelé au SI dans un certain nombre d'essais) et le SC-. Le SC- est un stimulus conditionné qui n'est jamais jumelé au SI et qui joue le rôle de « signal de sécurité » (Lissek et al., 2005). Dans ce type de paradigme, les réponses conditionnées de peur face au SC+ sont comparées aux réponses de peur face au SC- durant les phases de conditionnement et d'extinction de la peur. Ainsi, chez les individus sains, des réponses de peur accrues face au SC+ par rapport au SC- sont généralement observées durant le conditionnement. Durant l'extinction, les réponses de peur provoquées par le SC+ diminuent graduellement, ce qui diminue également la différence (ou niveau de discrimination) entre les réponses de peur face au SC+ et les réponses de peur face au SC- (Lissek et al., 2005). La plupart des études réalisées chez l'animal et chez l'humain adulte utilisent des stimuli hautement aversifs tels des chocs électriques (Milad, 2006 et 2012; Lissek et al, 2005. Or, ce type de stimulus ne peut être employé avec une population pédiatrique, pour des raisons déontologiques et pratiques.

Dans le cadre de la présente thèse, nous utiliserons un paradigme de conditionnement différentiel basé sur les tâches développées par Lau et collaborateurs (2008), employant (1) un SC+, soit la photo du visage d'une actrice (ou acteur pour la deuxième étude) affichant une expression émotionnellement neutre, apparié au SI (visage de la même actrice (acteur) exprimant la peur jumelé à un cri de peur) lors de 50% des essais et (2) un SC-, soit la photo du visage d'une autre actrice (ou acteur), affichant également une expression émotionnellement neutre et n'étant jamais jumelée au SI. Ces tâches se sont avérées efficaces pour susciter des réponses de peur et éliciter des activations au sein du circuit neuronal de la peur (Lau et al, 2011). Or, le fait que les visages soient exclusivement féminins pourrait engendrer un certain biais dans les résultats, dans la mesure où le sexe des stimuli modulerait les réponses de peur. Celui-ci pourrait également interagir avec le sexe des participants, ce qui pourrait, encore une fois, influencer les résultats dans une certaine mesure. Nous avons donc cherché, dans un premier temps, à examiner les influences individuelles et conjointes du sexe

des participants et du sexe des stimuli sur les réponses de peur durant le conditionnement et l'exinction de la peur chez une population jeune.

1.6.2 Conditionnement et extinction de la peur chez les jeunes en bonne santé : effets du sexe des participants et du sexe des stimuli

De nombreuses études chez l'adulte témoignent de différences sexuelles lors du traitement de stimuli émotionnels. De plus, la littérature suggère que le sexe des acteurs employés comme stimuli émotionnels faciaux peut également moduler le traitement des émotions chez les participants adultes, bien que ceci ait peu été étudié chez les jeunes.

1.6.2.1 Influences du sexe du participant sur le traitement émotionnel

Les résultats d'études antérieures rapportent des résultats variés par rapport aux différences sexuelles en termes de reconnaissance émotionnelle et des réactions aux émotions. Des études chez les rongeurs rapportent des niveaux de conditionnement supérieurs et une plus forte résistance à l'extinction chez les sujets mâles par rapport aux femelles. Par ailleurs, ces différences émergent autour de la puberté et seraient probablement liées aux influences des hormones sexuelles (Dalla & Shors, 2009).

Chez l'être humain adulte, des résultats contradictoires sont rapportés. D'une part, les femmes tendent à évaluer le SC+ et le SI comme étant davantage déplaisants, anxiogènes et/ou douloureux durant le conditionnement et l'extinction de la peur (Forsyth & Eifert, 1998; M. M. Kelly & Forsyth, 2007; Meulders, Vansteenwegen, & Vlaeyen, 2012). Par ailleurs, lorsque des réponses physiologiques sont employées (réponses électrodermales ou RÉD, activation cérébrale), les hommes semblent davantage réactifs que les femmes lors du traitement de stimuli menaçants, tout particulièrement lorsque ces stimuli sont constitués de visages masculins. Ces résultats ont été interprétés sous une perspective évolutive, suggérant que les

hommes, davantage que les femmes, doivent être prêts à se défendre contre d'éventuels rivaux masculins, afin d'assurer leur survie et leur reproduction (Kret & De Gelder, 2012; Milad, Goldstein, et al., 2006). En ce qui concerne le conditionnement de la peur, certaines études rapportent davantage de RÉDs en réponse aux stimuli faciaux menaçants chez les hommes par rapport aux femmes (Dimberg, 1996), alors que d'autres rapportent plutôt des réponses équivalentes entre les deux sexes (Kret & De Gelder, 2012; Navarrete et al., 2009).

Chez les jeunes, aucune étude n'a à ce jour examiné de façon explicite l'influence du sexe des participants sur le conditionnement et l'extinction de la peur. Néanmoins, des différences sexuelles au plan émotionnel ont été observées chez des enfants d'âge scolaire. Ainsi, les filles rapportent davantage d'inquiétudes et présentent des peurs de fréquence et d'intensité accrues par rapport aux garçons face à divers stimuli tels que l'obscurité, les animaux et certains objets, sons et expressions faciales (Gullone, 2000). Par ailleurs, diverses études employant des visages comme stimuli émotionnels rapportent davantage de réactions négatives face aux visages menaçants, ainsi que de meilleures aptitudes de reconnaissance émotionnelle en termes de vitesse et de précision, chez les filles par rapport aux garçons (Lee et al., 2013; voir revues par Kret & De Gelder, 2012; McClure, 2000). Cependant, d'autres auteurs rapportent une absence de différences sexuelles dans le traitement des émotions, tant chez des enfants que chez des adolescents (De Sonneville et al., 2002; Herba, Landau, Russell, Ecker, & Phillips, 2006; Kret & De Gelder, 2012; McClure, 2000; L. A. Thomas, De Bellis, Graham, & LaBar, 2007; Vicari, Reilly, Pasqualetti, Vizzotto, & Caltagirone, 2000).

1.6.2.2 Influences du sexe des stimuli sur le traitement émotionnel

Le sexe des acteurs/actrices employés comme stimuli émotionnels faciaux semble aussi influencer le traitement émotionnel. Ainsi, il a souvent été démontré que les visages masculins présentant une expression menaçante telle que la peur ou la colère suscitent davantage de réponses de peur que des visages homologues féminins, tant chez les enfants et les adolescents que chez les adultes (Aguado, Garcia-Gutierrez, & Serrano-Pedraza, 2009; Becker, Kenrick, Neuberg, Blackwell, & Smith, 2007; Egger et al., 2011; Goos L.M., 2002; Hess H., 1997; Navarrete et al., 2009; Seidel, Habel, Kirschner, Gur, & Derntl, 2010).

1.6.2.3 Influences du sexe du participant et du sexe des stimuli sur le traitement émotionnel : résumé

Les résultats de l'ensemble des études présentées à cette rubrique suggèrent l'existence d'un traitement émotionnel différentiel selon, d'une part, le sexe des participants et, d'autre part, le sexe des acteurs utilisés dans la constitution des stimuli émotionnels. Par ailleurs, peu d'études ont exploré ces différences à l'aide de tâches de conditionnement et d'extinction de la peur chez l'adulte et aucune ne s'y est intéressée chez une population jeune. Des différences liées au sexe des participants et/ou des stimuli pourraient constituer des facteurs confondants dans l'analyse et l'interprétation des résultats d'études utilisant des paradigmes de conditionnement et d'extinction de la peur, dans la mesure où celles-ci emploieraient des participants des deux sexes et/ou des visages (féminins ou masculins) comme SI/SC, tel que dans le cadre de la présente thèse. Le deuxième objectif de cette thèse vise donc à mieux caractériser l'influence du sexe des participants et du sexe des stimuli sur le conditionnement et l'extinction de la peur chez les adolescents.

1.6.3 Conditionnement et extinction de la peur : études en neuroimagerie chez les sujets sains

Chez l'adulte en bonne santé, diverses études démontrent une activation supérieure de l'amygdale face au SC+ comparativement au SC- durant le conditionnement de la peur (Buchel, Dolan, Armony, & Friston, 1999; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Sehlmeyer et al., 2009). Des résultats semblables ont été observés chez les jeunes dans une étude IRMf de conditionnement de la peur employant la tâche utilisée dans le cadre de la présente thèse (Lau et al., 2011). Cependant, de récentes revues de la littérature incluant des études effectuées sur des participants adultes sains rapportent des résultats inconstants d'une étude à l'autre en ce qui concerne l'implication de l'amygdale durant le conditionnement de la peur (Fullana et al., 2015; Mechias, Etkin, & Kalisch, 2010; Sehlmeyer et al., 2009). Ces divergences ont été attribuées à des différences méthodologiques, ainsi qu'aux patrons

d'habituation rapide de cette structure cérébrale (Fullana et al., 2015; Mechias et al., 2010; Sehlmeyer et al., 2009). En effet, l'activité de l'amygdale et les réponses de peur associées tendent à diminuer de façon rapide au cours du conditionnement (Buchel et al., 1998; LaBar et al., 1998; Quirk, Armony, & LeDoux, 1997). Ceci soulève l'importance de diviser le conditionnement et l'extinction de la peur en phases précoce et tardive, afin de mesurer adéquatement l'effet de ces tâches (Sehlmeyer et al., 2009), et d'utiliser un ratio partiel d'appariement SC+/SI (i.e. dans 50 ou 75% des essais), afin de limiter l'habituation (Mackintosh, 1974). Ces revues de la littérature ont aussi démontré l'implication d'autres structures du circuit neuronal de la peur, incluant l'hippocampe, l'insula, le GCAsg et le GCAd, durant le conditionnement de la peur (Fullana et al., 2015; Mechias et al., 2010; Sehlmeyer et al., 2009). D'autres études effectuées uniquement chez les adultes rapportent également une activité accrue de l'amygdale, de l'insula et du CPFvm/GCAsg lors de la présentation du SC+ vs. SC- durant l'extinction de la peur (Delgado, Olsson, & Phelps, 2006; Gottfried & Dolan, 2004; LaBar et al., 1998; Milad & Quirk, 2012; Milad, Rauch, et al., 2006; Phelps, Delgado, Nearing, & LeDoux, 2004; Sehlmeyer et al., 2009). L'implication du GCAsg semble par ailleurs être particulièrement importante pour l'extinction de la peur (Delgado et al., 2006; Milad & Quirk, 2012; Milad, Rauch, et al., 2006) chez l'adulte, alors que ceci n'a pas encore été vérifié chez le jeune.

1.6.4 Conditionnement et extinction de la peur : effets de l'adversité dans l'enfance et de l'anxiété

1.6.4.1 Adversité dans l'enfance, anxiété et conditionnement de la peur : Études comportementales

Les études de conditionnement et d'extinction de la peur démontrent la présence d'altérations du traitement de la peur chez les individus anxieux et/ou ayant vécu de l'adversité tôt dans la vie. Au plan comportemental, des niveaux accrus de peur subjective, ainsi que des réponses physiologiques (e.g., RÉDs, réflexes occulaires) plus rapides et/ou plus importantes face au SC+ (ou face au SC+ vs SC-) ont été rapportées chez les adultes

présentant un TSPT lié à un historique d'adversité dans l'enfance (Bremner et al., 2005), ainsi que chez les adultes et les jeunes en bonne santé psychologique mais étant à haut risque d'anxiété (en raison de traits de personnalité anxieux et/ou d'un historique d'anxiété dans la famille) (Barrett & Armony, 2009; Bremner et al., 2005; Glotzbach-Schoon et al., 2013; Indovina et al., 2011; Pejic, Hermann, Vaitl, & Stark, 2013; Waters, Peters, Forrest, & Zimmer-Gembeck, 2014), bien que certains auteurs ne rapportent pas ces différences au niveau physiologique (Bremner et al., 2005; Pejic et al., 2013). Chez les adultes et les jeunes atteints d'un trouble anxieux chez qui l'historique d'adversité n'était pas évalué, en revanche, une série d'études rapporte des niveaux subjectifs de peur et des RÉDs accrus face au SC- ou aux deux types de SCs (SC+ et SC-) dans un contexte de conditionnement différentiel équivalent (Britton et al., 2013; Craske, Waters, et al., 2008; Lau et al., 2008; Lissek, 2012; Lissek et al., 2005; Lissek et al., 2009; Waters, Henry, & Neumann, 2009). Une résistance à l'extinction des réponses de peur est aussi rapportée dans cette population (Craske, Waters, et al., 2008; Liberman, Lipp, Spence, & March, 2006; Milad, Rauch, et al., 2006; Waters et al., 2009).

Jusqu'à tout récemment, aucune étude n'avait investigué le conditionnement de la peur chez les jeunes, en lien avec un historique d'adversité. Néanmoins, une toute récente étude rapporte une réduction des réponses de peur face au SC+ durant la phase précoce de conditionnement chez des jeunes ayant été victimes de maltraitance par rapport aux jeunes du groupe contrôle et ce, indépendamment des symptômes d'anxiété et de la présence ou non d'un diagnostic de TSPT (McLaughlin, Sheridan, et al., 2015). Ces résultats sont surprenants, étant donné que la plupart des études rapportent plutôt une réactivité accrue face aux menaces chez les individus ayant un historique d'adversité dans l'enfance (Bremner et al., 2005; Maheu et al., 2010; Pine et al., 2005; Pollak & Sinha, 2002; Pollak & Tolley-Schell, 2003), et suggèrent qu'un historique d'adversité peut se manifester de manière indépendante aux niveaux d'anxiété.

1.6.4.2 Adversité dans l'enfance, anxiété et conditionnement de la peur : Études en neuroimagerie cérébrale

De façon similaire à ce qui a été rapporté au plan comportemental, une activité accrue du lobe temporal médian face au SC+ (ou SC+ vs SC-) a été observée chez des adultes atteints de TSPT lié à des abus dans l'enfance, ainsi que chez des adultes et des jeunes à haut risque d'anxiété (Barrett & Armony, 2009; Bremner et al., 2005; Craske, Waters, et al., 2008; Indovina et al., 2011; Pejic et al., 2013; Waters et al., 2009). En revanche, une généralisation de la peur au stimulus neutre (SC-), illustrée par des activations amygdaliennes accrues en réponse au SC- ou aux deux SCs dans un contexte de conditionnement différentiel de la peur équivalent, ont aussi été rapportées chez les jeunes et les adultes anxieux, indépendamment de leur historique d'adversité (Britton et al., 2013; Craske, Waters, et al., 2008; Gazendam, Kamphuis, & Kindt, 2013; Kindt & Soeter, 2014; Lau et al., 2008; Lissek, 2012; Lissek et al., 2005; Lissek et al., 2010; Lissek et al., 2009; Mahan & Ressler, 2012; Waters et al., 2009).

1.6.4.3 Adversité dans l'enfance, anxiété et extinction de la peur

Une résistance à l'extinction de la peur, illustrée par un maintien des réponses subjectives et physiologiques accrues face au SC+ vs. SC- durant la phase d'extinction, est également caractéristique de l'anxiété (Craske, Waters, et al., 2008; Liberman et al., 2006; Milad & Quirk, 2012; Milad, Rauch, et al., 2006; Waters et al., 2009). Celle-ci pourrait être expliquée par les hypoactivations du CPFvm et du GCAsg observées chez les adultes anxieux (Bremner et al., 2005; Erhardt & Spoormaker, 2013; Indovina et al., 2011; Lissek, 2012; Milad, Rauch, et al., 2006; Sehlmeyer et al., 2011), qui en retour seraient associées aux difficultés générales de régulation émotionnelle à la base des symptômes (Milad & Quirk, 2012). La résistance à l'extinction, ainsi que la généralisation des réponses de peur au SC-, ont été interprétées comme témoignant d'une difficulté chez les personnes anxieuses à distinguer les signaux de « sécurité », des stimuli signalant une « menace » potentielle (Britton et al., 2011; Lissek et al., 2005).

D'un autre côté, un risque d'anxiété chez des adultes en bonne santé psychologique a été associé à des activations accrues du CPFvm face au SC+ vs. SC- durant l'extinction (Barrett & Armony, 2009); ceci n'a pas encore été exploré chez les jeunes. De plus, une augmentation de la connectivité fonctionnelle entre l'amygdale et le CPFvm durant le conditionnement de la peur a été observée chez des jeunes à risque d'anxiété (Tzschoppe et al., 2014). Ces résultats renforcent l'hypothèse de l'existence de mécanismes compensatoires chez les individus à haut risque d'anxiété, via lesquels l'activation accrue du CPFvm et sa connectivité accrue avec l'amygdale et pourraient lui permettre de réguler efficacement les structures temporales hyperactives (Monk et al., 2006).

1.6.4.4 Adversité dans l'enfance, anxiété, conditionnement et extinction de la peur : conclusions

L'ensemble des études présentées à la rubrique précédente suggère la présence d'altérations du traitement de la peur chez les individus ayant un historique d'adversité dans l'enfance, ainsi que chez les individus anxieux. Par ailleurs, une seule étude comportementale (McLaughlin et al., 2015) a étudié le conditionnement et l'extinction de la peur chez les jeunes en lien avec un historique d'adversité, et aucune n'en a investigué les corrélats au plan du fonctionnement cérébral.

1.7 Adversité dans l'enfance, anxiété et fonctionnement du circuit neuronal de la peur : limites des études précédentes

L'ensemble des études en neuroimagerie chez les individus anxieux et/ou avec un historique d'adversité dans l'enfance suggère que des altérations du fonctionnement du circuit neuronal de la peur sont associées à l'adversité vécue durant l'enfance, de même qu'à l'anxiété, et renforcent l'hypothèse du rôle médiateur des différentes composantes du circuit

neuronal de la peur dans les liens entre l'anxiété et l'adversité. Cependant, la majorité des études mentionnées ci-haut proviennent de la littérature chez l'adulte, et la plupart d'entre elles ont examiné les corrélats neuronaux de l'anxiété OU de l'adversité exclusivement, sans s'intéresser à leurs influences mutuelles et à leurs interactions potentielles. Par ailleurs, la majorité de ces études, tant chez l'adulte que chez le jeune, ont employé des échantillons relativement petits ou hétérogènes, mélangeant des individus avec des historiques d'adversité de diverses origines (e.g. abus physique, sexuel ou négligence émotionnelle), et présentant des symptômes psychiatriques d'étiologie variable (Hart & Rubia, 2012; McCrory et al., 2011). Enfin, aucune de ces études ne s'est intéressée à cette forme plus légère mais malgré tout potentiellement délétère d'adversité que constituent les pratiques parentales coercitives. Cette thèse a donc pour but principal d'examiner les influences spécifiques de l'adversité dans l'enfance -- vécue de façon chronique sous la forme unique de pratiques parentales coercitives-- et de l'anxiété -- sous la forme de manifestations comportementales et de traits de personnalité anxieux élevés --, ainsi que leurs interactions potentielles, chez des jeunes en bonne santé, durant le conditionnement et l'extinction de la peur. Comprendre les liens entre l'adversité, l'anxiété et le circuit neuronal de la peur alors que les individus sont encore jeunes est crucial, afin d'identifier les jeunes étant le plus à risque et de rapidement implanter des interventions ciblées selon le type de risque encouru par le jeune et les processus neuronaux impliqués.

1.8 Objectifs et hypothèses de la présente thèse

1.8.1 Objectifs et hypothèses généraux

Étant donnée l'omniprésence des pratiques parentales coercitives et les nombreuses conséquences potentielles au plan psychopathologique (Hart & Rubia, 2012; Pine, 2003), il est important d'un point de vue clinique et de santé publique de mieux comprendre leurs influences sur le traitement émotionnel et sur le fonctionnement cérébral. Cette thèse a donc pour objectif principal de mieux comprendre les corrélats comportementaux, physiologiques, biologiques (incluant le sexe des participants), sociaux (incluant le sexe des visages utilisés

comme stimuli émotionnels) et neuronaux du traitement de la peur chez les jeunes en bonne santé physique et psychologique, en lien ou non avec un historique de pratiques parentales coercitives et d'anxiété. De plus, étant donné le risque d'évolution vers des comportements parentaux abusifs (Gershoff, 2002; Straus, 2000), nous chercherons, dans un premier temps, à mieux caractériser l'évolution longitudinale des pratiques parentales coercitives et à identifier les facteurs de risque associés, en nous concentrant spécifiquement sur la période allant de la petite enfance à l'âge de 6 ans, période ayant peu été explorée par le passé.

L'identification des facteurs de risque associés aux pratiques parentales coercitives d'une part, et, des corrélats neuronaux et comportementaux de l'anxiété et de l'adversité d'autre part, permettra éventuellement d'identifier les jeunes étant le plus à risque et de développer des interventions ciblées, afin de réduire les risques de psychopathologie à l'âge adulte.

1.8.2 Objectifs et hypothèses de l'article 1

L'objectif de l'article 3 est de mieux caractériser l'évolution longitudinale des pratiques parentales coercitives maternelles et les facteurs de risque associés, durant la période allant de la petite enfance à l'âge de 6 ans. Pour ce faire, nous étudierons un échantillon constitué de 2045 enfants et leurs mères, dont les niveaux de pratiques parentales coercitives ont été mesurés annuellement entre l'âge de 5 et 108 mois, et nous nous concentrerons sur la période de 17 à 72 mois. De cet objectif général découlent trois objectifs spécifiques :

Objectif spécifique 1 : Définir l'évolution longitudinale des pratiques parentales coercitives maternelles de la petite enfance (17 mois) à l'âge d'entrée à l'école (72 mois) à l'aide d'un modèle de courbe de croissance latente.

Objectif spécifique 2 : Identifier les facteurs de risque relatifs aux caractéristiques de l'enfant (le sexe et les comportements extériorisés et intériorisés), de la mère (le sentiment d'efficacité parentale et un historique de dépression) et du contexte familial (la suffisance du revenu familial et la satisfaction maritale telle que perçue par la mère) permettant de prédire des niveaux élevés des pratiques parentales coercitives entre 17 et 72 mois.

Hypothèse spécifique 2 : Le fait que l'enfant soit un garçon et présente une fréquence plus importante de comportements extériorisés et intériorisés, de même qu'un historique de dépression maternelle, des niveaux élevés d'insatisfaction maritale et une insuffisance du revenu tels que mesurés alors que l'enfant était âgé de 17 mois, seront associés à des niveaux plus élevés de pratiques parentales coercitives maternelles à 42 mois. Des niveaux élevés d'efficacité parentale perçue seront associés à des niveaux plus faibles de coercition maternelle.

Objectif spécifique 3 : Identifier les facteurs de risque permettant de prédire l'évolution longitudinale des pratiques parentales coercitives entre 17 et 72 mois.

Hypothèse spécifique 3: Les facteurs relatifs à l'enfant, soit le sexe et les comportements intériorisés et extériorisés seront associés à l'évolution longitudinale des pratiques parentales coercitives entre 17 et 72 mois.

1.8.3 Objectifs et hypothèses de l'article 2

Le second objectif de la présente thèse consiste à établir une méthodologie robuste permettant d'étudier le traitement de la peur et, dans la troisième étude, d'examiner le fonctionnement du circuit de la peur chez une population jeune. Pour ce faire, nous allons étudier, d'une part, l'influence du sexe des participants et, d'autre part, l'influence du sexe des visages constituant les stimuli cibles, ainsi que leurs potentielles interactions, sur le conditionnement et l'extinction de la peur chez des jeunes en bonne santé âgés de 10 à 17 ans. Dans cette optique, des tâches de conditionnement et d'extinction différentiels de la peur, développées par Lau et ses collaborateurs (2008) seront modifiées et utilisées. Pour la moitié des participants (filles et garçons), les stimuli originaux, soit les visages de deux actrices affichant une expression neutre (SC+ et SC-) ou effrayée (SI), seront utilisés. Pour l'autre moitié des jeunes (filles et garçons), des stimuli homologues masculins seront employés. Afin de mesurer les réponses de peur, deux types de mesures seront utilisés. D'une part, les niveaux subjectifs du degré de peur ressentie lors de la présentation de chaque stimulus seront mesurés pour chaque participant à l'aide d'une échelle en 5 points. De plus, les réponses électrodermales (RÉDs) seront enregistrées à l'aide de deux électrodes placées sur la plante du

pied des participants. Cette étude comporte les trois buts spécifiques et les hypothèses associées suivants :

But spécifique 1 : Investiguer l'influence du sexe des participants sur les réponses subjectives et physiologiques lors du conditionnement et de l'extinction de la peur.

Hypothèse 1.1 : Durant le conditionnement, les garçons et les filles devraient démontrer un conditionnement différentiel, illustré par de plus fortes réponses de peur face au SC+ vs. SC-.

Hypothèse 1.2 : Les filles devraient démontrer des niveaux de peur supérieurs aux garçons (face au SC+ et SC-), tels qu'évalués par les réponses subjectives de peur, durant le conditionnement et l'extinction de la peur.

Hypothèse 1.3 : Les garçons devraient démontrer des niveaux de peur supérieurs aux filles (face au SC+ et SC-), tels qu'évalués par les réponses électrodermales, durant le conditionnement et l'extinction de la peur, en particulier face aux stimuli masculins.

But spécifique 2 : Investiguer l'influence du sexe des stimuli faciaux sur le conditionnement et l'extinction de la peur.

Hypothèse 2 : Les visages masculins devraient susciter des réponses de peur supérieures chez les deux sexes par rapport aux visages féminins.

Hypothèse 3 : Durant l'extinction, les garçons et les filles devraient diminuer les réponses de peur subjectives et objectives, qui devraient devenir équivalentes entre le SC+ et le SC-. Ces réponses (SC+ et SC-) demeureront supérieures chez les filles par rapport aux garçons pour les réponses subjectives et supérieures chez les garçons pour les réponses objectives. Les réponses (subjectives et objectives) demeureront supérieures pour les visages masculins par rapport aux visages féminins.

1.8.4 Objectifs et hypothèses de l'article 3

Enfin, nous examinerons pour la première fois, dans l'article 3, les influences spécifiques et conjointes de (1) l'adversité dans l'enfance, prenant la forme de pratiques parentales coercitives, et (2) des niveaux d'anxiété, sous la forme de comportements et de traits anxieux, sur le conditionnement et l'extinction différentiels de la peur chez des jeunes âgés entre 12 et 16 ans. Pour ce faire, nous distribuerons 84 jeunes en bonne santé physique et

psychologique dans quatre groupes selon (1) le niveau de pratiques parentales coercitives de leur mère (faibles / élevés) et (2) leurs niveaux d'anxiété (faibles / élevés), mesurés de façon longitudinale de l'âge de 30 à 108 mois. Ces jeunes seront soumis aux mêmes tâches de conditionnement et d'extinction de la peur utilisées dans l'article 1, en n'employant que les stimuli féminins, durant une séance d'imagerie par résonnance magnétique fonctionnelle. Des évaluations subjectives du degré de peur ressentie lors de la présentation de chaque stimulus, de même que les RÉDs, seront aussi mesurées durant la passation des tâches. Cette étude comporte les buts spécifiques et les hypothèses associées suivants :

But spécifique 1: Déterminer si les réponses comportementales de peur (évaluations subjectives du degré de peur et RÉDs) et la réponse de l'amygdale, de l'hippocampe antérieur et de l'insula durant le conditionnement de la peur permettent de distinguer les jeunes (1) élevés dans un contexte de pratiques parentales coercitives et présentant des niveaux d'anxiété élevés (coercition élevée/anxiété élevée ou C-É/anx-É; n = 21), (2) élevés dans un contexte de pratiques parentales coercitives et des niveaux d'anxiété faibles (C-É/ anx-F; n = 20), (3) n'ayant pas été élevés dans un contexte de pratiques parentales coercitives et présentant des niveaux d'anxiété élevés (coercition faible/anxiété ou C-F/anx-É; n = 18), et les jeunes (4) n'ayant pas été élevés dans un contexte de pratiques parentales coercitives et présentant des niveaux d'anxiété faibles (C-F/anx-F; n = 21).

Hypothèse spécifique 1.1 : Durant le conditionnement de la peur, des niveaux accrus de conditionnement différentiel, reflétés par de plus fortes réponses en termes de RÉDs, d'évaluations subjectives de peur et d'activations de l'amygdale, de l'hippocampe antérieur et de l'insula face au SC+ vs. SC-, sont attendus chez les jeunes élevés dans un contexte de pratiques parentales coercitives (C-É/anx-É et C-É/anx-F) et/ou ayant des niveaux élevés d'anxiété (C-F/anx-É) par rapport aux jeunes du groupe C-F/anx-F.

Hypothèse spécifique1.2 : Les jeunes présentant des niveaux d'anxiété élevés (C-É-anx-É et C-F/anx-É) devraient présenter des réponses accrues (au plan neuronal, comportemental et physiologique) aux deux SCs par rapport aux groupes présentant des niveaux d'anxiété faibles (C-É/ anx-F, C-F/ anx-F).

Hypothèse spécifique 1.3 : Une connectivité réduite entre l'amygdale et le GCAsg/CPFvm est attendue chez les groupes présentant des niveaux d'anxiété élevés (C-É-anx-É et C-F/anx-É), par rapport aux groupes présentant des niveaux d'anxiété faibles (C-É/ anx-F, C-F/ anx-F). Chez les jeunes du groupe C-É/anx-F, une connectivité accrue est aussi attendue par rapport aux jeunes du groupe C-F/anx-F. Nous n'avions pas d'hypothèse spécifique concernant la connectivité amygdale-insula, en raison de l'absence de direction claire à ce sujet dans la littérature.

But spécifique 2 : Déterminer si les réponses comportementales de peur (évaluations subjectives du degré de peur et réponses électrodermales) et la réponse de l'amygdale, de l'hippocampe antérieur, de l'insula et du CPFvm durant l'extinction de la peur permettent de distinguer les jeunes (1) C-É/anx-É, (2) C-É/ anx-F, (3) C-F/anx-É, et (4) C-F/anx-F.

Hypothèse spécifique 2.1 : Durant l'extinction de la peur, les jeunes ayant des niveaux élevés d'anxiété (C-É/anx-É, C-F/anx-É) vont présenter une extinction réduite de la réponse de peur, reflétée par des évaluations subjectives de peur, des RÉDs et des activations du lobe temporal médian et de l'insula accrues face au SC+ vs. SC-, comparativement aux jeunes sans symptômes anxieux (C-É/ anx-F, C-F/ anx-F).

Hypothèse spécifique 2.2 : Les jeunes avec symptômes anxieux (C-É/anx-É, C-F/anx-É) démontreront une activation réduite du GCAsg/CPFvm par rapport aux jeunes avec des niveaux d'anxiété faibles (C-É/anx-F, C-F/anx-F), reflétant une régulation de l'amygdale moins efficace. De plus, les jeunes élevés dans un contexte de pratiques parentales coercitives mais qui ne présentent pas d'anxiété (C-É/anx-F) vont aussi démontrer une activation supérieure du GCAsg/CPFvm par rapport aux jeunes du groupe C-F/anx-F, malgré des niveaux équivalents de réponses subjectives de peur, de RÉDs et d'activations temporales médianes, reflétant un mécanisme compensatoire permettant l'inhibition adéquate de l'amygdale.

Chapitre 2

Articles

Article 1 : Maternal Harsh Parenting Practices: Developmental Evolution and Risk Factors from Early to Middle Childhood

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Maternal Harsh Parenting Practices: Developmental Evolution and Risk Factors from Early to Middle Childhood

Abstract

The present study modeled maternal harsh parenting (HP) evolution during early childhood, and identified associated risk factors. Maternal HP levels were assessed annually from 17 to 72 months (n= 2045 mother-child dyads). Child, mother, and family risk factors were measured at 17 months. A latent growth curve model was employed. Maternal HP followed a quadratic evolution, initially increasing from 17 to 42 months, then decreasing between 42 and 72 months. Child sex and internalizing and externalizing behaviors, as well as maternal depression and self-efficacy, predicted HP levels at 42 months. Child internalizing behaviors predicted HP decreases from 17 to 72 months, while child sex and externalizing behaviors, as well as maternal self-efficacy, moderated decreases after 42 months. These results provide potential targets for future interventions.

Key words: harsh parenting, risk factors, toddlerhood, preschool, longitudinal

Parenting practices are presumed to play a key role in emotional and social development during early childhood. Being sensitive and responsive to a child's needs and demands is related to a secure parent-child attachment relationship, which in turn creates a positive context for the successful development of a child's emotional and social competences (Gervai, 2009). In contrast, adopting harsh child-rearing behaviors, as reflected by hostile and punitive parenting practices, is associated with insecure attachment and a range of affective problems (Boivin et al., 2005; McKee et al., 2007). Although a majority of these previous studies have focused on abusive parenting behaviors that were chronic and severe enough to be reported to authorities, i.e., child maltreatment (Gracia, 1995), harsh parenting practices, a milder form of adversity, have also been related to negative socio-emotional outcomes (Gershoff, 2002; McKee et al., 2007), as well as to increased risks of psychopathology across the lifespan, such as anxiety, affective and conduct disorders (MacMillan et al., 1999).

Despite being linked to such negative developmental outcomes, harsh parenting is a relatively common practice amongst North American parents. Indeed, 11% of parents of children aged 0-17 years from a large community sample from Quebec, Canada, reported having used physical discipline practices (e.g. hitting their child on the buttocks), 49% reported the use of psychological aggression (e.g. scream at, threaten) three times or more in a year, and 29% reported both practices (Clément, M-É, F. Bernèche, C. Fontaine, & C. I. Chamberland, 2012b). In the United States, nearly two-thirds of parents of one- and two-year-olds and 80% of parents of fifth graders reported having used physical punishment, and 85% of adolescents reported having been victims of such practices (Gershoff, 2008).

Given the ubiquity of harsh parenting, and the possibility that it may lead to more abusive parenting behaviors (Gershoff, 2002; Straus, 2000), it is important from a clinical and public health perspective to understand how harsh parenting evolves over time in populations, and to identify its early risk factors during childhood, in order to prevent child maltreatment and psychopathology.

Developmental evolution of harsh parenting

Thus far, very few studies have examined the longitudinal evolution of harsh parenting practices in parents of young children. A prospective longitudinal study including a

population-based sample of 1,836 mothers and their children aged between five and 30 months showed striking general increases in harsh parenting despite varying initial and overall levels (Pierce et al., 2010). Similar findings were reported in two samples of approximately 500 at-risk mother-child dyads exposed to psychosocial adversity (Kim, Pears, Fisher, Connelly, & Landsverk, 2010; Windham et al., 2004).

Longitudinal research on harsh parenting practices has also focused on older children. For instance, Lansford and colleagues (Lansford et al., 2009) investigated maternal harsh physical discipline patterns in middle childhood children (children aged 6-9 years old; n= 499 mothers) and adolescents (youths aged 10-15 years; n= 258 mothers). Despite greatly differing initial levels of harsh parenting practices, similar evolution patterns were found across mothers, with levels either remaining stable (in 48% of the younger cohort and 67% of the older cohort) or decreasing (in 52% of the younger cohort and 33% of the older cohort) over time (Lansford et al., 2009).

Intriguingly, the developmental evolution of harsh parenting during toddler and preschool years has barely been investigated, with the exception of one study focusing exclusively on physical punishment, which employed a dichotomist scale that did not measure the severity of spanking but only its prevalence (MacKenzie, Nicklas, Waldfogel, & Brooks-Gunn, 2013). In this study, the prevalence of spanking was found to slightly decrease (from 57% to 52%) between the ages of 3 and 5 in a community sample of 1,933 American children and their parents (MacKenzie et al., 2013).

Data from cross-sectional studies show that the highest prevalence of psychological aggression, as well as of minor physical violence, is observed in mothers of children aged 3 to 6 years (M.-E. Clément, F. Bernèche, C. Fontaine, & C. Chamberland, 2012a). This period is characterized by many life challenges that are fundamental in the social, emotional, physical, and cognitive development of a child (e.g.: separating from parents and socializing at daycare and kindergarten, acquiring the prerequisites for reading and writing and basic mathematical operations, etc.). There are also important changes occurring in the structure and function of brain regions (e.g.: amygdala, hippocampus) underpinning socio-emotional and cognitive processing. Hence, this is a particularly sensitive period, and one in which harsh parenting could alter some of the brain's functions and thus increase the risk of later cognitive and emotional challenges, such as academic difficulties and psychopathology (Tottenham &

Sheridan, 2009). Given the absence of studies on this crucial developmental period, the first objective of this study was to investigate maternal harsh parenting of children of ages 1 ½ to 6 years (17, 30, 42, 60 and 72 months).

Risk factors for harsh parenting average levels

Three main classes of risk factors related to harsh rearing behaviors have typically been assessed in previous research: child, maternal, and family context characteristics (see Boivin et al., 2005).

Regarding child characteristics, previous studies report that high levels of child externalizing behaviors (e.g., aggressive, hyperactive, oppositional or rule-breaking behaviors) are linked with maternal harsh psychological and physical punitive behaviors in parents of preschoolers and school-age children (e.g., Bor & Sanders, 2004; Lansford et al., 2009). Internalizing behaviors in children may also elicit harsh parenting. Indeed, mothers of withdrawn and anxious preschoolers have been found to use more coercive strategies to address their children's behaviors (Rubin & Mills, 1990). This may be explained by the fact that parents of highly internalizing children display increased negative beliefs about their child (e.g. 'My child does not respect me'), which are in turn related to higher levels of aggressive and hostile verbal and physical discipline (Laskey & Cartwright-Hatton, 2009). The sex of the child has also been associated with coercive strategy use, with some studies reporting greater use of corporal punishment practices in young boys relative to girls (for a review see Gershoff, 2002). This finding is, however, highly disputed, and requires further research (Gershoff, 2002; Windham et al., 2004).

Previously documented maternal risk factors for harsh rearing practices include mothers' self-efficacy, i.e., mothers' perception of their capacity to care for their child. Mothers feeling self-effective tend to respond with greater warmth, sensitivity and responsiveness to their infants' needs, while mothers with low feelings of self-efficacy tend to respond to their children in a more hostile and punitive manner (Boivin et al., 2005; Bugental, Lewis, Lin, Lyon, & Kopeikin, 1999). These associations, however, were shown to decrease from infancy to toddlerhood, although self-efficacy levels remained relatively stable (Pierce et al., 2010), suggesting self-efficacy may be less predictive of harsh parenting evolution and levels as children grow up. This, however, remains to be explored. Studies also suggest that depressed mothers are more irritable, less responsive and less tolerant toward their offspring,

and tend to turn to hostile rearing practices when children become more demanding and behaviorally agitated (Boivin et al., 2005; Lovejoy, Graczyk, O'Hare, & Neuman, 2000; Shay & Knutson, 2008; Windham et al., 2004); this may be particularly apparent during toddlerhood and preschool years (Kim et al., 2010; Windham et al., 2004).

The last main category of risk factors for harsh parenting concerns family characteristics. Low familial income and marital dissatisfaction have both been associated with higher levels of severe maternal verbal and physical punishments in children of different ages (Atzaba-Poria & Pike, 2008; Gershoff, 2002; Gracia, 1995; Krishnakumar & Buehler, 2000; Lansford et al., 2009). Indeed, these situations are particularly stressful and adverse, and may elicit negative affects that may often spill over into the parent-child relationship (Atzaba-Poria & Pike, 2008; Gershoff, 2002; Krishnakumar & Buehler, 2000).

Risk factors associated with harsh parenting evolution

Among the previously mentioned factors, some could also be predictive of harsh parenting evolution from toddlerhood to preschool years. Indeed, both child internalizing and child externalizing behaviors have been shown to evolve substantially from early to middle childhood (Cote et al., 2009; R. E. Tremblay et al., 2005). Moreover, different developmental trajectories have been identified, with children that display the highest initial levels of either internalizing or externalizing behaviors showing the steepest increases over time (Cote et al., 2009; R. E. Tremblay et al., 2005). These factors may therefore be particularly linked to harsh parenting evolution over this period. For instance, child-externalizing behaviors were shown to predict differences in the developmental evolution of such practices from 6 to 9 years old (Lansford et al., 2009). Since sex differences become more marked as children grow older, sex of the child may also be linked with changes in harsh parenting over time.

In summary, child, parent and family characteristics seem to all play a key role in the modulation of harsh parenting practices. However, the associations of these factors to harsh parenting evolution from toddlerhood to the preschool years have not yet been examined, and none of the previous longitudinal studies has compared the predictive value of child, mother and family risk factors during this period in a large, community-based sample. Determining the key factors linked to higher levels of harsh parenting and longitudinal evolution is important for the development and implementation of targeted preventive interventions that

would modulate harsh parenting growth and potentially reduce the use of harsh parenting in mothers. This will in turn favor children's wellbeing and healthy development.

Aims and hypotheses

The present study has two objectives. Our first objective, as stated earlier, was to fill a gap in the literature by modeling, for the first time, the longitudinal evolution of harsh parenting practices in mothers of children from early to middle childhood (i.e., from 17 to 72 months) using data from a large representative population cohort. Our second objective was to determine the risk factors of harsh parenting average growth levels and, most importantly, of its evolution pattern, by examining the contribution of child characteristics (sex, externalizing behaviors, internalizing behaviors), mother characteristics (self-efficacy, depression), and family characteristics (low income, marital satisfaction) assessed at the beginning of toddlerhood (i.e. at 17 months). We expected that children that are male, and/or display higher levels of externalizing and internalizing behaviors, as well as a history of maternal depression and insufficient family income, would be associated with higher average levels of harsh parenting practices. In contrast, we hypothesized higher levels of maternal self-efficacy and marital satisfaction to be linked with lower average levels of harsh parenting. We also expected child characteristics (sex, internalizing and externalizing behaviors) to be specifically associated with harsh parenting evolution. We defined harsh parenting as including minor physical violence (defined by corporal punishment that is not considered to be physical abuse), as well as psychological aggression (defined as screaming at the child), as both have been linked with similar predictors and negative outcomes, and since they tend to co-occur in nearly 30% of parents (Clément et al., 2012a).

Method

Participants

Data were drawn from the Quebec Longitudinal Study of Child Development (QLSCD), a prospective longitudinal study conducted with a sample of children representative of singletons born in the province of Quebec (Canada) in 1997-1998. Children were excluded from the sample if: (1) they lived in the far North, Cree or Inuit regions, or in aboriginal reservations; (2) the duration of gestation could not be determined from birth record; (3) they were born at less than 24 weeks gestation; (4) they were born later than 42 weeks gestation,

because of the delay in receiving and processing birth record data from hospitals. A total of 2,940 children were selected through a region-based stratified sampling design. Of this initial sample, 2,223 families (75.6%) agreed to participate in the study. Children were followed yearly from 5 to 108 months of age. The present study, however, focuses on the periods of toddlerhood and preschool years, since developmental patterns have already been described in younger and older children (Kim et al., 2010; Lansford et al., 2009; Pierce et al., 2010; Windham et al., 2004). Hence, we used harsh parenting data collected in mothers when their children were aged 1 ½ -6 years old, with data collection occurring precisely at 17, 30, 42, 60 and 72 months. At every data collection, informed written consent was obtained from all participating parents. Trained interviewers conducted yearly home interviews with the mothers regarding children, maternal, and familial characteristics. Only the data analyzed in this study will be described. A total of 2,045 participants for which harsh parenting measures were available for at least one time point between 17-72 months were retained for growth curve and multivariate analyses. Table 1 presents the demographic characteristics of the sample.

---- Insert Table 1 approximately here ----

Measures

Outcome variable: Maternal harsh parenting practices. Maternal parenting practices were measured using a self-administered questionnaire when children were 17, 30, 42, 60 and 72 months old. This questionnaire measured a broad range of both positive, constructive parenting practices as well as negative, harsh parenting practices. Questions were selected from the Hostile/Ineffective scale used in the National Longitudinal Survey of Children and Youth (NLSCY; Statistics Canada, 1995) and in the Parental Cognitions and Conduct Toward the Infant Scale (PACOTIS, (Boivin et al., 2005)). These questions have been validated by a panel of 15 expert clinical and developmental psychologists for content, and have been previously shown to yield reliable individual differences in parenting in population-based samples, and to significantly converge on a general factor of hostile-ineffective parenting (Boivin et al., 2005; Boyle et al., 2004; Pierce et al., 2010).

Regarding the harsh parenting practices items, mothers were asked to rate themselves on a frequency scale indicating if they never (0), less than half the time (1), half the time (2),

more than half the time (3) or all the time (4): “got angry when punishing your child”; “spanked your child when he/she was difficult”; “raised your voice, scolded or yelled at your child when he/she broke the rules or did things he/she was not supposed to do”; “used physical punishment (e.g., shaking) when he/she broke the rules or did things he/she was not supposed to do”. These chosen items have shown adequate psychometric properties for the evaluation of maternal harsh parenting practices towards infants and up to school-age children (Boivin et al., 2005; Boyle et al., 2004; Pierce et al., 2010). Scores on the four items were added, so total values ranged between 0 and 16. The internal consistency value (alphas) was .73 at 17 months, .67 at 30 months, .66 at 42 months, .64 at 60 months and .64 at 72 months. Descriptive statistics (mean, SD, skew, kurtosis) for maternal harsh parenting practices at each time point are presented in Table 2.

---- Insert Table 2 approximately here ----

Risk factors

All of the risk factors were measured when children were aged 17 months, except for marital satisfaction, which was measured at 30 months.

1. Child Characteristics. Child externalizing (aggressive behavior, opposition and hyperactivity-impulsivity) and internalizing (anxiety and depression symptoms) behaviors were assessed with items selected from the early childhood behaviour scale from the Canadian National Longitudinal Study of Children and Youth (Statistics Canada (1995). This scale incorporates items from the Child Behavior Checklist (Achenbach, 1991), the Ontario Child Health Study Scales (Boyle et al., 1993) and the Preschool Behavior Questionnaire (Behar & Stringfield, 1974; R. E. Tremblay, Desmarais-Gervais, Gagnon, & Charlebois, 1987). Selected items from this scale have been previously used in large population studies and have shown adequate psychometric properties for the evaluation of emotional disorders in childhood (Boyle et al., 1993; Broidy et al., 2003; Cote et al., 2009; Galera et al., 2014; Japel, Tremblay, Vitaro, & Boulerice, 1999; R. E. Tremblay et al., 1987; R. E. Tremblay et al., 2005).

The following items were selected:

Aggressive behavior: 13 items: e.g. “kicks others”, “bites others”, “takes things away from others”, “pushes others”, “hits others”, “gets into fights with other children”, “bullies others”; internal consistency= .78 (R. Tremblay et al., 1999).

Opposition: 4 items: "was defiant or refused to comply with adults requests or rules", "didn't seem to feel guilty after misbehaving", "punishment didn't change his/her behavior", "had temper tantrums or hot temper"; internal consistency= .62 (Behar & Stringfield, 1974).

Hyperactivity-impulsivity: 5 items: "could not sit still, was restless or hyperactive", "could not stop fidgeting", "was impulsive, acted without thinking", "had difficulty waiting for his/her turn in games", "couldn't settle down to do anything for more than a few moments"; internal consistency= .74 (R. E. Tremblay et al., 1987).

Anxiety: 4 items: "is nervous high strung or tense, "is too fearlul or anxious", "appears worried"; "cries a lot"; internal consistency= .44, (R. E. Tremblay et al., 1987).

Depression: 4 items: "seemed to be unhappy or sad", "was not as happy as other children", "had no energy, was feeling tired", "had trouble enjoying him/herself"; internal consistency= .53 (Behar & Stringfield, 1974).

Items were rated by the mothers on a scale of never or not true (0), sometimes or somewhat true (1) and often or very true (2). Raw scores were standardized into z scores within behavioral domain, with higher scores indicating higher externalizing and internalizing behavior levels.

Sex was the final child characteristic taken into account in the analysis. *Sex* of the child was coded as 0 for boys and 1 for girls.

2. Mother Characteristics. *Maternal depression* was assessed through 15 items that measure depressive symptoms during worst episode of depression (e.g. "tired out", "fatigued, or no energy" , "insomnia or hypersomnia", "trouble concentrating", "loss of interest"; internal consistency= .62), which were extracted from the QLSCD Parental Depression Questionnaire, a scale measuring life-time depression and symptoms in adults with excellent construct validity (Roy et al., 2005). The scale ranged from 0 to 15 with higher scores indicating higher depression levels. *Maternal self-efficacy* was assessed via four questions (I feel that I am very good at "keeping my baby amused", "calming my baby down when s/he is upset, fussy or crying", "keeping my baby busy while I am doing other things", "attracting my baby's attention"; internal consistency= .73) taken from the Parental Cognitions and Conduct Toward the Infant Scale (PACOTIS) (Boivin et al., 2005). Item scales ranged from 0 to 10, with higher scores indicating higher perceived self-efficacy. Item scores for both maternal

variables were added and converted to z scores, with higher scores indicating higher depression/perceived self-efficacy in mothers.

3. Family Characteristics. *Low family income* was calculated according to Statistics Canada's guidelines (Canada, 2009), based on the proportion of family income spent on food, shelter and clothing, adjusted for family size. According to this criterion, familial income was either rated as (1) sufficient (77.9% of the sample) or (2) insufficient (20.1% of the sample; the remaining 2.0% of the sample were missing income information). *Marital satisfaction* was assessed through 7 items (e.g. "Things are going well between you and your partner"; "degree of happiness" on a scale ranging from –0 to 5) taken from the Dyadic Adjustment Scale (DAS; (Spanier, 1976)), a well-validated self-report questionnaire on mother's perceptions and attitudes towards their partner and the relationship itself. Item scores were added and converted into z scores, with higher global scores indicating higher marital satisfaction.

Data analysis

Our goal was to (1) model the longitudinal evolution of harsh parenting from ages 1 ½ to 6 years and (2) identify risk factors predictive of higher levels and evolution (increases and/or decreases) of harsh parenting across time. To characterize harsh parenting evolution in mothers, we constructed a latent growth curve model (LGCM), which examines intra-individual change and inter-individual differences in change across time (Wothke, 2000). We then combined the LGCM of harsh parenting with predictors of harsh parenting into one multivariate model to test the relation between harsh parenting intercept, slope and quadratic term, and each of the risk factors measured at 17 months (30 months for marital satisfaction).

Analyses were performed with Mplus version 5.21 (Muthen & Muthen, 1998-2008). Maximum Likelihood with Robust standard errors (MLR) was used to estimate the models, as this estimator has been shown to perform better than Maximum Likelihood (ML) when modeling low prevalent behaviors of non-normal data (Asparouhov & Muthen, 2005; Castellanos-Ryan, Parent, Vitaro, Tremblay, & Seguin, 2013). Full information maximum likelihood (FIML) was used to account for missing data. To test goodness of fit we used the Comparative Fit index (CFI; (Bentler, 1990)), the Tucker-Lewis index (TLI), the Root Mean Square Error of Approximation (RMSEA; (Browne & Cudeck, 1993), and the Standardized Root Mean Residual (SRMR).

Results

In order to assess whether there were significant individual differences in change in harsh parenting across time in this sample, a linear LGCM with harsh parenting scores from ages 17 to 72 months, centered at the first time point (17 months) was conducted (Mean intercept= 3.50; slope= 0.70; quadratic term= -0.20). This model did not fit the data well (χ^2(10, N= 2045)= 657.71; CFI= 0.75; TLI= 0.75; RMSEA= .18; SRMR= .10), suggesting change in harsh parenting was not linear across this time period. A quadratic LGCM model was therefore performed. Data fit (χ^2(10, N=2045)= 229.95; CFI= 0.92; TLI= 0.86; RMSEA= .14; SRMR= .05) was slightly improved but remained poor. A quadratic LGCM was then conducted in which the time score for the last time-point (72 months) was allowed to be freely estimated. This last time-score, and not others, was freed because raw means suggested that harsh parenting between 60 and 72 months was more stable (i.e. change was smaller) than across other time points. This model fit the data very well according to all fit criteria (χ^2(4, N= 2045)= 15.88; CFI= 1.00; TLI= 0.99; RMSEA= .04; SRMR= .02). The model explained 78% of the variance at 17 months ($p < .05$), and near 50% of the variance or over at subsequent time points (47%, 63%, 59% and 63% of the variance at 30, 42, 60 and 72 months, respective; all ps < .001).

All growth curve factor means (i.e., intercept= 3.21, linear slope= 1.46 and quadratic term= -0.40) differed significantly from zero at $p < .001$, and showed a tendency for harsh parenting behaviors to increase between 17 and 42 months of age, followed by a decrease between 42 and 72 months that was more important between 42 and 60 months. Growth curve factor variances (intercept = 4.67; linear slope = 3.93; quadratic term = 0.24) were also significant at $p < .001$, indicating there was significant individual variability in the level and change pattern of harsh parenting over time. There were high inter-correlations between intercept and slope ($r= -.57$, $p < .001$), intercept and quadratic term ($r= .43$, $p < .001$) and between slope and quadratic term ($r= -.96$, $p < .001$). Given these highly correlated factors, found often in quadratic latent growth curves centered at initial time point (Newsom, 2015), and to facilitate subsequent interpretation of the results, the intercept was re-centered at the middle time point (42 months) (Newsom, 2015), the time-point at which mothers reported the highest levels of harsh parenting. This procedure did not affect model fit indexes nor quadratic term mean and variance (respectively -.40 and .24, $p < .001$), but had an impact on intercept

(mean= 4.53, variance= 3.10, $p < .001$) and linear slope (mean= -0.14, variance= 0.27, $p < .001$). It also significantly reduced inter-correlations between factors: intercept and linear slope ($r= -.19$, $p < .001$); linear slope and quadratic term ($r= .10$, $p= .25$); intercept and quadratic term ($r= -.53$, $p < .001$). These inter-correlations suggest that higher mean levels of harsh parenting across time (or at 42 months) were associated with less linear increases (i.e. more stability) of harsh parenting across initial time points, but with steeper decreases or downturn later in development. See figure 1 for the development of hash parenting across time in this sample.

----Insert figure 1 approximately here ----

We included harsh parenting risk factors (child sex, externalizing and internalizing behaviors, maternal depression and self-efficacy, insufficient household income and marital satisfaction) to the previously described LGCM to test their association with the levels at 42 months (i.e., average level) and change in harsh parenting across 17 and 72 months. To do so, we included regression paths from these factors to the intercept, slope and quadratic term. The model fit the data very well ($\chi^2(18, N = 2045) = 43.68$; CFI = 0.99; TLI =0.98; RMSEA =.03; SRMR=.01). Figure 2 presents regression coefficients from risk factors to intercept, slope and quadratic term.

Results show that sex ($\beta = -0.08$, $p < .05$), externalizing ($\beta = 0.11$, $p < .001$) and internalizing behaviors of the child ($\beta = 0.12$, $p < .001$), and maternal depression ($\beta = 0.12$, $p <. 001$) and self-efficacy ($\beta = -0.13$, $p < 0.001$), were uniquely associated with mean levels of harsh parenting levels (intercept). Specifically, boys, and children with higher internalizing and externalizing behaviors at 17 months, as well as children of mothers with a history of lifetime depression, had mothers who used higher mean levels of harsh parenting. On the other hand, mothers with higher feelings of self-efficacy when the child was 17 months, reported lower mean levels of harsh parenting across time.

Additionally, child internalizing ($\beta = -0.18$, $p < .001$) behaviors were associated with lower linear growth between 17 and 72 months (slope). Child sex ($\beta = 0.08$, $p < .05$), internalizing ($\beta = -0.18$, $p < .001$) and externalizing ($\beta = 0.15$, $p < .001$) behaviors and maternal self-efficacy ($\beta = 0.33$, $p < .001$) were also associated with the quadratic term. This indicates that higher child internalizing behaviors at 17 months were associated with lower

increases or more stable low harsh parenting across initial periods of time which then had a steeper downturn at later time points. Being a boy was also associated with a more abrupt decline in harsh parenting after 42 months. On the other hand, higher maternal self-efficacy and child externalizing behaviors at child age 17 were associated with a less abrupt decrease or more stable harsh parenting over time.

---Insert figure 2 approximately here---

Discussion

We investigated maternal harsh parenting evolution from early to middle childhood (1 ½ to 6 years). Moreover, we identified and compared predictors of harsh parenting levels and evolution that are related to different spheres of a child's life.

Developmental evolution of harsh parenting from 17 to 72 months

Our results show that maternal harsh parenting levels when children are aged 17 months are highly variable amongst mothers, and follow a non-linear evolution from 17 to 72 months old. Accordingly, harsh parenting levels generally increase from 17 to 42 months of age. This initial increase is followed by a decrease between 42 and 72 months, which is more pronounced between 42 and 60 months, and flattens after 60 months. Increasing levels of harsh parenting during toddlerhood (17-42 months) are consistent with previous studies in mothers of younger children, which report important increases in harsh parenting from infancy to toddlerhood (i.e., 4.5 to 36 months) (Kim et al., 2010; Pierce et al., 2010; Windham et al., 2004). This increase may be explained by the new challenges elicited by developmental changes in children, who become much more independent and physically active after reaching toddlerhood. This requires constant monitoring and discipline from their mothers, who may use harsher discipline strategies in order to manage risky behaviors as well as oppositional behaviors and tantrums associated with their children's growing independence (Kim et al., 2010; Windham et al., 2004). Furthermore, as children gain autonomy and seek independence, their mothers may perceive them as less vulnerable and more accountable for their behavior (Pierce et al., 2010), leading to an increase in the use of disciplinary methods. Hence, levels of harsh parenting seem to increase between infancy and the end of toddlerhood.

From 42 months (3 1/2 years old) onwards, decreases in hostile parenting were observed in the mothers of our sample. This decrease parallels findings reported by Mackenzie and collaborators (MacKenzie et al., 2013), who found spanking rates to decrease from 3 to 5 years old. It also complements previous findings reported by Lansford and colleagues (Lansford et al., 2009), who showed decreases in the use of harsh parenting across time in mothers of school-aged children (6 to 9 years old) exhibiting moderate or high initial levels of harsh physical discipline. Again, this probably reflects maternal adaptive strategies to developmental changes in children. As their cognitive and language abilities increase, children become able to reason and to understand more sophisticated explanations (Lansford et al.,

2009). Parents may therefore decrease their use of harsh parenting strategies and increase the use of other nonphysical milder forms of discipline that can hardly be employed with younger children, such as reasoning, time-outs, and discussions on how their behavior may impact others. These changes in parental practices are rewarding for both parents and children, since it has been shown that strategies promoting inductive reasoning, such as offering explanations or providing guidance about rules and morals, are primordial for children to internalize morality and develop of emotional and social competence (e.g., (Kim et al., 2010; Kochanska & Thompson, 1997; Kuczynski & Hildebrandt, 1997) and should be employed as children grow and are able to understand them (Lansford et al., 2009). Of note, mothers displaying the highest levels of harsh parenting at 42 months showed the steeper decreases after this time-point.

Nevertheless, most of the mothers in our sample increased their levels of harsh parenting between child age 17 and 42 months and displayed important levels of harsh parenting at 42 months. Otherwise, the high variability in terms of harsh parenting intercept and slope indicates that the mothers did not use all the same levels of harsh parenting at 42 months and over time, with some of them exhibiting substantially higher levels than others, as well as distinct growth patterns.

Risk factors associated with average levels of harsh parenting

The mothers in our sample used the highest levels of harsh parenting when their child was aged 42 months. We investigated which earlier child, mother and family characteristics measured at child-age 17 months were associated with harsh parenting levels at 42 months.

As expected, greater child externalizing and internalizing behaviors were associated with greater average levels of maternal harsh parenting. Regarding child externalizing behaviors, these associations may be explained by the fact that mothers of highly aggressive and oppositional children may feel the need to exert harsher forms of discipline (e.g., physical punishment) in order to control their inappropriate behaviors (Bell & Chapman, 1986; Gershoff, 2002). Similarly, depression in preschool children has been found by some authors to express itself by significantly greater aggressiveness and irritability (Belden, Thomson, & Luby, 2008; Luby et al., 2009), and may lead to negative beliefs towards the child (Laskey & Cartwright-Hatton, 2009). In addition, violence and opposition from children may elicit negative feelings such as anger and resentment in their mothers, which may in turn lead to

higher levels of harsh parenting. The fact that prior levels of anxiety and depression in the children (measured at 17 months) predicted subsequent harsh parenting levels (measured at 42 months) suggests some directionality in the relation. However, one may not rule out the possibility that highly harsh mothers initially elicited or exacerbated internalizing behaviors in their children at age 17 months, which were in turn related to greater harsh parenting at age 42 months.

Sex of the child also significantly predicted average levels of harsh parenting at 42 months, with mothers of boys reporting higher levels of harsh parenting than mothers of girls, which is consistent with previous research (Gershoff, 2002; Straus & Stewart, 1999). However, we had not found such sex differences in 5-month-old infants (Boivin et al., 2005). Thus, it may be possible that the sex of the child has greater influences on maternal harsh parenting only for older children. Indeed, it has been suggested that boys receive more corporal punishment than girls because they tend to engage in behaviors that may elicit such practices, e.g. aggression (Gershoff, 2002). However the sex differences in terms of harsh parenting found here are over and above the differences predicted by externalizing behaviors, which suggests other factors may be implicated; for example, literature shows that parents nourish different sex-based beliefs about their children's education, such as wanting to "toughen up" their boys (Gershoff, 2002). As these attitudes are more prevalent as children get older and become more active and independent (i.e. during toddlerhood and preschool years), it is not surprising to find sex differences in harsh parenting in mothers of toddlers and preschoolers in this study but not in mothers of infants in a previous study

Maternal characteristics were also a predictor of harsh parenting. A history of lifetime depression and its severity in the mothers assessed when children were 17 months old were good predictors of harsh parenting levels at 42 months old. This is consistent with studies showing increased irritability and decreased patience in depressed mothers, leading them to adopt harsh punitive strategies when dealing with their children's demands and tantrums (Lovejoy et al., 2000; Shay & Knutson, 2008; Windham et al., 2004). Similarly, lower levels of maternal self-efficacy at child age 17 months were associated with higher levels of harsh parenting at 42 months, which is consistent with, our previous observation that mothers that felt less effective used more hostile parenting behaviors towards their 5 months old children (Boivin et al., 2005) and tended to use high and increasing levels of harsh parenting over time

as their children developed from infancy to toddlerhood (Pierce et al., 2010). It appears that feelings of low self-efficacy may bring mothers to perceive their child as being difficult, leading them to become irritated and to use punitive strategies when interacting with their offspring (Bugental, Blue, & Cruzcosa, 1989; Halpern, Anders, Coll, & Hua, 1994; Huesmann, Moise-Titus, Podolski, & Eron, 2003). Conversely, higher levels of maternal self-efficacy seem to constitute a protective factor against higher levels of harsh parenting.

Risk factors associated with harsh parenting evolution

Besides their relation with average harsh parenting levels, greater child externalizing behaviors at 17 months were also associated with less quadratic decline between 42 and 72 months. These results are in line with previous findings from Lansford and colleagues (Lansford et al., 2009), who reported child externalizing behaviors to be predictive of higher levels of harsh physical discipline over time in mothers of school-age children. Besides, since children displaying the highest levels of externalizing behaviors at 17 months were previously found to present the most important increases over time and the highest average levels at 42 months (R. E. Tremblay et al., 2005), it is not surprising their mothers also showed the lowest decreases after this time point.

Surprisingly, despite being associated with higher average levels, greater child internalizing behaviors were associated with lower increases in harsh parenting between 17 and 42 months, and with steeper decreases after 42 months. Our previous work shows that child internalizing symptoms tend to increase from infancy to preschool years (1 ½ to 5 years old), which was particularly true for the children who displayed the highest levels of internalizing symptoms to begin with (Cote et al., 2009). This indirectly suggests that increases in child internalizing symptoms are associated with decreases in harsh parenting levels, and could again reflect adaptive reactions from the mothers of more vulnerable children, in an attempt to manage increasing anxiety and depressive manifestations in their offspring. Moreover, internalizing symptoms may be less more tolerable and may elicit more warmth and compassion from the mothers relative to externalizing behaviors.

Similarly, mothers of boys were also found to show steeper decreases in harsh parenting relative to mothers of girls after 42 months, although they still displayed greater average levels of harsh parenting. One potential explanation is that mothers of girls already stable but low levels of harsh parenting at 42 months, limiting potential decreases. Steeper

decreases in mothers of boys may also suggest adaptations and changes in parental behavior and strategies after child-age 42 months, in an attempt to deal more effectively with boys' problematic behaviors.

Finally, although they were associated with lower harsh parenting average levels, higher maternal self-efficacy was also associated with less abrupt decreases after 42 months. This is probably explained by the fact that mothers with higher perceived self-efficacy displayed lower and more constant levels of harsh to begin with.

Characteristics unrelated to higher levels and/or evolution of harsh parenting

Finally, family risk factors did not predict harsh parenting levels and/or change over time. This suggests that child and maternal factors may simply be better predictors of harsh parenting during toddlerhood and preschool years, or may act as mediators in the relation between family characteristics and harsh parenting behaviors. As a matter of fact, Kim and collaborators (Kim et al., 2010) found no effect of family income on harsh parenting intercept (at 3 years of age) or slope (between 1 and 3 years of age), when other factors such as alcohol use and/or history of childhood abuse were included in the analysis.

Implications for interventions

Given the important childhood and adulthood consequences of harsh parenting, preventing and limiting the occurrence of such practices early is a crucial issue (Durrant & Ensom, 2012; Gershoff, 2002). In this study, we showed that levels and evolution of harsh parenting could be predicted by a set of factors related to the child and to the mother. Although it some harsh parenting predictors -- such as sex of the child --, prevention of harsh parenting may be achieved by identifying at-risk families and children, and by intervening on the manageable risk and protective factors. Among all of the manageable risk factors, maternal history of lifetime depression was a good predictor of harsh parenting levels, which highlights the need for social and psychological support for psychologically fragile mothers. Also, by helping mothers improve their feelings of self-efficacy or by teaching them skills to effectively deal with their children's difficult aggressive and oppositional, or anxious-depressive, behaviors during early childhood, interventions may reduce the use of hostile disciplinary strategies during the preschool years. Evidence shows that providing education and support to mothers positively impacts their competence, efficacy and psychological health, and can reduce their use of hostile disciplinary strategies (Durrant & Ensom, 2012).

Indeed, our results suggest a certain amount of willingness and efforts on the part of highly harsh mothers to change disciplinary strategies and adopt less coercive behaviors over time, particularly in mothers of highly internalizing children. This, however, was not observed in mothers of highly externalizing children, suggesting these families may be particularly at risk.

Limitations

The present findings have some limitations. First, harsh parenting practices were self-reported by the mothers. Hence, mothers may have under-evaluated their levels of harsh parenting, as self-report measures may be susceptible to social desirability, particularly when assessing behaviors that parents may feel uncomfortable to reveal (Boivin et al., 2005). Nonetheless, previous studies suggested self-report to be a valid and useful measure for etiologic research (Windham et al., 2004), and questions employed in the present study were well validated (Boivin et al., 2005), have been extensively used (e.g. Boivin et al., 2005; Guimond et al., 2012; Pierce et al., 2010; Vitaro, Barker, Boivin, Brendgen, & Tremblay, 2006), and have shown to effectively reveal individual differences in parenting in population-based samples (Boivin et al., 2005; Boyle et al., 2004; Pierce et al., 2010). Moreover, the levels of harsh parenting observed here were consistent with those reported by other authors (Lansford et al., 2009; Pierce et al., 2010). Further, care was taken to minimize potential social desirability effects on the evaluation of harsh parenting. Indeed, questions related to these negative behaviors were inserted in a questionnaire measuring positive and negative parenting practices altogether. However, future studies should include other measures of harsh parenting, such as child-reported records.

Second, all risk factor variables were also self-reported by the mothers, who may have over-rated or under-rated their child's behaviors and their own depressive manifestations (Briggs-Gowan, Carter, & Schwab-Stone, 1996). This approach may lead to problems of shared method variance and could be circumvented in future work by using more objective measures of parenting practices and of children and maternal behaviors, relying on independent observation or multiple informants.

A third limitation is that harsh parenting was measured in mothers only. Because there is evidence of some important differences in the use of hostile practices between mothers and fathers, with mothers often reporting more frequent use of corporal punishment (Gershoff,

2002), future studies should investigate developmental patterns and predictive factors of harsh parenting in fathers as well.

Another limitation resides in the fact that all risk factors were only measured at one time point. Hence, some of these factors, such as child externalizing and internalizing behaviors, may evolve and may interact with harsh parenting across time. Future studies targeting these specific behaviors should use transactional designs to explore potential interactions between variables over time.

Finally, some risk factors were not investigated. Indeed, none of the identified risk factors were predictive of harsh parenting linear increases, suggesting other variables may play a role in the increasing harsh parenting levels between 17 and 42 months of age. For instance, we did not measure the predictive impact of different maternal psychopathologies (e.g., drug abuse, bipolar depression symptoms) or of maternal history of childhood abuse on harsh parenting trajectories. Such variables could possibly be related to increases in harsh parenting levels (see Boivin, Perusse et al. 2005; Lansford, Criss et al. 2009; Kim, Pears et al. 2010), and should be investigated by future studies.

Regardless of these limitations, the strength of this study lies in the repeated assessments of harsh parenting over a 5-year period and extensive measures of risk factors investigated in a large and representative population-based cohort. This work replicates previous findings and extends them to the preschool period, filling an important gap in the literature by determining, for the first time, the evolution of maternal harsh parenting from early to middle childhood as well as its associated risk factors. Our findings provide guidelines to better identify families at high risk for harsh parenting, and to develop better-defined interventions for families in elevated harsh parenting contexts.

References

Achenbach, T. M. (1991). Child Behavior Checklist. . In U. o. V. Department of Psychiatry (Ed.). Burlington, VT:.

Asparouhov, T., & Muthen, B. (2005). *Multivariate statistical modeling with survey data.* Paper presented at the Federal Committee on Statistical Methodology (FCSM) Research Conference.

Atzaba-Poria, N., & Pike, A. (2008). Correlates of parental differential treatment: parental and contextual factors during middle childhood. *Child Dev, 79*(1), 217-232. doi: CDEV1121 [pii]10.1111/j.1467-8624.2007.01121.x

Behar, L., & Stringfield, S. (1974). A behavior rating scale for the preschool child. *Developmental Psychology, 10*(5), 601-610.

Belden, A. C., Thomson, N. R., & Luby, J. L. (2008). Temper tantrums in healthy versus depressed and disruptive preschoolers: defining tantrum behaviors associated with clinical problems. *J Pediatr, 152*(1), 117-122. doi: S0022-3476(07)00592-6 [pii]10.1016/j.jpeds.2007.06.030

Bell, R. Q., & Chapman, M. (1986). Child effects in studies using experimental of brief longitudinal approaches to socialization. *Developmental Psychology*(22), 595-603.

Bentler, P. M. (1990). Comparative fit indexes in structural models. *Psychol Bull, 107*(2), 238-246.

Boivin, M., Perusse, D., Dionne, G., Saysset, V., Zoccolillo, M., Tarabulsy, G. M., . . . Tremblay, R. E. (2005). The genetic-environmental etiology of parents' perceptions and self-assessed behaviours toward their 5-month-old infants in a large twin and singleton sample. *J Child Psychol Psychiatry, 46*(6), 612-630. doi: 10.1111/j.1469-7610.2004.00375.x

Bor, W., & Sanders, M. R. (2004). Correlates of self-reported coercive parenting of preschool-aged children at high risk for the development of conduct problems. *Aust N Z J Psychiatry, 38*(9), 738-745. doi: 10.1111/j.1440-1614.2004.01452.xANP1452 [pii]

Boyle, M. H., Jenkins, J. M., Georgiades, K., Cairney, J., Duku, E., & Racine, Y. (2004). Differential-maternal parenting behavior: estimating within- and between-family effects on children. *Child Dev, 75*(5), 1457-1476. doi: 10.1111/j.1467-8624.2004.00751.xCDEV751 [pii]

Boyle, M. H., Offord, D. R., Racine, Y., Fleming, J. E., Szatmari, P., & Sanford, M. (1993). Evaluation of the revised Ontario Child Health Study scales. *J Child Psychol Psychiatry, 34*(2), 189-213.

Briggs-Gowan, M. J., Carter, A. S., & Schwab-Stone, M. (1996). Discrepancies among mother, child, and teacher reports: examining the contributions of maternal depression and anxiety. *J Abnorm Child Psychol, 24*(6), 749-765.

Broidy, L. M., Nagin, D. S., Tremblay, R. E., Bates, J. E., Brame, B., Dodge, K. A., . . . Vitaro, F. (2003). Developmental trajectories of childhood disruptive behaviors and adolescent delinquency: a six-site, cross-national study. *Dev Psychol, 39*(2), 222-245.

Browne, M. W., & Cudeck, R. (1993). Alternative ways of assessing model fit. In K. A. Bollen & J. S. Long (Eds.), *Testing structural equation modeling.* (pp. 136-162.). CA,: Sage.

Bugental, D. B., Blue, J., & Cruzcosa, M. (1989). Perceived control over caregiving outcomes: Implications for child abuse. *Developmental Psychology, 25*(59), 532-539.

Bugental, D. B., Lewis, J. C., Lin, E., Lyon, J., & Kopeikin, H. (1999). In charge but not in control: the management of teaching relationships by adults with low perceived power. *Dev Psychol, 35*(6), 1367-1378.

Canada, S. (1995). Overview of Survey Instruments for 1994-1995 Data Collection, Cycle 1.

Canada, S. (2009). Income Trends in Canada: 1976-2007 Ottawa, ON, Canada: Author.

Castellanos-Ryan, N., Parent, S., Vitaro, F., Tremblay, R. E., & Seguin, J. R. (2013). Pubertal development, personality, and substance use: a 10-year longitudinal study from childhood to adolescence. *J Abnorm Psychol, 122*(3), 782-796. doi: 10.1037/a0033133

Clément, M.-E., Bernèche, F., Fontaine, C., & Chamberland, C. (2012a). Les attitudes parentales et les pratiques familiales. In G. Tardif (Ed.), *La violence familiale dans la vie des enfants du Québec*. Montreal, QC, Canada: Institut de la Statistique du Québec.

Clément, M.-E., Bernèche, F., Fontaine, C., & Chamberland, C. I. (2012b). Les attitudes parentales et les pratiques familiales. . In G. Tardif (Ed.), *La violence familiale dans la vie des enfants du Québec*. Montreal, QC, Canada,: Institut de la Statistique du Québec.

Cote, S. M., Boivin, M., Liu, X., Nagin, D. S., Zoccolillo, M., & Tremblay, R. E. (2009). Depression and anxiety symptoms: onset, developmental course and risk factors during early childhood. *J Child Psychol Psychiatry, 50*(10), 1201-1208. doi: JCPP2099 [pii]10.1111/j.1469-7610.2009.02099.x

Durrant, J., & Ensom, R. (2012). Physical punishment of children: lessons from 20 years of research. *CMAJ*. doi: 10.1503/cmaj.101314

Galera, C., Pingault, J. B., Michel, G., Bouvard, M. P., Melchior, M., Falissard, B., . . . Cote, S. M. (2014). Clinical and social factors associated with attention-deficit hyperactivity disorder medication use: population-based longitudinal study. *Br J Psychiatry, 205*(4), 291-297. doi: 10.1192/bjp.bp.113.141952

Gershoff, E. T. (2002). Corporal punishment by parents and associated child behaviors and experiences: a meta-analytic and theoretical review. *Psychol Bull, 128*(4), 539-579.

Gershoff, E. T. (2008). Report on Physical Punishment in the United States: What Research Tells Us About Its Effects on Children
. Columbus, OH.

Gervai, J. (2009). Environmental and genetic influences on early attachment. *Child Adolesc Psychiatry Ment Health, 3*(1), 25. doi: 10.1186/1753-2000-3-25

Gracia, E. (1995). Visible but unreported: a case for the "not serious enough" cases of child maltreatment. *Child Abuse Negl, 19*(9), 1083-1093. doi: 0145-2134(95)00070-O [pii]

Guimond, F. A., Brendgen, M., Forget-Dubois, N., Dionne, G., Vitaro, F., Tremblay, R. E., & Boivin, M. (2012). Associations of mother's and father's parenting practices with children's observed social reticence in a competitive situation: a monozygotic twin difference study. *J Abnorm Child Psychol, 40*(3), 391-402. doi: 10.1007/s10802-011-9573-8

Halpern, L. F., Anders, T. F., Coll, C. G., & Hua, J. (1994). Infant temperament: Is there a relation to sleep wake states and maternal nightime behavior ? *Infant Behavior and Development*(17), 255-268.

Huesmann, L. R., Moise-Titus, J., Podolski, C. L., & Eron, L. D. (2003). Longitudinal relations between children's exposure to TV violence and their aggressive and violent behavior in young adulthood. *Developmental Psychology, 39*(2), 201-221.

Japel, C., Tremblay, R. E., Vitaro, F., & Boulerice, B. (1999). Early parental separation and the psychosocial development of daughters 6-9 years old. *Am J Orthopsychiatry, 69*(1), 49-60.

Kim, H. K., Pears, K. C., Fisher, P. A., Connelly, C. D., & Landsverk, J. A. (2010). Trajectories of maternal harsh parenting in the first 3 years of life. *Child Abuse Negl, 34*(12), 897-906. doi: S0145-2134(10)00231-0 [pii]10.1016/j.chiabu.2010.06.002

Kochanska, G., & Thompson, R. A. (1997). The emergence and development of conscience in toddlerhood and early childhood. In Wiley (Ed.), *Parenting and children's internalization of rules: A handbook of contemporary theory* (pp. 53-77). New York.

Krishnakumar, A., & Buehler, C. (2000). Interparental Conflict and Parenting Behaviors: A Meta-Analytic Review. *Family Relations, 49*(1), 25-44.

Kuczynski, L., & Hildebrandt, N. (1997). Models of conformity and resistance in socialization theory. In Wiley (Ed.), Parenting and children's internalization of values: A handbook of contemporary theory. In J. E. Grusec & L. Kuczynski (Series Eds.), (pp. 227-256). New York.

Lansford, J. E., Criss, M. M., Dodge, K. A., Shaw, D. S., Pettit, G. S., & Bates, J. E. (2009). Trajectories of physical discipline: early childhood antecedents and developmental outcomes. *Child Dev, 80*(5), 1385-1402. doi: CDEV1340 [pii]10.1111/j.1467-8624.2009.01340.x

Laskey, B. J., & Cartwright-Hatton, S. (2009). Parental discipline behaviours and beliefs about their child: associations with child internalizing and mediation relationships. *Child Care Health Dev, 35*(5), 717-727. doi: CCH977 [pii]10.1111/j.1365-2214.2009.00977.x

Lovejoy, M. C., Graczyk, P. A., O'Hare, E., & Neuman, G. (2000). Maternal depression and parenting behavior: a meta-analytic review. *Clin Psychol Rev, 20*(5), 561-592. doi: S0272-7358(98)00100-7 [pii]

Luby, J. L., Essex, M. J., Armstrong, J. M., Klein, M. H., Zahn-Waxler, C., Sullivan, J. P., & Goldsmith, H. H. (2009). Gender differences in emotional reactivity of depressed and at-risk preschoolers: implications for gender specific manifestations of preschool depression. *J Clin Child Adolesc Psychol, 38*(4), 525-537. doi: 10.1080/15374410902976312

MacKenzie, M. J., Nicklas, E., Waldfogel, J., & Brooks-Gunn, J. (2013). Spanking and child development across the first decade of life. *Pediatrics, 132*(5), e1118-1125. doi: 10.1542/peds.2013-1227

MacMillan, H. L., Boyle, M. H., Wong, M. Y., Duku, E. K., Fleming, J. E., & Walsh, C. A. (1999). Slapping and spanking in childhood and its association with lifetime

prevalence of psychiatric disorders in a general population sample. *CMAJ, 161*(7), 805-809.
McKee, L., Jones, D. J., Roland, E., Coffelt, N., Rakow, A., & Forehand, R. (2007). Maternal HIV/AIDS and depressive symptoms among inner-city African American youth: the role of maternal depressive symptoms, mother-child relationship quality, and child coping. *Am J Orthopsychiatry, 77*(2), 259-266. doi: 10.1037/0002-9432.77.2.259
Muthen, L. K., & Muthen, B. O. (1998-2008). Mplus User's Guide. Los Angeles, CA: Muthen & Muthen
Newsom, T. J. (2015). Chapter 8: Nonlinear growth curve models *Longitudinal structural equation modelling: A comprehensive introduction* (pp. 434): Routledge.
Pierce, T., Boivin, M., Frenette, E., Forget-Dubois, N., Dionne, G., & Tremblay, R. E. (2010). Maternal self-efficacy and hostile-reactive parenting from infancy to toddlerhood. *Infant Behav Dev, 33*(2), 149-158. doi: S0163-6383(09)00113-1 [pii]10.1016/j.infbeh.2009.12.005

Roy, C. A., Zoccolillo, M., Gruber, R., Boivin, M., Perusse, D., & Tremblay, R. E. (2005). Construct validity of an instrument to assess major depression in parents in epidemiologic studies. *Can J Psychiatry, 50*(12), 784-791.
Rubin, K. H., & Mills, R. S. (1990). Maternal beliefs about adaptive and maladaptive social behaviors in normal, aggressive, and withdrawn preschoolers. *J Abnorm Child Psychol, 18*(4), 419-435.
Shay, N. L., & Knutson, J. F. (2008). Maternal depression and trait anger as risk factors for escalated physical discipline. *Child Maltreat, 13*(1), 39-49. doi: 13/1/39 [pii]10.1177/1077559507310611

Spanier, A. H. (1976). Measuring Dyadic Adjustment: New Scales for Assessing the Quality of Marriage and Similar Dyads. *Journal of Marriage and Family, 38*(1), 15-28.
Straus, M. A. (2000). Corporal punishment and primary prevention of physical abuse. *Child Abuse Negl, 24*(9), 1109-1114. doi: S0145-2134(00)00180-0 [pii]
Straus, M. A., & Stewart, J. H. (1999). Corporal punishment by American parents: national data on prevalence, chronicity, severity, and duration, in relation to child and family characteristics. *Clin Child Fam Psychol Rev, 2*(2), 55-70.
Tottenham, N., & Sheridan, M. A. (2009). A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. *Front Hum Neurosci, 3*, 68. doi: 10.3389/neuro.09.068.2009
Tremblay, R., Japel, C., Pérusse, D., McDuff, P., Boivin, M., Zoccolillo, M., & Montplaisir, J. (1999). he search for the age of "onset" of physical aggression: Rousseau and Bandura revisited. *Criminal Behavior and Mental Health, 9*(1), 8-23.
Tremblay, R. E., Desmarais-Gervais, L., Gagnon, C., & Charlebois, P. (1987). The Preschool Behaviour Questionnaire: Stability of its factor structure between cultures, sexes, ages and socioeconomic classes. *International Journal of Behavioral Development,, I*(10), 467-484.
Tremblay, R. E., Nagin, D. S., Seguin, J. R., Zoccolillo, M., Zelazo, P. D., Boivin, M., . . . Japel, C. (2005). Physical aggression during early childhood: trajectories and predictors. *Can Child Adolesc Psychiatr Rev, 14*(1), 3-9.

Vitaro, F., Barker, E. D., Boivin, M., Brendgen, M., & Tremblay, R. E. (2006). Do early difficult temperament and harsh parenting differentially predict reactive and proactive aggression? *J Abnorm Child Psychol, 34*(5), 685-695. doi: 10.1007/s10802-006-9055-6

Windham, A. M., Rosenberg, L., Fuddy, L., McFarlane, E., Sia, C., & Duggan, A. K. (2004). Risk of mother-reported child abuse in the first 3 years of life. *Child Abuse Negl, 28*(6), 645-667. doi: 10.1016/j.chiabu.2004.01.003S014521340400105X [pii]

Wothke, W. (2000). *Longitudinal and multigroup modeling with missing data Modeling longitudinal and multilevel data: Practical issues, applied approaches, and specific examples.* Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers.

Figures

Figure 1. Observed and estimated mean maternal harsh parenting levels from 17 to 72 months (n = 2045)

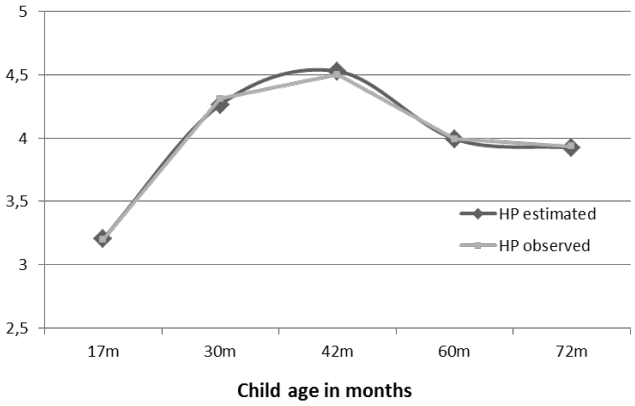
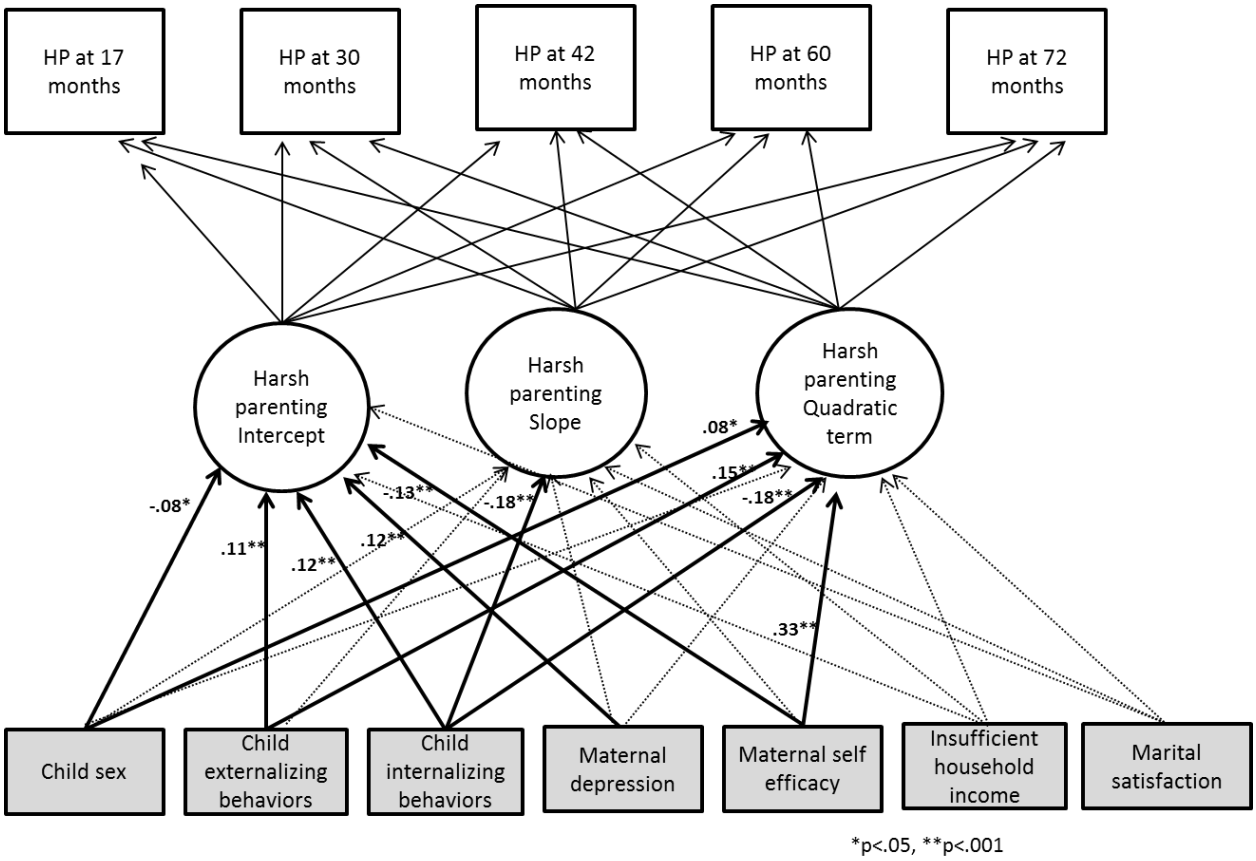


Figure 2. Predictors of harsh parenting intercept, linear and quadratic evolution from 17 to 72 months.



Data courtesy of the Institut de la Statistique du Québec

Tables

Table 1. Demographic characteristics of the sample at 17 months

	N= 2045	%
Sex of the child		
Boys	1035	50.6
Girls	1010	49.4
Family income		
Sufficient	1593	77.9
Insufficient	411	20.1
Missing	41	2.0

Data courtesy of the Institut de la Statistique du Québec

Table 2. Descriptive statistics (mean, SD, skewness) for maternal harsh parenting practices at each time point.

	Age in months				
	17	30	42	60	72
Mean	3.39	4.38	4.57	4.07	3.94
SD	2.40	2.54	2.13	1.97	1.96
Skewness	0.48	0.66	0.43	0.41	0.43

Data courtesy of the Institut de la Statistique du Québec

The conditioning and extinction of fear in youths:

What's sex got to do with it?

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Article 2 : The conditioning and extinction of fear in youths: What's sex got to do with it?

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The conditioning and extinction of fear in youths:
What's sex got to do with it?

Abstract

Adult work shows differences in emotional processing influenced by sexes of both the viewer and expresser of facial expressions. We investigated this in 120 healthy youths (57 boys; 10-17 years old) randomly assigned to fear conditioning and extinction tasks using either neutral male or female faces as the conditioned threat and safety cues, and a fearful face paired with a shrieking scream as the unconditioned stimulus. Fear ratings and skin conductance responses (SCRs) were assessed. Male faces triggered increased fear ratings in all participants during conditioning and extinction. Greater differential SCRs were observed in boys viewing male faces and in girls viewing female faces during conditioning. During extinction, differential SCR findings remained significant in boys viewing male faces. Our findings demonstrate how sex of participant and sex of target interact to shape fear responses in youths, and how the type of measure may lead to distinct profiles of fear responses.

Keywords

Sex, Gender, Youth, Fear conditioning, Fear extinction, Skin conductance.

Introduction

A wealth of work performed in adults reports that sex may influence emotional processing. Not only are there differences in the way men and women recognize and process emotions, there are also differences in the way the sex of facial targets used in tasks may modulate the analysis of emotional cues (Kret & De Gelder, 2012; Kring & Gordon, 1998; Pattwell, Lee, & Casey, 2013). Little is known about the influence sexes of participants and targets may have on emotional processing in younger population. In the current study, we aim at better understanding the influence of sex of participant and sex of target on fear conditioning and extinction in youths, as these tasks are often used to study emotions and emotion-related brain function in healthy and psychiatric paediatric populations.

Fear conditioning refers to the process by which a neutral stimulus is paired with an aversive unconditional stimulus (US; e.g. electric shocks), becoming a conditioned stimulus (CS+) eliciting a conditioned fear response when presented independently of the US. In humans, this response is usually measured with subjective fear ratings and/or skin conductance responses (SCR) (Lissek et al., 2005). Fear extinction, in comparison, refers to the diminution of the fear response after repeated presentation of the CS+ without the US. In discrimination fear conditioning and extinction, fear responses to the CS+ are compared to fear responses to a CS never paired with the US (CS-), which serves as a safety signal.

When using such classical fear conditioning and extinction paradigms in rodents, males show greater fear conditioning and more resistance to fear extinction than females, differences that emerge around puberty, presumably due to effects of sex hormones (Dalla & Shors, 2009). In human youths, no prior work examined sex differences during fear conditioning and extinction; however, tasks using intrinsically evocative faces were employed. Findings from this work report mixed observations. An important amount of studies demonstrated that female children and adolescents are more negatively aroused by threatening faces, as well as faster and more accurate in labelling and recognizing these cues, compared to male children and adolescents ((Lee et al., 2013); see reviews by Kret & De Gelder, 2012; McClure, 2000). Some other work, however, did not observe sex differences in emotional processing, neither in child nor adolescent samples (De Sonneville et al., 2002; Herba, Landau, Russell, Ecker, & Phillips, 2006; Kret & De Gelder, 2012; McClure, 2000; Thomas, De Bellis, Graham, & LaBar, 2007; Vicari, Reilly, Pasqualetti, Vizzotto, & Caltagirone, 2000). In adults, conflicting

findings are also observed. Women are shown to rate the CS+ and the US as more distressing and unpleasant than men during fear conditioning and extinction (Forsyth & Eifert, 1998; Kelly & Forsyth, 2007). Increased fear ratings of pain during movement-related conditioning are also observed in women relative to men (Meulders, Vansteenwegen, & Vlaeyen, 2012). When using physiological responses (SCRs, brain activation), however, men have often been reported as more physiologically reactive during the processing of threatening stimuli - especially male facial cues - compared to women. These findings were interpreted in an evolutionary perspective, with men prepping defence responses towards other threatening rival males, in relation with reproduction and survival (Kret & De Gelder, 2012; Milad et al., 2006). Regarding fear conditioning specifically, physiological data are less clear-cut as some findings show greater SCRs to facial threat cues in men relative to women (Dimberg, 1996), whereas other work report similar SCRs to facial threat cues in both men and women (Kret & De Gelder, 2012; Navarrete et al., 2009).

Concerning the influence sex of facial targets may have on emotional processing, threatening male facial expressions (anger, fear) have consistently been demonstrated to activate greater fearful responses than threatening female facial expressions. This was observed in both youths and adults (Aguado, Garcia-Gutierrez, & Serrano-Pedraza, 2009; Becker, Kenrick, Neuberg, Blackwell, & Smith, 2007; Egger et al., 2011; Goos L.M., 2002; Hess H., 1997; Navarrete et al., 2009; Seidel, Habel, Kirschner, Gur, & Derntl, 2010).

In the current study, we aimed at examining, firstly, the influence of sex of participants, and secondly, the influence of sex of target, on fear learning and extinction in boys and girls aged 10-17 years old. To reach this goal, we used a discrimination fear conditioning and extinction paradigm recently developed by Lau and collaborators (Lau et al., 2011; Lau et al., 2008). This unique paradigm uses a paediatrically-safe US shown to be as efficient as the US usually employed in animals and adults, electric shocks, which may not be used in youths due to ethical considerations. Head shots of two different actresses constitute the CS+ and CS- (neutral facial expressions) and the US is constituted of the CS+ actress's picture depicting a fearful facial expression, which is simultaneously presented with a shrieking female scream. Hence, here, we capitalized on the intrinsic aversiveness of witnessing fear in others. With this task, Lau and collaborators were successful in triggering fear acquisition and extinction, as measured through fear ratings and SCRs in healthy and

anxious youths (Lau et al., 2011; Lau et al., 2008). However, the influence of sexes of participants and targets was not measured in these previous studies.

Taking these two variables into account, and based on the above mentioned findings (especially those concerning human youths), we hypothesized that during conditioning, (1) boys and girls would show differential learning, manifested as greater fear evoked by the CS+ *vs*. CS-, (2) girls would show greater overall fear responses (CS+ and CS-) compared to boys, and (3) male fearful facial expressions would trigger greater fear responses in both sexes compared to female faces. During extinction, both boys and girls should extinguish fear, with levels of fear responses being similar for both the CS+ and CS-. Overall fear responses (CS+ and CS-) should remain higher in girls compared to boys, and for male faces relative to female faces in both sexes.

Method

Participants

A total of 120 healthy participants completed the study. Participants ranged in age from 10 to 17 years. Exclusion criteria for participation in the study were any type of past or present mental disorders, medical illness and use of medication as assessed by self-report in youths and one of their parents. Subjects were recruited in community centres (e.g., libraries, day camps) as well as schools of the Montreal greater area using flyers. The study protocol was approved by the Research Ethics Boards of the CHU Ste-Justine, Montreal, Canada. Participants and their parents gave informed assent and consent, respectively, and youths were compensated for their participation. Of the initial 120 participants recruited, two abandoned before completing the study, and data for one participant were lost due to technical problems. Hence, analyses were carried on 117 youths, 56 boys (Mean age = 14.05 ± 2.11) and 61 girls (Mean age = 13.77 ± 1.93).

Experimental Design

The paradigm lasted 17 minutes and comprised two phases: a fear conditioning phase and a fear extinction phase (Lau et al., 2011; Lau et al., 2008). During each phase, participants saw head shots of individuals presenting neutral emotional expressions. These photos were selected from the NimStim Set of Facial Expressions (Tottenham et al., 2009). One individual was randomly selected to serve as the conditioned stimulus (CS+) for each participant, whereas the other served as the CS- (safety signal). During conditioning, the CS+ was paired

with the US on 50% of trials. Because fear conditioning is a process inducing a fear response that tends to naturally decrease over time, a partial reinforcement contingency ratio was used to prevent habituation to the US (Mackintosh, 1974). The US was constituted of the photo of the same actor/actress selected for the CS+, but depicting a fearful expression and presented simultaneously with a 90dB shrieking male or female scream. Participants were not aware of the CS+ - US association prior to the experiment. The other actor/actress served as a conditioned stimulus unpaired (CS-) with the aversive US. In the present study, 49 participants (24 boys, 25 girls) saw photos of males posing as the CS+ and CS-, while 68 participants (32 boys, 36 girls) saw photos of females posing as the CS+ and CS-. Four groups were constituted: Group 1- boys viewing male facial expressions; Group 2- girls viewing male facial expressions; Group 3- boys viewing female facial expressions; Group 4- girls viewing female facial expressions. During extinction, task procedures were identical to that of the conditioning session except that no US were presented, and only 14 CS+ unpaired and 14 CS- were shown.

Fear ratings and SCRs served as the behavioural dependent measures, i.e., the fear responses to the CS+ and CS- during conditioning and extinction. Fear ratings were performed during each presentation of the photographs (CS+ before apparition of US, CS-), in both the conditioning and extinction phases (Figure 1). Participants were asked to indicate on a 5-point likert scale the degree to which they felt afraid when viewing the actor/actress in the CS+ and CS- photos (Are you afraid?; 1= not at all, 5= extremely). Fear ratings were recorded with a right hand-held button response box developed to allow for a graded range of responses (Current designs, Philadelphia).

Overall, 84 stimuli were presented (Figure 1). Conditioning trials (n=56) comprised one of three events: CS+ paired (n=14), CS+ unpaired (n=14) or CS- stimuli (n=28). The CS+ paired events consisted of the presentation of a neutral face stimulus (3-s), a rating response (3-s), and a fearful face stimulus (1.1-s) paired with the auditory stimulus (1-s). The CS+ unpaired and CS- events consisted of the presentation of the neutral face stimulus (3-s), followed by the rating response (3-s). Events were presented for durations of 6 (CS+-unpaired and CS-) or 7.1 (CS+-US-paired) seconds with inter-stimulus intervals of 3, 4, 5, 6, 8, 10 or 12 seconds. During extinction, 14 CS+ unpaired (3s- face presentation, 3s- rating response) and 14 CS- (3s- face presentation, 3s- rating response) were shown. Trials were presented in a

pseudorandom order and the assignment of actors or actresses (either blond or brown hair) to *CS-type* (CS+, CS-) was counterbalanced across participants.

Insert Figure 1 here

Before testing, participants were familiarized with the discrimination conditioning and extinction tasks to ensure understanding of picture rating. The pictures presented during the practice session were different from the ones used during the actual fear conditioning and extinction paradigm to prevent habituation to the CS+, US and CS-. Before practice and testing sessions, participants were told they would see two different images and hear sounds, but no details were given on the images or sounds. Visual and auditory stimuli were presented through a laptop computer using E-Prime software (PST, Inc., Pittsburgh, PA) and headphones were placed on the ears of the participants.

Following completion of the conditioning and extinction tasks, photos of the actors or actresses used for the CS+ and CS-, and depicting a neutral facial expression, were presented again to participants, who were asked to rate their fear levels on the 5-point Likert scale one last time. During this post-experiment interview, participants were also debriefed and asked about their contingency awareness of the CS – US relationship. Specifically, youths were asked if the blond- and/or brown-haired actor/actress screamed. Contingency awareness (1= yes, 0= no) was granted if participants correctly identified which actor/actress had been paired with the scream (CS+), and which represented the safety signal (CS-).

Physiological Measurements

Skin conductance, an index of sympathetic nervous system activity, was used to measure physiological responses to the fear-related (CS+) and safe (CS-) cues during fear conditioning and extinction. Skin conductance responses were recorded using non-invasive procedures, i.e., two 10-mm EDA isotonic gel radio-translucent electrodes placed on the plantar surface of the right foot of participants. Collection and preprocessing of the SCR data were performed according to Dubé and collaborators (Dubé et al., 2009). Hence, physiological

data were amplified, digitized, and recorded at 1000 Hz using a computerized data acquisition system (MP150-BIOPAC System), and SCR analyses were performed using Acknowledge Analysis Software (version 4.2 BIOPAC). Preprocessing of the data included 500ms mean smoothing, 1 s delay signal subtraction, and replacement of negative values by 0 (Dubé et al., 2009). The area under the differential curve was extracted for a 3 sec-window following cue onset, delayed by 1 to 3 sec to account for the latency of the SCR, for each stimulus presented (CS+ and CS-) in every participant. This index, reflecting the amplitude of the SCR, is highly sensitive to rapid increases in phasic skin conductance (positive slope;(Dawson, 2000). The extracted area under the differential curve was limited to the first 3 sec following cue onset in order to avoid contamination with skin conductance activity triggered by the motor response performed during stimulus rating, which occurred in the last 3 sec-segment of each stimulus presentation (cf. Figure 1).

Primary analysis. Because high variability characterizes SCRs from one event to the other in each participant, amplitude of the SCRs was standardized within each subject, for both the conditioning and extinction phases, using Z transformations. Means were calculated over SCRs during both the CS+ and CS- events, separately for the conditioning and extinction phases. This allowed for statistical analysis comparing SCRs to the CS+ *vs.* CS- within each group, during conditioning as well as extinction.

Secondary analysis. Because absence of differential conditioning (CS+ > CS-) in two of the groups (boys viewing female faces and girls viewing male faces) was observed (cf. *Results* section), we proceeded in calculating the number of *significant* SCRs to both the CS+ and CS- in each participant of all four groups. This was done in order to determine if similar levels of physiological reactivity were triggered by the stimuli (CS+ and CS-), or if the absence of differential conditioning in these two groups was due to an absence of physiological reactivity and thus, of fear learning. A participant's SCRs were considered *significant* if they were two times larger (and thus, presumably in reaction to the CS+ and CS- events) than his "noise-level" (i.e., non-significant) SCRs. The noise-level SCR was determined based on the rest period occurring before the onset of the conditioning task. Specifically, within the 6 sec-segment before the end of the rest period, the amplitude of the SCR was extracted for a 3 sec-window, in each participant. The significant SCRs, thus personalized for every youth, were coded 1, and noise-level (non-significant) SCRs were

coded 0. For every participant, the sum of significant SCRs was calculated separately for the CS+ and CS- events, and separately for the conditioning and extinction phases.

Data Analyses

Demographic, behavioral and physiological data analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL).

Demographic characteristic data. Demographic characteristic data of participants met sphericity and normality assumptions in the four groups. To investigate whether an equal number of male and female facial expressions were viewed by both boys and girls, and to determine if an equal number of boys and girls were evaluated, chi-squares for quantitative measures were used. Age of participants was compared between the four groups using a one-way analysis of variance (ANOVA).

Behavioral and physiological measures. Sphericity was met for both the fear ratings and SCRs, but normality was met only for the SCRs. Subjective fear rating data were therefore log transformed. Subjective fear ratings, SCR amplitude data and number of significant SCRs were analyzed in distinct ANOVAs, and conditioning and extinction phases were analyzed separately. Four-way repeated-measures ANOVAs with *sex of participants* (boys *vs.* girls) and *sex of target* (male *vs.* female faces) as between-subjects factors, and *CS-type* (CS+, CS-) and *time of cue presentation* (early *vs.* late; for conditioning, early: 14 first cues, late: 14 last cues; for extinction, early: 7 first cues, late: 7 last cues) as the within-subjects factor were conducted on the dependent variables subjective fear ratings and SCRs. For the number of significant SCR data, the pattern of results was not affected by the factor *Time of cue presentation*, in both the conditioning and extinction phases. Therefore, the results presented are based on ANOVAs with two between-subjects factors (*sex of participants*, *sex of target*) and one within-subjects factor (*CS-type*). Post-hoc comparisons performed on significant ANOVA findings were done using Tukey group comparisons test at an alpha level of 0.05.

Results

Demographic Characteristics

The final sample consisted of 117 youths: 24 boys viewing male faces (Mean age = 13.71 ± 2.26), 25 girls viewing male faces (Mean age = 13.96 ± 2.07), 32 boys viewing female faces (Mean age = 14.31 ± 2.01), 36 girls viewing female faces (Mean age = 13.64 ± 1.84). An

equal number of male and female facial expressions were seen by boys, as well as by girls (χ^2 = .04, p = .83). Groups did not differ in terms of age ($F_{3,116}$ = 0.72, p = .54).

Behavioral and Physiological Measures

Fear ratings and SCRs were unrelated (all rs < .19, all ps > .05). Means and standard deviations of fear ratings and SCRs to the CS+ and CS- during conditioning and extinction are displayed in Table 1.

Insert Table 1 here

Fear ratings. Eight participants presented multivariate outlier data to both the CS+ and CS- (unusual pattern of responses – i.e., much higher scores – compared to the mean CS+ and CS- scores of their respective group; as per Achim, 2012), and were rejected from the subjective fear ratings analysis; hence, analyses were performed on 109 participants. During conditioning, there were significant main effects of *CS-type* ($F_{1,105}$ = 84.00, p < .001; η^2 = .44) and *time of cue presentation* ($F_{1,105}$ = 55.00, p < .001; η^2 = .34), which were subsumed by a significant two-way interaction of *CS-type X time of cue presentation* ($F_{1,105}$ = 16.09, p < .001; η^2 = .13). Post hoc analyses showed that subjective fear ratings were higher for the CS+ during early compared to late conditioning (p < .001; Figure 2A). No early *vs.* late differences in CS- ratings were observed (p > .05). The ANOVA also revealed a significant main effect for *sex of target*, with greater fear ratings to the male faces compared to female faces ($F_{1,105}$ = 11.67, p = .001; η^2 = .10; Figure 2B). No main effect of *sex of participants* ($F_{1,105}$ = 2.40, p = .12), and no other two- or three-way interactions (all $Fs_{1,105}$ < 3.25; all ps > .07) were observed.

Insert Figure 2 here

During extinction, there were main effects for *CS-type* ($F_{1,105}$ = 61.65, p < .001, η^2 = .37) and *time of cue presentation* ($F_{1,105}$ = 23.47, p < .001; η^2 = .18), as well as a *CS-type X*

time of cue presentation interaction ($F_{1,105} = 16.17$, $p < .001$; $\eta^2 = .13$), which were subsumed by a *CS-type X time of cue presentation X sex of participants* interaction ($F_{1, 105} = 4.68$, $p = .03$; $\eta^2 = .04$). Summarized post hoc findings show greater differential fear learning (CS+ *vs.* CS-) for ratings during early and late extinction in both boys and girls (*ps* < .001). Additionally, in early compared to late extinction, fear ratings were more elevated in both sexes for the CS+ condition (*ps* ≤ .001), but more elevated in girls relative to boys for the CS- condition ($p = .03$; Figure 3A). The ANOVA also revealed a main effect of *sex of target* ($F_{1,105} = 5.79$, $p = .02$; $\eta^2 = .05$), which was subsumed by a *CS-type X sex of target* interaction ($F_{1,105} = 10.43$, $p = .002$, $\eta^2 = .09$). Post hoc analyses showed that the CS+ triggered greater fear ratings for male faces compared to female faces in both boys and girls ($p = .002$; Figure 3B). No other main effect or two- or three-way interactions were found (all $Fs_{1,105} < 3.6$; all *ps* > .06).

Insert Figure 3 here

Skin conductance responses. Five participants were excluded from the SCR analyses because they showed no SCRs or because of bad quality data (e.g. noise); hence analyses were carried on 112 participants.

SCR amplitude during conditioning. During conditioning, we observed a main effect of *time of cue presentation*, with greater SCRs observed during early relative to late conditioning ($F_{1,108} = 46.79$, $p < .001$; $\eta^2 = .30$). The ANOVA also revealed a main effect of *CS-type* ($F_{1,108} = 11.52$, $p = .001$; $\eta^2 = .10$), which was subsumed by a *CS-type X sex of participant X sex of target* interaction ($F_{1, 108} = 8.10$, $p = .005$, $\eta^2 = .07$; Figure 4A). Post hoc analyses showed greater SCRs triggered by the CS+ *vs.* CS- in boys viewing male faces ($p < .001$), and in girls viewing female faces ($p = .03$). No other main effects, or two- or three-way interactions were found (all $Fs_{1,108} < 3.43$; all *ps* > .07).

Number of SCRs during conditioning. No significant main effects were observed during conditioning ($Fs_{1, 108} < 3.72$, $p > .05$). However, a *CS-type X sex of participants X sex of target* was observed ($F_{1, 108} = 7.50$, $p = .007$; $\eta^2 = .07$; Figure 4B). Post hoc analyses

showed that there was a greater number of SCRs for the CS+ compared to the CS- in boys viewing male faces (p = .01), and in girls viewing female faces (p = .05). As can be seen in figure 4B, there were SCRs to the CS+ and CS- in boys viewing female faces and in girls viewing male faces, however this reactivity was of similar level for both stimuli. Thus, the observed absence of differential learning in the SCR amplitude data is not due to failed fear conditioning, but to comparable SCRs to both events. No other two- or three-way interactions were found (all $Fs_{1,108} < .55$; all $ps > .46$).

Insert Figure 4 here

SCR amplitude during extinction. During extinction, no significant main effects were observed (all $Fs_{1,\ 108} < 2.40$, all $ps > .13$). However, a *CS-type X sex of participants X sex of target* interaction was found ($F_{1,\ 108} = 6.78$, $p = .01$; $\eta^2 = .06$). Post hoc analyses showed greater SCRs triggered by the CS+ *vs.* CS- for male faces in boys (p = .05; Figure 5A). We also observed a *CS-type X time of cue presentation X sex of target* interaction ($F_{1,\ 108} = 4.23$, p = .04; η^2 = .04); however, no *CS-type* differences (CS+ *vs.* CS-) were observed in any of the groups (all $ps > .14$). No other two- or three-way interactions were found (all $Fs_{1,108} < 1.25$, all $ps > .27$).

Number of SCRs during extinction. We observed a main effect of *sex of target* during extinction, with a greater number of SCRs observed for female faces compared to male faces ($F_{1,108} = 7.87$, $p = .006$; $\eta^2 = .07$; Figure 5B). No other main effects or two- or three-way interactions were found (all $Fs_{1,108} < 2.22$; all $ps > .14$).

Insert Figure 5 here

Post-experiment questionnaire. Over 95% of participants showed contingency awareness of the CS – US relationship. The chi-squared analysis of participants showing correct *vs.* incorrect contingency awareness didn't differ across groups ($\chi 2 = 1.23$, $p = .05$).

Moreover, excluding data of the 3 unaware participants did not affect the pattern of results for the fear ratings or SCRs during conditioning and extinction. Ratings obtained with the post-experiment questionnaire (cf. means and standard deviations in Table 2) led to similar conclusions as those observed with ratings collected during the task, i.e., greater fear levels manifested to the CS+ *vs.* CS- ($F_{1,100}$ = 130.72, p < .001; η^2 = .57; as observed during both conditioning and extinction), and greater fear levels triggered by male faces relative to female faces ($F_{1,100}$ = 7.28, p = .008; η^2 = .07; as observed during conditioning and extinction). Moreover, a *CS-type X sex of target* interaction was found ($F_{1,100}$ = 5.32, p = .02, η^2 = .05), showing greater fear ratings triggered by the CS+ for male faces compared to female faces in both boys and girls (p = .003; as observed during conditioning and extinction).

Insert Table 2 here

Discussion

To our knowledge, this is the first study to explicitly investigate the influence of sex of participants and sex of target on discrimination fear conditioning and extinction in youths. Two key findings emerge from the conditioning rating data. Firstly, greater fear ratings to the CS+ in early relative to late trials were observed in both boys and girls. Decreased fear responses in late conditioning trials are expected as habituation to threat-related cues occurs over time. Fear ratings to the CS- remained low from early to late trials, confirming that all participants correctly identified the safety cue. Secondly, fear ratings to both the CS+ and CS- during conditioning were greater for male faces compared to female faces, in both boys and girls. Two key findings also emerge regarding the physiological reactivity measured during conditioning. First, similarly to the rating findings, SCRs were greater in early relative to late trials in all groups, suggesting elevation of fear reactivity that eventually habituated over time. Secondly, differential fear learning as reflected by SCR amplitude data was characterized by an "own-sex" effect, as boys showed greater physiological reactivity to the CS+ relative to the CS- only when viewing male faces and girls, only when viewing female faces. In contrast, when conditioned with stimuli from the opposite sex, no difference was observed between

CS+ and CS- in boys viewing female faces and in girls viewing male faces. This suggests that participants failed to efficiently recognize safety cues when they were depicted by facial features of the opposite sex.

During extinction, the absence of attenuation in fear ratings (i.e., CS+ > CS-) from early to late trials was observed in both boys and girls. Girls were also slow in minimizing fear ratings to the safety cues (CS-) during early trials. Moreover, as observed during conditioning, male faces triggered greater fear ratings than female faces in the CS+ condition, in both sexes. Finally, in terms of SCRs, only an "own-sex" effect reflecting greater physiological reactivity to the CS+ relative to the CS- in boys viewing male faces was maintained.

Findings from subjective fear ratings analyses show that both boys and girls reported being more afraid of male neutral facial expressions than of female neutral faces, during conditioning and extinction. This confirms adult work showing that male neutral faces are perceived as more threatening than female neutral facial expressions (Adams, Nelson, Soto, Hess, & Kleck, 2012), and that male facial expressions perceived as threatening trigger longer-lasting fear and hostile responses (Becker et al., 2007; Kret & De Gelder, 2012; Navarrete et al., 2009; Ohman, 2009; Rotteveel & Phaf, 2004). This may be explained by the physiognomy of men – heavier and lower eyebrows, angular facial features (e.g., jaw), thinner lips, larger nose – which naturally connotes greater hostility and threat than that of women (Becker et al., 2007; Hess H., 1997). Additionally, the fact that more crime and violence are linked to men than women reinforces the stereotypic feelings of threat conveyed by male facial expressions (Becker et al., 2007; Daly, 1994; Dimberg, 1996; Kret & De Gelder, 2012).

Contrary to our predictions, however, girls did not show greater subjective fear ratings than boys, and this was true for both conditioning and extinction phases. Such findings are not necessarily in contradiction with the literature as conflicting results regarding sex differences in emotional processing are reported (De Sonneville et al., 2002; Herba et al., 2006; Thomas et al., 2007; Vicari et al., 2000); cf.(Kret & De Gelder, 2012). The female advantage is indeed characterized as being quite modest, and could be influenced by some methodological factors (Kret & De Gelder, 2012; McCarthy & Konkle, 2005). For example, sex differences, to the advantage of females, are thought to be particularly apparent when the intensity of the emotion portrayed is maximal, as opposed to the neutral facial expressions presented in the current study (Kret & De Gelder, 2012). The female advantage is also thought to be particularly

salient when using verbal instead of visuo-spatial cues (as in the current paradigm, which employed photos; (Herba et al., 2006). Finally, a sex advantage in emotional processing may vary according to the wax and wane of hormonal levels, as observed during puberty or phases of girls' menstrual cycle, and according to differences in the maturation of brain structure and function. In the present study, youths were tested in different puberty stages, phases of their menstrual cycle or states of brain maturation. Not having controlled for these aspects, it is possible that the different biological states in which were the participants at the time of testing dampened the girls' reactivity to the fear-related cues (CS+; (Guapo et al., 2009; Kret & De Gelder, 2012; Little, 2013).

Regarding physiological fear responses during conditioning, an "own-sex" effect characterized SCRs, with boys showing greater physiological reactivity to the CS+ *vs.* CS- for male faces and girls, for female faces. This parallels findings from other physiological studies showing greater SCRs or electroencephalogram-measured cortical activity in males processing or being conditioned to male facial features, and in females processing female facial features (Doi, Amamoto, Okishige, Kato, & Shinohara, 2010; Kret & De Gelder, 2012; Mazurski, Bond, Siddle, & Lovibond, 1996; Suyama, Hoshiyama, Shimizu, & Saito, 2008). An "own-sex" bias was also observed for neural brain activation during memory encoding, with greater right amygdala activity being triggered in men for male faces and greater left amygdala activation being triggered in women for female faces (Armony & Sergerie, 2007). Our findings, as that of the above mentioned studies, could be accounted for by early developmental socialization processes. Indeed, young adolescents tend to spend more time with same-sex mates. As proposed by previous work, this could lead to better decoding of same-sex facial expressions, and a more thorough identification of the emotional cues transmitted (Cellerino, Borghetti, & Sartucci, 2004; McClure, 2000). Such behavior is of particular importance since a more efficient analysis of emotional cues warning of potential self-related threat, as those efficiently transmitted by individuals of one's own-sex, may enhance chances of survival.

In contrast, when participants were conditioned with stimuli from the opposite sex, no difference was observed in SCRs between CS+ and CS-. Despite the absence of differential learning (CS+ > CS-), it is difficult to argue that conditioning failed to occur in these two groups (boys viewing female faces and girls viewing male faces). Firstly, the contingency

awareness data indicate clear stimulus distinction for practically all participants in the current study (i.e., CS+ perceived as threat-related and CS-, as a safety cue). Secondly, as demonstrated by the number of significant SCRs depicted in Fig. 4B, all participants showed SCRs to both CS+ and CS-. Amplitude of SCRs was, however, similar in both conditions. Therefore, the observed equivalent increases in SCRs for both the CS+ and CS- are most probably best explained by fear generalization, which occurs when the CS- (in this study, a neutral facial expression), by being perceptually similar to the CS+ (also a neutral facial expression in this study), triggers similar or even greater fear responses than the CS+ itself (Dunsmoor, Prince, Murty, Kragel, & LaBar, 2011; Lissek et al., 2005).

Such enhanced physiological fear reactivity to faces of the "out-group" (the social group to which one does not identify, e.g., because of sex, ethnicity or social category) has often been reported, explained by difficulties in accurately discriminating facial features of the "out-group" as opposed to that of the "in-group", especially when threatening emotions are being displayed (Aleman & Swart, 2008; Navarrete et al., 2009; Rotteveel & Phaf, 2004; van der Schalk et al., 2011). Because neutral facial expressions are ambiguous and often misinterpreted as threatening (Cellerino et al., 2004; McClure, 2000), the opposite-sex effect observed in two of our groups (boys viewing female faces, girls viewing male faces) could be due to difficulties in efficiently discriminating opposite-sex neutral facial features. This could be explained, as mentioned above, by youths tending to spend more time with same-sex friends. Additionally, youths are in a period of the lifespan during which important changes in brain development are occurring, especially in the prefrontal cortex (Blakemore, 2012; Kret & De Gelder, 2012; Lenroot & Giedd, 2010). This region being a key player in the processing and interpretation of socio-affective cues, it is possible that the less familiar opposite-sex neutral facial cues (CS+ and CS-) were both perceived as threatening. Hence, important physiological reactivity was triggered by the opposite-sex targets, with boys not efficiently discriminating the threat-related CS+ from the safe CS- when depicted by female facial features (and vice-versa for girls), explaining why fear was transferred from the CS+ to the CS-, and why fear generalization occurred only in those two groups.

Regarding differences in SCRs relative to ratings during conditioning, such discrepancies are not uncommon. As reported by a wealth of data, physiological responses are unconscious, automatic reflex-like responses triggered by the brain's amygdala, which allows

for rapid processing of crudely analysed information that are transmitted by downstream connections (e.g., with the midbrain and brainstem) and the thalamus. Hence, when the information is finally processed more thoroughly by the cortex, discrepancies easily arise between the automatic physiological responses and the cognitive appraisal of the same cue (LeDoux, 2014; Ohman, Carlsson, Lundqvist, & Ingvar, 2007).

Findings from the extinction phase led to another discrepancy, as we did not observe the same attenuation of fear responses in our young participants as that usually observed in adults (see reviews in (Delgado, Olsson, & Phelps, 2006; Dimberg, 1996; Jovanovic, Nylocks, & Gamwell, 2013; Ohman, 2009; Sehlmeyer et al., 2009). Indeed, resistance to fear extinction was observed in fear ratings for male faces in both boys and girls, and in SCRs of boys who viewed male faces. Lack of fear extinction has been reported before, notably by Lau and collaborators, who used a very similar version of the task presented here in adolescents (Haddad, Lissek, Pine, & Lau, 2011; Lau et al., 2008). Such resistance to fear extinction could be related to social desirability and participants' impression that the CS+ commanded elevated subjective fear responses. However, though this explanation seems fitted for the cognitive fear rating data, it seems more difficult to reconcile with the observed elevations in physiological responses, which depend on automatic, reflex-like mechanisms (LeDoux, 2014; Ohman et al., 2007). Another explanation related to task methodology could be suggested. In the current study, a 50% partial reinforcement schedule was used in order to prevent habituation to the US (Mackintosh, 1974). Such schedules have been linked to slower extinction of fear responses. But again, it is unlikely that this may explain our findings as other previous adolescent work using over 50% contingency reinforcement ratios (i.e., 75-100%) also report resistance to fear extinction (Lau et al., 2008; Neumann, Waters, Westbury, & Henry, 2008; Pattwell et al., 2012; Pattwell et al., 2013).

Most likely, a developmental bias may explain the lack of fear extinction observed. Healthy adults are generally quite efficient in suppressing fear responses (diminution of CS+ fear levels to that of the CS-; (Delgado et al., 2006; Dimberg, 1996; Lissek et al., 2005; Ohman, 2009), even with a 50% contingency reinforcement ratio (e.g., (Barrett & Armony, 2009; Gottfried & Dolan, 2004; Phelps, Delgado, Nearing, & LeDoux, 2004). As suggested by recent developmental fear conditioning and extinction studies performed in rodents and humans (Li, Kim, & Richardson, 2012; Pattwell et al., 2012; Pattwell et al., 2013), the

persistent fear responses observed during extinction in youths may be due to differences in emotion processing between youths and adults. Work on normal brain development indeed demonstrates that youths are characterized by a mature limbic lobe but an under-developed frontal cortex, whereas both structures are optimally developed in adults. This normal protracted development of frontal regions relative to limbic areas in youths may have prevented the efficient regulation of the prefrontal cortex over the amygdala, leading to blunted cognitive and physiological regulation of amygdala-dependent fear responses and lack of fear extinction (Casey et al., 2010; Gogtay & Thompson, 2010; Pattwell et al., 2013).

Finally, though SCRs amplitude to male and female faces for the extinction phase were equivalent, the number of significant SCRs was significantly greater for female faces relative to male faces in all participants (Fig. 5B). Cautious interpretation of the number of significant SCRs is required since they do not reflect the magnitude of the responses. This finding could be reconciled with the extensively investigated perception that females are more emotional, fragile and vulnerable – especially when in a threat-related context – than males, a judgment based on implicit stereotypes, and social prejudice and desirability (Fisher, 1993; Friedman & Zebrowitz, 1992). This implicit stereotyped perception may have triggered unconscious, automatic reflex-like SCRs more often in participants.

Limitations and Recommendations

Our findings should be considered in light of some limitations. Firstly, we did not control for hormonal puberty and menstrual cycle variations, the possible use of oral contraception, or differences in the maturation of brain structure and function. Since sex differences related to fear learning and extinction were recently shown to be influenced by these variables (Merz, Stark, Vaitl, Tabbert, & Wolf, 2013; Merz et al., 2012; Milad et al., 2006; Zeidan et al., 2011), further studies should take these factors into account. Secondly, a more thorough investigation of emotional difficulties in participants, using more standard mood and anxiety disorders questionnaires or interviews, could have helped control for confounding emotional symptoms which may have influenced participants' performance on our fear-related task.

Conclusion

Despite these limitations, this first study of the influence of sex of participants and sex of target on fear conditioning and extinction in youths suggests that important differences exist

in terms of how boys and girls react to male and female threatening cues. Both boys and girls were similarly conditioned to fear, and showed resistance to fear extinction. Moreover, even though both male and female faces triggered conditioning effects, resistance to fear extinction was observed only for male faces in boys and girls. Additionally, findings also reveal that fear responses, depending on whether they were measured subjectively or objectively, lead to different perspectives as to whether cues were perceived as threatening or safe in youths. These findings underline three important points: firstly, that male and female faces do not have the same impact on fear conditioning and extinction, with female faces triggering more comparable levels of fear learning and extinction in boys and girls, compared to male faces. Secondly, that the sex of the participant may interact with the sex of the target and lead to different fear conditioning and extinction responses. Third, that findings obtained via subjective measures (e.g., ratings) do not necessarily mirror findings obtained via objective measures (e.g., SCRs), suggesting that our conscious interpretation of threat may not match our automatic physiological reactivity to the same emotionally negative cues. These conclusions underlie the importance of carefully choosing the sex of target, depending on the effects one desires to obtain, and the necessity of using both types of measures in order to obtain a more complete comprehension of fear learning and extinction in youths.

References

Adams, R. B., Jr., Nelson, A. J., Soto, J. A., Hess, U., & Kleck, R. E. (2012). Emotion in the neutral face: a mechanism for impression formation? *Cogn Emot, 26*(3), 431-441. doi: 10.1080/02699931.2012.666502

Aguado, L., Garcia-Gutierrez, A., & Serrano-Pedraza, I. (2009). Symmetrical interaction of sex and expression in face classification tasks. *Atten Percept Psychophys, 71*(1), 9-25. doi: 71/1/9 [pii]10.3758/APP.71.1.9

Aleman, A., & Swart, M. (2008). Sex differences in neural activation to facial expressions denoting contempt and disgust. *PLoS One, 3*(11), e3622. doi: 10.1371/journal.pone.0003622

Armony, J. L., & Sergerie, K. (2007). Own-sex effects in emotional memory for faces. *Neurosci Lett, 426*(1), 1-5. doi: S0304-3940(07)00886-5 [pii]10.1016/j.neulet.2007.08.032

Barrett, J., & Armony, J. L. (2009). Influence of trait anxiety on brain activity during the acquisition and extinction of aversive conditioning. *Psychol Med, 39*(2), 255-265. doi: 10.1017/S0033291708003516

Becker, D. V., Kenrick, D. T., Neuberg, S. L., Blackwell, K. C., & Smith, D. M. (2007). The confounded nature of angry men and happy women. *J Pers Soc Psychol, 92*(2), 179-190. doi: 2007-00654-002 [pii]10.1037/0022-3514.92.2.179

Blakemore, S. J. (2012). Development of the social brain in adolescence. *J R Soc Med, 105*(3), 111-116. doi: 10.1258/jrsm.2011.110221

Casey, B. J., Jones, R. M., Levita, L., Libby, V., Pattwell, S. S., Ruberry, E. J., . . . Somerville, L. H. (2010). The storm and stress of adolescence: insights from human imaging and mouse genetics. *Dev Psychobiol, 52*(3), 225-235. doi: 10.1002/dev.20447

Cellerino, A., Borghetti, D., & Sartucci, F. (2004). Sex differences in face gender recognition in humans. *Brain Res Bull, 63*(6), 443-449. doi: 10.1016/j.brainresbull.2004.03.010S0361923004001017 [pii]

Dalla, C., & Shors, T. J. (2009). Sex differences in learning processes of classical and operant conditioning. *Physiol Behav, 97*(2), 229-238. doi: S0031-9384(09)00075-4 [pii]10.1016/j.physbeh.2009.02.035

Daly, M., Wilson, M. (1994). Evolutionary psychology of male violence. In C. Routledge (Ed.), *Male violence*. New York: In J. Archer (Ed.).

Dawson, M. E., Schell, A.M., Filion, D.L. (2000). The electrodermal system. In J. T. Cacioppo, Tassinary, L.G., Bernston, G.G. (Ed.), *Handbook of Psychophysiology* (2nd ed., pp. 200-223). USA: Cambridge University Press.

De Sonneville, L. M., Verschoor, C. A., Njiokiktjien, C., Op het Veld, V., Toorenaar, N., & Vranken, M. (2002). Facial identity and facial emotions: speed, accuracy, and processing strategies in children and adults. *J Clin Exp Neuropsychol, 24*(2), 200-213. doi: 10.1076/jcen.24.2.200.989

Delgado, M. R., Olsson, A., & Phelps, E. A. (2006). Extending animal models of fear conditioning to humans. *Biol Psychol, 73*(1), 39-48. doi: 10.1016/j.biopsycho.2006.01.006

Dimberg, U., Öhman, A. (1996). Behold the Wrath: Psychophysiological Responses to Facial Stimuly. *Motivation and Emotion, 20*(2).

Doi, H., Amamoto, T., Okishige, Y., Kato, M., & Shinohara, K. (2010). The own-sex effect in facial expression recognition. *Neuroreport, 21*(8), 564-568. doi: 10.1097/WNR.0b013e328339b61a

Dubé, A. A., Duquette, M., Roy, M., Lepore, F., Duncan, G., & Rainville, P. (2009). Brain activity associated with the electrodermal reactivity to acute heat pain. *Neuroimage, 45*(1), 169-180. doi: 10.1016/j.neuroimage.2008.10.024

Dunsmoor, J. E., Prince, S. E., Murty, V. P., Kragel, P. A., & LaBar, K. S. (2011). Neurobehavioral mechanisms of human fear generalization. *Neuroimage, 55*(4), 1878-1888. doi: 10.1016/j.neuroimage.2011.01.041

Egger, H. L., Pine, D. S., Nelson, E., Leibenluft, E., Ernst, M., Towbin, K. E., & Angold, A. (2011). The NIMH Child Emotional Faces Picture Set (NIMH-ChEFS): a new set of children's facial emotion stimuli. *Int J Methods Psychiatr Res, 20*(3), 145-156. doi: 10.1002/mpr.343

Fisher, A. H. (1993). Sex Differences in Emotionality: Fact of Stereotype ? *Feminism & Psychology, 3*(3), 303-318.

Forsyth, J. P., & Eifert, G. H. (1998). Response intensity in content-specific fear conditioning comparing 20% versus 13% CO2-enriched air as unconditioned stimuli. *J Abnorm Psychol, 107*(2), 291-304.

Friedman, H., & Zebrowitz, L. A. (1992). The Contribution of Typical Sex Differences in Facial Maturity to Sex Role Stereotypes. *Society for Personality and Social Psychology, 18*, 430-438.

Gogtay, N., & Thompson, P. M. (2010). Mapping gray matter development: implications for typical development and vulnerability to psychopathology. *Brain Cogn, 72*(1), 6-15. doi: 10.1016/j.bandc.2009.08.009

Goos L.M., S. I. (2002). Sex related factors in the perception of threatening facial expressions. *Journal of Nonverbal Behavior, 26*(1).

Gottfried, J. A., & Dolan, R. J. (2004). Human orbitofrontal cortex mediates extinction learning while accessing conditioned representations of value. *Nat Neurosci, 7*(10), 1144-1152. doi: 10.1038/nn1314

Guapo, V. G., Graeff, F. G., Zani, A. C., Labate, C. M., dos Reis, R. M., & Del-Ben, C. M. (2009). Effects of sex hormonal levels and phases of the menstrual cycle in the processing of emotional faces. *Psychoneuroendocrinology, 34*(7), 1087-1094. doi: 10.1016/j.psyneuen.2009.02.007

Haddad, A. D., Lissek, S., Pine, D. S., & Lau, J. Y. (2011). How do social fears in adolescence develop? Fear conditioning shapes attention orienting to social threat cues. *Cogn Emot, 25*(6), 1139-1147. doi: 10.1080/02699931.2010.524193

Herba, C. M., Landau, S., Russell, T., Ecker, C., & Phillips, M. L. (2006). The development of emotion-processing in children: effects of age, emotion, and intensity. *J Child Psychol Psychiatry, 47*(11), 1098-1106. doi: 10.1111/j.1469-7610.2006.01652.x

Hess H., B. S., Kleck R.E. (1997). The intensity of emotional facial expressions and decoding accuracy. *Journal of Nonverbal Behavior, 21*(4).

Jovanovic, T., Nylocks, K. M., & Gamwell, K. L. (2013). Translational neuroscience measures of fear conditioning across development: applications to high-risk children and adolescents. *Biol Mood Anxiety Disord, 3*(1), 17. doi: 10.1186/2045-5380-3-17

Kelly, M. M., & Forsyth, J. P. (2007). Observational fear conditioning in the acquisition and extinction of attentional bias for threat: an experimental evaluation. *Emotion, 7*(2), 324-335. doi: 10.1037/1528-3542.7.2.324

Kret, M. E., & De Gelder, B. (2012). A review on sex differences in processing emotional signals. *Neuropsychologia, 50*(7), 1211-1221. doi: S0028-3932(12)00002-4 [pii]10.1016/j.neuropsychologia.2011.12.022

Kring, A. M., & Gordon, A. H. (1998). Sex differences in emotion: expression, experience, and physiology. *J Pers Soc Psychol, 74*(3), 686-703.

Lau, J. Y., Britton, J. C., Nelson, E. E., Angold, A., Ernst, M., Goldwin, M., . . . Pine, D. S. (2011). Distinct neural signatures of threat learning in adolescents and adults. *Proc Natl Acad Sci U S A, 108*(11), 4500-4505. doi: 1005494108 [pii]10.1073/pnas.1005494108

Lau, J. Y., Lissek, S., Nelson, E. E., Lee, Y., Roberson-Nay, R., Poeth, K., . . . Pine, D. S. (2008). Fear conditioning in adolescents with anxiety disorders: results from a novel experimental paradigm. *J Am Acad Child Adolesc Psychiatry, 47*(1), 94-102. doi: 10.1097/chi.0b01e31815a5f01S0890-8567(09)62089-X [pii]

LeDoux, J. E. (2014). Coming to terms with fear. *Proc Natl Acad Sci U S A, 111*(8), 2871-2878. doi: 10.1073/pnas.1400335111

Lee, N. C., Krabbendam, L., White, T. P., Meeter, M., Banaschewski, T., Barker, G. J., . . . Shergill, S. S. (2013). Do you see what I see? Sex differences in the discrimination of facial emotions during adolescence. *Emotion, 13*(6), 1030-1040. doi: 10.1037/a0033560

Lenroot, R. K., & Giedd, J. N. (2010). Sex differences in the adolescent brain. *Brain Cogn, 72*(1), 46-55. doi: 10.1016/j.bandc.2009.10.008

Li, S., Kim, J. H., & Richardson, R. (2012). Differential involvement of the medial prefrontal cortex in the expression of learned fear across development. *Behav Neurosci, 126*(2), 217-225. doi: 10.1037/a0027151

Lissek, S., Powers, A. S., McClure, E. B., Phelps, E. A., Woldehawariat, G., Grillon, C., & Pine, D. S. (2005). Classical fear conditioning in the anxiety disorders: a meta-analysis. *Behav Res Ther, 43*(11), 1391-1424. doi: S0005-7967(04)00251-7 [pii]10.1016/j.brat.2004.10.007

Little, A. C. (2013). The influence of steroid sex hormones on the cognitive and emotional processing of visual stimuli in humans. *Front Neuroendocrinol, 34*(4), 315-328. doi: 10.1016/j.yfrne.2013.07.009

Mackintosh, N. J. (1974). *The psychology of animal learning*. London: Academic Press.

Mazurski, E. J., Bond, N. W., Siddle, D. A., & Lovibond, P. F. (1996). Conditioning with facial expressions of emotion: effects of CS sex and age. *Psychophysiology, 33*(4), 416-425.

McCarthy, M. M., & Konkle, A. T. (2005). When is a sex difference not a sex difference? *Front Neuroendocrinol, 26*(2), 85-102. doi: 10.1016/j.yfrne.2005.06.001

McClure, E. B. (2000). A meta-analytic review of sex differences in facial expression processing and their development in infants, children, and adolescents. *Psychol Bull, 126*(3), 424-453.

Merz, C. J., Stark, R., Vaitl, D., Tabbert, K., & Wolf, O. T. (2013). Stress hormones are associated with the neuronal correlates of instructed fear conditioning. *Biol Psychol, 92*(1), 82-89. doi: S0301-0511(12)00039-7 [pii]10.1016/j.biopsycho.2012.02.017

Merz, C. J., Tabbert, K., Schweckendiek, J., Klucken, T., Vaitl, D., Stark, R., & Wolf, O. T. (2012). Oral contraceptive usage alters the effects of cortisol on implicit fear learning. *Horm Behav, 62*(4), 531-538. doi: S0018-506X(12)00208-5 [pii]10.1016/j.yhbeh.2012.09.001

Meulders, A., Vansteenwegen, D., & Vlaeyen, J. W. (2012). Women, but not men, report increasingly more pain during repeated (un)predictable painful electrocutaneous stimulation: Evidence for mediation by fear of pain. *Pain, 153*(5), 1030-1041. doi: 10.1016/j.pain.2012.02.005

Milad, M. R., Goldstein, J. M., Orr, S. P., Wedig, M. M., Klibanski, A., Pitman, R. K., & Rauch, S. L. (2006). Fear conditioning and extinction: influence of sex and menstrual cycle in healthy humans. *Behav Neurosci, 120*(6), 1196-1203. doi: 10.1037/0735-7044.120.5.1196

Navarrete, C. D., Olsson, A., Ho, A. K., Mendes, W. B., Thomsen, L., & Sidanius, J. (2009). Fear extinction to an out-group face: the role of target gender. *Psychol Sci, 20*(2), 155-158. doi: 10.1111/j.1467-9280.2009.02273.x

Neumann, D. L., Waters, A. M., Westbury, H. R., & Henry, J. (2008). The use of an unpleasant sound unconditional stimulus in an aversive conditioning procedure with 8- to 11-year-old children. *Biol Psychol, 79*(3), 337-342. doi: 10.1016/j.biopsycho.2008.08.005

Ohman, A. (2009). Of snakes and faces: an evolutionary perspective on the psychology of fear. *Scand J Psychol, 50*(6), 543-552. doi: 10.1111/j.1467-9450.2009.00784.x

Ohman, A., Carlsson, K., Lundqvist, D., & Ingvar, M. (2007). On the unconscious subcortical origin of human fear. *Physiol Behav, 92*(1-2), 180-185. doi: 10.1016/j.physbeh.2007.05.057

Pattwell, S. S., Duhoux, S., Hartley, C. A., Johnson, D. C., Jing, D., Elliott, M. D., . . . Lee, F. S. (2012). Altered fear learning across development in both mouse and human. *Proc Natl Acad Sci U S A, 109*(40), 16318-16323. doi: 10.1073/pnas.1206834109

Pattwell, S. S., Lee, F. S., & Casey, B. J. (2013). Fear learning and memory across adolescent development: Hormones and Behavior Special Issue: Puberty and Adolescence. *Horm Behav, 64*(2), 380-389. doi: 10.1016/j.yhbeh.2013.01.016

Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: role of the amygdala and vmPFC. *Neuron, 43*(6), 897-905. doi: 10.1016/j.neuron.2004.08.042

Rotteveel, M., & Phaf, R. H. (2004). Automatic affective evaluation does not automatically predispose for arm flexion and extension. *Emotion, 4*(2), 156-172. doi: 10.1037/1528-3542.4.2.156

Sehlmeyer, C., Schoning, S., Zwitserlood, P., Pfleiderer, B., Kircher, T., Arolt, V., & Konrad, C. (2009). Human fear conditioning and extinction in neuroimaging: a systematic review. *PLoS One, 4*(6), e5865. doi: 10.1371/journal.pone.0005865

Seidel, E. M., Habel, U., Kirschner, M., Gur, R. C., & Derntl, B. (2010). The impact of facial emotional expressions on behavioral tendencies in women and men. *J Exp Psychol Hum Percept Perform, 36*(2), 500-507. doi: 2010-06263-017 [pii]10.1037/a0018169

Suyama, N., Hoshiyama, M., Shimizu, H., & Saito, H. (2008). Event-related potentials for gender discrimination: an examination between differences in gender discrimination between males and females. *Int J Neurosci, 118*(9), 1227-1237. doi: 10.1080/00207450601047176

Thomas, L. A., De Bellis, M. D., Graham, R., & LaBar, K. S. (2007). Development of emotional facial recognition in late childhood and adolescence. *Dev Sci, 10*(5), 547-558. doi: 10.1111/j.1467-7687.2007.00614.x

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., . . . Nelson, C. (2009). The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Res, 168*(3), 242-249. doi: 10.1016/j.psychres.2008.05.006

van der Schalk, J., Fischer, A., Doosje, B., Wigboldus, D., Hawk, S., Rotteveel, M., & Hess, U. (2011). Convergent and divergent responses to emotional displays of ingroup and outgroup. *Emotion, 11*(2), 286-298. doi: 10.1037/a0022582

Vicari, S., Reilly, J. S., Pasqualetti, P., Vizzotto, A., & Caltagirone, C. (2000). Recognition of facial expressions of emotions in school-age children: the intersection of perceptual and semantic categories. *Acta Paediatr, 89*(7), 836-845.

Zeidan, M. A., Igoe, S. A., Linnman, C., Vitalo, A., Levine, J. B., Klibanski, A., . . . Milad, M. R. (2011). Estradiol modulates medial prefrontal cortex and amygdala activity during fear extinction in women and female rats. *Biol Psychiatry, 70*(10), 920-927. doi: S0006-3223(11)00545-2 [pii]10.1016/j.biopsych.2011.05.016

Figures

Figure 1. A schematic depiction of the fear conditioning and extinction tasks using female and male facial cues. CS+: conditioned stimulus, CS-: safety cue, US: unconditioned stimulus.

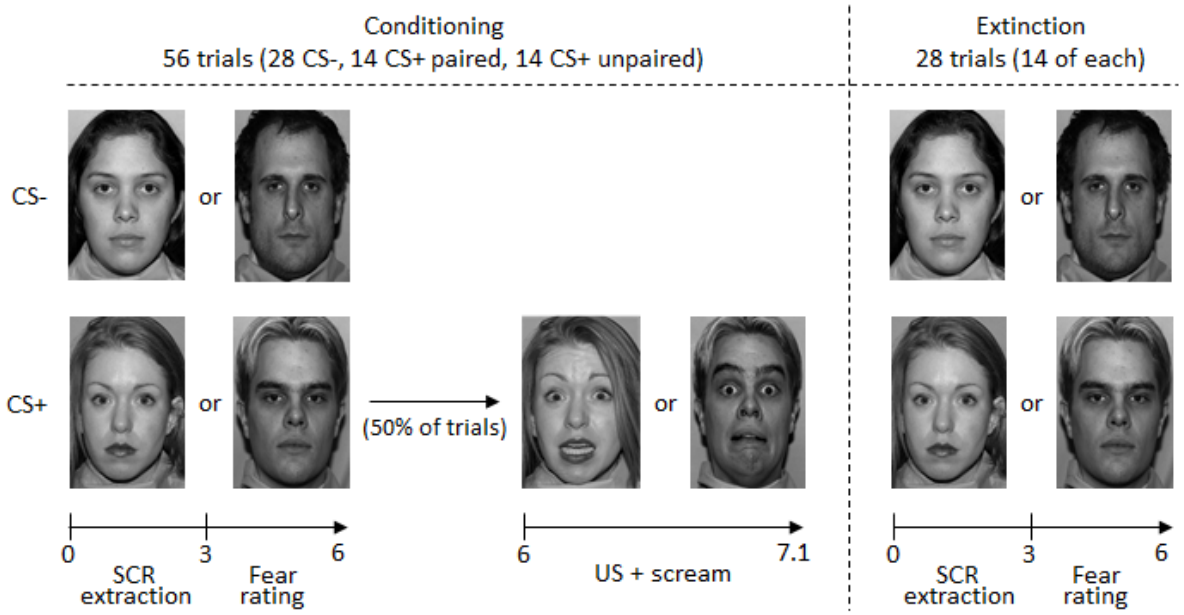


Figure 2. Mean fear ratings during early and late conditioning for the CS+ and CS- in all groups; **(A)** Greater fear ratings during early *vs.* late conditioning for the CS+ ($p < .001$); **(B)** Greater fear ratings for male faces compared to female faces ($p = .001$). ***$p \leq .001$.

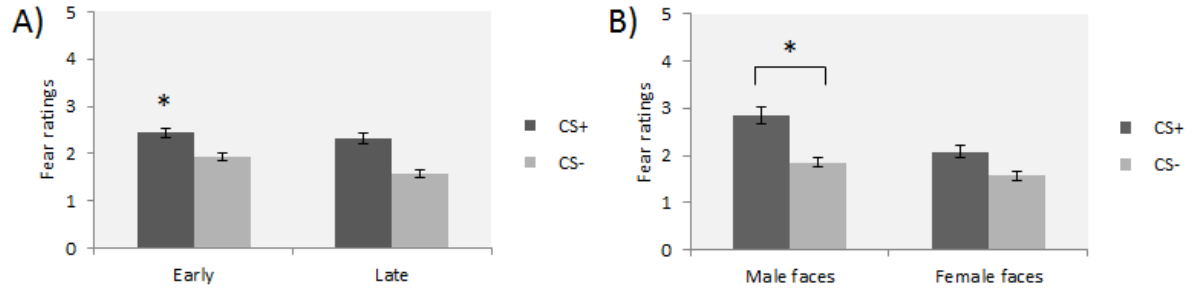


Figure 3. Mean fear ratings during early and late extinction for CS+ and CS- in all groups; **(A)** Resistance to fear extinction as demonstrated by greater ratings to CS+ compared to CS- during early and late extinction for both boys and girls (all *ps* < .001); Greater fear ratings to

CS+ in early *vs.* late extinction for both boys and girls (all *ps* ≤ .001); Greater fear ratings to CS- for girls relative to boys during early extinction (*p* = .03); **(B)** Greater fear ratings for male faces *vs.* female faces in the CS+ condition, in both boys and girls (*p* = .002). *$p < .05$, **$p < .01$, ***$p < .001$.

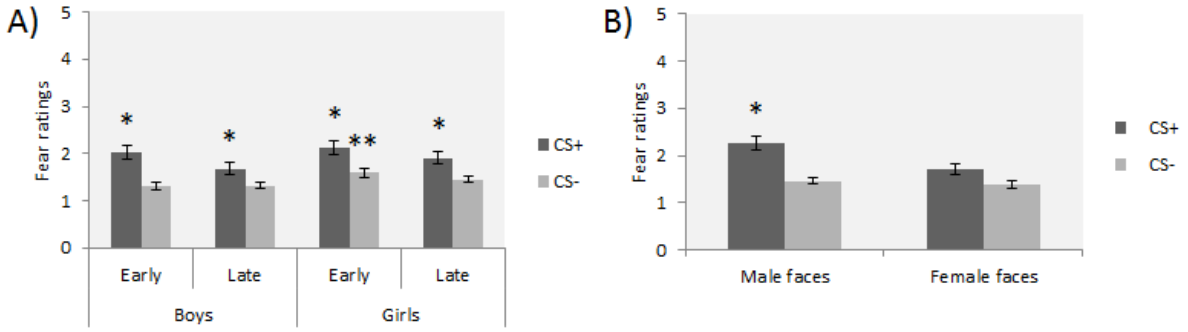


Figure 4. Mean skin conductance responses during conditioning for CS+ and CS- in all groups; **(A)** Greater differential fear conditioning (CS+ > CS-) in boys viewing male faces (*p* < .001) and in girls viewing female faces (*p* = .03). **(B)** Greater number of significant SCRs for the CS+ relative to the CS- in boys viewing male faces (*p* = .01) and in girls viewing female faces (*p* = .05). *$p < .05$, **$p < .01$, ***$p < .001$.

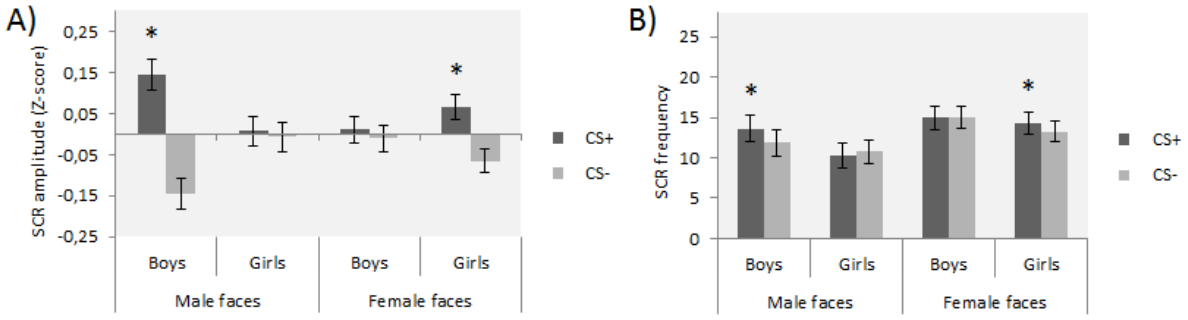
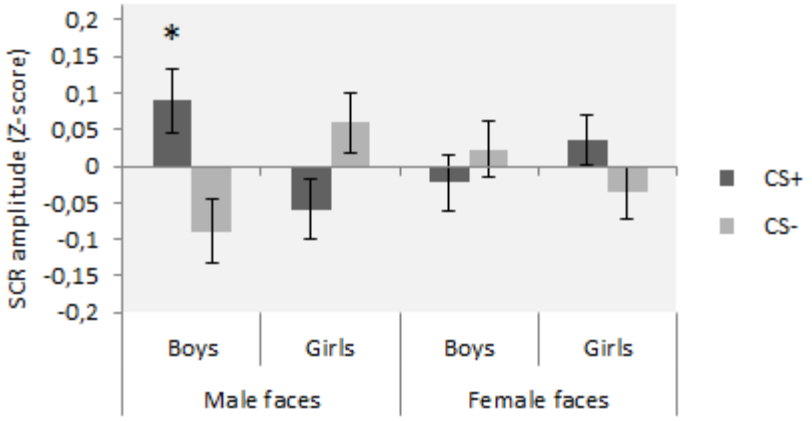


Figure 5. Mean skin conductance responses during extinction for CS+ and CS- in all groups; **(A)** Greater SCRs to CS+ *vs.* CS- for male faces in boys (p = .05). **(B)** Greater number of significant SCRs for female faces compared to male faces (p = .006). *p < .05, **p < .01.



Tables

Table 1. Means and Standard Deviations of Fear Ratings and Skin Conductance Responses to the CS+ and CS- during Conditioning and Extinction.

	Conditioning					Extinction				
Variable	CS+		CS-		p	CS+		CS-		p
Ratings, mean (SD)										
Male faces										
Early										
Boys	2.54	(0.92)	2.06	(0.71)	***	2.17	(1.03)	1.38	(0.51)	***
Girls	3.11	(1.10)	2.20	(0.76)	***	2.65	(1.25)	1.61	(0.68)	***
Late										
Boys	2.53	(1.30)	1.61	(0.55)	***	1.79	(0.83)	1.30	(0.42)	**
Girls	2.98	(1.16)	1.79	(0.66)	***	2.43	(1.21)	1.55	(0.55)	***
Mean										
Boys	2.54	(1.06)	1.83	(0.59)	***	1.98	(0.90)	1.34	(0.44)	**
Girls	3.04	(1.11)	1.99	(0.68)	***	2.54	(1.21)	1.58	(0.55)	***
Female faces										
Early										
Boys	2.07	(0.94)	1.66	(0.73)	**	1.90	(1.12)	1.26	(0.50)	***
Girls	2.22	(1.05)	1.86	(0.95)	**	1.76	(0.90)	1.58	(0.82)	
Late										
Boys	2.00	(1.14)	1.32	(0.51)	***	1.60	(0.88)	1.33	(0.60)	*
Girls	1.97	(0.92)	1.63	(0.94)	*	1.55	(0.71)	1.39	(0.56)	
Mean										
Boys	2.03	(1.01)	1.49	(0.58)	***	1.75	(0.97)	1.30	(0.53)	***
Girls	2.09	(0.97)	1.75	(0.92)	***	1.66	(0.79)	1.48	(0.67)	
SCR, mean (SD)										
Male faces										
Early										
Boys	.30	(.24)	-.07	(.28)	***	.17	(.45)	-.09	(.26)	
Girls	.13	(.34)	.11	(.28)		-.001	(.36)	-.006	(.34)	
Late										
Boys	-.02	(.24)	-.22	(.23)	**	.007	(.34)	-.09	(.36)	
Girls	-.11	(.24)	-.12	(.27)		-.12	(.22)	.12	(.28)	*
Mean										
Boys	.14	(.17)	-.14	(.17)	***	.09	(.20)	-.09	(.20)	*
Girls	.007	(.20)	-.007	(.20)		-.06	(.17)	.06	(.17)	
Female faces										
Early										
Boys	.14	(.32)	.08	(.33)		-.04	(.35)	.11	(.37)	
Girls	.21	(.32)	.02	(.31)	*	.08	(.36)	-.02	(.43)	
Late										
Boys	-.11	(.26)	-.10	(.26)		-.006	(.36)	-.06	(.31)	
Girls	-.08	(.26)	-.15	(.23)		-.01	(.37)	-.09	(.33)	
Mean										
Boys	.01	(.15)	-.01	(.15)		-.02	(.19)	.02	(.13)	
Girls	.07	(.18)	-.07	(.18)	*	.04	(.24)	-,04	(.24)	

Note. SD = Standard deviation; *** = $p < .001$; ** = $p < .01$; * = $p < .05$

Table 2. Means and Standard Deviations of Post-questionnaire Fear Ratings to the CS+ and CS-.

	Male faces		Female faces	
Variable	Boys (n = 23)	Girls (n = 23)	Boys (n = 29)	Girls (n = 29)
Post-questionnaire, mean (SD)				
CS+	2.80 (1.15)	3.15 (1.36)	2.10 (0.99)	2.29 (1.11)
CS-	1.43 (0.59)	1.43 (0.66)	1.24 (0.51)	1.40 (0.56)

Note. SD = Standard deviation

Article 3 : Harsh Parenting and Anxiety Predict Fear Circuitry Function and Connectivity Patterns in Healthy Adolescents During Fear Conditioning and Extinction

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Harsh Parenting and Anxiety Predict Fear Circuitry Function and Connectivity Patterns in Healthy Adolescents During Fear Conditioning and Extinction

Abstract

Background: Adverse care-giving may increase risk for anxiety disorders, possibly reflecting anomalies in the "fear" circuit, a neural system including the amygdala and anterior hippocampus, the insula, and prefrontal cortex. Previous fMRI studies reported altered fear circuitry responses during fear conditioning and extinction in adults with a history of childhood adversity, and in anxious children and adults. To date, however, no study has used these tasks in youths with a history of early adversity, and most of the existing studies in adults and/or using other tasks in youths investigated correlates of anxiety or of early adversity exclusively, without examining joint influences or interactions. **Objectives:** In the present study, we investigated fear circuitry activations and connectivity patterns in healthy youths displaying high (HA) or low (LA) levels of anxiety with or without a history of early and chronic adversity, taking the form of high (HH) or low (LH) maternal harsh parenting, both measured yearly from 2.5 to 9 years old. **Methods:** 84 youths aged 12-17 were split in 4 groups according to anxiety and mother's harsh parenting practices levels: LH/LA, LH/HA, HH/LA and HH/HA. We used valid fMRI discrimination fear conditioning and extinction tasks and performed standard and PPI analyses during contrast CS+ vs. CS-. Left amygdala was selected as seed region for PPI analyses**. Results:** During conditioning, standards analyses show that high harsh parenting levels were associated with decreased medial temporal lobe deactivations to CS+ and CS-. PPI analyses show less amygdala-insula functional connectivity to CS+>CS-, in high relative to low harsh parenting. Interestingly, we also found opposite anxiety differences in amygdala-rostral ACC connectivity depending on harsh parenting levels. During extinction, higher anxiety levels were linked with increased dorsal anterior cingulate (dACC) activations, possibly reflecting increased cognitively-driven fear responses. In a dACC cluster, however, anxiety differences in activations associated with anxiety varied according to harsh parenting levels. **Conclusions:** Besides the individual influences of harsh parenting and anxiety, our results also suggest that a history of harsh parenting is linked with a unique anxious phenotype, which is separate from anxious manifestations of other etiology. This highlights the need to consider both risk factors when

planning interventions, as the underlying neural mechanisms may differ according to early adversity and anxiety histories.

Key words: fear, conditioning, extinction, adolescents, fMRI, amygdala, psycho-physiological interactions

Introduction

Extensive evidence links early adversity with impaired socio-emotional development and long-lasting psychopathology (Care., 2000; McKee et al., 2007; Pine, 2003; Pine & Cohen, 2002; Solomon & Serres, 1999). Most studies to date on adverse caregiving have focused on maltreated or neglected children; however, youths exposed to harsh parenting, a milder form of maltreatment that is defined by hostile and coercive child-rearing behaviors, are also at a high risk of anxiety disorders and other negative socio-emotional outcomes (MacMillan et al., 1999; McLeod, Wood, & Weisz, 2007; Wood, McLeod, Sigman, Hwang, & Chu, 2003).

In both adults and youths, early-life adversity is related to greater sensitivity to threatening cues; (for a review of the literature, see (Hart & Rubia, 2012). Such altered threat processing, in turn, is closely associated with anxiety disorders (Hofmann, Ellard, & Siegle, 2012). These links may be mediated by alterations in the "fear circuitry", a neural system particularly sensitive to early-life adversity (Hart & Rubia, 2012; E. McCrory, De Brito, & Viding, 2011; Tottenham & Sheridan, 2009). This system plays a key role in fear learning and expression, which rely mainly on activity in medial temporal lobe structures (i.e. amygdala and anterior hippocampus) and also in the insula and dorsal anterior cingulate cortex (dACC) (Milad & Quirk, 2012; W. K. Simmons et al., 2013), and in emotion regulation, which depends on ventro medial prefrontal cortex (vmPFC) (including the subgenual anterior cingulate cortex (sgACC)) activity (Buchel & Dolan, 2000; Buchel, Morris, Dolan, & Friston, 1998; LeDoux, 2000; Marek, Strobel, Bredy, & Sah, 2013; Milad & Quirk, 2012; Milad, Rauch, Pitman, & Quirk, 2006; Ohman, 2005). In the present study, we investigated fear circuitry activations and connectivity patterns in youths displaying high or low levels of chronic, non-clinical anxiety with and without a history of maternal harsh parenting, so as to shed light on the neural mechanisms that link early adversity and anxiety in healthy adolescents.

Fear conditioning and extinction tasks are extensively used in the study of fear circuitry function in humans and animals (Charney, 2004; Lissek et al., 2005; Pine, Helfinstein, Bar-Haim, Nelson, & Fox, 2009). Fear conditioning is a process by which a conditioned stimulus (CS+; e.g., a neutral face), after repeated pairing with an aversive unconditioned stimulus (US; e.g., electrical shocks), elicits a conditioned fear response; this

response can be extinguished by repeatedly presenting the CS+ without the US. In discrimination fear conditioning, a second CS, the CS-, is never paired with the US, and serves as a safety signal. Conditioned responses are measured as the difference between CS+ and CS.

Conditioning and extinction paradigms have demonstrated alterations of fear processing in individuals with early-life adversity histories and/or high anxiety levels, although the majority of results come from studies with adult samples. At the behavioral level, increased subjective distress levels, and faster and/or increased physiological responses to CS+ (or increased CS+ vs. CS- differences) have been reported in adults with post-traumatic stress disorder (PTSD) related to a history of early adversity, as well as in healthy adults and youths at risk of anxiety (Barrett & Armony, 2009; Bremner et al., 2005; Glotzbach-Schoon et al., 2013; Indovina, Robbins, Nunez-Elizalde, Dunn, & Bishop, 2011; Pejic, Hermann, Vaitl, & Stark, 2013), although other studies have failed to find such differences at the physiological level (Bremner et al., 2005; Pejic et al., 2013). In clinically anxious adults and youths whose history of early adversity was not reported, a wealth of data shows greater overall subjective fear ratings and skin conductance responses (SCRs) to CS- or to both types of stimuli (CS+ and CS-) in a context of equivalent discrimination conditioning (Britton et al., 2013; Craske et al., 2008; Lau et al., 2008; Lissek, 2012; Lissek et al., 2005; Lissek et al., 2009; Waters, Henry, & Neumann, 2009), as well as resistance in extinguishing fear responses (Craske et al., 2008; Liberman, Lipp, Spence, & March, 2006; Milad, Rauch, et al., 2006; Waters et al., 2009). This suggests anxious individuals may have difficulties in differentiating threat-signaling from safety cues (Lissek, 2012; Lissek et al., 2005; Lissek et al., 2010; Lissek et al., 2009; Mahan & Ressler, 2012).

Similarly, at the neural level, medial temporal lobe hyperactivity to CS+ (or CS+ vs. CS-) has been observed in adults with PTSD related to a history of early adversity and in other healthy but at-risk individuals (Barrett & Armony, 2009; Bremner et al., 2005; Craske et al., 2008; Indovina et al., 2011; Pejic et al., 2013; Waters et al., 2009). Increased amygdala responses to CS- and increased overall responses to both CSs in a context of equivalent discrimination conditioning have also been reported in anxious adults and youths, regardless of adversity history (Britton et al., 2013; Craske et al., 2008; Gazendam, Kamphuis, & Kindt, 2013; Kindt & Soeter, 2014; Lau et al., 2008; Lissek, 2012; Lissek et al., 2005; Lissek et al., 2010; Lissek et al., 2009; Mahan & Ressler, 2012; Waters et al., 2009). As well, difficulties in

extinguishing fear responses have been associated with reduced vmPFC activity in anxious adults (Bremner et al., 2005; Erhardt & Spoormaker, 2013; Indovina et al., 2011; Lissek, 2012; Milad, Rauch, et al., 2006; Sehlmeyer et al., 2011).

To our knowledge, no fMRI studies have investigated fear conditioning or extinction in children and adolescents with a history of early adversity. However, studies employing other emotion-evoking stimuli (e.g. facial pictures) have shown increased activations in the amygdala, hippocampus and insula in youths with histories of early adversity relative to controls, although most of these children displayed normal levels of anxiety (Maheu et al., 2010; E. J. McCrory et al., 2013; E. J. McCrory et al., 2011; McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015; Tottenham et al., 2011).

Regarding functional connectivity, recent studies reported reduced amygdala-PFC coupling in adults with a history of childhood trauma (Fan et al., 2014; Herringa et al., 2013), an anxiety disorder (Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010; Hahn et al., 2011; Pannekoek et al., 2013), or both (Birn, Patriat, Phillips, Germain, & Herringa, 2014). Similar results were recently reported in maltreated children, who also displayed increased anxiety levels relative to controls (Thomason et al., 2015). On the other hand, increased vmPFC activity and/or increased amygdala-vmPFC connectivity have been observed in psychiatrically healthy adults and adolescents at high risk of anxiety disorders (Barrett & Armony, 2009; Carrion, Garrett, Menon, Weems, & Reiss, 2008; Hardee et al., 2013; Mueller et al., 2010; Telzer et al., 2008; Tzschoppe et al., 2014), and have also been associated with reduced anxiety symptoms (Birn et al., 2014; Burghy et al., 2012; Fan et al., 2014; Gee, Gabard-Durnam, et al., 2013; Herringa et al., 2013; Monk et al., 2006; Thomason et al., 2015). Insula findings are less clear, with some studies reporting increased amygdala-insula connectivity in populations with anxiety and/or a history of early adversity (McClure et al., 2007; Rabinak et al., 2011; Roy et al., 2013; Thomason et al., 2015), while others report opposite patterns (Etkin, Prater, Schatzberg, Menon, & Greicius, 2009; Fonzo et al., 2013; Fonzo et al., 2010; A. N. Simmons et al., 2008; van der Werff et al., 2013).

The majority of the previously mentioned studies, however, were performed on adults, and most of them investigated correlates of anxiety OR of early adversity exclusively, without examining joint influences or interactions. Additionally, most of these studies, whether performed in adults or youths, used small or heterogeneous samples, which mixed individuals

with early-life adversity of different origins (e.g., maltreatment, institutionalization), and with psychiatric symptoms of different disorders (Hart & Rubia, 2012; E. McCrory et al., 2011). In the present study, we examined the specific and conjoined influences of early and chronic life adversity – in the unique form of chronic highly harsh parenting – and chronic, non-clinical, anxiety levels, both measured yearly from 2.5 to 9 years old, on fear circuitry function and connectivity in a sample of 84 healthy adolescents. Participants were split into 4 groups according to maternal harsh parenting levels and anxiety levels: high harsh parenting and high anxiety levels (HH/HA), high harsh parenting and low anxiety levels (HH/LH), low harsh parenting and high anxiety levels (LH/HA), and low harsh parenting and low anxiety levels (LH/LA). Youths were submitted to fear conditioning and extinction tasks developed by Lau and collaborators (Lau et al., 2011; Lau et al., 2008), using a pediatrically safe US shown to be successful in triggering fear responses in youths (Chauret et al., 2014; Lau et al., 2011; Lau et al., 2008).

During *fear conditioning,* we expected greater discrimination conditioning, reflected by increased fear ratings and SCRs responses, as well as by greater amygdala, anterior hippocampus and insula activations to CS+> CS-, in HH/HA, HH/LA and LH/HA relative to low harsh parenting groupsLH/LA. Increased overall fear ratings to both CS+ and CS- were also expected in high relative to low anxiety groups. In terms of connectivity, decreased amygdala-sgACC connectivity was expected in high relative to low anxiety groups. Youths in the HH/LA group were also expected to show increased amygdala-sgACC connectivity relative to youths in the LH/LA group. Because of the absence of clear evidence in the literature, there was no specific hypothesis concerning amygdala-insula connectivity. **During *fear extinction,*** increased subjective fear ratings, SCRs, and medial temporal lobe activation, as well as reduced sgACC activation to CS+ > CS-, were expected in high relative to low anxiety groups. Youths in the HH/LA were also expected to show increased sgACC activations relative to the LH/LA group, despite equivalent medial temporal lobe activations, fear ratings and SCRs.

Materials and Methods

Participants

Participants were recruited in two related cohorts from two prospective longitudinal studies: *In 2001, I was 5 years old* and *The Quebec Longitudinal Study of Children's Development,* through the Research Unit on **Children's Psychosocial Maladjustment** in collaboration with the Quebec Statistical Institute ("Institut de la statistique du Québec"). These cohorts include a total of 2,174 healthy children – and their mothers -- representative of singletons born in the province of Quebec (Canada) between 1996 and 1998 (children from the far North, Cree or Inuit regions, and aboriginal reservations were excluded). Longitudinal data regarding youths and their parents' socio-demographic profile, psychological development (including anxiety levels), familial interactions (including harsh parenting practices) and health status were collected yearly from the time the youths were 5 months old. A developmental trajectory methodology (Nagin, 2005) was employed to determine how to distribute youths according to maternal harsh parenting and child anxiety levels into the four following groups: LH/LA, LH/HA, HH/LA and HH/HA.

Assignation to groups. For the purpose of this study, we narrowed down the cohorts to 1,761 possible participants, after selecting only those for whom data on their anxiety profile and their parents' harsh parenting practices were collected at least three times between the ages of 2.5 and 9 years (the most recent data point at which both variables were measured). At least one of those measurements had to have been taken in the last two times they were evaluated, at ages 8 and 9 years.

We used a developmental trajectory methodology to distribute the 1,761 youths into our four groups of interest. This is an empirical method that identifies groups of children who follow similar developmental patterns over time. When employing this method, a semi-parametric, group-based mixture model is computed using all available data points across time. The model assigns individuals to trajectory groups on the basis of a posterior probability rule (Nagin, 2005). Developmental trajectories were computed based on youths' anxiety symptoms (as evaluated by their mothers), and maternal harsh parenting practices collected across time (i.e., when youths were 2.5-9 years old). A two-group (high vs. low) solution was selected as the best-fitting model that minimized the Bayesian Information Criterion (Nagin, 2005) for both youths' anxiety symptoms and mothers' harsh parenting practices (see Figure

1). Developmental trajectories for both variables were then computed simultaneously to get a valid estimation of the proportion of youths in each of the four groups of interest.

------ Insert Figure 1 approximately here -------

Inclusion and exclusion criteria measures. For each group, participants were recruited among those having a 70% or higher chance of belonging to that group (see Table 1 for group distribution). Youths that met the inclusion criteria and had the highest probability of belonging to any of the four cells were included in the study first. To ensure that their current profile matched the group they supposedly belonged to, selected youths were re-evaluated on both variables using the SCARED anxiety level questionnaire (Birmaher et al., 1997) and the parenting practices questionnaire (NLSCY; Canada, 1994; Boivin et al., 2005). Exclusion criteria for youths in this study included: (a) current or past neurological or psychiatric diagnostic, as measured by the *Kiddie Schedule for Affective Disorders and Schizophrenia* (K-SADS) (Kaufman et al., 1997), a structured clinical psychiatric assessment based on DSM-IV criteria that was administered to all youths and their parents separately; (b) current use of psychotropic medication, or psychological treatment, for psychiatric illness; (c) past head trauma; (d) past or current abuse; (e) contraindications for MRI (e.g., braces); and (f) Verbal IQ scores < 70 assessed with the *Peabody Picture Vocabulary Test-Revised* (PPVT) ((Dunn & Dunn, 1981).

Final sample. A total of 112 youths and their parents accepted to participate in the study. Of these, 10 were excluded because of MRI contraindications (e.g. braces), and 8 were excluded after screening because of the presence of a psychiatric disorder. In total, 94 youths aged between 13 and 16 years at the time of testing went through the MRI procedure. Of these youth, 91 had complete functional MRI data. The data of a further seven youths were removed, because of excessive motion during the scanning sessions. Hence, the final sample was comprised of 84 youths (see Table 1 for the sample's demographic and psychological characteristics).

Measures

Harsh parenting practices. A questionnaire including different subscales investigating parenting practices (e.g., maternal self-efficacy, perceived parental impact,

parental overprotection) was administered to mothers when youths were 30, 42, 48, 60, 72, 96 and 108 months old. Questions on harsh parenting were selected from the Hostile/Ineffective scale used in the National Longitudinal Survey of Children and Youth (NLSCY; Canada, 1994) and from the Parental Cognitions and Conduct Toward the Infant Scale (PACOTIS, (Boivin et al., 2005)). Regarding harsh parenting practices, mothers were asked to rate themselves on a frequency scale indicating if they never (0), less than half the time (1), half the time (2), more than half the time (3) or all the time (4): "got angry when punishing your child"; "spanked your child when he/she was difficult"; "raised your voice, scolded or yelled at your child when he/she broke the rules or did things he/she was not supposed to do"; and "used physical punishment (e.g., shaking) when he/she broke the rules or did things he/she was not supposed to do". These chosen items have been validated by a panel of 15 expert clinical and developmental psychologists for content, have been used in several large population studies (e.g. Boivin, 2005, Pierce, 2010; Vitaro, 2006, Barker, Boivin et al, 2006; Guimond, Bredgen et al, 2012), and have shown adequate psychometric properties for the evaluation of maternal harsh parenting practices towards infants up to school-age children (Boivin et al., 2005; Boyle et al., 2004; Pierce et al., 2010). Scores on each of the 4 items were added so that final scores ranged between 0 and 16. The internal consistency value (alphas) was .66, .67, .62, .64, .64, .46, .56 at 30, 42,48, 60, 72, 96 and 108 months, respectively. Harsh parenting levels were re-assessed during the screening session using the same questionnaire.

Anxiety levels. The items evaluating youths' anxiety symptoms were selected from the anxious/depressed and emotionally reactive subscales of the *Child Behaviour Checklist* (Achenbach, 1991). Mothers indicated on a two-point scale ranging from 0 (never) to 2 (often) if their child exhibited the following symptoms: "is nervous, high strung or tense", "appears fearful or anxious", and "appears worried". These chosen items have been used in large population studies and have shown adequate psychometric properties for the evaluation of anxiety levels in early childhood up to adolescence (Boyle et al., 1993; Cote et al., 2009; Galera et al., 2014). Mothers answered questions when youths were 30, 42, 48, 60, 72, 84, 96 and 108 months old. The coefficients of internal consistency for the child's anxiety symptoms items were weaker at very young ages, and fair to satisfactory by age 60 months (0.5, 0.6, 0.6, 0.7, 0.7, 0.8, 0.7, 0.8 at 30, 42, 48, 60, 72, 84, 96 and 108 months, respectively). Current anxiety levels were re-assessed at the time of scanning with the *Screen for Child Anxiety*

Related Emotional Disorders (SCARED), a questionnaire that measures five dimensions of anxiety symptoms in children and adolescents, and that has been proven to possess adequate psychometric properties (Birmaher et al., 1997). This questionnaire was filled by the mothers (parent version) and by the participants themselves (child version).

Other demographic characteristics. Socio-economic status (SES) was measured using the 4-factors Hollingshead scale, which combines scales for maternal and paternal education and occupation (Hollingshead, 1973). Pubertal stage was assessed with the *Tanner scale* (Tanner & Whitehouse, 1976) at the time of testing. Youths were asked to circle pictures that best resembled their current stages of physical development (in terms of pubic hair, breast development in girls and testicle development in boys). Finally, to rule out the presence of depression, depression symptoms were assessed with the *Child Depression Inventory* (CDI) (Kovacs, 1984).

------Insert table 1 approximately here ------

Procedure

Recruitment and screening. First, letters were sent to participants and their mothers to explain the aims and conditions of the study. Participants' mothers were then contacted by telephone, and home interviews were conducted with interested participants and their mothers to screen for possible exclusion criteria and complete the KSADS interview and all questionnaires. Subjects that fulfilled both the inclusion and exclusion criteria were invited to the fMRI session.

Experimental fMRI design. We used a 17-minute paradigm comprised of two phases: fear conditioning, and fear extinction (Lau et al., 2008, 2011). During each phase, participants saw headshots of two actresses presenting neutral emotional expressions. For each participant, one actress was randomly selected to serve as the conditioned stimulus (CS+), and the other served as the safety signal (CS-). During conditioning, the CS+ was paired on 50% of trials with the unconditioned stimulus (US), which consisted of a photography of the actress selected for the CS+ depicting a fearful expression and presented simultaneously with a 90 dB shrieking scream. A partial reinforcement contingency ratio was used to prevent habituation to the US (Mackintosh, 1974). The other actress served as a conditioned stimulus unpaired with

the aversive US (CS-). Participants were unaware of the CS+ – US association prior to the experiment. Subjective fear ratings and skin conductance responses (SCRs) were recorded during the whole procedure. Specific details on experimental design are presented elsewhere (Chauret et al., 2014).

Scanning procedure. Functional MRI scans were performed at the Montreal Geriatric University Institute (IUGM). Before testing, participants had been familiarized with the MRI environment and with the experimental paradigm in a mock scanner, to ensure that they understood how to rate the pictures. To prevent habituation to the stimuli, the pictures and sounds presented during this practice session were different from the ones used during the actual fear conditioning and extinction tasks. Once the fMRI tasks were completed, a nine-minute structural MRI scan was performed. After the scan, participants were debriefed in a short interview, where they were also asked to identify the actress associated with the scream, to ensure contingency awareness.

Data acquisition and analysis. Demographic, behavioral and physiological data analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL). All data were checked for normality of the distribution and outliers. When needed, data were square root or log transformed.

Demographic and psychological data. To ensure participants were classified in the right membership group, separate two-way analyses of variance (ANOVAs) with harsh parenting (high vs. low) and anxiety levels (high vs. low) as between-subjects factors were used to compare groups in terms of current harsh parenting levels, as measured with the parenting practices questionnaire, and in terms of current anxiety levels, as measured with the SCARED-R (parent and child versions). Participants were also compared in terms of age, socio-economic status (SES), verbal IQ, and mean depression levels (CDI) using separate two-way ANOVAs, with harsh parenting and anxiety used as between-subjects factors. Chi-squares for quantitative measures were used to investigate potential group differences in terms of sex and pubertal status (Tanner stage) of participants.

Subjective fear ratings acquisition. In both the conditioning and extinction phases, nervousness ratings were recorded during each presentation of the stimuli (CS+ before (potential) apparition of US, and CS−) using a right hand-held button response box developed to allow for a graded range of responses (Current Designs, Philadelphia, PA). Participants

were asked to indicate on a 5-point Likert scale the degree to which they felt afraid when viewing the actress in the CS+ and CS− photos (Are you afraid? 1 = not at all, 5 = extremely).

Skin conductance rates (SCRs) acquisition and preprocessing. Mean SCRs for all the CS+ and CS- trials served as physiological dependent measures of fear conditioning and extinction. The procedures to measure SCRs in the fMRI scanner were developed by Dr. Pierre Rainville (U Montreal) (Dube et al., 2009). SCRs were recorded during the functional scan using two 10-mm radio-translucent electrodes placed on the plantar surface of the subject's right foot and connected to hardware filters that prevent the cross-contamination of signals (see http://www.biopac.com/mri-compatible-transducer-filtered-cables-specifications). SCRs data were amplified, digitized, and recorded at 1000 Hz using a computerized data acquisition system (MP150-BIOPAC). For specific details on SCR processing, see (Chauret et al., 2014).

SCR intra-subject data analysis. Due to technical issues, the data of 21 participants were lost. Analyses were performed on the remaining 63 participants (66% of the sample). In a first step, the amplitude of the SCRs, for both the conditioning and extinction phases, was standardized within each subject using Z transformations. This was performed to account for the high intra-subject variability of SCRs from one event to the other. We used mean SCRs to both the CS+ and CS− events, measured separately during the conditioning and extinction phases, to allow for statistical analysis comparing SCRs to the CS+ > CS− within each group and during each phase.

SCR and subjective fear ratings group analyses. SCR and subjective fear ratings were analyzed in distinct ANOVAs. Conditioning and extinction data were analyzed separately using SPSS. Four-way repeated-measures ANOVAs with harsh parenting (low vs. high) and anxiety (low vs. high) as between-subjects factors, and CS-type (CS+, CS−) and time of cue presentation (early vs. late; for conditioning, early: 14 first cues, late: 14 last cues; for extinction, early: 7 first cues, late: 7 last cues) as within-subjects factors were conducted. Post hoc Tukey group comparisons test set at an alpha level of 0.05 were further performed on significant ANOVA findings.

fMRI data acquisition parameters. Functional and structural MRI data were acquired using echo planar imaging (EPI) sequences with a Siemens TRIO 3-Tesla scanner equipped with a standard head coil. Visual and auditory stimuli were presented on a laptop computer

using E-Prime software (PST, Inc., Pittsburgh, PA), and images were projected onto a screen at the foot of the scanner while sounds were transmitted via MRI-compatible headphones. The following parameters were used for functional scans: 32 ascending 3.3 mm axial slices covering the entire brain and parallel to the AC-PC plane using a single-shot gradient echo T2* weighting with a TR: 2300 ms, TE: 30 ms, voxel dimensions: 3.8 x 3.8 x 3.3 mm, matrix size: 64 x 64 mm, and field of view (FOV): 24 cm. Volumetric data for spatial normalization was acquired with the following parameters: MP-RAGE sequence with 176 1 mm axial slices, TR: 2300 ms, TE: 2.98 ms, TI: 900 ms, flip angle: 9°, NEX = 1, matrix size of 256 x 256 mm, bandwidth = 240 Hz/Px, and FOV: 256 mm.

fMRI data analysis. Data were pre-processed and analysed with SPM8 (SPM8, http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (Mathworks). For each subject, pre-processing included: slice timing correction, realignment of functional time series, co-registration of functional and anatomical images, spatial normalization in Montreal Neurological Institute (MNI) space, spatial smoothing with a 6 mm full-width half-maximum Gaussian smoothing kernel, and high- and low-pass filtering. Data of participants who moved over 4.5 mm in any plane were excluded from analyses (n = 7).

A two-level hierarchical model using fixed-effects (single subject level) and mixed-effects (group-level) analyses was then conducted. For subject level analyses, a general linear model (GLM) was used to estimate changes in brain regional responses using 12 regressors: CS+ and CS- during habituation phase, CS+ unpaired with US and CS- during early (first 7 CS+ unpaired and 14 CS-) and late (last 7 CS+ unpaired and 14 CS-) conditioning and early (first 7 CS+ and CS-) and late (last 7 CS+ and CS-) extinction, and US; the 0-3 seconds following unpaired CS+ and CS- presentation were also modeled as conditions of no interest, to avoid contamination of baseline due to US expectancy (Dunsmoor & LaBar, 2012; Linnman, Rougemont-Bucking, Beucke, Zeffiro, & Milad, 2011). Data were adjusted for noise and motion artefacts using RobustWLS Toolbox (Diedrichsen & Shadmehr, 2005). Contrast images for CS+ > CS- (early and late conditioning or extinction together) were estimated during conditioning and extinction separately for each subject.

The average effects of condition were assessed for conditioning and extinction. To assess the main effects of harsh parenting and/or anxiety and/or anxiety x harsh parenting interactions, contrast images were entered in two-way ANOVAs with harsh parenting (low vs.

high) and anxiety (low vs. high) as between-subjects factors for conditioning and extinction separately. Extinction was further subdivided into early and late phases, which were examined separately. Based on our a priori hypothesis, we used a region of interest (ROI) approach with small volume corrections. Right and left anterior hippocampus ROIs were defined with masks selected from a previous study (Maheu et al., 2010). Left and right amygdala, insula, and prefrontal/anterior cingulate cortex (regions BAs 11, 24, 25, 32 and 47) ROIs were created using the WFU PickAtlas software, version 3.0.5 (http://fmri.wfubmc.edu/cms/software#PickAtlas). A statistical threshold of $p < 0.05$, family-wise error small-volume corrected was used. Individual signal change values at the peak voxel coordinates of structures with significant SPM results were extracted, to plot effect directionality and conduct post hoc analyses with SPSS. SPM values were extracted for all conditions of interest (e.g. CS+ unpaired with US during early conditioning vs. baseline, CS- during early conditioning vs. baseline, CS+ unpaired with US during late conditioning vs. baseline, CS- during late conditioning vs. baseline, etc.).

Post hoc repeated-measures ANOVAs were performed for conditioning and extinction separately, with harsh parenting (low vs. high) and/or anxiety (low vs. high) as between-subjects factors, and CS-type (CS+ vs. CS−) and time of cue presentation (early vs. late) as within-subjects factors. Post hoc Tukey group comparisons test set at an alpha level of 0.05 were further performed on significant ANOVA findings.

Additionally, separate contrast weights for CS+ and CS- during conditioning were computed for each participant, and average effects of conditions were estimated for each condition during conditioning in bilateral amygdalae and hippocampi for exploratory analyses, to look only for significant activations (and not deactivations) in these regions. Mean percentage signal changes at peak activation voxels were plotted for visualization purposes.

Psycho-physiological interactions (PPI) analysis. To look for group differences in fear circuitry connectivity, we performed a psycho-physiological interaction analysis (PPI; (Friston et al., 1997) in SPM8. PPIs test whether functional coupling -- defined as positive (for positive PPI) or negative (for negative PPI) correlations between a specific region (selected as seed) and other brain regions -- changes significantly as a function of task condition (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). In the present study, the left amygdala was selected as seed region, since group differences from standard GLM analyses emerged in

this region. Only participants with significant amygdala activations during conditioning were included in the analyses (n=76; 90.5% of the sample). Because of the absence of amygdala activation during extinction, analyses focused exclusively on the conditioning phase. As for standard analyses, a two-level hierarchical model using fixed-effects (single subject level) and mixed-effects (group-level) analyses was conducted. BOLD time-series were first extracted for each participant from voxels within a sphere with a 4 mm radius surrounding the left amygdala activation peak (xyz= -24 -4 -22), with the strongest task effect in group comparisons for contrast CS+ > CS-. For each participant, this time-series was entered as a regressor into a GLM analysis. Amygdala time-course and main effect of task (CS+ > CS-) were extracted and entered as regressors of no interest.

To test for harsh parenting and/or anxiety effects or interactions, all PPI individual discrimination contrasts reflecting the positive and negative interactions (PPI regressor) between the psychological (CS+ > CS-) and the physiological (amygdala time-course) variables were entered in two-way repeated measures ANOVAs in SPM (one ANOVA for positive and another for negative connectivity), with harsh parenting (low vs. high) and anxiety (low vs. high) as between-subjects factors. We used a ROI approach with small volume corrections to extract changes in connectivity between the amygdala and other fear circuitry regions. We used the same prefrontal (BA 11, 24, 25, 32 and 47) and insula masks as for standard analyses. A statistical threshold of $p < 0.05$, family-wise error small-volume corrected was used. Individual PPI-related signal change values at the peak voxel coordinates of structures with significant SPM results were extracted, to plot effect directionality and conduct post hoc analyses with SPSS, when needed.

Results

Demographic and psychological characteristics

There were no main effects of harsh parenting or anxiety or significant harsh parenting x anxiety interactions for age, SES, IQ, Tanner stage, sex, or depression levels (all ps > .05) indicating groups were equivalent in these areas. Main effects of harsh parenting were found for current harsh parenting levels, with higher scores found in high vs. low harsh parenting groups ($F(1,80) = 17.56$, $p < .001$, $\eta^2 = .18$). Main effects of anxiety were found for parent-reported SCARED-R scores ($F(1, 75) = 7.21$, $p = .009$, $\eta^2 = .09$), showing significantly greater current anxiety levels in the high vs. low anxiety groups. Differences were not

significant for child-reported SCARED-R scores. There were no other significant effects or interactions for harsh parenting and/or anxiety measures (all ps >.05).

Behavioral and physiological results

Table 2 shows mean subjective ratings and SCRs for each group during conditioning and extinction.

Subjective fear ratings and contingency awareness. All participants (100%) were contingency-aware.

Conditioning. Significant main effects were found for CS type ($F(1, 80) = 30.27$, $p < .001$, $\eta^2 = .28$) and time of cue presentation ($F(1, 80) = 36.27$, $p < .001$, $\eta^2 = .31$). These effects were subsumed by a CS type x time of cue presentation two-way interaction ($F(1,80) = 4.68$, $p = .03$, $\eta^2 = .06$). Post hoc analyses showed that ratings to both CS+ and CS- were higher during early vs. late conditioning (both ps < .001), and that ratings were higher to CS+ > CS- during both early and late phases (both ps < .001), with discrimination conditioning (CS+ > CS-) being greater during late conditioning ($p = .04$). Results also showed a significant anxiety x CS type interaction ($F(1,80) = 4.59$, $p = .04$, $\eta^2 = .05$). Post hoc analyses indicated discrimination conditioning (CS+ > CS-) was acquired in both anxiety groups (respectively $p < .001$ in low anxiety and $p = .02$ in high anxiety), and higher ratings to CS- were observed in high relative to low anxiety ($p = .03$). Finally, a significant harsh parenting x anxiety interaction was found ($F(1, 80) = 8.19$, $p = .005$, $\eta^2 = .09$). Post hoc tests indicated that in the low harsh parenting groups, higher anxiety levels (LH/HA) were associated with greater fear ratings to both CSs ($p = .005$) relative to low anxiety (LH/LA), while no differences were observed between high (HH/HA) and low anxiety (LH/LA) in the high harsh parenting groups ($p = .27$). Moreover, subjective fear ratings were significantly higher in LH/HA group relative to the HH/HA group ($p = .006$).

Extinction. Main effects of time of cue presentation were found, with greater subjective fear ratings during early vs. late extinction ($F(1,80) = 19.88$, $p < .001$, $\eta^2 = .20$). A main effect of CS type ($F(1,80) = 20.48$, $p < .001$, $\eta^2 = .20$) and a harsh parenting x anxiety interaction ($F(1,80) = 6.85$, $p = .01$, $\eta^2 = .08$) were found, that were subsumed by a CS type x harsh parenting x anxiety interaction ($F(1,80) = 5.19$, $p = .03$, $\eta^2 = .06$). Post hoc analyses showed resistance to fear extinction illustrated by greater subjective fear responses to CS+ > CS- in low harsh parenting / high anxiety ($p < .001$) and in high harsh parenting / low anxiety

(p = .004) groups. Moreover, in low harsh parenting groups, high anxiety was related to higher fear responses to both CS+ (p = .004) and CS- (p = .03), while no anxiety differences were observed in the high harsh parenting groups. Finally, subjective fear ratings to CS+ were significantly higher in the low harsh parenting / high anxiety group relative to the high harsh parenting / high anxiety group (p = .008).

SCRs

Conditioning. Main effects of CS type and time of cue presentation were found, with greater SCRs observed for CS+ > CS- ($F(1, 58) = 11.68$, $p = .001$, $\eta^2 = .17$), and during early vs. late conditioning ($F(1,58) = 12.26$, $p = .001$, $\eta^2 = .18$). No other significant main effects or interactions were found (all ps > .05).

Extinction. No main effects of CS type, time of cue presentation, harsh parenting or anxiety, or significant interactions were found (all ps > .05).

----Insert table 2 approximately here ------

----Insert figures 2 to 4 approximately here ----

fMRI results

Standard GLM analyses

Overall conditioning effects. During conditioning, main effects of condition showed significant activations to CS+> CS- in bilateral amygdalae, hippocampi, insulae, and sgACC/vmPFC (BAs 24 and 32) across subjects (all at $p \leq .01$ FWE-corrected; see Table 3 for exact coordinates and statistics for each ROI).

Group comparisons in limbic regions during conditioning. SPM group comparisons of activations to CS+ vs. CS- revealed a significant main effect of harsh parenting in the left amygdala (xyz = -24 -4 -22) and in the left (xyz= -26 -8 -20) and right (xyz= 36 -14 -16) anterior hippocampi (all at $p < .05$ FWE-corrected; see Table 3 for exact statistics). Follow-up ANOVAs using SPSS on the signal changes in the identified peak suprathreshold voxels revealed similar results for the three structures. First, a main effect of time was found, with greater activations (or less deactivations) during late vs. early conditioning (respectively ($F(1, 82) = 4.92$, $p = .04$, $\eta^2 = .05$ for left amygdala, $F(1,82) = 10.53$, $p = .002$, $\eta^2 = .11$ for left anterior hippocampus, and $F(1,82) = 17.55$, $p < .001$, $\eta^2 = .18$ for right anterior hippocampus).

A main effect of CS type was found ($F(1, 82) = 23.38$, $p < .001$, $\eta^2 = .22$ for left amygdala, $F(1,82) = 31.60$, $p < .001$, $\eta^2 = .28$ for left anterior hippocampus, and $F(1,82) = 25.72$, $p < .001$, $\eta^2 = .24$ for right anterior hippocampus), as well as a significant CS type x harsh parenting interaction ($F(1,82) = 13.99$, $p < .001$, $\eta^2 = .15$ for left amygdala, $F(1,82) = 14.41$, $p < .001$, $\eta^2 = .15$ for left anterior hippocampus and $F(1,82) = 11.80$, $p = .001$, $\eta^2 = .13$ for right anterior hippocampus). Post hoc analyses revealed significant CS+ > CS- differences in low harsh parenting only. Specifically, in the low harsh parenting groups, greater deactivations were observed for CS+ relative to CS- for all structures (all ps <.001) while no CS+/CS- differences appeared in the high harsh parenting groups. (all ps > .1). Figure 5 presents the main results of group comparisons.

Supplementary analyses on limbic regions during conditioning. Average effects of conditions for CS+ and CS- analyzed separately showed significant overall activations in bilateral amygdalae and hippocampi for both stimuli relative to baseline (all ps < .01 FWE-corrected; see Table 6 for exact coordinates and statistics for each ROI and figure 6 for brain activations and percentage signal change), suggesting these areas were positively activated during conditioning, despite the deactivations observed in group comparisons.

Groups comparisons on vmPFC regions during conditioning. No effects of harsh parenting or anxiety, or harsh parenting x anxiety interactions were observed in prefrontal regions, suggesting comparable activations in these regions across groups during conditioning.

In summary, conditioning results show a history of high harsh parenting is associated with lower deactivations in left amygdala and bilateral hippocampus relative to low harsh parenting, while no differences are observed in vmPFC regions.

Overall extinction effects. During extinction, increased overall activations to CS+ > CS- were observed in bilateral insulae (both ps ≤ .01) and right BA47 ($p < .001$), while when considering early extinction only, additional significant activations were found in the dACC (BA24) and ventrolateral PFC (BA 47) (all ps ≤ .05; see Table 4 for exact coordinates and statistics for each ROI).

Group comparisons in limbic regions during extinction. Group differences in terms of CS+ > CS- activations were only observed during the early extinction phase in the dACC encompassing left (xyz = -12 10 36) and right (xyz = 6 16 32) Brodmann area 24 and right Brodman area 32 (xyz = 4 18 34) (all ps ≤ .01; see Table 4 for exact statistics). Further

ANOVAS on SPSS showed similar patterns across the three significant peaks. An anxiety x CS type interaction was found (All Fs(1, 82) > 16, ps < .001 and η^2 > .16), with significantly greater activations to CS+ > CS- found in the high anxiety groups only (all ps < .001), while there were no differences between activations to CS+> CS- in the low anxiety groups (all ps > .05). A significant harsh parenting x anxiety interaction was also found in a smaller right dACC cluster (BA24; xyz = 16 14 30). ANOVAs performed on SPSS revealed a significant harsh parenting x anxiety x CS type interaction ($F(1,82) = 14.54$, $p < .001$, $\eta^2 = .15$). Post hoc comparisons showed that in low harsh parenting, high anxiety (LH/HA) was associated with greater activations to CS+ > CS- relative to low anxiety (LH/LA) (p = .001), while in high harsh parenting, high (HH/HA) relative to low (HH/LA) anxiety was related to decreased CS+ > CS- activations (p = .03). Figure 7 presents the main results of group comparisons.

Group comparisons in vmPFC regions during extinction. No group differences emerged in more ventral and rostral regions of the PFC during extinction (all ps >.05).

In short, although no differences were observed in the medial temporal lobe or in the vmPFC, high anxiety levels are related to increased dACC activations during extinction. However, in a smaller cluster of this region, opposite anxiety differences are observed in low harsh parenting groups.

---Insert tables 3 and 4 approximately here----

---Insert figures 5 to 7 approximately here----

PPI GLM analyses

Positive connectivity. SPM PPI analyses revealed main effects of harsh parenting (all at p < .05 FWE corrected) for positive PPIs between left amygdala and left (xyz = -38 6 14) and right (xyz = 42 4 14) insula (see Table 5 for exact statistics for each ROI). Extracted beta weights show greater positive connectivity between left amygdala and all regions to CS+ > CS- in low vs. high harsh parenting (see Figure 8).

A harsh parenting x anxiety interaction was found for positive amygdala- rostral ACC (rACC/ BA 24; xyz = 6 32 4) connectivity. Subsequent ANOVAs performed on SPSS with extracted beta weights confirmed the harsh parenting x anxiety interaction ($F(1,77) = 13.98$, $p < .001$, $\eta^2 = .15$). Post hoc analyses showed that in low harsh parenting, high anxiety levels

(LH/HA) were associated with lower amygdala-rACC positive coupling to CS+ > CS-, relative to low anxiety levels (LH/LA) ($p = .003$). In high harsh parenting, however, high anxiety (HH/HA) was associated with greater amygdala-rACC positive connectivity relative to low anxiety (HH/LA) ($p = .03$) (see Figure 8).

Negative connectivity. SPM analyses also revealed main effects of harsh parenting for negative PPIs between amygdala and left and right insula (all at $p < .05$ FWE corrected). Extracted beta weights showed increased negative coupling between left amygdala and left and right insulae to CS+ > CS- in low harsh parenting relative to high harsh parenting (see Figure 8).

In summary, PPI results show lower positive and negative amygdala-insulae connectivity in high relative to low harsh parenting, as well as opposite anxiety effects on amygdala-rACC coupling depending on harsh parenting levels.

------Insert table 5 approximately here -----

----Insert figure 8 approximately here---

Discussion

To our knowledge, this is the first study to investigate the separate and conjoined influences of harsh parenting and anxiety on fear conditioning and extinction in psychiatrically healthy youths. At the neural level, differences related to harsh parenting were observed during conditioning in terms of medial temporal lobe activations and connectivity with the insulae, while differences related to anxiety were observed during extinction in terms of dACC activations. Interestingly, harsh parenting and anxiety interactions were found at the behavioral level, as well as with regard to amygdala-rACC coupling during conditioning, and to activations in a dACC cluster during extinction.

Overall, subjective fear ratings, SCRs, and medial temporal lobe activations to CS+ > CS- suggest discrimination conditioning was effectively acquired across participants. In terms of time effects, behavioral and physiological data show that although CS+ > CS- differences were established from the beginning, and, despite a general habituation to both CSs, the threat-safety conscious differentiation increased with increased exposition to both CSs. In terms of medial temporal lobe responses, higher overall activations to both CSs were found during late

relative to early conditioning. During extinction, fear ratings showed a gradual reduction of fear responses, although this was not the case for SCRs, where the overall absence of CS+/CS- differences during the whole phase shows an effective suppression of physiological fear responses independently of timing. Similarly, the absence of medial temporal lobe activations during extinction suggests an overall proper extinction at the physiological level.

As expected, greater medial temporal lobe (left amygdala and bilateral anterior hippocampus) activations to CS+ > CS- were found in high relative to low harsh parenting during the conditioning phase. This is consistent with previous studies suggesting increased sensitivity to threat in adversely-reared individuals and in persons carrying other risks for anxiety (Barrett & Armony, 2009; Bremner et al., 2005; Craske et al., 2008; Indovina et al., 2011; Maheu et al., 2010; E. J. McCrory et al., 2013; E. J. McCrory et al., 2011; Pejic et al., 2013; Tottenham et al., 2011; Waters et al., 2009), which probably reflects hypervigilance mechanisms that prepare them to face potential dangers from a threatening environment.

Surprisingly, these differences were due to greater deactivations to the CS+ relative to the CS- in low harsh parenting. Moreover, beta weights indicate amygdala and anterior hippocampus deactivations to the CS+ and CS- in both groups, as soon as the early conditioning phase. This may reflect rapid habituation processes, as previously demonstrated in the literature (Buchel et al., 1998; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Quirk, Armony, & LeDoux, 1997).

Medial temporal lobe deactivations could also be due to higher baseline activation in our participants, owing to increased arousal levels triggered by the scanning procedure. This may explain the reduction in deactivations observed over time, as participants became used to the machine and procedures. However, exploratory analyses show that other more lateral amygdala and anterior hippocampus clusters were significantly activated across groups to CS+ (and CS-) relative to baseline, although harsh parenting differences were only observed in deactivated clusters. Animal studies have shown that the amygdala can be subdivided in several regions, two of which are particularly involved in fear conditioning processes: the basolateral and the centromedial amygdala complexes (Duvarci & Pare, 2014). Through connections with the thalamus, sensory cortices, and PFC regions, the basolateral amygdala receives and evaluates sensory information, signals the threat value of a stimulus, and modulates the encoding of fear memories (Davis & Whalen, 2001; Duvarci & Pare, 2014;

Jovanovic & Ressler, 2010; Pitkanen, Jolkkonen, & Kemppainen, 2000). Through excitatory and inhibitory connections, this region also modulates centromedial activity (Duvarci & Pare, 2014). The centromedial amygdala, on the other hand, is responsible for fear expression (Duvarci & Pare, 2014), and has a critical role in the modulation of attention and vigilance (Boll, Gamer, Gluth, Finsterbusch, & Buchel, 2013). Although it is impossible to delimitate specific amygdala subregions in the present study because of image resolution limitations, we could speculate that the clusters significantly activated by CSs in our subjects belonged to the basolateral amygdala, while deactivated clusters, in which harsh parenting differences emerged, corresponded to centromedial regions. Centromedial amygdala deactivations in our healthy youth sample may reflect inhibitory inputs from the basolateral amygdala and other higher order regions such as the sgACC, which was also significantly activated across groups. In the low harsh parenting groups, these inputs targeted specifically the threat-signaling stimulus (i.e. CS+), while this was not the case in the high harsh parenting groups. Hence, a harsh parenting history may predispose youths for psychopathology not only because of a hypersensitivity to threat, but also due to a less targeted suppression of fear responses and/or a less efficient modulation of attention to threat.

Given its strong interconnections with the amygdala (Strange & Dolan, 2006), it is not surprising that similar patterns were observed in the anterior hippocampus. Amygdala and hippocampus deactivations during threat processing have been previously reported in healthy individuals (McClure et al., 2007; Petrovic, Carlsson, Petersson, Hansson, & Ingvar, 2004; Schneider et al., 1999; Thomas et al., 2001), and have been suggested to reflect mechanisms for the attenuation of stress responses (Petrovic et al., 2004). Of note, hippocampus hypoactivations have been linked to increased anxiety symptoms during stress-evoking situations in trauma-exposed youths, while no such relation was found in control subjects (Elsey et al., 2015). The authors interpreted this as a blunting of stress responses in trauma-exposed youths, due to repetitive exposure to stress (Elsey et al., 2015). Therefore, decreased medial temporal lobe function may reflect adaptive responses to threat in the low harsh parenting participants, while it may be detrimental to the high harsh parenting youths.

Lower functional connectivity between left amygdala and bilateral insula in response to CS+ > CS- was also found in high relative to low harsh parenting during conditioning. Previous studies demonstrated the insula's role in the perception of interoceptive states (Craig,

2009; Jones, Ward, & Critchley, 2010; Simmons et al., 2013), as well as in the integration of interoceptive information with perceptual and high-level cognitive representations, through heavy connections with somatosensory regions and limbic system structures such as the amygdala, PFC and ACC regions (Simmons et al., 2013). This may help evaluate the self-relevance of internal and external information, which may in turn be critical for producing appropriate affective responses (Simmons et al., 2013). Decreased amygdala-insula functional connectivity has indeed been reported in anxious and depressive patients, and in healthy individuals with high levels of neuroticism, a risk factor for anxiety and depressive disorders (Aghajani et al., 2014; Etkin et al., 2009; Perlman et al., 2012; Zeng et al., 2012). It has been suggested that these alterations reflect the impaired integration of emotions generated by the amygdala into conscious processing by the insula (Perlman et al., 2012). Reduced amygdala-insula connectivity in the high harsh parenting groups may therefore indirectly impair proper regulation of amygdala responses to CS+ through a poor awareness of emotional states, which therefore cannot be effectively communicated to emotion-regulation regions.

As expected, no further differences were observed between high and low anxiety groups, independently of harsh parenting levels, in terms of discrimination conditioning both at the neural and at the behavioral/physiological levels during the conditioning phase. However, increased fear ratings to CS- were found in high relative to low anxiety during this phase, despite equivalent levels of discrimination conditioning. These findings are consistent with previous studies that suggest a generalization of fear responses to the safety signal (i.e. CS-) in high anxiety individuals (Lissek, 2012; Lissek et al., 2005; Lissek et al., 2010; Lissek et al., 2009). Behavioral resistance to fear extinction observed in this group also suggests difficulties in distinguishing safety signals from threat signals in anxious individuals (Milad, Goldstein, et al., 2006; Milad & Quirk, 2012). These features, however, seem to be present only in a context of low adversity. Indeed, anxiety differences seemed to be driven by the low harsh parenting groups, suggesting that harsh parenting has a modulatory influence on anxiety. Moreover, high anxiety was related to increased overall fear ratings of both CS+ and CS- relative to low anxiety during conditioning and extinction, but only in the low harsh parenting groups. This suggests that a history of harsh parenting may lead to a unique anxious phenotype, which is separate from anxious manifestations of other sources.

Along the same lines, in the current study, functional connectivity during conditioning showed inverse anxiety differences related to harsh parenting contexts. In low harsh parenting groups, high relative to low anxiety levels were associated with lower amygdala-rostral ACC (rACC) positive functional connectivity, while in a context of high harsh parenting, high anxiety levels were associated with higher amygdala-rACC connectivity. Reduced amygdala-mPFC/rACC connectivity has been reported in clinically anxious adults (Burghy et al., 2012; Etkin et al., 2010; Hahn et al., 2011; Hilbert, Lueken, & Beesdo-Baum, 2014; Klumpp, Angstadt, & Phan, 2012; Pannekoek et al., 2013), as well as in adults and youths with a history of childhood maltreatment, in which it was associated with increased anxiety symptoms (Birn et al., 2014; Fan et al., 2014; Herringa et al., 2013; Thomason et al., 2015). Hence, reduced connectivity in youths of the LH/HA group may predispose them towards later anxiety disorders.

However, the increased connectivity observed in the HH/HA group is quite unexpected. An alternative explanation may be that higher positive amygdala-rACC connectivity is not necessarily beneficial, especially in a context of early and chronic adversity. In maltreated children and adolescents, negative amygdala-mPFC/rACC connectivity has been associated with a reduction in anxiety symptoms, possibly reflecting developmental adaptation mechanisms that aim to regulate a hyper-responsive amygdala (Gee et al, 2013). By contrast, positive amygdala-mPFC connectivity has been associated with immature neural function and increased emotional reactivity (Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013). As a matter of fact, a recent review highlighted the role of rACC in the cognitive dimensions of anxiety, including conscious threat appraisal, worrying and catastrophizing (Kalisch & Gerlicher, 2014). Reduced positive amygdala-rACC functional connectivity in the two groups carrying only one risk factor (i.e. HH/LA and LH/HA) may thus represent a protective mechanism that may prevent later psychopathology development. This reduction was not observed in the HH/HA group; this may put youths in this group at greater risk of future anxiety disorders.

A last potential explanation is that this increased functional connectivity may have a different impact according to harsh parenting history, because of the observed differences in amygdala function. Hence, in a context of a well-regulated amygdala, as encountered in low harsh parenting, increased positive amygdala-rACC connectivity is associated with low

anxiety symptoms, whereas in high harsh parenting, where the amygdala is not properly regulated, increased connectivity with rACC may lead to increased worries and catastrophizing, and thus be associated with increased anxiety levels.

During the early extinction phase, higher activations to CS+ > CS- were observed in the bilateral dorsal ACC in high relative to low anxiety. While ventral and rostral regions of the ACC are typically related to emotion regulation mechanisms, more dorsal portions of the ACC are involved in fear responses to unconditioned and conditioned stimuli (Milad & Quirk, 2012), and in general emotional reactions to threats, including negative affect and fear communication (Barbas, 2009; Shackman et al., 2011). Higher activations in dACC may thus reflect increased cognitively-driven emotional arousal in high anxiety groups. Besides general anxiety differences, harsh parenting and anxiety interactions were also observed in a smaller dACC cluster during extinction. In low harsh parenting groups, high relative to low anxiety levels were associated with higher activations to threat relative to safety (CS+ > CS) signals, while an opposite pattern was observed in high harsh parenting (i.e. lower activations to CS+ > CS- in high relative to low anxiety). While increased dACC activations have been reported in non trauma-related anxiety (i.e. specific phobia), possibly reflecting increased cognitively-driven fear responses to fear-evoking stimuli, dACC hypoactivations have been consistently observed in PTSD (Etkin & Wager, 2007). In this context, it has been suggested that, because dACC may help to evoke sgACC emotion regulation mechanisms by eliciting fear responses, decreased dACC activation may indirectly contribute to emotional dysregulation in PTSD, by eliciting less emotion regulation mechanisms (Etkin & Wager, 2007). Hence, in a context of early and chronic adversity such as harsh parenting, dACC hypoactivation may be related to lower emotional regulation, whereas in a context of low adversity, emotional dysregulation is associated with dACC hyperactivation, as observed in non-trauma related anxiety.

Contrary to our expectations, and to existing literature (e.g.(Barrett & Armony, 2009; Bremner et al., 2005; Erhardt & Spoormaker, 2013; Indovina et al., 2011; Lissek, 2012; Milad, Rauch, et al., 2006; Sehlmeyer et al., 2011), no harsh parenting or anxiety differences were observed in terms of vmPFC/sgACC activations during extinction (or conditioning). However, previous studies showing vmPFC or sgACC differences during fear conditioning and extinction in anxious and/or anxiety-at-risk individuals were performed in adults (Barrett & Armony, 2009; Bremner et al., 2005; Erhardt & Spoormaker, 2013; Indovina et al., 2011;

Lissek, 2012; Milad, Rauch, et al., 2006; Sehlmeyer et al., 2011). Absence of sgACC/vmPFC anxiety differences during extinction in the present study may thus reflect developmental differences with adult samples, as the prefrontal cortex was not fully developed in our younger sample (Gogtay et al., 2004). However, recent studies using other tasks reported prefrontal hyperactivity in youths with histories of important adversity (i.e. physical abuse and severe emotional neglect) (Elsey et al., 2015; Mueller et al., 2010). This suggests that the nature of the paradigms employed, as well as the severity of adversity, may also influence the differences observed in the vmPFC.

Taken together, the present findings suggest specific contributions of harsh parenting and anxiety to fear circuitry function, as well as interactions between the two risk factors. Hence, a history of chronic elevated harsh parenting levels is associated with decreased medial temporal lobe regulation, and with decreased amygdala-insula functional connectivity during threat signals processing. In turn, higher anxiety levels are linked to increased dorsal anterior cingulate activations during extinction, possibly reflecting increased cognitively-driven fear responses. In some rostral and dorsal ACC regions, however, anxiety differences varied according to harsh parenting levels, highlighting the need to consider both risk factors when planning interventions, as the underlying neural mechanisms may differ according to early adversity and anxiety histories.

This study has some limitations. First, anxiety and harsh parenting differences were observed during conditioning and extinction for fear ratings and brain activations, but not for SCR measures. Discrepancies between SCR and rating measures have been previously reported (e.g., (Chauret et al., 2014; Pejic et al., 2013), and may be explained by distinct underlying neural mechanisms. Indeed, physiological responses are unconscious and automatic responses that allow for rapid processing of information and are triggered mainly by the amygdala, whereas fear ratings represent conscious cognitive responses relying on prefrontal regions (LeDoux, 2014; Ohman, Carlsson, Lundqvist, & Ingvar, 2007). In the present study, behavioral resistance to fear extinction was indeed observed in the two groups showing increased dACC activations relative to the others (i.e. LH/HA and HH/LA), while at the physiological and amygdala levels, extinction was observed across groups. Besides, an absence of SCR differences between anxious and non-anxious participants in a context of behavioral and/or brain activation differences is not uncommon (e.g. (Gazendam et al., 2013;

Liberman et al., 2006; Tzschoppe et al., 2014; Waters et al., 2009; Waters, Peters, Forrest, & Zimmer-Gembeck, 2014).

Second, harsh parenting practices were self-reported, so mothers may have under-evaluated their levels of harsh parenting, as self-reporting may be susceptible to social desirability (Boivin et al., 2005). Nevertheless, previous studies suggested self-report to be a valid and useful measure for etiologic research (Windham et al., 2004). Moreover, the harsh parenting questions employed in the previous study have been extensively used (e.g. Boivin, 2005, Pierce, 2010; Vitaro, 2006, Barker, Boivin et al, 2006; Guimond, Bredgen et al, 2012), and the levels of harsh parenting observed here were consistent with those of previous research (Lansford et al., 2009; Pierce et al., 2010). The fact that harsh parenting was measured in mothers only is another limitation of this study, since mothers often report more frequent use of corporal punishment relative to fathers (Gershoff, 2002). However, previous studies in the same cohorts reported paternal and maternal harsh parenting levels to be positively correlated, suggesting that similar levels would most probably have been observed in our subjects' fathers (Guimond et al., 2012).

Another important limitation is that we did not investigate parental history of anxiety or other psychiatric disorders. Genetic background has been shown to influence anxiety disorders development (Casey et al., 2011) and fear circuitry function (Redlich et al., 2015), and may interact with early adversity factors (E. McCrory et al., 2011; Redlich et al., 2015).

Finally, one must keep in mind that all of our participants were psychiatrically healthy and showed subclinical levels of anxiety, since the purpose of this study was to investigate the neural correlates of chronic anxiety in an at-risk non-clinical population, with an aim of prevention. This limits the interpretation of the observed differences regarding potential relations with later psychopathology. Future studies should include measures of familial psychopathology background and paternal harsh parenting levels, and should follow youths further and into adulthood.

Regardless of these limitations, this study sheds light for the first time on the individual and conjoined influences of harsh parenting and anxiety on fear processing in youth. The strength of this study lies in the repeated assessments of harsh parenting and anxiety levels over a 10-year period in a large and representative population-based cohort. This work partially replicates previous findings in adults with histories of anxiety and/or childhood

adversity and in anxious children, and provides new insights into neural mechanisms underlying the risks of and resiliency to future psychopathology, providing guidelines to better identify the most at-risk youths and to develop better-targeted interventions.

References

Achenbach, T. M. (1991). Child Behavior Checklist. . In U. o. V. Department of Psychiatry (Ed.). Burlington, VT:.

Aghajani, M., Veer, I. M., van Tol, M. J., Aleman, A., van Buchem, M. A., Veltman, D. J., . . . van der Wee, N. J. (2014). Neuroticism and extraversion are associated with amygdala resting-state functional connectivity. *Cogn Affect Behav Neurosci, 14*(2), 836-848. doi: 10.3758/s13415-013-0224-0

Barbas, H. (2009). Prefrontal Cortex: Structure and Anatomy *Encyclopedia of Neuroscience* (Vol. 7, pp. 909-918). Oxford: Academic Press.

Barrett, J., & Armony, J. L. (2009). Influence of trait anxiety on brain activity during the acquisition and extinction of aversive conditioning. *Psychol Med, 39*(2), 255-265. doi: 10.1017/S0033291708003516

Birmaher, B., Khetarpal, S., Brent, D., Cully, M., Balach, L., Kaufman, J., & Neer, S. M. (1997). The Screen for Child Anxiety Related Emotional Disorders (SCARED): scale construction and psychometric characteristics. *J Am Acad Child Adolesc Psychiatry, 36*(4), 545-553. doi: 10.1097/00004583-199704000-00018

Birn, R. M., Patriat, R., Phillips, M. L., Germain, A., & Herringa, R. J. (2014). Childhood maltreatment and combat posttraumatic stress differentially predict fear-related fronto-subcortical connectivity. *Depress Anxiety, 31*(10), 880-892. doi: 10.1002/da.22291

Boivin, M., Perusse, D., Dionne, G., Saysset, V., Zoccolillo, M., Tarabulsy, G. M., . . . Tremblay, R. E. (2005). The genetic-environmental etiology of parents' perceptions and self-assessed behaviours toward their 5-month-old infants in a large twin and singleton sample. *J Child Psychol Psychiatry, 46*(6), 612-630. doi: JCPP375 [pii]10.1111/j.1469-7610.2004.00375.x

Boll, S., Gamer, M., Gluth, S., Finsterbusch, J., & Buchel, C. (2013). Separate amygdala subregions signal surprise and predictiveness during associative fear learning in humans. *Eur J Neurosci, 37*(5), 758-767. doi: 10.1111/ejn.12094

Boyle, M. H., Jenkins, J. M., Georgiades, K., Cairney, J., Duku, E., & Racine, Y. (2004). Differential-maternal parenting behavior: estimating within- and between-family effects on children. *Child Dev, 75*(5), 1457-1476. doi: 10.1111/j.1467-8624.2004.00751.xCDEV751 [pii]

Boyle, M. H., Offord, D. R., Racine, Y., Fleming, J. E., Szatmari, P., & Sanford, M. (1993). Evaluation of the revised Ontario Child Health Study scales. *J Child Psychol Psychiatry, 34*(2), 189-213.

Bremner, J. D., Vermetten, E., Schmahl, C., Vaccarino, V., Vythilingam, M., Afzal, N., . . . Charney, D. S. (2005). Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual-abuse-related post-traumatic stress disorder. *Psychol Med, 35*(6), 791-806.

Britton, J. C., Grillon, C., Lissek, S., Norcross, M. A., Szuhany, K. L., Chen, G., . . . Pine, D. S. (2013). Response to learned threat: An FMRI study in adolescent and adult anxiety. *Am J Psychiatry, 170*(10), 1195-1204. doi: 10.1176/appi.ajp.2013.12050651

Buchel, C., & Dolan, R. J. (2000). Classical fear conditioning in functional neuroimaging. *Curr Opin Neurobiol, 10*(2), 219-223.

Buchel, C., Morris, J., Dolan, R. J., & Friston, K. J. (1998). Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron, 20*(5), 947-957.

Burghy, C. A., Stodola, D. E., Ruttle, P. L., Molloy, E. K., Armstrong, J. M., Oler, J. A., . . . Birn, R. M. (2012). Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. *Nat Neurosci, 15*(12), 1736-1741. doi: 10.1038/nn.3257

Care., A. A. o. P. C. o. E. C. a. A. a. D. (2000). Developmental issues for young children in foster care. *Pediatrics, 106*(5), 1145-1150.

Carrion, V. G., Garrett, A., Menon, V., Weems, C. F., & Reiss, A. L. (2008). Posttraumatic stress symptoms and brain function during a response-inhibition task: an fMRI study in youth. *Depress Anxiety, 25*(6), 514-526. doi: 10.1002/da.20346

Casey, B. J., Ruberry, E. J., Libby, V., Glatt, C. E., Hare, T., Soliman, F., . . . Tottenham, N. (2011). Transitional and translational studies of risk for anxiety. *Depress Anxiety, 28*(1), 18-28. doi: 10.1002/da.20783

Charney, D. S. (2004). Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *Am J Psychiatry, 161*(2), 195-216.

Chauret, M., La Buissonniere-Ariza, V., Lamoureux Tremblay, V., Suffren, S., Servonnet, A., Pine, D. S., & Maheu, F. S. (2014). The conditioning and extinction of fear in youths: what's sex got to do with it? *Biol Psychol, 100*, 97-105. doi: 10.1016/j.biopsycho.2014.06.001

Cote, S. M., Boivin, M., Liu, X., Nagin, D. S., Zoccolillo, M., & Tremblay, R. E. (2009). Depression and anxiety symptoms: onset, developmental course and risk factors during early childhood. *J Child Psychol Psychiatry, 50*(10), 1201-1208. doi: JCPP2099 [pii]10.1111/j.1469-7610.2009.02099.x

Craig, A. D. (2009). How do you feel--now? The anterior insula and human awareness. *Nat Rev Neurosci, 10*(1), 59-70. doi: 10.1038/nrn2555

Craske, M. G., Waters, A. M., Lindsey Bergman, R., Naliboff, B., Lipp, O. V., Negoro, H., & Ornitz, E. M. (2008). Is aversive learning a marker of risk for anxiety disorders in children? *Behav Res Ther, 46*(8), 954-967. doi: 10.1016/j.brat.2008.04.011

Davis, M., & Whalen, P. J. (2001). The amygdala: vigilance and emotion. *Mol Psychiatry, 6*(1), 13-34.

Diedrichsen, J., & Shadmehr, R. (2005). Detecting and adjusting for artifacts in fMRI time series data. *Neuroimage, 27*(3), 624-634. doi: 10.1016/j.neuroimage.2005.04.039

Dube, A. A., Duquette, M., Roy, M., Lepore, F., Duncan, G., & Rainville, P. (2009). Brain activity associated with the electrodermal reactivity to acute heat pain. *Neuroimage, 45*(1), 169-180. doi: 10.1016/j.neuroimage.2008.10.024

Dunn, L. M., & Dunn, L. (1981). *Peabody Picture Vocabulary Test-Revised (PPVT): Manual for Forms L and M*. Circle Pines, MN: American Guidance Service.

Dunsmoor, J. E., & LaBar, K. S. (2012). Brain activity associated with omission of an aversive event reveals the effects of fear learning and generalization. *Neurobiol Learn Mem, 97*(3), 301-312. doi: 10.1016/j.nlm.2012.02.003

Duvarci, S., & Pare, D. (2014). Amygdala microcircuits controlling learned fear. *Neuron, 82*(5), 966-980. doi: 10.1016/j.neuron.2014.04.042

Elsey, J., Coates, A., Lacadie, C. M., McCrory, E. J., Sinha, R., Mayes, L. C., & Potenza, M. N. (2015). Childhood trauma and neural responses to personalized stress, favorite-food and neutral-relaxing cues in adolescents. *Neuropsychopharmacology, 40*(7), 1580-1589. doi: 10.1038/npp.2015.6

Erhardt, A., & Spoormaker, V. I. (2013). Translational approaches to anxiety: focus on genetics, fear extinction and brain imaging. *Curr Psychiatry Rep, 15*(12), 417. doi: 10.1007/s11920-013-0417-9

Etkin, A., Prater, K. E., Hoeft, F., Menon, V., & Schatzberg, A. F. (2010). Failure of anterior cingulate activation and connectivity with the amygdala during implicit regulation of emotional processing in generalized anxiety disorder. *Am J Psychiatry, 167*(5), 545-554. doi: 10.1176/appi.ajp.2009.09070931

Etkin, A., Prater, K. E., Schatzberg, A. F., Menon, V., & Greicius, M. D. (2009). Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. *Arch Gen Psychiatry, 66*(12), 1361-1372. doi: 10.1001/archgenpsychiatry.2009.104

Etkin, A., & Wager, T. D. (2007). Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry, 164*(10), 1476-1488. doi: 10.1176/appi.ajp.2007.07030504

Fan, Y., Herrera-Melendez, A. L., Pestke, K., Feeser, M., Aust, S., Otte, C., . . . Grimm, S. (2014). Early life stress modulates amygdala-prefrontal functional connectivity: implications for oxytocin effects. *Hum Brain Mapp, 35*(10), 5328-5339. doi: 10.1002/hbm.22553

Fonzo, G. A., Flagan, T. M., Sullivan, S., Allard, C. B., Grimes, E. M., Simmons, A. N., . . . Stein, M. B. (2013). Neural functional and structural correlates of childhood maltreatment in women with intimate-partner violence-related posttraumatic stress disorder. *Psychiatry Res, 211*(2), 93-103. doi: 10.1016/j.pscychresns.2012.08.006

Fonzo, G. A., Simmons, A. N., Thorp, S. R., Norman, S. B., Paulus, M. P., & Stein, M. B. (2010). Exaggerated and disconnected insular-amygdalar blood oxygenation level-dependent response to threat-related emotional faces in women with intimate-partner violence posttraumatic stress disorder. *Biol Psychiatry, 68*(5), 433-441. doi: 10.1016/j.biopsych.2010.04.028

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage, 6*(3), 218-229. doi: 10.1006/nimg.1997.0291

Galera, C., Pingault, J. B., Michel, G., Bouvard, M. P., Melchior, M., Falissard, B., . . . Cote, S. M. (2014). Clinical and social factors associated with attention-deficit hyperactivity disorder medication use: population-based longitudinal study. *Br J Psychiatry, 205*(4), 291-297. doi: 10.1192/bjp.bp.113.141952

Gazendam, F. J., Kamphuis, J. H., & Kindt, M. (2013). Deficient safety learning characterizes high trait anxious individuals. *Biol Psychol, 92*(2), 342-352. doi: 10.1016/j.biopsycho.2012.11.006

Gee, D. G., Gabard-Durnam, L. J., Flannery, J., Goff, B., Humphreys, K. L., Telzer, E. H., . . . Tottenham, N. (2013). Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. *Proc Natl Acad Sci U S A, 110*(39), 15638-15643. doi: 10.1073/pnas.1307893110

Gee, D. G., Humphreys, K. L., Flannery, J., Goff, B., Telzer, E. H., Shapiro, M., . . . Tottenham, N. (2013). A developmental shift from positive to negative connectivity in human amygdala-prefrontal circuitry. *J Neurosci, 33*(10), 4584-4593. doi: 10.1523/JNEUROSCI.3446-12.2013

Gershoff, E. T. (2002). Corporal punishment by parents and associated child behaviors and experiences: a meta-analytic and theoretical review. *Psychol Bull, 128*(4), 539-579.
Glotzbach-Schoon, E., Tadda, R., Andreatta, M., Troger, C., Ewald, H., Grillon, C., . . . Muhlberger, A. (2013). Enhanced discrimination between threatening and safe contexts in high-anxious individuals. *Biol Psychol, 93*(1), 159-166. doi: 10.1016/j.biopsycho.2013.01.011
Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., . . . Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A, 101*(21), 8174-8179. doi: 10.1073/pnas.0402680101 [pii]
Guimond, F. A., Brendgen, M., Forget-Dubois, N., Dionne, G., Vitaro, F., Tremblay, R. E., & Boivin, M. (2012). Associations of mother's and father's parenting practices with children's observed social reticence in a competitive situation: a monozygotic twin difference study. *J Abnorm Child Psychol, 40*(3), 391-402. doi: 10.1007/s10802-011-9573-8
Hahn, A., Stein, P., Windischberger, C., Weissenbacher, A., Spindelegger, C., Moser, E., . . . Lanzenberger, R. (2011). Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder. *Neuroimage, 56*(3), 881-889. doi: 10.1016/j.neuroimage.2011.02.064
Hardee, J. E., Benson, B. E., Bar-Haim, Y., Mogg, K., Bradley, B. P., Chen, G., . . . Perez-Edgar, K. (2013). Patterns of neural connectivity during an attention bias task moderate associations between early childhood temperament and internalizing symptoms in young adulthood. *Biol Psychiatry, 74*(4), 273-279. doi: 10.1016/j.biopsych.2013.01.036
Hart, H., & Rubia, K. (2012). Neuroimaging of child abuse: a critical review. *Front Hum Neurosci, 6*, 52. doi: 10.3389/fnhum.2012.00052
Herringa, R. J., Birn, R. M., Ruttle, P. L., Burghy, C. A., Stodola, D. E., Davidson, R. J., & Essex, M. J. (2013). Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. *Proc Natl Acad Sci U S A, 110*(47), 19119-19124. doi: 10.1073/pnas.1310766110
Hilbert, K., Lueken, U., & Beesdo-Baum, K. (2014). Neural structures, functioning and connectivity in Generalized Anxiety Disorder and interaction with neuroendocrine systems: a systematic review. *J Affect Disord, 158*, 114-126. doi: 10.1016/j.jad.2014.01.022
Hofmann, S. G., Ellard, K. K., & Siegle, G. J. (2012). Neurobiological correlates of cognitions in fear and anxiety: a cognitive-neurobiological information-processing model. *Cogn Emot, 26*(2), 282-299. doi: 10.1080/02699931.2011.579414
Hollingshead, A. B. (1973). *Four-factor index of social status*. New Haven: Yale University Press.
Indovina, I., Robbins, T. W., Nunez-Elizalde, A. O., Dunn, B. D., & Bishop, S. J. (2011). Fear-conditioning mechanisms associated with trait vulnerability to anxiety in humans. *Neuron, 69*(3), 563-571. doi: 10.1016/j.neuron.2010.12.034
Jones, C. L., Ward, J., & Critchley, H. D. (2010). The neuropsychological impact of insular cortex lesions. *J Neurol Neurosurg Psychiatry, 81*(6), 611-618. doi: 10.1136/jnnp.2009.193672

Jovanovic, T., & Ressler, K. J. (2010). How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD. *Am J Psychiatry, 167*(6), 648-662. doi: 10.1176/appi.ajp.2009.09071074

Kalisch, R., & Gerlicher, A. M. (2014). Making a mountain out of a molehill: on the role of the rostral dorsal anterior cingulate and dorsomedial prefrontal cortex in conscious threat appraisal, catastrophizing, and worrying. *Neurosci Biobehav Rev, 42*, 1-8. doi: 10.1016/j.neubiorev.2014.02.002

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., . . . Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry, 36*(7), 980-988. doi: 10.1097/00004583-199707000-00021

Kindt, M., & Soeter, M. (2014). Fear inhibition in high trait anxiety. *PLoS One, 9*(1), e86462. doi: 10.1371/journal.pone.0086462

Klumpp, H., Angstadt, M., & Phan, K. L. (2012). Insula reactivity and connectivity to anterior cingulate cortex when processing threat in generalized social anxiety disorder. *Biol Psychol, 89*(1), 273-276. doi: 10.1016/j.biopsycho.2011.10.010

Kovacs, E. (1984). The Children′s Depression Inventory (CDI) *Psychopharmacol. Bull.*(21), 995-998.

LaBar, K. S., Gatenby, J. C., Gore, J. C., LeDoux, J. E., & Phelps, E. A. (1998). Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron, 20*(5), 937-945.

Lansford, J. E., Criss, M. M., Dodge, K. A., Shaw, D. S., Pettit, G. S., & Bates, J. E. (2009). Trajectories of physical discipline: early childhood antecedents and developmental outcomes. *Child Dev, 80*(5), 1385-1402. doi: CDEV1340 [pii]10.1111/j.1467-8624.2009.01340.x

Lau, J. Y., Britton, J. C., Nelson, E. E., Angold, A., Ernst, M., Goldwin, M., . . . Pine, D. S. (2011). Distinct neural signatures of threat learning in adolescents and adults. *Proc Natl Acad Sci U S A, 108*(11), 4500-4505. doi: 1005494108 [pii]10.1073/pnas.1005494108

Lau, J. Y., Lissek, S., Nelson, E. E., Lee, Y., Roberson-Nay, R., Poeth, K., . . . Pine, D. S. (2008). Fear conditioning in adolescents with anxiety disorders: results from a novel experimental paradigm. *J Am Acad Child Adolesc Psychiatry, 47*(1), 94-102. doi: 10.1097/chi.0b01e31815a5f01S0890-8567(09)62089-X [pii]

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annu Rev Neurosci, 23*, 155-184. doi: 10.1146/annurev.neuro.23.1.155

LeDoux, J. E. (2014). Coming to terms with fear. *Proc Natl Acad Sci U S A, 111*(8), 2871-2878. doi: 10.1073/pnas.1400335111

Liberman, L. C., Lipp, O. V., Spence, S. H., & March, S. (2006). Evidence for retarded extinction of aversive learning in anxious children. *Behav Res Ther, 44*(10), 1491-1502. doi: S0005-7967(05)00231-7 [pii]10.1016/j.brat.2005.11.004

Linnman, C., Rougemont-Bucking, A., Beucke, J. C., Zeffiro, T. A., & Milad, M. R. (2011). Unconditioned responses and functional fear networks in human classical conditioning. *Behav Brain Res, 221*(1), 237-245. doi: 10.1016/j.bbr.2011.02.045

Lissek, S. (2012). Toward an account of clinical anxiety predicated on basic, neurally mapped mechanisms of Pavlovian fear-learning: the case for conditioned overgeneralization. *Depress Anxiety, 29*(4), 257-263. doi: 10.1002/da.21922

Lissek, S., Powers, A. S., McClure, E. B., Phelps, E. A., Woldehawariat, G., Grillon, C., & Pine, D. S. (2005). Classical fear conditioning in the anxiety disorders: a meta-analysis. *Behav Res Ther, 43*(11), 1391-1424. doi: S0005-7967(04)00251-7 [pii]10.1016/j.brat.2004.10.007

Lissek, S., Rabin, S., Heller, R. E., Lukenbaugh, D., Geraci, M., Pine, D. S., & Grillon, C. (2010). Overgeneralization of conditioned fear as a pathogenic marker of panic disorder. *Am J Psychiatry, 167*(1), 47-55. doi: 10.1176/appi.ajp.2009.09030410

Lissek, S., Rabin, S. J., McDowell, D. J., Dvir, S., Bradford, D. E., Geraci, M., . . . Grillon, C. (2009). Impaired discriminative fear-conditioning resulting from elevated fear responding to learned safety cues among individuals with panic disorder. *Behav Res Ther, 47*(2), 111-118. doi: 10.1016/j.brat.2008.10.017

Mackintosh, N. (1974). *The psychology of animal learning.* . London:: Academic Press.

MacMillan, H. L., Boyle, M. H., Wong, M. Y., Duku, E. K., Fleming, J. E., & Walsh, C. A. (1999). Slapping and spanking in childhood and its association with lifetime prevalence of psychiatric disorders in a general population sample. *CMAJ, 161*(7), 805-809.

Mahan, A. L., & Ressler, K. J. (2012). Fear conditioning, synaptic plasticity and the amygdala: implications for posttraumatic stress disorder. *Trends Neurosci, 35*(1), 24-35. doi: 10.1016/j.tins.2011.06.007

Maheu, F. S., Dozier, M., Guyer, A. E., Mandell, D., Peloso, E., Poeth, K., . . . Ernst, M. (2010). A preliminary study of medial temporal lobe function in youths with a history of caregiver deprivation and emotional neglect. *Cogn Affect Behav Neurosci, 10*(1), 34-49. doi: 10.3758/CABN.10.1.34

Marek, R., Strobel, C., Bredy, T. W., & Sah, P. (2013). The amygdala and medial prefrontal cortex: partners in the fear circuit. *J Physiol, 591*(Pt 10), 2381-2391. doi: 10.1113/jphysiol.2012.248575

McClure, E. B., Monk, C. S., Nelson, E. E., Parrish, J. M., Adler, A., Blair, R. J., . . . Pine, D. S. (2007). Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder. *Arch Gen Psychiatry, 64*(1), 97-106. doi: 10.1001/archpsyc.64.1.97

McCrory, E., De Brito, S. A., & Viding, E. (2011). The impact of childhood maltreatment: a review of neurobiological and genetic factors. *Front Psychiatry, 2*, 48. doi: 10.3389/fpsyt.2011.00048

McCrory, E. J., De Brito, S. A., Kelly, P. A., Bird, G., Sebastian, C. L., Mechelli, A., . . . Viding, E. (2013). Amygdala activation in maltreated children during pre-attentive emotional processing. *Br J Psychiatry, 202*(4), 269-276. doi: 10.1192/bjp.bp.112.116624

McCrory, E. J., De Brito, S. A., Sebastian, C. L., Mechelli, A., Bird, G., Kelly, P. A., & Viding, E. (2011). Heightened neural reactivity to threat in child victims of family violence. *Curr Biol, 21*(23), R947-948. doi: 10.1016/j.cub.2011.10.015

McKee, L., Jones, D. J., Roland, E., Coffelt, N., Rakow, A., & Forehand, R. (2007). Maternal HIV/AIDS and depressive symptoms among inner-city African American youth: the role of maternal depressive symptoms, mother-child relationship quality, and child coping. *Am J Orthopsychiatry, 77*(2), 259-266. doi: 10.1037/0002-9432.77.2.259

McLaughlin, K. A., Peverill, M., Gold, A. L., Alves, S., & Sheridan, M. A. (2015). Child Maltreatment and Neural Systems Underlying Emotion Regulation. *J Am Acad Child Adolesc Psychiatry, 54*(9), 753-762. doi: 10.1016/j.jaac.2015.06.010

McLeod, B. D., Wood, J. J., & Weisz, J. R. (2007). Examining the association between parenting and childhood anxiety: a meta-analysis. *Clin Psychol Rev, 27*(2), 155-172. doi: 10.1016/j.cpr.2006.09.002

Milad, M. R., Goldstein, J. M., Orr, S. P., Wedig, M. M., Klibanski, A., Pitman, R. K., & Rauch, S. L. (2006). Fear conditioning and extinction: influence of sex and menstrual cycle in healthy humans. *Behav Neurosci, 120*(6), 1196-1203. doi: 10.1037/0735-7044.120.5.1196

Milad, M. R., & Quirk, G. J. (2012). Fear extinction as a model for translational neuroscience: ten years of progress. *Annu Rev Psychol, 63*, 129-151. doi: 10.1146/annurev.psych.121208.131631

Milad, M. R., Rauch, S. L., Pitman, R. K., & Quirk, G. J. (2006). Fear extinction in rats: implications for human brain imaging and anxiety disorders. *Biol Psychol, 73*(1), 61-71. doi: 10.1016/j.biopsycho.2006.01.008

Monk, C. S., Nelson, E. E., McClure, E. B., Mogg, K., Bradley, B. P., Leibenluft, E., . . . Pine, D. S. (2006). Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *Am J Psychiatry, 163*(6), 1091-1097. doi: 10.1176/appi.ajp.163.6.1091

Mueller, S. C., Maheu, F. S., Dozier, M., Peloso, E., Mandell, D., Leibenluft, E., . . . Ernst, M. (2010). Early-life stress is associated with impairment in cognitive control in adolescence: an fMRI study. *Neuropsychologia, 48*(10), 3037-3044. doi: 10.1016/j.neuropsychologia.2010.06.013

Nagin, D. S. (2005). *Group-based modeling of development over the life course*. Cambridge.

O'Reilly, J. X., Woolrich, M. W., Behrens, T. E., Smith, S. M., & Johansen-Berg, H. (2012). Tools of the trade: psychophysiological interactions and functional connectivity. *Soc Cogn Affect Neurosci, 7*(5), 604-609. doi: 10.1093/scan/nss055

Ohman, A. (2005). The role of the amygdala in human fear: automatic detection of threat. *Psychoneuroendocrinology, 30*(10), 953-958. doi: 10.1016/j.psyneuen.2005.03.019

Ohman, A., Carlsson, K., Lundqvist, D., & Ingvar, M. (2007). On the unconscious subcortical origin of human fear. *Physiol Behav, 92*(1-2), 180-185. doi: 10.1016/j.physbeh.2007.05.057

Pannekoek, J. N., Veer, I. M., van Tol, M. J., van der Werff, S. J., Demenescu, L. R., Aleman, A., . . . van der Wee, N. J. (2013). Resting-state functional connectivity abnormalities in limbic and salience networks in social anxiety disorder without comorbidity. *Eur Neuropsychopharmacol, 23*(3), 186-195. doi: 10.1016/j.euroneuro.2012.04.018

Pejic, T., Hermann, A., Vaitl, D., & Stark, R. (2013). Social anxiety modulates amygdala activation during social conditioning. *Soc Cogn Affect Neurosci, 8*(3), 267-276. doi: 10.1093/scan/nsr095

Perlman, G., Simmons, A. N., Wu, J., Hahn, K. S., Tapert, S. F., Max, J. E., . . . Yang, T. T. (2012). Amygdala response and functional connectivity during emotion regulation: a study of 14 depressed adolescents. *J Affect Disord, 139*(1), 75-84. doi: 10.1016/j.jad.2012.01.044

Petrovic, P., Carlsson, K., Petersson, K. M., Hansson, P., & Ingvar, M. (2004). Context-dependent deactivation of the amygdala during pain. *J Cogn Neurosci, 16*(7), 1289-1301. doi: 10.1162/0898929041920469

Pierce, T., Boivin, M., Frenette, E., Forget-Dubois, N., Dionne, G., & Tremblay, R. E. (2010). Maternal self-efficacy and hostile-reactive parenting from infancy to toddlerhood. *Infant Behav Dev, 33*(2), 149-158. doi: S0163-6383(09)00113-1 [pii]10.1016/j.infbeh.2009.12.005

Pine, D. S. (2003). Developmental psychobiology and response to threats: relevance to trauma in children and adolescents. *Biol Psychiatry, 53*(9), 796-808.

Pine, D. S., & Cohen, J. A. (2002). Trauma in children and adolescents: risk and treatment of psychiatric sequelae. *Biol Psychiatry, 51*(7), 519-531.

Pine, D. S., Helfinstein, S. M., Bar-Haim, Y., Nelson, E., & Fox, N. A. (2009). Challenges in developing novel treatments for childhood disorders: lessons from research on anxiety. *Neuropsychopharmacology, 34*(1), 213-228. doi: npp2008113 [pii]10.1038/npp.2008.113

Pitkanen, A., Jolkkonen, E., & Kemppainen, S. (2000). Anatomic heterogeneity of the rat amygdaloid complex. *Folia Morphol (Warsz), 59*(1), 1-23.

Quirk, G. J., Armony, J. L., & LeDoux, J. E. (1997). Fear conditioning enhances different temporal components of tone-evoked spike trains in auditory cortex and lateral amygdala. *Neuron, 19*(3), 613-624.

Rabinak, C. A., Angstadt, M., Welsh, R. C., Kenndy, A. E., Lyubkin, M., Martis, B., & Phan, K. L. (2011). Altered amygdala resting-state functional connectivity in post-traumatic stress disorder. *Front Psychiatry, 2*, 62. doi: 10.3389/fpsyt.2011.00062

Redlich, R., Stacey, D., Opel, N., Grotegerd, D., Dohm, K., Kugel, H., . . . Dannlowski, U. (2015). Evidence of an IFN-gamma by early life stress interaction in the regulation of amygdala reactivity to emotional stimuli. *Psychoneuroendocrinology, 62*, 166-173. doi: 10.1016/j.psyneuen.2015.08.008

Roy, A. K., Fudge, J. L., Kelly, C., Perry, J. S., Daniele, T., Carlisi, C., . . . Ernst, M. (2013). Intrinsic functional connectivity of amygdala-based networks in adolescent generalized anxiety disorder. *J Am Acad Child Adolesc Psychiatry, 52*(3), 290-299 e292. doi: 10.1016/j.jaac.2012.12.010

Schneider, F., Weiss, U., Kessler, C., Muller-Gartner, H. W., Posse, S., Salloum, J. B., . . . Birbaumer, N. (1999). Subcortical correlates of differential classical conditioning of aversive emotional reactions in social phobia. *Biol Psychiatry, 45*(7), 863-871.

Sehlmeyer, C., Dannlowski, U., Schoning, S., Kugel, H., Pyka, M., Pfleiderer, B., . . . Konrad, C. (2011). Neural correlates of trait anxiety in fear extinction. *Psychol Med, 41*(4), 789-798. doi: 10.1017/S0033291710001248

Shackman, A. J., Salomons, T. V., Slagter, H. A., Fox, A. S., Winter, J. J., & Davidson, R. J. (2011). The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci, 12*(3), 154-167. doi: 10.1038/nrn2994

Simmons, A. N., Paulus, M. P., Thorp, S. R., Matthews, S. C., Norman, S. B., & Stein, M. B. (2008). Functional activation and neural networks in women with posttraumatic stress disorder related to intimate partner violence. *Biol Psychiatry, 64*(8), 681-690. doi: 10.1016/j.biopsych.2008.05.027

Simmons, W. K., Avery, J. A., Barcalow, J. C., Bodurka, J., Drevets, W. C., & Bellgowan, P. (2013). Keeping the body in mind: insula functional organization and functional

connectivity integrate interoceptive, exteroceptive, and emotional awareness. *Hum Brain Mapp, 34*(11), 2944-2958. doi: 10.1002/hbm.22113
Solomon, C. R., & Serres, F. (1999). Effects of parental verbal aggression on children's self-esteem and school marks. *Child Abuse Negl, 23*(4), 339-351. doi: S0145-2134(99)00006-X [pii]
Strange, B. A., & Dolan, R. J. (2006). Anterior medial temporal lobe in human cognition: memory for fear and the unexpected. *Cogn Neuropsychiatry, 11*(3), 198-218. doi: 10.1080/13546800500305096
Tanner, J. M., & Whitehouse, R. H. (1976). Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. *Arch Dis Child, 51*(3), 170-179.
Telzer, E. H., Mogg, K., Bradley, B. P., Mai, X., Ernst, M., Pine, D. S., & Monk, C. S. (2008). Relationship between trait anxiety, prefrontal cortex, and attention bias to angry faces in children and adolescents. *Biol Psychol, 79*(2), 216-222. doi: 10.1016/j.biopsycho.2008.05.004
Thomas, K. M., Drevets, W. C., Dahl, R. E., Ryan, N. D., Birmaher, B., Eccard, C. H., . . . Casey, B. J. (2001). Amygdala response to fearful faces in anxious and depressed children. *Arch Gen Psychiatry, 58*(11), 1057-1063.
Thomason, M. E., Marusak, H. A., Tocco, M. A., Vila, A. M., McGarragle, O., & Rosenberg, D. R. (2015). Altered amygdala connectivity in urban youth exposed to trauma. *Soc Cogn Affect Neurosci, 10*(11), 1460-1468. doi: 10.1093/scan/nsv030
Tottenham, N., Hare, T. A., Millner, A., Gilhooly, T., Zevin, J. D., & Casey, B. J. (2011). Elevated amygdala response to faces following early deprivation. *Dev Sci, 14*(2), 190-204. doi: 10.1111/j.1467-7687.2010.00971.x
Tottenham, N., & Sheridan, M. A. (2009). A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. *Front Hum Neurosci, 3*, 68. doi: 10.3389/neuro.09.068.2009
Tzschoppe, J., Nees, F., Banaschewski, T., Barker, G. J., Buchel, C., Conrod, P. J., . . . consortium, I. (2014). Aversive learning in adolescents: modulation by amygdala-prefrontal and amygdala-hippocampal connectivity and neuroticism. *Neuropsychopharmacology, 39*(4), 875-884. doi: 10.1038/npp.2013.287
van der Werff, S. J., Pannekoek, J. N., Veer, I. M., van Tol, M. J., Aleman, A., Veltman, D. J., . . . van der Wee, N. J. (2013). Resting-state functional connectivity in adults with childhood emotional maltreatment. *Psychol Med, 43*(9), 1825-1836. doi: 10.1017/S0033291712002942
Waters, A. M., Henry, J., & Neumann, D. L. (2009). Aversive Pavlovian conditioning in childhood anxiety disorders: impaired response inhibition and resistance to extinction. *J Abnorm Psychol, 118*(2), 311-321. doi: 10.1037/a0015635
Waters, A. M., Peters, R. M., Forrest, K. E., & Zimmer-Gembeck, M. (2014). Fear acquisition and extinction in offspring of mothers with anxiety and depressive disorders. *Dev Cogn Neurosci, 7*, 30-42. doi: 10.1016/j.dcn.2013.10.007
Windham, A. M., Rosenberg, L., Fuddy, L., McFarlane, E., Sia, C., & Duggan, A. K. (2004). Risk of mother-reported child abuse in the first 3 years of life. *Child Abuse Negl, 28*(6), 645-667. doi: 10.1016/j.chiabu.2004.01.003S014521340400105X [pii]
Wood, J. J., McLeod, B. D., Sigman, M., Hwang, W. C., & Chu, B. C. (2003). Parenting and childhood anxiety: theory, empirical findings, and future directions. *J Child Psychol Psychiatry, 44*(1), 134-151.

Zeng, L. L., Shen, H., Liu, L., Wang, L., Li, B., Fang, P., . . . Hu, D. (2012). Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis. *Brain, 135*(Pt 5), 1498-1507. doi: 10.1093/brain/aws059

Figures

Figure 1. Trajectory groups for anxiety and harsh parenting (n=1761)

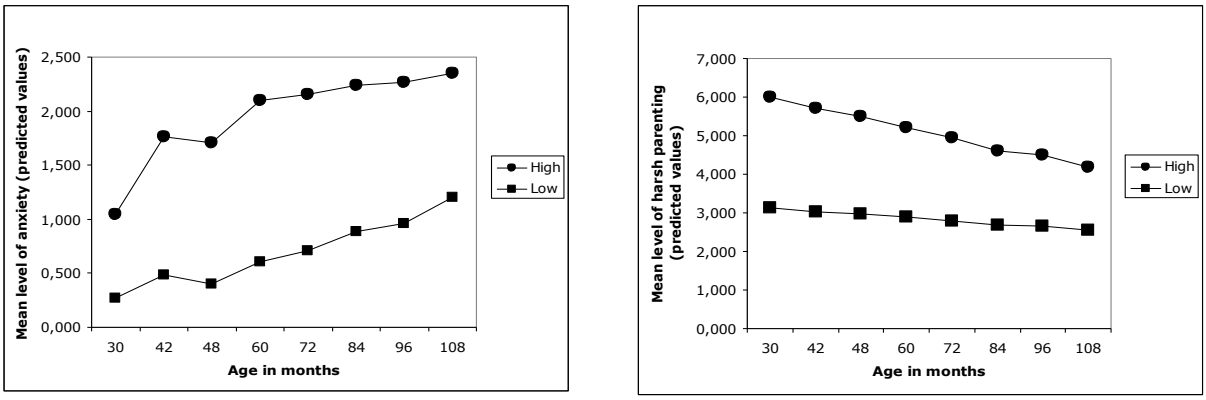


Figure 2. Subjective fear ratings during conditioning phase. Graph bars represent average ratings (scale ranging from 1 not afraid to 5 very afraid). A) CS type x time of cue presentation interaction. B) Anxiety x CS type interaction. C) Harsh parenting x anxiety interaction. Graph bars show the anxiety x CS type interaction in B is driven by the low harsh parenting groups.

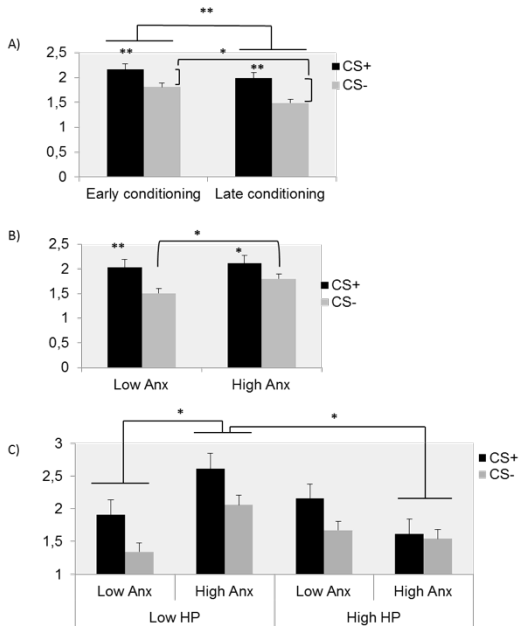


Figure 3. Subjective fear ratings during extinction phase. Graph bars represent average ratings (scale ranging from 1 not afraid to 5 very afraid). A) Main effect of time of cue presentation. B) Harsh parenting x anxiety x CS type interaction.

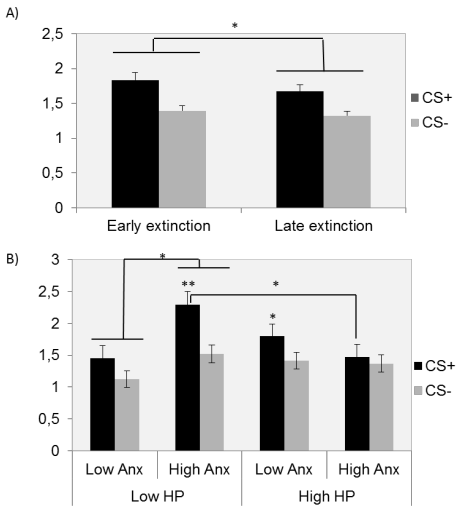


Figure 4. SCRs during conditioning and extinction phases. Graph bars represent average Z-scored SCRs. A) Main effects of CS type and time of cue presentation during conditioning phase. B) CS type and time differences no longer exist during extinction.

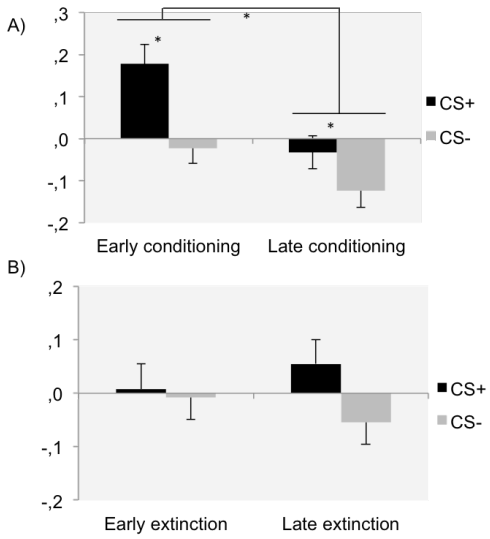


Figure 5. Amygdala and anterior hippocampus activation to CS+ > CS- during conditioning. Images presented at an uncorrected $p < .005$ threshold. Graph bars represent mean % BOLD signal change. A) Greater activation to CS+ vs. CS- in high vs. low harsh parenting in left

amygdala (xyz = -24 -4 -22), and in B) left (xyz = -26 -8 -20) and C) right (xyz = 36 -14 -16) anterior hippocampus.

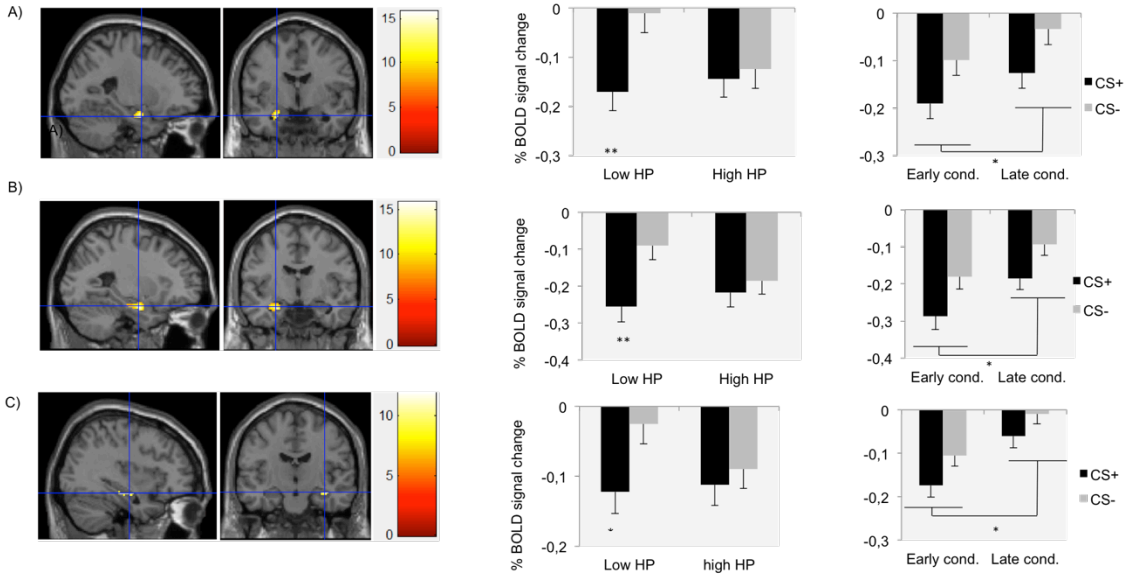


Figure 6. Average effects of CS+ > baseline (all subjects together) during conditioning in left and right amygdalae. Images presented at an uncorrected p < .001 threshold. Graph bars represent mean % signal change to CS+ and CS- in left amygdala (xyz = -24 0 -12).

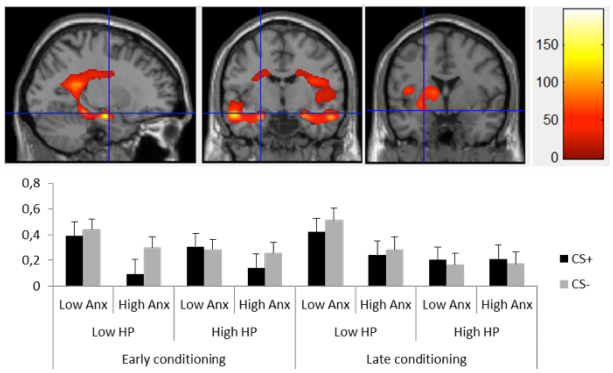


Figure 7. Anterior cingulate activation to CS+ > CS- during early extinction. Images presented at an uncorrected p < .005 threshold. Graph bars represent mean % BOLD signal change. A) Greater activation in high vs. low anxiety in left (xyz= -12 10 36) and B) right (xyz = 6 16 32) BA 24 and in C) right BA 32 (xyz = 4 18 34). D) Harsh parenting x anxiety interaction in left BA 24 (xyz = 16 14 30).

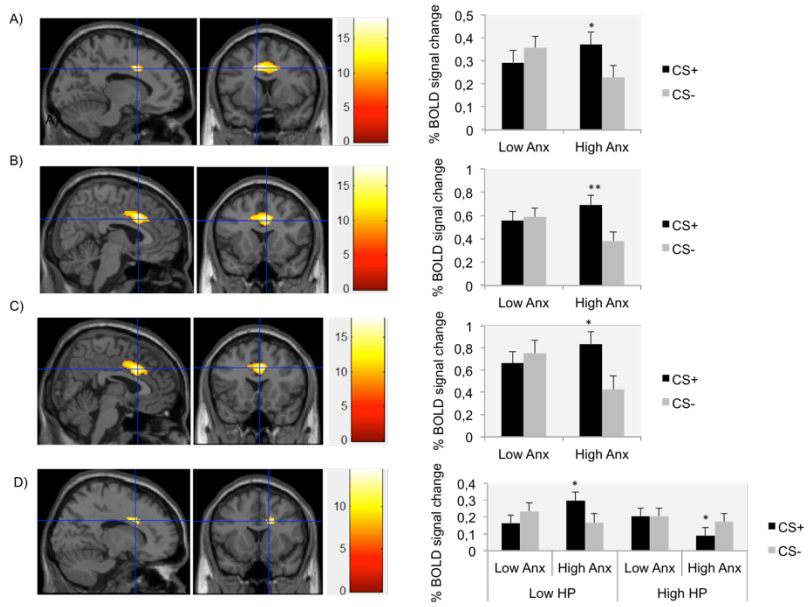
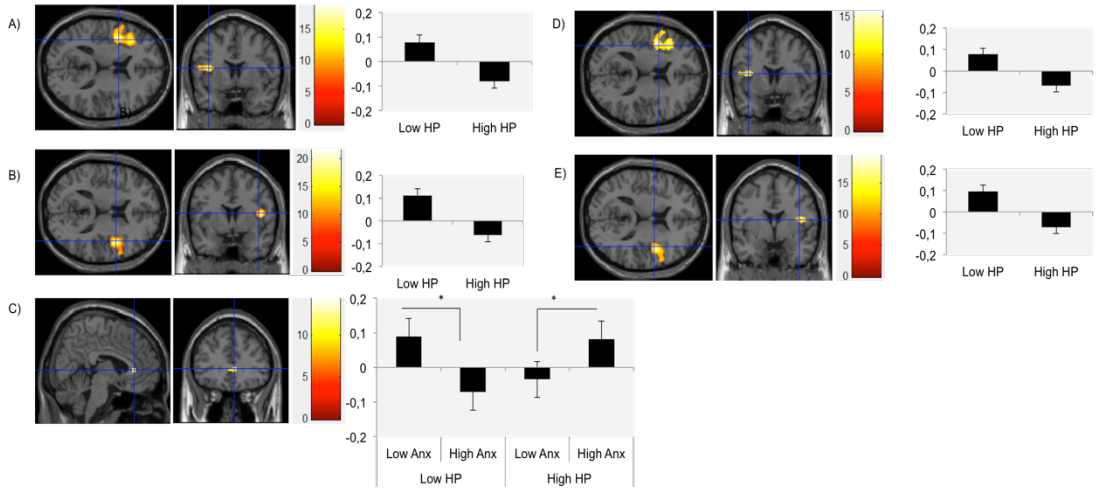


Figure 8. Positive (A, B, C) and negative (D, E) CS+ > CS- PPIs with left amygdala (xyz= -24 -4 -22) as seed region during conditioning. Images presented at an uncorrected $p < .005$ threshold. Graph bars represent mean % BOLD signal change. Increased positive and negative connectivity with amygdala in in A) left (A; xyz = -38 6 14 and D; xyz = -38 6 14) and right (B; xyz = 42 4 14 and E; xyz = 42 0 14) insula in low vs. high harsh parenting. C) Harsh parenting x anxiety interaction on positive connectivity with BA 24 (xyz = 6 32 4).



Tables

Table 1. Demographic and psychological characteristics of the final sample per group

	Low harsh parenting		**High harsh parenting**	
	Low anxiety	**High anxiety**	**Low anxiety**	**High anxiety**
N	21	19	23	21
Sex (female/male)	10/11	14/5	11/12	10/11
Age	14.10 (0.75)	13.92 (0.63)	13.87 (0.54)	14.21 (0.74)
Tanner stage	3.76 (0.71)	4.07 (0.75)	3.88 (0.83)	4.05 (0.63)
Verbal IQ (PPVT-R)	111 (14.49)	111 (13.88)	108 (9.97)	103 (13.80)
SES	34.93 (9.10)	36.84 (14.94)	37.07 (10.38)	43.29 (12.92)
CDI T-scores	44.14 (5.92)	44.26 (6.31)	44.56 (5.89)	46.58 (6.70)
Current harsh parenting scores	6.86 (2.29)	6.05 (1.72)	8.35 (1.99)	8.43 (2.36)
Current anxiety levels (SCARED-R parent version)	8.07 (8.61)	12.45 (7.03)	11.24 (7.21)	16.09 (10.67)
Current anxiety levels (SCARED-R child version)	16.86 (7.66)	20.39 (8.77)	19.20 (10.46)	19.48 (10.75)

Note. Means and (standard deviations). PPVT-R = Peabody Picture Vocabulary Test-Revised; SES = Socio-Economic Status; CDI= Child Depression Inventory.

Table 2. Mean subjective fear ratings and SCRs (Z-scores) during early and late conditioning and extinction for each group

	Conditioning				**Extinction**			
	Early		**Late**		**Early**		**Late**	
	CS+	**CS-**	**CS+**	**CS-**	**CS+**	**CS-**	**CS+**	**CS-**
Ratings, mean (SD)								
Low harsh parenting								
Low anxiety	2.00	1.52	1.83	1.16	1.56	1.14	1.34	1.11
	(1.14)	(0.68)	(1.06)	(0.26)	(0.94)	(0.26)	(0.64)	(0.25)
High anxiety	2.71	2.22	2.51	1.90	2.39	1.61	2.19	1.43
	(1.25)	(0.83)	(1.21)	(0.79)	(1.16)	(0.79)	(1.13)	(0.56)
High harsh parenting								
Low anxiety	2.27	1.81	2.06	1.53	1.89	1.42	1.70	1.41
	(1.14)	(0.85)	(1.17)	(0.75)	(0.99)	(0.78)	(0.84)	(0.78)
High anxiety	1.67	1.70	1.56	1.38	1.92	.40	1.45	1.34
	(0.61)	(0.68)	(0.74)	(0.56)	(1.09)	(0.64)	(0.83)	(0.60)
SCRs								
Low harsh parenting								
Low anxiety	0.20	-0.01	-0.07	-0.11	0.01	-0.04	0.09	-0.07
	(0.33)	(0.31)	(0.28)	(0.28)	(0.35)	(0.37)	(0.35)	(0.30)
High anxiety	0.25	-0.05	-0.05	-0.15	-0.05	0.09	0.00	-0.04
	(0.23)	(0.27)	(0.30)	(0.22)	(0.41)	(0.26)	(0.37)	(0.27)
High harsh parenting								
Low anxiety	0.23	-0.15	0.02	-0.10	0.01	-0.01	0.02	-0.02
	(0.45)	(0.26)	(0.35)	(0.37)	(0.36)	(0.27)	(0.35)	(0.33)
High anxiety	0.03	0.13	-0.02	-0.14	0.06	-0.08	0.11	-0.08
	(0.31)	(0.28)	(0.27)	(0.34)	(0.37)	(0.35)	(0.34)	(0.38)

Table 3. Peak voxels for contrast CS+ vs. CS- during conditioning

Region	Cluster size (voxels)	MNI coordinates x	y	z	F	FWE corrected p
Average effect of condition						
Left amygdala	60	-26	-6	-18	26.61	< .0001
Right amygdala	53	30	-4	-28	21.73	< .001
Left anterior hippocampus	209	-26	-14	-18	41.99	< .00001
Right anterior hippocampus	253	34	-18	-18	47.57	< .000001
Left insula	462	-36	-6	12	17.94	.01
Right insula	963	46	-16	12	31.10	< .001
Left BA24	43	-6	32	-6	17.75	< .01
Right BA 24	46	8	24	-6	28.63	<. 001
Left BA 32	301	-10	38	-10	41.31	< .00001
Right BA 32	278	6	44	-10	36.73	< .0001
Main effect of harsh parenting						
Left amygdala	33	-24	-4	-22	14.85	.005
Left anterior hippocampus	95	-26	-8	-20	15.79	.005
Right anterior hippocampus	36	36	-14	-16	11.52	.03

Cluster size at uncorrected p < .005. Coordinates at most significant peak for each region.

Table 4. Peak voxels for main effects of anxiety and harsh parenting (HP) * anxiety interaction for contrast CS+ vs. CS- during extinction

Region	Cluster size (voxels)	MNI coordinates			F	FWE corrected p
		x	y	z		
Average effect of condition						
Right BA 47	17	32	26	2	19.96	< .01
Left insula	117	-40	2	-4	17.41	.01
Right insula	461	40	0	-4	27.82	< .001
Early extinction only						
Average effect of condition						
Right BA 24	57	4	16	28	14.52	.03
Right BA 47	25	38	26	2	24.32	< .001
Left insula	195	-28	26	2	16.94	.02
Right insula	424	32	28	2	25.99	< .001
Main effect of anxiety						
Left BA 24	186	-12	10	36	17.95	.009
Right BA 24	233	6	16	32	16.84	.01
Right BA 32	341	4	18	34	17.51	.01
HP * Anxiety interaction						
Right BA 24	16	16	14	30	14.45	.04

Cluster size at uncorrected p < .005

Table 5. Peak voxels for groups comparisons for CS+ vs. CS- positive and negative PPI contrasts with left amygdala as seed region during conditioning

	Positive PPI					Negative PPI				
Region	**Cluster size (voxels)**	**MNI coordinates x y z**			**F**	**FWE corrected p**	**Cluster size (voxels)**	**MNI coordinates x y z**			**F**	**FWE corrected p**
Main effect of HP												
Left insula	110	-38	6	14	16.79	.02	47	-38	6	14	14.40	.04
Right insula	102	42	4	14	17.86	.02	83	42	0	14	17.05	.02
HP* Anxiety interaction												
Right BA 24	31	6	32	4	14.40	.04						

Cluster size at uncorrected p < .005

Table 6. Exploratory analyses: peak activation voxels to CS+ vs. baseline and CS- vs. baseline

	CS+ vs. baseline						CS- vs. baseline					
Region	**Cluster size (voxels)**	**MNI coordinates x y z**			**F**	**FWE corrected p**	**Cluster size (voxels)**	**MNI coordinates x y z**			**F**	**FWE corrected p**
Average effect of condition												
Left amygdala	37	-24	-8	-16	48.67	< .000001	22	-24	0	-12	60.33	< .000001
	11	-24	0	-12	30.79	< .0001	11	-24	-8	-16	14.94	< .01
Right amygdala	72	30	-4	-20	44.41	< .000001	23	32	-4	-20	20.23	< .01
Left ant. hippo.	195	-24	-12	-18	104.02	< .000001	152	-24	-12	-18	46.26	< .000001

Right ant. hippo.	256	24 -12 -18	83.40	< .000001	190	24 -12 -18	40.48	< .00001

in amygdalae and hippocampi during conditioning

Cluster size at uncorrected $p < .005$

Chapitre 3

Discussion générale

L'objectif principal de la présente thèse était de mieux comprendre les corrélats comportementaux, physiologiques, biologiques, sociaux et neuronaux du traitement de la peur chez les jeunes en bonne santé, en lien ou non avec un historique d'adversité et d'anxiété. Pour ce faire, nous avons d'abord examiné l'évolution longitudinale ainsi que les facteurs de risque des pratiques parentales coercitives entre l'âge de 17 mois et 6 ans. Nous avons ensuite investigué les influences du sexe des participants et du sexe des acteurs/actrices employés dans la constitution des stimuli émotionnels, sur le conditionnement et l'extinction de la peur, en termes de réponses comportementales et physiologiques, chez des jeunes en bonne santé physique et psychologique. Finalement, nous avons exploré les influences conjointes et individuelles des pratiques parentales coercitives et de l'anxiété non clinique sur les réponses comportementales, physiologiques et l'activité cérébrale durant le conditionnement et l'extinction de la peur, toujours chez des adolescents en bonne santé. Diverses conclusions peuvent être tirées de ces trois études.

3.1 Évolution et facteurs de risque des pratiques parentales coercitives de 17 mois à 6 ans

3.1.1 Évolution des pratiques parentales coercitives

3.1.1.1 Augmentation de la coercition maternelle de 17 à 42 mois

Les résultats de l'article 3 démontrent une évolution non-linéaire des pratiques parentales coercitives maternelles de la petite enfance à l'âge de 6 ans. Conformément à ce qui a été observé par d'autres équipes dans différentes études (Kim et al., 2010; Pierce et al., 2010; Windham et al., 2004), les pratiques parentales coercitives augmentent de façon graduelle entre 17 et 30 mois. Par ailleurs, cette augmentation se poursuit jusqu'à 42 mois, âge auquel la coercition maternelle atteint un plafond. Cette augmentation est probablement expliquée par le fait que les enfants, en grandissant, sont davantage en quête d'indépendance et deviennent plus

actifs physiquement (Kim et al., 2010; Windham et al., 2004), pouvant ainsi présenter davantage de comportements risqués et/ou inappropriés. Ceci requiert une surveillance et une discipline accrues de la part de la mère, qui peut en retour faire usage de stratégies plus coercitives afin de contrôler les comportements risqués, l'opposition et/ou les crises de l'enfant (Kim et al., 2010). Qui plus est, la perception qu'à la mère de son enfant peut se modifier à mesure que l'enfant acquiert autonomie et indépendance; la mère peut ainsi le considérer comme étant moins vulnérable et davantage responsable de son comportement qu'auparavant (Pierce et al., 2010).

3.1.1.2 Réduction de la coercition maternelle de 42 à 72 mois

À partir de 42 mois, une diminution de la fréquence des pratiques coercitives est observée; celle-ci est davantage prononcée entre 42 et 60 mois et se poursuit jusqu'à 72 mois. Cette réduction supporte les résultats obtenus par Mackenzie et ses collaborateurs (2013) démontrant une réduction du taux d'usage de la fessée entre 3 et 5 ans, et suggère que le déclin observé par Lansford et collaborateurs (2009) s'amorce dès l'âge de trois ans et demi. Ceci pourrait encore une fois illustrer une adaptation des stratégies maternelles face aux changements observés chez l'enfant. Ainsi, alors que leurs habiletés cognitives et langagières évoluent, les enfants deviennent davantage capables de raisonnement et d'abstraction (Lansford et al., 2009). Les mères peuvent ainsi diminuer l'usage de pratiques coercitives pour laisser place à des stratégies telles que le retrait, le raisonnement et les discussions, qui sont plus difficiles à employer avec des enfants plus jeunes. Il est important de souligner que les mères démontrant les niveaux de coercition les plus élevés à 42 mois sont celles qui ont les ont le plus réduits par la suite, ce qui suggère encore une fois la présence de stratégies d'adaptation et une certaine normalisation avec le temps.

3.1.2 Facteurs de risque des pratiques parentales coercitives

3.1.2.1 Facteurs de risque de niveaux élevés de coercition maternelle à 42 mois

Tel qu'attendu, des niveaux élevés de comportements extériorisés et intériorisés chez l'enfant à 17 mois, le fait que l'enfant soit un garçon, de même qu'un historique de dépression chez la mère, ont été associés à des niveaux accrus de coercition maternelle à l'âge de 42 mois, alors que des niveaux élevés d'efficacité maternelle étaient associés à une réduction de la coercition.

Ainsi, il est probable que les mères d'enfants agressifs et/ou opposants ressentent le besoin d'avoir recours à des stratégies disciplinaires coercitives, afin de contrôler les comportements inappropriés de leurs enfants (Bell & Chapman, 1986; Gershoff, 2002) et/ou en raison de sentiments de colère suscités par les comportements de l'enfant. Par ailleurs, la dépression chez l'enfant d'âge préscolaire peut s'exprimer par une agressivité et une irritabilité accrues (Belden, Thomson, & Luby, 2008; Luby et al., 2009), en plus d'être associée à des sentiments négatifs à l'égard de l'enfant (Laskey & Cartwright-Hatton, 2009), qui en retour sont associés à l'adoption de pratiques parentales coercitives.

En ce qui concerne le sexe de l'enfant, nos résultats sont compatibles avec un ensemble d'études effectuées chez des enfants de divers âges, qui suggèrent un usage de coercition accru à l'égard des garçons (Gershoff, 2002; Straus & Stewart, 1999). Le fait que nous n'ayons pas observé ces associations alors que les enfants étaient âgés de 5 mois (Boivin et al., 2005) peut s'expliquer par des différences développementales. Ainsi, il est probable que le sexe de l'enfant ne soit associé à des différences en termes de pratiques parentales qu'à partir d'un certain âge, auquel les différences sexuelles au plan du comportement deviennent plus marquées. De fait, il a été suggéré que les garçons sont davantage victimes de coercition en raison de la fréquence accrue de comportements problématiques tels que l'agressivité chez ces derniers (Gershoff, 2002). De même, l'adoption de stratégies éducatives différentes basées sur des croyances stéréotypées chez les parents, telles que le désir d'endurcir leurs enfants mâles, peut également moduler l'usage de coercition (Gershoff, 2002). Ces phénomènes sont

davantage observés alors que les enfants grandissent et deviennent plus indépendants et actifs, tel qu'observé durant la période de 17 à 72 mois.

Par ailleurs, l'augmentation des demandes d'indépendance et des crises normalement observée chez les jeunes enfants peut être particulièrement difficile à gérer pour les mères plus fragiles sur le plan psychologique, ce qui peut expliquer l'usage plus fréquent de pratiques parentales coercitives observé chez les mères ayant souffert de dépression (Lovejoy et al., 2000; Shay & Knutson, 2008; Windham et al., 2004). De façon similaire, les mères qui se perçoivent comme étant moins efficaces dans leurs interventions durant la petite enfance ont utilisé davantage de pratiques coercitives par la suite, tel qu'observé alors que ces enfants étaient âgés de 5 mois (Boivin et al., 2005; Pierce et al, 2010). De fait, les impressions d'une faible efficacité parentale peuvent entrainer des sentiments de frustration chez les mères et les amener à percevoir leurs enfants comme étant plus difficiles, ce qui, en retour, peut être associé à l'adoption de stratégies punitives (Bugental, Blue, & Cruzcosa, 1989; Halpern, Anders, Coll, & Hua, 1994; Huesmann, Moise-Titus, Podolski, & Eron, 2003). Au contraire, un fort sentiment d'efficacité maternelle semble constituer un facteur de protection contre l'adoption de ce genre de pratique.

3.1.2.2 Facteurs de risque associés à l'évolution de la coercition maternelle de 42 à 72 mois

En plus d'être associées à des niveaux élevés de coercition maternelle, les caractéristiques relatives à l'enfant ont toutes prédit de façon significative l'évolution longitudinale des pratiques parentales coercitives.

Ainsi, des niveaux élevés de comportements extériorisés chez l'enfant à l'âge de 17 mois étaient associés à un déclin quadratique moins prononcé entre 42 et 72 mois. Il a précédemment été observé, chez la même cohorte, que les enfants présentant les niveaux initiaux les plus élevés de comportements extériorisés à 17 mois sont ceux qui ont connu les augmentations les plus importantes par la suite et les niveaux moyens les plus élevés à l'âge de 42 mois (Tremblay et al., 2005). Il n'est donc pas surprenant que les mères de ces enfants soient aussi celles qui réduisent le moins leur usage de pratiques parentales coercitives.

De façon étonnante, les troubles intériorisés, bien qu'étant associés à des niveaux accrus de coercition maternelle à l'âge de 42 mois, ont aussi été associés à une augmentation moindre entre 17 et 42 mois et à un déclin plus prononcé à partir de 42 mois. Similairement à ce qui a été rapporté pour les troubles extériorisés, la fréquence et la sévérité des comportements intériorisés tend à augmenter de la petite enfance à l'âge préscolaire, et ceci est particulièrement vrai chez les enfants présentant les niveaux initiaux les plus élevés (Cote et al., 2009). Ceci suggère de manière indirecte que l'augmentation des comportements anxio-dépressifs chez l'enfant est associée à une réduction de l'emploi de pratiques parentales coercitives à travers le temps. Ceci pourrait refléter une modification des stratégies disciplinaires des mères face à la vulnérabilité perçue chez leurs enfants, dans une tentative de réduire l'anxiété grandissante chez ceux-ci.

Les mères de garçons ont aussi diminué leurs niveaux de pratiques parentales coercitives de manière plus prononcée que les mères de filles à partir de 42 mois, malgré le fait qu'elles présentaient aussi les niveaux les plus élevés à 42 mois. Une explication possible est que les mères de fillettes utilisaient déjà des niveaux très faibles et relativement stables de coercition à 42 mois, ce qui limite l'ampleur des diminutions potentielles. Les réductions abruptes chez les mères de garçons peuvent par ailleurs également refléter des adaptations et des changements dans les stratégies disciplinaires à partir de 42 mois, dans le but de gérer de manière plus efficace les comportements problématiques chez les garçons.

Finalement, les niveaux d'efficacité parentale perçue, bien que négativement associés aux niveaux de coercition à 42 mois, étaient aussi associés à un déclin moins abrupt entre 42 et 72 mois. Ceci est probablement expliqué par le fait que les mères présentant les niveaux les plus élevés d'efficacité parentale à 42 mois ont aussi présenté des niveaux très faibles et constants de pratiques parentales coercitives à travers le temps, limitant l'ampleur potentielle des réductions subséquentes.

3.1.3 Conclusions sur l'évolution et les facteurs de risque des pratiques parentales coercitives de 17 à 72 mois

Trois conclusions peuvent être tirées du troisième article constituant cette thèse. Premièrement, les pratiques parentales coercitives suivent une évolution non linéaire de la petite enfance à l'âge de 6 ans. Ainsi, une augmentation est initialement observée jusqu'à 42 mois; celle-ci est suivie d'une diminution, qui est plus prononcée entre 42 et 60 mois. Ensuite, les facteurs de risque relatifs à l'enfant, soit le sexe et les niveaux de comportements intériorisés et extériorisés, de même que les facteurs de risque maternels, soit un historique de dépression et l'efficacité parentale perçue, tels que mesurés à 17 mois, permettent de prédire les niveaux de coercition à 42 mois. Finalement, l'ensemble des facteurs de risque relatifs à l'enfant, ainsi que l'efficacité maternelle perçue, prédisent également l'évolution des pratiques parentales coercitives entre 17 et 72 mois. En revanche, les facteurs de risque familiaux, soit la satisfaction conjugale et la suffisance du revenu, ne sont associés ni aux niveaux moyens, ni à l'évolution de la coercition maternelle, suggérant que ces facteurs jouent un rôle moins important durant cette période développementale.

3.2 Conditionnement et extinction de la peur: effets du sexe des participants et du sexe des stimuli

3.2.1 Conditionnement et extinction de la peur : réponses subjectives équivalentes entre les garçons et les filles

Contrairement à notre hypothèse prédisant des niveaux subjectifs de peur plus élevés chez les filles par rapport aux garçons, aucune différence sexuelle n'a été observée en termes de réponses subjectives de peur durant le conditionnement et l'extinction de la peur dans

l'article 1. Bien que plusieurs études aient démontré des différences sexuelles dans le traitement de stimuli menaçants chez les jeunes et les adultes, d'autres rapportent des résultats contraires (pour revues voir Kret & De Gelder, 2012; McClure, 2000). Ceci suggère que les différences sexuelles sont en réalité modestes et peuvent être influencées par divers aspects méthodologiques (Kret & De Gelder, 2012; McCarthy & Konkle, 2005), tels que l'intensité des émotions véhiculées par les stimuli (Kret & De Gelder, 2012) ou la modalité de présentation de ces derniers (Herba et al., 2006). Par ailleurs, le fait que nos participants, âgés entre 10 et 16 ans, aient été évalués à différents stades du développement pubertaire et à différentes phases du cycle menstruel chez les filles, peut également, dans une certaine mesure, avoir masqué des différences sexuelles, puisqu'il a été démontré que ces facteurs peuvent moduler les réponses émotionnelles (Guapo et al., 2009; Kret & De Gelder, 2012; Little, 2013).

3.2.2 Conditionnement et extinction de la peur : les stimuli masculins perçus comme étant plus effrayants

En ce qui concerne le sexe des acteurs et actrices employés comme stimuli émotionnels, nos hypothèses ont été confirmées pour ce qui est des réponses subjectives de peur. Ainsi, les stimuli masculins ont suscité des niveaux subjectifs de peur plus élevés par rapport aux stimuli féminins, tant chez les filles que chez les garçons durant le conditionnement et l'extinction de la peur, similairement à ce qui a été observé chez l'adulte (Adams, Nelson, Soto, Hess, & Kleck, 2012; Becker et al., 2007; Kret & De Gelder, 2012; Navarrete et al., 2009; Ohman, 2009; Rotteveel & Phaf, 2004). Une résistance à l'extinction en termes de RÉDs a aussi été observée chez les garçons, lorsque confrontés à des stimuli masculins. Ces différences pourraient être attribuables, d'une part, à une physionomie masculine (p.ex. traits du visage anguleux et prononcés, sourcils plus épais) pouvant sembler davantage menaçante (Becker et al., 2007; Hess H., 1997) et, d'autre part, au fait que davantage de crimes violents sont perpétrés par des hommes, ce qui renforce encore une fois la

connotation menaçante des stimuli masculins (Becker et al., 2007; Daly, 1994; Dimberg, 1996; Kret & De Gelder, 2012).

3.2.3 Conditionnement et extinction de la peur : les stimuli féminins associés à une fréquence accrue de réactions physiologiques

D'un autre côté, bien que la magnitude des RÉDs soit équivalente entre les deux types de stimuli, le nombre de réponses significatives (i.e. supérieures à 0) était supérieur pour les visages féminins, relativement aux visages masculins. Ceci pourrait s'expliquer par le fait que les femmes sont souvent perçues comme étant davantage vulnérables et émotives en comparaison aux hommes, particulièrement dans un contexte de menace potentielle (Fisher, 1993; Friedman & Zebrowitz, 1992). Cette perception implicite et stéréotypée peut ainsi avoir suscité davantage de réactions physiologiques inconscientes et automatiques chez les participants. Cependant, ces résultats doivent être interprétés avec précaution, puisque cette mesure ne reflète pas la magnitude des réponses, mais seulement leur fréquence.

3.2.4 Conditionnement et extinction de la peur : interactions entre le sexe des participants et le sexe des stimuli émotionnels

3.2.4.1 Effets du « même sexe »

Contrairement à ce qui a été observé au plan des réponses subjectives, les réponses physiologiques de peur suggèrent plutôt un effet du « même sexe », caractérisé par des réponses de conditionnement différentiel (SC+ vs. SC-) face aux stimuli du même sexe que le participant, mais pas face aux stimuli du sexe opposé. Ainsi, les garçons ont présenté une augmentation des RÉDs face au SC+ vs. SC- lors du conditionnement et de l'extinction pour

les stimuli masculins uniquement, alors qu'un patron inverse a été observé chez les filles au conditionnement. Des résultats similaires ont précédemment été rapportés chez l'adulte (Armony & Sergerie, 2007; Doi, Amamoto, Okishige, Kato, & Shinohara, 2010; Kret & De Gelder, 2012; Mazurski, Bond, Siddle, & Lovibond, 1996; Suyama, Hoshiyama, Shimizu, & Saito, 2008) et pourraient être expliqués par les processus de socialisation dans l'enfance. Les enfants et les jeunes adolescents ont en effet tendance à fréquenter davantage de pairs du même sexe, ce qui peut en retour faciliter le décodage des émotions communiquées par les individus de même sexe (Cellerino, Borghetti, & Sartucci, 2004; McClure, 2000).

3.2.4.2 Effets du « sexe opposé»

En revanche, chez les jeunes ayant été conditionnés à des stimuli du sexe opposé, une absence de conditionnement différentiel a été observée, suggérant une généralisation des réponses de peur au SC- illustrée par des réponses équivalentes face aux deux stimuli (Dunsmoor, Prince, Murty, Kragel, & LaBar, 2011; Lissek et al., 2005). Une augmentation de la réactivité physiologique face aux visages d'un « autre groupe », soit un groupe social auquel l'individu ne s'identifie pas, en raison de différences sexuelles, ethniques ou sociodémographiques par exemple, a précédemment été observée (Aleman & Swart, 2008; Navarrete et al., 2009; Rotteveel & Phaf, 2004; van der Schalk et al., 2011). Celle-ci a été expliquée par des difficultés à discriminer les caractéristiques faciales de l'« autre groupe » par rapport aux individus du même groupe social, particulièrement lors de la communication d'une menace potentielle (Aleman & Swart, 2008; Navarrete et al., 2009; Rotteveel & Phaf, 2004; van der Schalk et al., 2011). Les expressions faciales neutres étant ambigües et pouvant être interprétées comme menaçantes (Cellerino et al., 2004; McClure, 2000), les effets du « sexe opposé » observés dans deux de nos groupes peuvent donc être dus à des difficultés à discriminer adéquatement les traits faciaux des visages neutres de sexe opposé. Encore une fois, ceci peut être attribué, du moins en partie, à des différences liées à la socialisation dans l'enfance. D'autre part, les jeunes se trouvaient dans une période de vie caractérisée par d'importants changements au plan neuronal, notamment au sein du cortex préfrontal (Blakemore, 2012; Kret & De Gelder, 2012; Lenroot & Giedd, 2010). Cette région jouant un rôle-clé dans le traitement et l'interprétation des stimuli socio-émotionnels, il n'est pas étonnant que des stimuli moins familiers (i.e. de sexe opposé), aient été moins bien

discriminés par un CPF en développement et aient donc été perçus comme étant également menaçants.

3.2.5 Influences du sexe sur le traitement de la peur chez les jeunes : conclusions

Trois conclusions peuvent être tirées de l'article 1. Premièrement, les visages masculins et féminins n'ont pas le même impact sur le conditionnement et l'extinction de la peur chez les jeunes, alors que les stimuli féminins suscitent des réponses de peur plus constantes et davantage comparables chez les garçons et les filles par rapport aux stimuli masculins. Deuxièmement, le sexe des participants et le sexe des stimuli émotionnels employés dans les tâches de conditionnement et d'extinction de la peur peuvent interagir et moduler les réponses de peur. Enfin, les réponses subjectives de peur ne sont pas nécessairement équivalentes aux réponses obtenues par des mesures plus objectives (telles que les RÉDs), suggérant que l'interprétation consciente de la connotation menaçante d'un stimulus ne correspond pas nécessairement aux réactions physiologiques automatiques face à celui-ci. Ces résultats soulèvent l'importance de porter une attention particulière au choix du sexe des stimuli émotionnels en fonction des questions auxquelles on souhaite répondre et des effets que l'on souhaite obtenir (p.ex. une résistance à l'extinction), d'utiliser des mesures de contrôle pour le sexe des participants (p. ex. s'assurer de l'équivalence entre les groupes) et d'utiliser les deux types de mesures afin d'obtenir un portrait plus complet des réponses de conditionnement et d'extinction de la peur chez une population jeune.

3.3 Conditionnement et extinction de la peur: effets des pratiques parentales coercitives et de l'anxiété

3.3.1 Pratiques parentales coercitives et conditionnement de la peur

3.3.1.1 Régulation altérée du lobe temporal médian

Tel qu'attendu, durant le conditionnement de la peur, des activations supérieures dans l'amygdale et l'hippocampe antérieur face au stimulus menaçant (SC+ vs SC-) ont été observées chez les jeunes ayant été élevés dans un contexte de pratiques parentales coercitives par rapport aux jeunes n'ayant pas été élevés dans un tel contexte. Cependant, ces différences étaient dues non pas à une hyperactivité temporale médiane chez le premier groupe, mais plutôt à une inhibition mieux ciblée de cette région chez le second, reflétée par des déactivations supérieures face au SC+ vs. SC-.

Ces déactivations pourraient être attribuables aux processus d'habituation rapide de l'amygdale, tel que précédemment démontré dans la littérature (Buchel et al., 1998; LaBar et al., 1998; Quirk et al., 1997). Elles pourraient également être expliquées par des niveaux d'activation de base particulièrement élevés, en raison de l'agitation suscitée par la procédure d'IRMf. Ceci expliquerait la réduction des déactivations observée avec le temps, au fur et à mesure que les participants sont devenus plus familiers avec le scanner et la tâche. Néanmoins, des analyses exploratoires démontrent la présence d'activations significatives face au SC+ (et au SC-) relativement aux niveaux de base dans certaines régions plus latérales de l'amygdale et de l'hippocampe antérieur, même si les différences de groupes n'ont été notées que dans les régions déactivées. Des études effectuées chez l'animal démontrent que l'amygdale peut se subdiviser en différentes régions, dont deux sont particulièrement impliquées dans les processus de conditionnement de la peur : les régions basolatérale et centromédiane (Duvarci & Pare, 2014). Via ses connexions avec le thalamus, les cortex somatosensoriels et les régions préfrontales, l'amygdale basolatérale reçoit et évalue l'information sensorielle, signale la nature menaçante d'un stimulus et module l'apprentissage de la peur (Davis & Whalen, 2001;

Duvarci & Pare, 2014; Jovanovic & Ressler, 2010; Pitkanen, Jolkkonen, & Kemppainen, 2000). De plus, par le biais de connexions excitatrices et inhibitrices, cette région peut également moduler l'activité de l'amygdale centromédiane (Duvarci & Pare, 2014). L'amygdale centromédiane est en retour responsable de l'expression de la peur, ainsi que de la modulation des ressources attentionnelles et de la vigilance (Boll, Gamer, Gluth, Finsterbusch, & Buchel, 2013; Duvarci & Pare, 2014). Bien qu'il soit impossible, dans la présente thèse, de délimiter de manière précise les différentes subdivisions de l'amygdale, en raison de contraintes méthodologiques liées à la résolution spatiale, nous pouvons supposer que les régions significativement activées par les SCs chez nos sujets font partie de l'amygdale basolatérale, alors que les régions déactivées appartiennent plutôt à l'amygdale centromédiane. Les déactivations observées dans cette région pourraient ainsi refléter les influences inhibitrices de l'amygdale basolatérale et d'autres régions de plus haut niveau telles que le CPFvm, qui était également activé chez l'ensemble de nos participants. Bien entendu, ces hypothèses demeurent spéculatives et d'autres études seront nécessaires pour les mettre à l'épreuve.

Par ailleurs, les connexions massives entre l'hippocampe et l'amygdale (Strange & Dolan, 2006) expliquent sans doute les déactivations également observées dans l'hippocampe antérieur. Des déactivations dans l'amygdale et/ou dans l'hippocampe ont été observées chez des individus psychiatriquement sains durant le traitement de stimuli menaçants (McClure et al., 2007; Petrovic, Carlsson, Petersson, Hansson, & Ingvar, 2004; Schneider et al., 1999; K. M. Thomas et al., 2001); il a été suggéré que celles-ci constituaient des mécanismes d'atténuation des réponses de stress face aux menaces (Petrovic et al., 2004). Ainsi, chez les participants présentant des niveaux faibles de coercition maternelle, ces mécanismes semblent cibler de façon spécifique le stimulus signalant une menace (i.e. le SC+), alors que cela n'est pas le cas chez les participants ayant un historique de coercition élevée. Ces résultats sont compatibles avec ceux de Mclaughlin et ses collaborateurs (2015), qui ont récemment rapporté une réduction de la différentiation SC+/SC- en termes de RÉDs chez des jeunes victimes de maltraitance. Cette réduction était en retour associée à des niveaux accrus de symptômes extériorisés. Un historique de pratiques parentales coercitives pourrait donc prédisposer les jeunes à des risques accrus de psychopathologie non seulement en raison d'une

hypersensibilité face aux menaces, mais également en raison d'une suppression moins ciblée des réponses de peur et/ou d'une modulation moins efficace de l'attention face aux menaces.

Par ailleurs, des hypoactivations hippocampiques ont récemment été associées à une augmentation des symptômes anxieux durant l'exécution de tâches anxiogènes chez des jeunes exposés à des évènements traumatiques, alors que cela n'était pas le cas chez les jeunes du groupe contrôle (Elsey et al., 2015). Il a été suggéré que ces déactivations seraient liées à un émoussement émotionnel chez les participants traumatisés, consécutif à une exposition répétée au stress (Elsey et al., 2015). Ainsi, une atténuation des réponses temporales médianes pourrait refléter des mécanismes adaptatifs face aux menaces chez les participants dont les mères n'exercent pas de pratiques parentales coercitives, alors qu'elle pourrait être néfaste chez les jeunes ayant un historique d'adversité.

3.3.1.2 Réduction de la connectivité fonctionnelle amygdale-insula

Durant le conditionnement de la peur, une réduction de la connectivité fonctionnelle amygdale-insula face au SC+ vs SC- a aussi été observée chez les participants dont les mères exercent des niveaux élevés de pratiques parentales coercitives. Des résultats similaires ont été rapportés chez des patients anxieux ou dépressifs, ainsi que chez des individus présentant des traits de névrotisme élevés (Aghajani et al., 2014; Etkin et al., 2009; Perlman et al., 2012; Zeng et al., 2012) et pourraient témoigner de processus déficitaires d'intégration des émotions générées par l'amygdale au traitement émotionnel conscient réalisé par l'insula (Perlman et al., 2012). Par ailleurs, l'insula est largement connectée à diverses structures sous-corticales et corticales, incluant le CPFvm et le GCAsg (Simmons et al., 2013). Une réduction de la connectivité amygdale-insula pourrait ainsi indirectement nuire à la régulation des réponses de l'amygdale face au SC+, par le biais d'une conscience lacunaire des états émotionnels résultant en une communication appauvrie de ces derniers au CPFvm/GCAsg.

3.3.2 Anxiété et extinction de la peur

3.3.2.1 Activation accrue du GCA dorsal

Contrairement à ce qui était attendu, nous n'avons pas observé d'activations persistantes au niveau du lobe temporal médian chez les participants plus anxieux durant l'extinction. Cependant, durant la première partie de cette phase, des activations accrues du GCAd face au SC+ vs. SC- ont été observées chez ces jeunes, relativement aux jeunes moins anxieux. Le GCAd est impliqué dans les réactions émotionnelles conscientes face aux menaces telles que les affects négatifs, la communication de la peur à autrui et les réactions physiologiques conséquentes à ces réactions (Barbas, 2009; Shackman et al., 2011) et jouerait également un rôle dans les réponses aux SI et SC (Milad & Quirk, 2012). L'activation accrue du GCAd durant l'extinction reflète donc probablement l'état d'agitation émotionnelle consciente accrue chez les participants plus anxieux, malgré l'absence d'activation temporale médiane.

3.3.3 Interactions des pratiques parentales coercitives et de l'anxiété durant le conditionnement et l'extinction de la peur

3.3.3.1 Évaluations subjectives de peur durant le conditionnement et l'extinction

Des niveaux équivalents de conditionnement différentiel ont été observés entre les deux niveaux d'anxiété, au plan comportemental, physiologique et neuronal. Des réponses subjectives de peur accrues face au stimulus neutre (SC-) ont aussi été observées chez les participants présentant des niveaux d'anxiété élevés relativement aux jeunes présentant des niveaux faibles d'anxiété. Ces résultats suggèrent une généralisation des réponses de peur au

stimulus neutre, tel qu'observé précédemment dans la littérature chez les individus anxieux et tel que prédit par nos hypothèses (Lissek et al., 2005). Par ailleurs, ces différences étaient principalement dues aux groupes de jeunes élevés par des mères non coercitives. Dans ce contexte, des niveaux élevés d'anxiété ont aussi été associés à une augmentation globale des réponses de peur durant le conditionnement et l'extinction de la peur, de même qu'à une résistance à l'extinction, suggérant une difficulté à distinguer les stimuli représentant une menace des stimuli sécurisants, tel qu'observé précédemment chez les individus anxieux (Lissek, 2012; Lissek et al., 2005; Lissek et al., 2010; Lissek et al., 2009; Milad & Quirk, 2012). Dans un contexte de pratiques parentales coercitives élevées, en revanche, aucune différence n'a été observée entre les différents niveaux d'anxiété en termes d'évaluations subjectives de peur. Ceci suggère que l'anxiété liée à un historique d'adversité constitue un phénotype unique se manifestant de manière différente à l'anxiété d'une autre origine.

3.3.3.2 Connectivité fonctionnelle amygdale-GCA rostral durant le conditionnement

Des interactions entre les pratiques parentales coercitives et les niveaux d'anxiété ont aussi été observées en termes de connectivité fonctionnelle durant le conditionnement. Ainsi, chez les jeunes ayant des mères non coercitives, des niveaux élevés d'anxiété étaient associés à une connectivité fonctionnelle réduite entre l'amygdale et le GCA rostral (GCAr) au niveau périgénual, alors que des résultats opposés (i.e. une connectivité accrue chez les plus anxieux) ont été observés chez les jeunes élevés dans un contexte de pratiques parentales coercitives. Une connectivité amygdale-GCA réduite pourrait constituer un facteur de risque du développement d'un trouble anxieux, tel qu'observé chez l'adulte (Birn et al., 2014; Burghy et al., 2012; Etkin et al., 2010; Fan et al., 2014; Hahn et al., 2011; Herringa et al., 2013; Hilbert, Lueken, & Beesdo-Baum, 2014; Klumpp, Angstadt, & Phan, 2012; Pannekoek et al., 2013). Cependant, cette hypothèse parait contradictoire avec les résultats observés chez les jeunes vivant dans un contexte de pratiques parentales coercitives (C-É/anx-É).

Une explication potentielle est qu'une augmentation de la connectivité fonctionnelle positive entre l'amygdale et le GCAr ne soit pas nécessairement bénéfique, surtout dans un contexte d'adversité. Une récente revue de la littérature a de ce fait souligné le rôle spécifique

de la partie rostrale du GCA dans des dimensions cognitives de l'anxiété telles que l'évaluation consciente des menaces potentielles, les inquiétudes et la tendance à la « catastrophisation » (Kalisch & Gerlicher, 2014). Ainsi, une connectivité réduite chez les deux groupes porteurs d'un seul facteur de risque (i.e. (C-É/anx-F et C-F/anx-É) pourrait constituer un mécanisme de protection permettant de prévenir l'émergence d'un trouble anxieux chez ces jeunes. Ce dernier ne serait pas présent chez les jeunes du groupe C-É/anx-É, qui seraient de ce fait particulièrement à risque de développer un trouble anxieux dans le futur.

Une explication alternative est celle d'un impact différent de la connectivité fonctionnelle amygdale-GCAr selon l'historique de pratiques parentales coercitives, en raison des différences observées au plan du fonctionnement de l'amygdale. Ainsi, dans la mesure ou l'amygdale est régulée de façon adéquate, tel qu'observé dans un contexte de pratiques parentales non coercitives, une connectivité amygdale-GCAr accrue est associée à une réduction de l'anxiété, alors que dans un contexte de coercition élevée, où l'amygdale est moins bien régulée, une connectivité accrue pourrait mener vers une augmentation des inquiétudes et de la dramatisation et être ainsi associée à une augmentation des niveaux d'anxiété.

3.3.3.3 Réponses du GCA dorsal durant l'extinction

En dehors des différences générales liées à l'anxiété observées durant la première partie de l'extinction, des interactions entre les niveaux de pratiques parentales coercitives et d'anxiété ont aussi été observées au sein d'une sous-section du GCAd durant cette phase. Ainsi, chez les participants élevés sans coercition maternelle, des niveaux élevés d'anxiété ont été associés à des activations accrues face au SC+ vs SC-, alors que des résultats opposés ont été observés chez les participants élevés par des mères coercitives (i.e. des activations réduites du GCAd chez les plus anxieux). Des activations accrues du GCAd ont été rapportées chez les individus atteints d'un trouble anxieux non relié à un historique d'adversité (i.e. phobie spécifique), probablement en lien avec une augmentation des réponses cognitives de peur (Etkin & Wager, 2007). En revanche, chez les individus atteints de TSPT, des hypoactivations du GCAd ont plutôt été observées de façon récurrente (Etkin & Wager, 2007). Les auteurs ont

suggéré que puisque le GCAd peut faciliter le déclenchement des mécanismes de régulation émotionnelle du GCAsg, en élicitant les réponses de peur, une réduction de son activité peut ainsi entraver les processus régulateurs et pourrait expliquer l'émoussement affectif souvent observé chez les individus atteints de TSPT (Etkin & Wager, 2007). Ainsi, dans un contexte d'adversité précoce et chronique tel que des pratiques parentales coercitives, l'hypoactivation du GCAd pourrait être associée à une pauvre régulation émotionnelle, alors que dans un contexte de faible adversité, c'est plutôt l'hyperactivation du GCAd qui témoignerait de difficultés d'autorégulation.

3.3.4 Absence de différences d'activation du CPFvm durant l'extinction (et le conditionnement) de la peur

Contrairement à ce qui était attendu, aucune différence associée aux pratiques parentales coercitives ou à l'anxiété n'a été observée en termes d'activité préfrontale médiane. Ceci est contraire aux résultats d'études effectuées chez l'adulte anxieux et/ou à haut risque d'anxiété durant le conditionnement et l'extinction de la peur (Barrett & Armony, 2009; Bremner et al., 2005; Erhardt & Spoormaker, 2013; Indovina et al., 2011; Lissek, 2012; Milad, Goldstein, et al., 2006; Milad & Quirk, 2012; Sehlmeyer et al., 2011). Une explication possible est que l'absence de différences dans l'activité du CPFvm/GCAsg soit le reflet de différences développementales par rapport aux échantillons d'adultes étudiés dans les études précédentes, chez qui, contrairement à nos jeunes, le développement préfrontal était terminé (Gogtay et al., 2004). Des différences à ce niveau pourraient ainsi n'émerger qu'ultérieurement. Par ailleurs de récentes études employant des tâches autres que le conditionnement et l'extinction de la peur rapportent une hyperactivité préfrontale chez des jeunes ayant vécu sous des conditions hautement aversives (i.e. la maltraitance et la négligence émotionnelle) (Elsey et al., 2015; Mueller et al., 2010), ce qui suggère que le type de paradigme employé, de même que le niveau de sévérité de l'adversité vécue, pourraient également jouer un rôle dans les différences d'activation observées au sein du CPFvm.

3.3.5 Influences des pratiques parentales coercitives et de l'anxiété sur le traitement de la peur chez les jeunes : conclusions

Trois principales conclusions peuvent être tirées de l'article 2. En premier lieu, l'adversité, sous la forme de pratiques parentales coercitives, influence de manière spécifique le fonctionnement du lobe temporal médian, de même que les interactions entre ce dernier et l'insula, durant le conditionnement de la peur chez les jeunes en bonne santé physique et psychologique. En revanche, durant la première partie de l'extinction de la peur, les niveaux d'anxiété exercent une influence spécifique sur les réponses du GCA dorsal. Plus intéressant encore, les pratiques parentales coercitives et l'anxiété peuvent également interagir et viennent moduler les différences de connectivité fonctionnelle entre l'amygdale et le GCA rostral durant le conditionnement, l'activation d'une sous-région du GCAd durant l'extinction, de même que les réponses subjectives de peur durant les deux phases, suggérant que l'anxiété associée à un historique d'adversité représente un phénotype distinct à l'anxiété d'une autre origine.

3.4 Conditionnement et extinction de la peur chez les jeunes en bonne santé : conclusions générales

3.4.1 Différences entre les mesures subjectives et objectives

De façon générale, deux constats émergent des deux premières études constituant cette thèse. Premièrement, les deux mesures dépendantes du conditionnement employées dans ces études, soit les réponses électrodermales et les évaluations subjectives de peur, ne mènent pas nécessairement à des résultats équivalents. Il n'est pas rare de retrouver ce genre de différence

durant le conditionnement et l'extinction de la peur (p.ex. Gazendam et al., 2013; Liberman et al., 2006; Tzschoppe et al., 2014; Waters et al., 2009; Waters et al., 2014). En effet, les réponses physiologiques sont des réponses inconscientes et automatiques suscitées d'abord par l'amygdale, qui permet un traitement rapide de l'information qui est ensuite transmise au thalamus par des connections descendantes (LeDoux, 2014; Ohman, Carlsson, Lundqvist, & Ingvar, 2007). Les évaluations subjectives de peur représentent en revanche un traitement conscient réalisé par les régions préfrontales (LeDoux, 2014). Il est ainsi possible que des différences émergent entre, d'une part, des réponses automatiques et incontrôlables et, d'autre part, des réponses conscientes et davantage sujettes à la désirabilité sociale. De fait, dans la deuxième étude, une résistance subjective à l'extinction est observée dans les deux groupes démontrant une activation accrue du GCAd, alors qu'en termes de RÉDs, l'extinction a lieu chez l'ensemble des participants, conformément à l'absence globale d'activation temporale médiane observée.

3.4.2 Absence d'extinction des réponses de peur chez certains jeunes

Ceci nous amène au deuxième constat, soit la présence d'une résistance à l'extinction au plan subjectif chez certains groupes dans chacune des études. Dans la première étude, cette résistance a été observée exclusivement pour les stimuli masculins, suggérant que ce type de stimulus engendre des réponses davantage persistantes par rapport aux stimuli féminins. Par contre, dans la deuxième étude, employant des stimuli féminins uniquement, une résistance à l'extinction a de nouveau été observée chez deux groupes. Tel que mentionné précédemment, des réponses persistantes de peur durant l'extinction sont fréquemment retrouvées chez les individus anxieux (Britton et al., 2011; Milad & Quirk, 2012), ce qui peut expliquer certains résultats de la deuxième étude. Cependant, il faut préciser que tous les jeunes étaient en bonne santé psychologique (les niveaux d'anxiété étant sous-cliniques) et que l'absence d'extinction a aussi été observée chez l'un des groupes de jeunes faiblement anxieux, ce qui suggère que d'autres facteurs pourraient aussi être impliqués.

Alors qu'une réduction significative des réponses de peur face au SC+ vs. SC- est typiquement observée durant l'extinction chez l'adulte (pour revues de la littérature voir Delgado et al., 2006; Dimberg, 1996; Jovanovic, Nylocks, & Gamwell, 2013; Ohman, 2009; Sehlmeyer et al., 2009), une absence d'extinction a précédemment été rapportée chez les jeunes conditionnés à l'aide de tâches très similaires à la tâche employée dans la présente thèse (Haddad, Lissek, Pine, & Lau, 2011; Lau et al., 2008). Cette résistance pourrait s'expliquer par une certaine désirabilité sociale qui pourrait être plus importante durant cette période de bouleversements aux plans social et affectif qu'est l'adolescence (Casey et al., 2010; Silvers et al., 2012), et par l'impression chez certains jeunes de devoir continuer à évaluer le SC+ comme étant plus effrayant, malgré l'absence de peur ressentie. Cependant, dans la première étude, une résistance à l'extinction a aussi été observée en termes de RÉDs, qui sont des réponses automatiques et inconscientes (LeDoux, 2014; Ohman et al., 2007) qui ne sont pas sujettes à la désirabilité sociale.

L'absence d'extinction retrouvée dans certains groupes pourrait aussi être expliquée par des considérations méthodologiques. En effet, l'utilisation de ratios d'appariement SC+/SI partiels tel que dans le cadre de la présente thèse (i.e. 50%) a été associée à une vitesse ralentie d'extinction des réponses (Mackintosh, 1974). Néanmoins, d'autres études employant des ratios de contingence plus élevés (i.e. 75-100%) ont aussi rapporté une résistance à l'extinction chez des participants jeunes (Lau et al., 2008; Neumann, Waters, Westbury, & Henry, 2008; Pattwell et al., 2012; Pattwell, Lee, & Casey, 2013).

Une troisième hypothèse permettant d'expliquer la résistance à l'extinction observée chez certains jeunes est celle de différences développementales par rapport aux adultes au plan du traitement des émotions, tel que suggéré par de récentes études effectuées chez l'humain et l'animal (Li, Kim, & Richardson, 2012; Pattwell et al., 2012; Pattwell et al., 2013). Ainsi, chez les adolescents, le développement cérébral se caractérise par un lobe temporal médian mature mais par un CPF en développement, contrairement aux adultes chez qui les deux systèmes ont atteint la maturité (Gogtay et al., 2004). Le débalancement développemental entre les structures limbiques et le CPF pourrait ainsi empêcher une régulation optimale de l'amygdale par le CPF durant l'extinction et donner lieu à des réponses de peur persistantes chez certains jeunes (Casey et al., 2010; Gogtay & Thompson, 2010; Pattwell et al., 2013). Qui plus est,

bien que des activations aient été observées au sein du CPF ventral chez l'ensemble des participants durant l'extinction, nous n'avons pas observé d'activations globales et/ou de différences de groupe au niveau du GCA subgénual, site spécifiquement impliqué dans l'extinction de la peur chez l'adulte (Milad & Quirk, 2012), ce qui pourrait encore une fois être le reflet de différences développementales.

3.5 Implications pour les interventions

Les résultats des deux dernières études de la présente thèse sont particulièrement intéressants d'un point de vue interventionniste. La deuxième étude démontre que les pratiques parentales coercitives et l'anxiété chronique sont non seulement associées de façon individuelle à des différences dans le traitement de la peur, mais peuvent également interagir. Ainsi, l'anxiété associée à un historique d'adversité pourrait constituer un phénotype distinct des manifestations anxieuses d'une différente étiologie, telle que le bagage génétique, par exemple. Ceci souligne l'importance de considérer ces deux facteurs lors de la planification d'interventions chez les jeunes anxieux, puisque les mécanismes neuronaux sous-jacents peuvent différer en fonction de l'historique d'adversité.

Parmi les différentes interventions visant à traiter les troubles anxieux pédiatriques, les thérapies par exposition figurent au premier plan (James, James, Cowdrey, Soler, & Choke, 2013; Walkup et al., 2008). Ces interventions reposent sur les principes d'extinction des réponses de peur suite à la présentation répétée des stimuli évocateurs d'anxiété (Craske, Kircanski, et al., 2008) et ont pour prémisse que la persistance de l'anxiété est liée, du moins en partie, à des mécanismes inefficaces d'extinction de la peur (Beesdo et al., 2007; Pine et al., 2009). Or, bien que ce type de traitement s'avère efficace pour la majorité, environ 40% des jeunes n'observent pas d'amélioration significative de leurs symptômes suite au traitement et d'autres expérimentent un retour des symptômes après un certain temps (Kendall, Hudson, Gosch, Flannery-Schroeder, & Suveg, 2008; Walkup et al., 2008; Wood, Piacentini, Southam-Gerow, Chu, & Sigman, 2006). Ainsi, des différences dans les mécanismes cérébraux associés aux symptômes anxieux, en fonction de l'historique d'adversité, pourraient possiblement expliquer pourquoi certains jeunes répondent de façon favorable au traitement, alors que

d'autres demeurent symptomatiques. Par exemple, nous avons observé que des niveaux élevés d'anxiété sont associés à des réponses subjectives de peur persistantes à une activité accrue du GCAd durant l'extinction, mais uniquement chez les jeunes sans historique de pratiques parentales coercitives, alors qu'une réduction de l'activité du GCAd est plutôt observée chez les jeunes anxieux et ayant un historique d'adversité. Les thérapies par exposition standard s'avèreraient donc probablement plus efficaces pour le premier groupe de jeunes. En revanche, les réductions de la différenciation SC+/SC- dans le lobe temporal médian et de la connectivité fonctionnelle avec l'insula observées chez les jeunes victimes de coercition, suggèrent un certain émoussement émotionnel face aux menaces; celui-ci se poursuit à l'extinction pour les plus anxieux, chez qui des réductions de l'activité du GCAd sont observées. Cet émoussement pourrait en retour être associé à des difficultés comportementales, tel que démontré dans une récente étude (McLaughlin, Sheridan, et al., 2015). Des interventions ciblant de manière plus spécifique à réduire les mécanismes d'évitement de la peur et favorisant une meilleure conscience des états émotionnels pourraient ainsi s'avérer plus adéquates pour traiter l'anxiété chez ces jeunes. De fait, de récentes études ont démontré l'utilité de cibler de manière spécifique les mécanismes d'évitement de la peur dans le traitement du TSPT chez l'adulte (Andersen, Ravn, & Roessler, 2015; Dunne, Kenardy, & Sterling, 2012).

D'autre part, il ne faut pas oublier que les jeunes ayant été victimes de coercition maternelle, mais ne présentant pas des niveaux élevés d'anxiété, pourraient également être à risque de psychopathologie future, puisque des différences dans l'activité des structures limbiques ont aussi été observées. Des interventions préventives, s'adressant davantage aux mères, pourraient s'avérer bénéfiques pour les jeunes de ce groupe.

À cet effet, les résultats de la troisième étude suggèrent que des facteurs de risque mesurés dès la petite enfance permettent de prédire les niveaux ultérieurs et l'évolution de la coercition maternelle. Ainsi, bien qu'il soit difficile, voire parfois impossible d'agir sur certains facteurs tels que le sexe de l'enfant ou la suffisance du revenu, identifier les familles à risque et intervenir sur les facteurs de risque et de protection malléables pourrait permettre de prévenir, ou du moins, de diminuer l'emploi de ce genre de pratique chez les mères. Par exemple, nous avons observé que les mères ayant un historique de dépression ont plus souvent tendance à adopter ce type de pratique, soulevant l'importance d'apporter un support

psychologique et social aux mères plus psychologiquement fragiles. De plus, en aidant les mères à augmenter leur sensibilité à l'égard de l'enfant et leurs sentiments d'efficacité parentale, et en leur enseignant à mieux gérer les comportements agressifs et opposants de leurs enfants durant la petite enfance, et en travaillant à améliorer la relation-mère enfant, il est possible de réduire leur usage de coercition à l'âge préscolaire et par la suite. En effet, il a été démontré que le fait d'offrir de l'information et du support aux mères a un impact positif sur leurs compétences parentales, leur efficacité et leur bienêtre psychologique et permet de réduire l'usage de pratiques coercitives et punitives (Durrant & Ensom, 2012).

Par ailleurs, nos résultats suggèrent une certaine volonté et des efforts chez les mères hautement coercitives d'adapter leurs stratégies disciplinaires et de réduire leurs niveaux de coercition avec le temps. Cela est particulièrement le cas chez les mères d'enfants présentant des niveaux élevés de symptômes anxio-dépressifs, ce qui suggère une certaine sensibilité chez les mères face à la détresse de leur enfant. Néanmoins, ces réductions n'ont pas été observées chez les mères d'enfants plus agressifs et opposants, qui avaient plutôt tendance à maintenir des niveaux élevés de coercition après 42 mois. Il est donc important d'intervenir auprès de ces familles qui sont particulièrement à risque et chez qui la coercition maternelle pourrait potentiellement se transformer en abus physique (Gershoff, 2002; Straus, 2000).

3.6 Limites et perspectives futures

Les études présentées dans le cadre de cette thèse comportent bien évidemment certaines limites. Une première limite de l'étude 1 est le fait que nous n'ayons pas évalué le stade pubertaire chez nos jeunes participants, de même que la phase du cycle menstruel et/ou la prise de contraceptifs oraux chez les filles. Ces facteurs pourraient moduler les différences sexuelles lors du conditionnement et de l'extinction de la peur tel qu'observé chez l'adulte (Merz, Stark, Vaitl,Tabbert, & Wolf, 2013; Merz et al., 2012; Milad et al., 2006; Zeidanet al., 2011) et devraient être pris en compte dans de futures études. Nous n'avons pas non plus évalué de façon objective la présence de psychopathologie chez les participants, de même que l'historique d'anxiété et d'adversité. Ces facteurs, tel que démontré de façon extensive dans les diverses sections de cette thèse, peuvent aussi avoir influencé les réponses subjectives et

objectives de peur chez nos participants et devraient également être mieux contrôlés dans les études ultérieures.

En ce qui concerne les deux dernières études, une des principales limites est l'utilisation de mesures auto-rapportées des pratiques parentales coercitives. Les mères peuvent ainsi avoir sous-estimé leur usage de coercition, ce type de mesure étant particulièrement sujet à la désirabilité sociale (Boivin et al., 2005). Dans un même ordre d'idées, les différents facteurs de risque de l'étude 3 ont aussi été évalués exclusivement par les mères, ce qui pourrait entrainer des problèmes de variance commune. De plus, les mères peuvent avoir sous ou surévalué les difficultés comportementales et psychologiques chez leurs enfants et/ou leurs propres symptômes dépressifs (Briggs-Gowan, Carter, & Schwab-Stone, 1996). Il faut cependant préciser que les questionnaires utilisés dans le cadre de la présente thèse ont tous démontré des propriétés psychométriques satisfaisantes (Behar & Stringfield, 1974; Birmaher et al., 1997; Boivin et al., 2005; Tremblay, Desmarais-Gervais, Gagnon, & Charlebois, 1987) et ont été employés de manière efficace dans des études précédentes (e.g., Boivin et al., 2005; Boyle et al., 2004; Cote et al., 2009; Guimond et al., 2012; Pierce et al., 2010; Tremblay et al., 2004; Vitaro, Barker, Boivin, Brendgen, & Tremblay, 2006). Néanmoins, les études subséquentes devraient utiliser des mesures complémentaires et plus objectives de la coercition maternelle et des autres variables étudiées, telles que les observations d'une tierce personne et/ou des questionnaires adressés à aux enfants, dans la mesure où ces derniers possèderaient la maturité suffisante pour y répondre. Elles devraient également mesurer les niveaux de coercition paternelle, ainsi que les facteurs de risque associés.

Une autre limite importante concernant la deuxième étude est l'absence d'évaluation des antécédents psychiatriques familiaux chez nos participants. Il a été démontré que le bagage génétique peut influencer le développement de l'anxiété (Casey et al., 2011) et le fonctionnement du circuit neuronal de la peur (Redlich et al., 2015) et peut interagir avec des conditions d'adversité vécue tôt dans la vie (E. McCrory et al., 2011; Redlich et al., 2015). Cette limite devrait être contournée dans les études futures, en ajoutant des mesures de psychopathologie parentale actuelle et antérieure.

Toujours par rapport à l'étude 2, il est important de spécifier que tous les participants étaient en bonne santé psychologique, les niveaux d'anxiété étant tous sous-cliniques, ce qui limite la portée des interprétations quant à la valeur prédictive des différences observées au plan du fonctionnement cérébral sur le développement ultérieur d'une psychopathologie. Il serait nécessaire de suivre les jeunes de manière longitudinale jusqu'à l'âge adulte, afin d'identifier ceux qui développeront un trouble anxieux et/ou tout autre forme de psychopathologie et d'ainsi mettre à l'épreuve le pouvoir prédictif des différences observées au niveau cérébral. Des études cliniques effectuées chez les jeunes chez qui les niveaux d'anxiété atteindront un seuil clinique seront aussi nécessaires, afin de déterminer si l'historique d'adversité aura ou non un impact sur l'issue des interventions.

3.7 Conclusions

Les résultats des études présentées dans le cadre de la présente thèse soulèvent trois conclusions importantes. Dans un premier temps, nous avons démontré que les pratiques parentales coercitives suivent une évolution non linéaire de la petite enfance à l'âge de six ans et que certains facteurs relatifs à l'enfant, notamment les niveaux d'anxiété, et à la mère, permettent de prédire leurs niveaux et leur évolution. Nous avons ensuite démontré, pour une première fois, que le sexe des participants, ainsi que le sexe des acteurs constituant les stimuli émotionnels, influencent les réponses subjectives et physiologiques durant le conditionnement et l'extinction de la peur chez les jeunes. Cette étude nous a permis d'établir une méthodologie solide afin de réaliser la troisième étude, qui nous a permis de démontrer que les historiques d'adversité et d'anxiété chroniques sont associées à des différences dans le traitement de la peur, au plan subjectif, physiologique et cérébral. Ainsi, non seulement l'anxiété et les pratiques parentales coercitives s'influencent l'une l'autre, mais elles interagissent tout au long de l'enfance, modulent le traitement de la peur et peuvent mener à des profils phénotypiques distincts au plan cérébral. Ces résultats ajoutent une pièce au casse-tête des neurosciences développementales et fournissent des pistes intéressantes pour le choix et le développement d'interventions plus efficaces et mieux ciblées.

Bibliographie

Adams, R. B., Jr., Nelson, A. J., Soto, J. A., Hess, U., & Kleck, R. E. (2012). Emotion in the neutral face: a mechanism for impression formation? *Cogn Emot, 26*(3), 431-441. doi: 10.1080/02699931.2012.666502

Aghajani, M., Veer, I. M., van Tol, M. J., Aleman, A., van Buchem, M. A., Veltman, D. J., . . . van der Wee, N. J. (2014). Neuroticism and extraversion are associated with amygdala resting-state functional connectivity. *Cogn Affect Behav Neurosci, 14*(2), 836-848. doi: 10.3758/s13415-013-0224-0

Aguado, L., Garcia-Gutierrez, A., & Serrano-Pedraza, I. (2009). Symmetrical interaction of sex and expression in face classification tasks. *Atten Percept Psychophys, 71*(1), 9-25. doi: 71/1/9 [pii]10.3758/APP.71.1.9

Aleman, A., & Swart, M. (2008). Sex differences in neural activation to facial expressions denoting contempt and disgust. *PLoS One, 3*(11), e3622. doi: 10.1371/journal.pone.0003622

Andersen, T. E., Ravn, S. L., & Roessler, K. K. (2015). Value-based cognitive-behavioural therapy for the prevention of chronic whiplash associated disorders: protocol of a randomized controlled trial. *BMC Musculoskelet Disord, 16*, 232. doi: 10.1186/s12891-015-0687-y

Armony, J. L., & Sergerie, K. (2007). Own-sex effects in emotional memory for faces. *Neurosci Lett, 426*(1), 1-5. doi: S0304-3940(07)00886-5[pii]10.1016/j.neulet.2007.08.032

Atzaba-Poria, N., & Pike, A. (2008). Correlates of parental differential treatment: parental and contextual factors during middle childhood. *Child Dev, 79*(1), 217-232. doi: CDEV1121 [pii]10.1111/j.1467-8624.2007.01121.x

Banihashemi, L., Sheu, L. K., Midei, A. J., & Gianaros, P. J. (2015). Childhood physical abuse predicts stressor-evoked activity within central visceral control regions. *Soc Cogn Affect Neurosci, 10*(4), 474-485. doi: 10.1093/scan/nsu073

Barbas, H. (2009). Prefrontal Cortex: Structure and Anatomy *Encyclopedia of Neuroscience* (Vol. 7, pp. 909-918). Oxford: Academic Press.

Barrett, J., & Armony, J. L. (2009). Influence of trait anxiety on brain activity during the acquisition and extinction of aversive conditioning. *Psychol Med, 39*(2), 255-265. doi: 10.1017/S0033291708003516

Becker, D. V., Kenrick, D. T., Neuberg, S. L., Blackwell, K. C., & Smith, D. M. (2007). The confounded nature of angry men and happy women. *J Pers Soc Psychol, 92*(2), 179-190. doi: 2007-00654-002 [pii]10.1037/0022-3514.92.2.179

Beesdo, K., Bittner, A., Pine, D. S., Stein, M. B., Hofler, M., Lieb, R., & Wittchen, H. U. (2007). Incidence of social anxiety disorder and the consistent risk for secondary depression in the first three decades of life. *Arch Gen Psychiatry, 64*(8), 903-912. doi: 10.1001/archpsyc.64.8.903

Behar, L., & Stringfield, S. (1974). A behavior rating scale for the preschool child. *Developmental Psychology, 10*(5), 601-610.

Belden, A. C., Thomson, N. R., & Luby, J. L. (2008). Temper tantrums in healthy versus depressed and disruptive preschoolers: defining tantrum behaviors associated with

clinical problems. *J Pediatr, 152*(1), 117-122. doi: S0022-3476(07)00592-6 [pii]10.1016/j.jpeds.2007.06.030

Bell, R. Q., & Chapman, M. (1986). Child effects in studies using experimental of brief longitudinal approaches to socialization. *Developmental Psychology*(22), 595-603.

Birmaher, B., Khetarpal, S., Brent, D., Cully, M., Balach, L., Kaufman, J., & Neer, S. M. (1997). The Screen for Child Anxiety Related Emotional Disorders (SCARED): scale construction and psychometric characteristics. *J Am Acad Child Adolesc Psychiatry, 36*(4), 545-553. doi: 10.1097/00004583-199704000-00018

Birn, R. M., Patriat, R., Phillips, M. L., Germain, A., & Herringa, R. J. (2014). Childhood maltreatment and combat posttraumatic stress differentially predict fear-related fronto-subcortical connectivity. *Depress Anxiety, 31*(10), 880-892. doi: 10.1002/da.22291

Blakemore, S. J. (2012). Development of the social brain in adolescence. *J R Soc Med, 105*(3), 111-116. doi: 10.1258/jrsm.2011.110221

Boivin, M., Perusse, D., Dionne, G., Saysset, V., Zoccolillo, M., Tarabulsy, G. M., . . . Tremblay, R. E. (2005). The genetic-environmental etiology of parents' perceptions and self-assessed behaviours toward their 5-month-old infants in a large twin and singleton sample. *J Child Psychol Psychiatry, 46*(6), 612-630. doi: JCPP375 [pii]10.1111/j.1469-7610.2004.00375.x

Boll, S., Gamer, M., Gluth, S., Finsterbusch, J., & Buchel, C. (2013). Separate amygdala subregions signal surprise and predictiveness during associative fear learning in humans. *Eur J Neurosci, 37*(5), 758-767. doi: 10.1111/ejn.12094

Bor, W., & Sanders, M. R. (2004). Correlates of self-reported coercive parenting of preschool-aged children at high risk for the development of conduct problems. *Aust N Z J Psychiatry, 38*(9), 738-745. doi: 10.1111/j.1440-1614.2004.01452.xANP1452 [pii]

Boyle, M. H., Jenkins, J. M., Georgiades, K., Cairney, J., Duku, E., & Racine, Y. (2004). Differential-maternal parenting behavior: estimating within- and between-family effects on children. *Child Dev, 75*(5), 1457-1476. doi: 10.1111/j.1467-8624.2004.00751.xCDEV751 [pii]

Bremner, J. D., Vermetten, E., Schmahl, C., Vaccarino, V., Vythilingam, M., Afzal, N., . . . Charney, D. S. (2005). Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual-abuse-related post-traumatic stress disorder. *Psychol Med, 35*(6), 791-806.

Briggs-Gowan, M. J., Carter, A. S., & Schwab-Stone, M. (1996). Discrepancies among mother, child, and teacher reports: examining the contributions of maternal depression and anxiety. *J Abnorm Child Psychol, 24*(6), 749-765.

Britton, J. C., Grillon, C., Lissek, S., Norcross, M. A., Szuhany, K. L., Chen, G., . . . Pine, D. S. (2013). Response to learned threat: An FMRI study in adolescent and adult anxiety. *Am J Psychiatry, 170*(10), 1195-1204. doi: 10.1176/appi.ajp.2013.12050651

Britton, J. C., Lissek, S., Grillon, C., Norcross, M. A., & Pine, D. S. (2011). Development of anxiety: the role of threat appraisal and fear learning. *Depress Anxiety, 28*(1), 5-17. doi: 10.1002/da.20733

Buchel, C., & Dolan, R. J. (2000). Classical fear conditioning in functional neuroimaging. *Curr Opin Neurobiol, 10*(2), 219-223.

Buchel, C., Dolan, R. J., Armony, J. L., & Friston, K. J. (1999). Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. *J Neurosci, 19*(24), 10869-10876.

Buchel, C., Morris, J., Dolan, R. J., & Friston, K. J. (1998). Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron, 20*(5), 947-957.

Bugental, D. B., Blue, J., & Cruzcosa, M. (1989). Perceived control over caregiving outcomes: Implications for child abuse. *Developmental Psychology, 25*(59), 532-539.

Bugental, D. B., Lewis, J. C., Lin, E., Lyon, J., & Kopeikin, H. (1999). In charge but not in control: the management of teaching relationships by adults with low perceived power. *Dev Psychol, 35*(6), 1367-1378.

Burghy, C. A., Stodola, D. E., Ruttle, P. L., Molloy, E. K., Armstrong, J. M., Oler, J. A., . . . Birn, R. M. (2012). Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. *Nat Neurosci, 15*(12), 1736-1741. doi: 10.1038/nn.3257

Carrion, V. G., Garrett, A., Menon, V., Weems, C. F., & Reiss, A. L. (2008). Posttraumatic stress symptoms and brain function during a response-inhibition task: an fMRI study in youth. *Depress Anxiety, 25*(6), 514-526. doi: 10.1002/da.20346

Carrion, V. G., Weems, C. F., & Reiss, A. L. (2007). Stress predicts brain changes in children: a pilot longitudinal study on youth stress, posttraumatic stress disorder, and the hippocampus. *Pediatrics, 119*(3), 509-516. doi: 10.1542/peds.2006-2028

Casey, B. J., Jones, R. M., Levita, L., Libby, V., Pattwell, S. S., Ruberry, E. J., . . . Somerville, L. H. (2010). The storm and stress of adolescence: insights from human imaging and mouse genetics. *Dev Psychobiol, 52*(3), 225-235. doi: 10.1002/dev.20447

Casey, B. J., Ruberry, E. J., Libby, V., Glatt, C. E., Hare, T., Soliman, F., . . . Tottenham, N. (2011). Transitional and translational studies of risk for anxiety. *Depress Anxiety, 28*(1), 18-28. doi: 10.1002/da.20783

Cellerino, A., Borghetti, D., & Sartucci, F. (2004). Sex differences in face gender recognition in humans. *Brain Res Bull, 63*(6), 443-449. doi: 10.1016/j.brainresbull.2004.03.010S0361923004001017 [pii]

Charney, D. S. (2004). Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *Am J Psychiatry, 161*(2), 195-216.

Clément, M.-E., Bernèche, F., Fontaine, C., & Chamberland, C. (2012). Les attitudes parentales et les pratiques familiales. In G. Tardif (Ed.), *La violence familiale dans la vie des enfants du Québec*. Montreal, QC, Canada: Institut de la Statistique du Québec.

Cote, S. M., Boivin, M., Liu, X., Nagin, D. S., Zoccolillo, M., & Tremblay, R. E. (2009). Depression and anxiety symptoms: onset, developmental course and risk factors during early childhood. *J Child Psychol Psychiatry, 50*(10), 1201-1208. doi: JCPP2099 [pii]10.1111/j.1469-7610.2009.02099.x

Craig, A. D. (2009). How do you feel--now? The anterior insula and human awareness. *Nat Rev Neurosci, 10*(1), 59-70. doi: 10.1038/nrn2555

Craske, M. G., Kircanski, K., Zelikowsky, M., Mystkowski, J., Chowdhury, N., & Baker, A. (2008). Optimizing inhibitory learning during exposure therapy. *Behav Res Ther, 46*(1), 5-27. doi: 10.1016/j.brat.2007.10.003

Craske, M. G., Waters, A. M., Lindsey Bergman, R., Naliboff, B., Lipp, O. V., Negoro, H., & Ornitz, E. M. (2008). Is aversive learning a marker of risk for anxiety disorders in children? *Behav Res Ther, 46*(8), 954-967. doi: 10.1016/j.brat.2008.04.011

Dalla, C., & Shors, T. J. (2009). Sex differences in learning processes of classical and operant conditioning. *Physiol Behav, 97*(2), 229-238. doi: S0031-9384(09)00075-4 [pii]10.1016/j.physbeh.2009.02.035

Daly, M., Wilson, M. (1994). Evolutionary psychology of male violence. In C. Routledge (Ed.), *Male violence*. New York: In J. Archer (Ed.).

Davidson, R. J. (2004). Well-being and affective style: neural substrates and biobehavioural correlates. *Philos Trans R Soc Lond B Biol Sci, 359*(1449), 1395-1411. doi: 10.1098/rstb.2004.1510

Davis, M., & Whalen, P. J. (2001). The amygdala: vigilance and emotion. *Mol Psychiatry, 6*(1), 13-34.

De Bellis, M., Keshavan, M., Clark, D., Casey, B., Giedd, J., Boring, A., . . . Ryan, N. D. (1999). Developmental traumatology part II: Brain development *Biol Psychiatry*(45), 1271-1284.

De Bellis, M., Keshavan, M., Shifflett, H., Iyengar, S., Beers, S., Hall, J., & Moritz, G. (2002). Brain structures in pediatric maltreatment-related posttraumatic stress disorder: A sociodemographically matched study. *Biol Psychiatry*(2), 1066-1078.

De Sonneville, L. M., Verschoor, C. A., Njiokiktjien, C., Op het Veld, V., Toorenaar, N., & Vranken, M. (2002). Facial identity and facial emotions: speed, accuracy, and processing strategies in children and adults. *J Clin Exp Neuropsychol, 24*(2), 200-213. doi: 10.1076/jcen.24.2.200.989

Delgado, M. R., Olsson, A., & Phelps, E. A. (2006). Extending animal models of fear conditioning to humans. *Biol Psychol, 73*(1), 39-48. doi: 10.1016/j.biopsycho.2006.01.006

Dennison, M., Whittle, S., Yucel, M., Vijayakumar, N., Kline, A., Simmons, J., & Allen, N. B. (2013). Mapping subcortical brain maturation during adolescence: evidence of hemisphere- and sex-specific longitudinal changes. *Dev Sci, 16*(5), 772-791. doi: 10.1111/desc.12057

Dimberg, U., Öhman, A. (1996). Behold the Wrath: Psychophysiological Responses to Facial Stimuly. *Motivation and Emotion, 20*(2).

Doi, H., Amamoto, T., Okishige, Y., Kato, M., & Shinohara, K. (2010). The own-sex effect in facial expression recognition. *Neuroreport, 21*(8), 564-568. doi: 10.1097/WNR.0b013e328339b61a

Dunne, R. L., Kenardy, J., & Sterling, M. (2012). A randomized controlled trial of cognitive-behavioral therapy for the treatment of PTSD in the context of chronic whiplash. *Clin J Pain, 28*(9), 755-765. doi: 10.1097/AJP.0b013e318243e16b

Dunsmoor, J. E., Prince, S. E., Murty, V. P., Kragel, P. A., & LaBar, K. S. (2011). Neurobehavioral mechanisms of human fear generalization. *Neuroimage, 55*(4), 1878-1888. doi: 10.1016/j.neuroimage.2011.01.041

Durrant, J., & Ensom, R. (2012). Physical punishment of children: lessons from 20 years of research. *CMAJ*. doi: 10.1503/cmaj.101314

Duvarci, S., & Pare, D. (2014). Amygdala microcircuits controlling learned fear. *Neuron, 82*(5), 966-980. doi: 10.1016/j.neuron.2014.04.042

Egger, H. L., Pine, D. S., Nelson, E., Leibenluft, E., Ernst, M., Towbin, K. E., & Angold, A. (2011). The NIMH Child Emotional Faces Picture Set (NIMH-ChEFS): a new set of children's facial emotion stimuli. *Int J Methods Psychiatr Res, 20*(3), 145-156. doi: 10.1002/mpr.343

Elsey, J., Coates, A., Lacadie, C. M., McCrory, E. J., Sinha, R., Mayes, L. C., & Potenza, M. N. (2015). Childhood trauma and neural responses to personalized stress, favorite-food and neutral-relaxing cues in adolescents. *Neuropsychopharmacology, 40*(7), 1580-1589. doi: 10.1038/npp.2015.6

Erhardt, A., & Spoormaker, V. I. (2013). Translational approaches to anxiety: focus on genetics, fear extinction and brain imaging. *Curr Psychiatry Rep, 15*(12), 417. doi: 10.1007/s11920-013-0417-9

Etkin, A. (2012). Neurobiology of anxiety: from neural circuits to novel solutions? *Depress Anxiety, 29*(5), 355-358. doi: 10.1002/da.21957

Etkin, A., Prater, K. E., Hoeft, F., Menon, V., & Schatzberg, A. F. (2010). Failure of anterior cingulate activation and connectivity with the amygdala during implicit regulation of emotional processing in generalized anxiety disorder. *Am J Psychiatry, 167*(5), 545-554. doi: 10.1176/appi.ajp.2009.09070931

Etkin, A., Prater, K. E., Schatzberg, A. F., Menon, V., & Greicius, M. D. (2009). Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. *Arch Gen Psychiatry, 66*(12), 1361-1372. doi: 10.1001/archgenpsychiatry.2009.104

Etkin, A., & Wager, T. D. (2007). Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry, 164*(10), 1476-1488. doi: 10.1176/appi.ajp.2007.07030504

Fan, Y., Herrera-Melendez, A. L., Pestke, K., Feeser, M., Aust, S., Otte, C., . . . Grimm, S. (2014). Early life stress modulates amygdala-prefrontal functional connectivity: implications for oxytocin effects. *Hum Brain Mapp, 35*(10), 5328-5339. doi: 10.1002/hbm.22553

Fisher, A. H. (1993). Sex Differences in Emotionality: Fact of Stereotype ? *Feminism & Psychology, 3*(3), 303-318.

Fonzo, G. A., Flagan, T. M., Sullivan, S., Allard, C. B., Grimes, E. M., Simmons, A. N., . . . Stein, M. B. (2013). Neural functional and structural correlates of childhood maltreatment in women with intimate-partner violence-related posttraumatic stress disorder. *Psychiatry Res, 211*(2), 93-103. doi: 10.1016/j.pscychresns.2012.08.006

Fonzo, G. A., Simmons, A. N., Thorp, S. R., Norman, S. B., Paulus, M. P., & Stein, M. B. (2010). Exaggerated and disconnected insular-amygdalar blood oxygenation level-dependent response to threat-related emotional faces in women with intimate-partner violence posttraumatic stress disorder. *Biol Psychiatry, 68*(5), 433-441. doi: 10.1016/j.biopsych.2010.04.028

Forsyth, J. P., & Eifert, G. H. (1998). Response intensity in content-specific fear conditioning comparing 20% versus 13% CO2-enriched air as unconditioned stimuli. *J Abnorm Psychol, 107*(2), 291-304.

Friedman, H., & Zebrowitz, L. A. (1992). The Contribution of Typical Sex Differences in Facial Maturity to Sex Role Stereotypes. *Society for Personality and Social Psychology, 18*, 430-438.

Fries, A. B., & Pollak, S. D. (2004). Emotion understanding in postinstitutionalized Eastern European children. *Dev Psychopathol, 16*(2), 355-369.

Fullana, M. A., Harrison, B. J., Soriano-Mas, C., Vervliet, B., Cardoner, N., Avila-Parcet, A., & Radua, J. (2015). Neural signatures of human fear conditioning: an updated and extended meta-analysis of fMRI studies. *Mol Psychiatry*. doi: 10.1038/mp.2015.88

Gazendam, F. J., Kamphuis, J. H., & Kindt, M. (2013). Deficient safety learning characterizes high trait anxious individuals. *Biol Psychol, 92*(2), 342-352. doi: 10.1016/j.biopsycho.2012.11.006

Gee, D. G., Gabard-Durnam, L. J., Flannery, J., Goff, B., Humphreys, K. L., Telzer, E. H., . . . Tottenham, N. (2013). Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. *Proc Natl Acad Sci U S A, 110*(39), 15638-15643. doi: 10.1073/pnas.1307893110

Gershoff, E. T. (2002). Corporal punishment by parents and associated child behaviors and experiences: a meta-analytic and theoretical review. *Psychol Bull, 128*(4), 539-579.

Gervai, J. (2009). Environmental and genetic influences on early attachment. *Child Adolesc Psychiatry Ment Health, 3*(1), 25. doi: 10.1186/1753-2000-3-25

Glotzbach-Schoon, E., Tadda, R., Andreatta, M., Troger, C., Ewald, H., Grillon, C., . . . Muhlberger, A. (2013). Enhanced discrimination between threatening and safe contexts in high-anxious individuals. *Biol Psychol, 93*(1), 159-166. doi: 10.1016/j.biopsycho.2013.01.011

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., . . . Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A, 101*(21), 8174-8179. doi: 10.1073/pnas.0402680101 [pii]

Gogtay, N., & Thompson, P. M. (2010). Mapping gray matter development: implications for typical development and vulnerability to psychopathology. *Brain Cogn, 72*(1), 6-15. doi: 10.1016/j.bandc.2009.08.009

Goos L.M., S. I. (2002). Sex related factors in the perception of threatening facial expressions. *Journal of Nonverbal Behavior, 26*(1).

Gottfried, J. A., & Dolan, R. J. (2004). Human orbitofrontal cortex mediates extinction learning while accessing conditioned representations of value. *Nat Neurosci, 7*(10), 1144-1152. doi: 10.1038/nn1314

Gracia, E. (1995). Visible but unreported: a case for the "not serious enough" cases of child maltreatment. *Child Abuse Negl, 19*(9), 1083-1093. doi: 0145-2134(95)00070-O [pii]

Guapo, V. G., Graeff, F. G., Zani, A. C., Labate, C. M., dos Reis, R. M., & Del-Ben, C. M. (2009). Effects of sex hormonal levels and phases of the menstrual cycle in the processing of emotional faces. *Psychoneuroendocrinology, 34*(7), 1087-1094. doi: 10.1016/j.psyneuen.2009.02.007

Guimond, F. A., Brendgen, M., Forget-Dubois, N., Dionne, G., Vitaro, F., Tremblay, R. E., & Boivin, M. (2012). Associations of mother's and father's parenting practices with children's observed social reticence in a competitive situation: a monozygotic twin difference study. *J Abnorm Child Psychol, 40*(3), 391-402. doi: 10.1007/s10802-011-9573-8

Gullone, E. (2000). The development of normal fear: a century of research. *Clin Psychol Rev, 20*(4), 429-451.

Haddad, A. D., Lissek, S., Pine, D. S., & Lau, J. Y. (2011). How do social fears in adolescence develop? Fear conditioning shapes attention orienting to social threat cues. *Cogn Emot, 25*(6), 1139-1147. doi: 10.1080/02699931.2010.524193

Hahn, A., Stein, P., Windischberger, C., Weissenbacher, A., Spindelegger, C., Moser, E., . . . Lanzenberger, R. (2011). Reduced resting-state functional connectivity between

amygdala and orbitofrontal cortex in social anxiety disorder. *Neuroimage, 56*(3), 881-889. doi: 10.1016/j.neuroimage.2011.02.064

Halpern, L. F., Anders, T. F., Coll, C. G., & Hua, J. (1994). Infant temperament: Is there a relation to sleep wake states and maternal nightime behavior ? *Infant Behavior and Development*(17), 255-268.

Hardee, J. E., Benson, B. E., Bar-Haim, Y., Mogg, K., Bradley, B. P., Chen, G., . . . Perez-Edgar, K. (2013). Patterns of neural connectivity during an attention bias task moderate associations between early childhood temperament and internalizing symptoms in young adulthood. *Biol Psychiatry, 74*(4), 273-279. doi: 10.1016/j.biopsych.2013.01.036

Hart, H., & Rubia, K. (2012). Neuroimaging of child abuse: a critical review. *Front Hum Neurosci, 6*, 52. doi: 10.3389/fnhum.2012.00052

Herba, C. M., Landau, S., Russell, T., Ecker, C., & Phillips, M. L. (2006). The development of emotion-processing in children: effects of age, emotion, and intensity. *J Child Psychol Psychiatry, 47*(11), 1098-1106. doi: 10.1111/j.1469-7610.2006.01652.x

Herringa, R. J., Birn, R. M., Ruttle, P. L., Burghy, C. A., Stodola, D. E., Davidson, R. J., & Essex, M. J. (2013). Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. *Proc Natl Acad Sci U S A, 110*(47), 19119-19124. doi: 10.1073/pnas.1310766110

Hess H., B. S., Kleck R.E. (1997). The intensity of emotional facial expressions and decoding accuracy. *Journal of Nonverbal Behavior, 21*(4).

Hilbert, K., Lueken, U., & Beesdo-Baum, K. (2014). Neural structures, functioning and connectivity in Generalized Anxiety Disorder and interaction with neuroendocrine systems: a systematic review. *J Affect Disord, 158*, 114-126. doi: 10.1016/j.jad.2014.01.022

Hofmann, S. G., Ellard, K. K., & Siegle, G. J. (2012). Neurobiological correlates of cognitions in fear and anxiety: a cognitive-neurobiological information-processing model. *Cogn Emot, 26*(2), 282-299. doi: 10.1080/02699931.2011.579414

Holzschneider, K., & Mulert, C. (2011). Neuroimaging in anxiety disorders. *Dialogues Clin Neurosci, 13*(4), 453-461.

Huesmann, L. R., Moise-Titus, J., Podolski, C. L., & Eron, L. D. (2003). Longitudinal relations between children's exposure to TV violence and their aggressive and violent behavior in young adulthood. *Developmental Psychology, 39*(2), 201-221.

Indovina, I., Robbins, T. W., Nunez-Elizalde, A. O., Dunn, B. D., & Bishop, S. J. (2011). Fear-conditioning mechanisms associated with trait vulnerability to anxiety in humans. *Neuron, 69*(3), 563-571. doi: 10.1016/j.neuron.2010.12.034

Ipser, J. C., Singh, L., & Stein, D. J. (2013). Meta-analysis of functional brain imaging in specific phobia. *Psychiatry Clin Neurosci, 67*(5), 311-322. doi: 10.1111/pcn.12055

James, A. C., James, G., Cowdrey, F. A., Soler, A., & Choke, A. (2013). Cognitive behavioural therapy for anxiety disorders in children and adolescents. *Cochrane Database Syst Rev, 6*, CD004690. doi: 10.1002/14651858.CD004690.pub3

Jones, C. L., Ward, J., & Critchley, H. D. (2010). The neuropsychological impact of insular cortex lesions. *J Neurol Neurosurg Psychiatry, 81*(6), 611-618. doi: 10.1136/jnnp.2009.193672

Jovanovic, T., Nylocks, K. M., & Gamwell, K. L. (2013). Translational neuroscience measures of fear conditioning across development: applications to high-risk children and adolescents. *Biol Mood Anxiety Disord, 3*(1), 17. doi: 10.1186/2045-5380-3-17

Jovanovic, T., & Ressler, K. J. (2010). How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD. *Am J Psychiatry, 167*(6), 648-662. doi: 10.1176/appi.ajp.2009.09071074

Kalisch, R., & Gerlicher, A. M. (2014). Making a mountain out of a molehill: on the role of the rostral dorsal anterior cingulate and dorsomedial prefrontal cortex in conscious threat appraisal, catastrophizing, and worrying. *Neurosci Biobehav Rev, 42*, 1-8. doi: 10.1016/j.neubiorev.2014.02.002

Keding, T. J., & Herringa, R. J. (2014). Abnormal Structure of Fear Circuitry in Pediatric Post-Traumatic Stress Disorder. *Neuropsychopharmacology*. doi: 10.1038/npp.2014.239

Kelly, M. M., & Forsyth, J. P. (2007). Observational fear conditioning in the acquisition and extinction of attentional bias for threat: an experimental evaluation. *Emotion, 7*(2), 324-335. doi: 10.1037/1528-3542.7.2.324

Kelly, P. A., Viding, E., Wallace, G. L., Schaer, M., De Brito, S. A., Robustelli, B., & McCrory, E. J. (2013). Cortical thickness, surface area, and gyrification abnormalities in children exposed to maltreatment: neural markers of vulnerability? *Biol Psychiatry, 74*(11), 845-852. doi: 10.1016/j.biopsych.2013.06.020

Kendall, P. C., Hudson, J. L., Gosch, E., Flannery-Schroeder, E., & Suveg, C. (2008). Cognitive-behavioral therapy for anxiety disordered youth: a randomized clinical trial evaluating child and family modalities. *J Consult Clin Psychol, 76*(2), 282-297. doi: 10.1037/0022-006X.76.2.282

Kim, H. K., Pears, K. C., Fisher, P. A., Connelly, C. D., & Landsverk, J. A. (2010). Trajectories of maternal harsh parenting in the first 3 years of life. *Child Abuse Negl, 34*(12), 897-906. doi: S0145-2134(10)00231-0 [pii]
10.1016/j.chiabu.2010.06.002

Kindt, M., & Soeter, M. (2014). Fear inhibition in high trait anxiety. *PLoS One, 9*(1), e86462. doi: 10.1371/journal.pone.0086462

Kitayama, N., Quinn, S., & Bremner, J. D. (2006). Smaller volume of anterior cingulate cortex in abuse-related posttraumatic stress disorder. *J Affect Disord, 90*(2-3), 171-174. doi: 10.1016/j.jad.2005.11.006

Klumpp, H., Angstadt, M., & Phan, K. L. (2012). Insula reactivity and connectivity to anterior cingulate cortex when processing threat in generalized social anxiety disorder. *Biol Psychol, 89*(1), 273-276. doi: 10.1016/j.biopsycho.2011.10.010

Kret, M. E., & De Gelder, B. (2012). A review on sex differences in processing emotional signals. *Neuropsychologia, 50*(7), 1211-1221. doi: S0028-3932(12)00002-4 [pii]10.1016/j.neuropsychologia.2011.12.022

Krishnakumar, A., & Buehler, C. (2000). Interparental Conflict and Parenting Behaviors: A Meta-Analytic Review. *Family Relations, 49*(1), 25-44.

LaBar, K. S., Gatenby, J. C., Gore, J. C., LeDoux, J. E., & Phelps, E. A. (1998). Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron, 20*(5), 937-945.

Lansford, J. E., Criss, M. M., Dodge, K. A., Shaw, D. S., Pettit, G. S., & Bates, J. E. (2009). Trajectories of physical discipline: early childhood antecedents and developmental

outcomes. *Child Dev, 80*(5), 1385-1402. doi: CDEV1340 [pii]10.1111/j.1467-8624.2009.01340.x

Laskey, B. J., & Cartwright-Hatton, S. (2009). Parental discipline behaviours and beliefs about their child: associations with child internalizing and mediation relationships. *Child Care Health Dev, 35*(5), 717-727. doi: CCH977 [pii]10.1111/j.1365-2214.2009.00977.x

Lau, J. Y., Britton, J. C., Nelson, E. E., Angold, A., Ernst, M., Goldwin, M., . . . Pine, D. S. (2011). Distinct neural signatures of threat learning in adolescents and adults. *Proc Natl Acad Sci U S A, 108*(11), 4500-4505. doi: 1005494108 [pii]10.1073/pnas.1005494108

Lau, J. Y., Lissek, S., Nelson, E. E., Lee, Y., Roberson-Nay, R., Poeth, K., . . . Pine, D. S. (2008). Fear conditioning in adolescents with anxiety disorders: results from a novel experimental paradigm. *J Am Acad Child Adolesc Psychiatry, 47*(1), 94-102. doi: 10.1097/chi.0b01e31815a5f01S0890-8567(09)62089-X [pii]

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annu Rev Neurosci, 23*, 155-184. doi: 10.1146/annurev.neuro.23.1.155

LeDoux, J. E. (2014). Coming to terms with fear. *Proc Natl Acad Sci U S A, 111*(8), 2871-2878. doi: 10.1073/pnas.1400335111

Lee, N. C., Krabbendam, L., White, T. P., Meeter, M., Banaschewski, T., Barker, G. J., . . . Shergill, S. S. (2013). Do you see what I see? Sex differences in the discrimination of facial emotions during adolescence. *Emotion, 13*(6), 1030-1040. doi: 10.1037/a0033560

Lenroot, R. K., & Giedd, J. N. (2010). Sex differences in the adolescent brain. *Brain Cogn, 72*(1), 46-55. doi: 10.1016/j.bandc.2009.10.008

Li, S., Kim, J. H., & Richardson, R. (2012). Differential involvement of the medial prefrontal cortex in the expression of learned fear across development. *Behav Neurosci, 126*(2), 217-225. doi: 10.1037/a0027151

Liberman, L. C., Lipp, O. V., Spence, S. H., & March, S. (2006). Evidence for retarded extinction of aversive learning in anxious children. *Behav Res Ther, 44*(10), 1491-1502. doi: S0005-7967(05)00231-7 [pii]10.1016/j.brat.2005.11.004

Lissek, S. (2012). Toward an account of clinical anxiety predicated on basic, neurally mapped mechanisms of Pavlovian fear-learning: the case for conditioned overgeneralization. *Depress Anxiety, 29*(4), 257-263. doi: 10.1002/da.21922

Lissek, S., Powers, A. S., McClure, E. B., Phelps, E. A., Woldehawariat, G., Grillon, C., & Pine, D. S. (2005). Classical fear conditioning in the anxiety disorders: a meta-analysis. *Behav Res Ther, 43*(11), 1391-1424. doi: S0005-7967(04)00251-7 [pii]10.1016/j.brat.2004.10.007

Lissek, S., Rabin, S., Heller, R. E., Lukenbaugh, D., Geraci, M., Pine, D. S., & Grillon, C. (2010). Overgeneralization of conditioned fear as a pathogenic marker of panic disorder. *Am J Psychiatry, 167*(1), 47-55. doi: 10.1176/appi.ajp.2009.09030410

Lissek, S., Rabin, S. J., McDowell, D. J., Dvir, S., Bradford, D. E., Geraci, M., . . . Grillon, C. (2009). Impaired discriminative fear-conditioning resulting from elevated fear responding to learned safety cues among individuals with panic disorder. *Behav Res Ther, 47*(2), 111-118. doi: 10.1016/j.brat.2008.10.017

Little, A. C. (2013). The influence of steroid sex hormones on the cognitive and emotional processing of visual stimuli in humans. *Front Neuroendocrinol, 34*(4), 315-328. doi: 10.1016/j.yfrne.2013.07.009

Lovejoy, M. C., Graczyk, P. A., O'Hare, E., & Neuman, G. (2000). Maternal depression and parenting behavior: a meta-analytic review. *Clin Psychol Rev, 20*(5), 561-592. doi: S0272-7358(98)00100-7 [pii]

Luby, J. L., Essex, M. J., Armstrong, J. M., Klein, M. H., Zahn-Waxler, C., Sullivan, J. P., & Goldsmith, H. H. (2009). Gender differences in emotional reactivity of depressed and at-risk preschoolers: implications for gender specific manifestations of preschool depression. *J Clin Child Adolesc Psychol, 38*(4), 525-537. doi: 10.1080/15374410902976312

MacKenzie, M. J., Nicklas, E., Waldfogel, J., & Brooks-Gunn, J. (2013). Spanking and child development across the first decade of life. *Pediatrics, 132*(5), e1118-1125. doi: 10.1542/peds.2013-1227

Mackintosh, N. (1974). *The psychology of animal learning*. . London:: Academic Press.

Mackintosh, N. J. (1974). *The psychology of animal learning*. London: Academic Press.

MacMillan, H. L., Boyle, M. H., Wong, M. Y., Duku, E. K., Fleming, J. E., & Walsh, C. A. (1999). Slapping and spanking in childhood and its association with lifetime prevalence of psychiatric disorders in a general population sample. *CMAJ, 161*(7), 805-809.

Mahan, A. L., & Ressler, K. J. (2012). Fear conditioning, synaptic plasticity and the amygdala: implications for posttraumatic stress disorder. *Trends Neurosci, 35*(1), 24-35. doi: 10.1016/j.tins.2011.06.007

Maheu, F. S., Dozier, M., Guyer, A. E., Mandell, D., Peloso, E., Poeth, K., . . . Ernst, M. (2010). A preliminary study of medial temporal lobe function in youths with a history of caregiver deprivation and emotional neglect. *Cogn Affect Behav Neurosci, 10*(1), 34-49. doi: 10.3758/CABN.10.1.34

Marchand, J. F., Hock, E. , Widaman, K. . (2002). Mutual relations between mothers' depressive symptoms and hostile-controlling behavior and young children's externalizing and internalizing behavior problems. *Parenting: Science and Practice*(2), 335–353.

Marek, R., Strobel, C., Bredy, T. W., & Sah, P. (2013). The amygdala and medial prefrontal cortex: partners in the fear circuit. *J Physiol, 591*(Pt 10), 2381-2391. doi: 10.1113/jphysiol.2012.248575

Masten, C. L., Guyer, A. E., Hodgdon, H. B., McClure, E. B., Charney, D. S., Ernst, M., . . . Monk, C. S. (2008). Recognition of facial emotions among maltreated children with high rates of post-traumatic stress disorder. *Child Abuse Negl, 32*(1), 139-153. doi: S0145-2134(07)00263-3 [pii]10.1016/j.chiabu.2007.09.006

Mazurski, E. J., Bond, N. W., Siddle, D. A., & Lovibond, P. F. (1996). Conditioning with facial expressions of emotion: effects of CS sex and age. *Psychophysiology, 33*(4), 416-425.

McCarthy, M. M., & Konkle, A. T. (2005). When is a sex difference not a sex difference? *Front Neuroendocrinol, 26*(2), 85-102. doi: 10.1016/j.yfrne.2005.06.001

McClure, E. B. (2000). A meta-analytic review of sex differences in facial expression processing and their development in infants, children, and adolescents. *Psychol Bull, 126*(3), 424-453.

McClure, E. B., Monk, C. S., Nelson, E. E., Parrish, J. M., Adler, A., Blair, R. J., . . . Pine, D. S. (2007). Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder. *Arch Gen Psychiatry, 64*(1), 97-106. doi: 10.1001/archpsyc.64.1.97

McCrory, E., De Brito, S. A., & Viding, E. (2011). The impact of childhood maltreatment: a review of neurobiological and genetic factors. *Front Psychiatry, 2*, 48. doi: 10.3389/fpsyt.2011.00048

McCrory, E. J., De Brito, S. A., Kelly, P. A., Bird, G., Sebastian, C. L., Mechelli, A., . . . Viding, E. (2013). Amygdala activation in maltreated children during pre-attentive emotional processing. *Br J Psychiatry, 202*(4), 269-276. doi: 10.1192/bjp.bp.112.116624

McCrory, E. J., De Brito, S. A., Sebastian, C. L., Mechelli, A., Bird, G., Kelly, P. A., & Viding, E. (2011). Heightened neural reactivity to threat in child victims of family violence. *Curr Biol, 21*(23), R947-948. doi: 10.1016/j.cub.2011.10.015

McKee, L., Jones, D. J., Roland, E., Coffelt, N., Rakow, A., & Forehand, R. (2007). Maternal HIV/AIDS and depressive symptoms among inner-city African American youth: the role of maternal depressive symptoms, mother-child relationship quality, and child coping. *Am J Orthopsychiatry, 77*(2), 259-266. doi: 10.1037/0002-9432.77.2.259

McLaughlin, K. A., Peverill, M., Gold, A. L., Alves, S., & Sheridan, M. A. (2015). Child Maltreatment and Neural Systems Underlying Emotion Regulation. *J Am Acad Child Adolesc Psychiatry, 54*(9), 753-762. doi: 10.1016/j.jaac.2015.06.010

McLaughlin, K. A., Sheridan, M. A., Gold, A. L., Duys, A., Lambert, H. K., Peverill, M., . . . Pine, D. S. (2015). Maltreatment Exposure, Brain Structure, and Fear Conditioning in Children and Adolescents. *Neuropsychopharmacology*. doi: 10.1038/npp.2015.365

McLeod, B. D., Wood, J. J., & Weisz, J. R. (2007). Examining the association between parenting and childhood anxiety: a meta-analysis. *Clin Psychol Rev, 27*(2), 155-172. doi: 10.1016/j.cpr.2006.09.002

Mechias, M. L., Etkin, A., & Kalisch, R. (2010). A meta-analysis of instructed fear studies: implications for conscious appraisal of threat. *Neuroimage, 49*(2), 1760-1768. doi: 10.1016/j.neuroimage.2009.09.040

Mehta, M. A., Golembo, N. I., Nosarti, C., Colvert, E., Mota, A., Williams, S. C., . . . Sonuga-Barke, E. J. (2009). Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian Adoptees study pilot. *J Child Psychol Psychiatry, 50*(8), 943-951. doi: 10.1111/j.1469-7610.2009.02084.x

Meulders, A., Vansteenwegen, D., & Vlaeyen, J. W. (2012). Women, but not men, report increasingly more pain during repeated (un)predictable painful electrocutaneous stimulation: Evidence for mediation by fear of pain. *Pain, 153*(5), 1030-1041. doi: 10.1016/j.pain.2012.02.005

Milad, M. R., Goldstein, J. M., Orr, S. P., Wedig, M. M., Klibanski, A., Pitman, R. K., & Rauch, S. L. (2006). Fear conditioning and extinction: influence of sex and menstrual cycle in healthy humans. *Behav Neurosci, 120*(6), 1196-1203. doi: 10.1037/0735-7044.120.5.1196

Milad, M. R., & Quirk, G. J. (2012). Fear extinction as a model for translational neuroscience: ten years of progress. *Annu Rev Psychol, 63*, 129-151. doi: 10.1146/annurev.psych.121208.131631

Milad, M. R., Rauch, S. L., Pitman, R. K., & Quirk, G. J. (2006). Fear extinction in rats: implications for human brain imaging and anxiety disorders. *Biol Psychol, 73*(1), 61-71. doi: S0301-0511(06)00026-3 [pii]10.1016/j.biopsycho.2006.01.008

Monk, C. S., Nelson, E. E., McClure, E. B., Mogg, K., Bradley, B. P., Leibenluft, E., . . . Pine, D. S. (2006). Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *Am J Psychiatry, 163*(6), 1091-1097. doi: 10.1176/appi.ajp.163.6.1091

Mueller, S. C., Maheu, F. S., Dozier, M., Peloso, E., Mandell, D., Leibenluft, E., . . . Ernst, M. (2010). Early-life stress is associated with impairment in cognitive control in adolescence: an fMRI study. *Neuropsychologia, 48*(10), 3037-3044. doi: 10.1016/j.neuropsychologia.2010.06.013

Navarrete, C. D., Olsson, A., Ho, A. K., Mendes, W. B., Thomsen, L., & Sidanius, J. (2009). Fear extinction to an out-group face: the role of target gender. *Psychol Sci, 20*(2), 155-158. doi: 10.1111/j.1467-9280.2009.02273.x

Neumann, D. L., Waters, A. M., Westbury, H. R., & Henry, J. (2008). The use of an unpleasant sound unconditional stimulus in an aversive conditioning procedure with 8- to 11-year-old children. *Biol Psychol, 79*(3), 337-342. doi: 10.1016/j.biopsycho.2008.08.005

Ohman, A. (2005). The role of the amygdala in human fear: automatic detection of threat. *Psychoneuroendocrinology, 30*(10), 953-958. doi: 10.1016/j.psyneuen.2005.03.019

Ohman, A. (2009). Of snakes and faces: an evolutionary perspective on the psychology of fear. *Scand J Psychol, 50*(6), 543-552. doi: 10.1111/j.1467-9450.2009.00784.x

Ohman, A., Carlsson, K., Lundqvist, D., & Ingvar, M. (2007). On the unconscious subcortical origin of human fear. *Physiol Behav, 92*(1-2), 180-185. doi: 10.1016/j.physbeh.2007.05.057

Pannekoek, J. N., Veer, I. M., van Tol, M. J., van der Werff, S. J., Demenescu, L. R., Aleman, A., . . . van der Wee, N. J. (2013). Resting-state functional connectivity abnormalities in limbic and salience networks in social anxiety disorder without comorbidity. *Eur Neuropsychopharmacol, 23*(3), 186-195. doi: 10.1016/j.euroneuro.2012.04.018

Pattwell, S. S., Duhoux, S., Hartley, C. A., Johnson, D. C., Jing, D., Elliott, M. D., . . . Lee, F. S. (2012). Altered fear learning across development in both mouse and human. *Proc Natl Acad Sci U S A, 109*(40), 16318-16323. doi: 10.1073/pnas.1206834109

Pattwell, S. S., Lee, F. S., & Casey, B. J. (2013). Fear learning and memory across adolescent development: Hormones and Behavior Special Issue: Puberty and Adolescence. *Horm Behav, 64*(2), 380-389. doi: 10.1016/j.yhbeh.2013.01.016

Pears, K. C., & Fisher, P. A. (2005). Emotion understanding and theory of mind among maltreated children in foster care: evidence of deficits. *Dev Psychopathol, 17*(1), 47-65.

Pejic, T., Hermann, A., Vaitl, D., & Stark, R. (2013). Social anxiety modulates amygdala activation during social conditioning. *Soc Cogn Affect Neurosci, 8*(3), 267-276. doi: 10.1093/scan/nsr095

Perlman, G., Simmons, A. N., Wu, J., Hahn, K. S., Tapert, S. F., Max, J. E., . . . Yang, T. T. (2012). Amygdala response and functional connectivity during emotion regulation: a study of 14 depressed adolescents. *J Affect Disord, 139*(1), 75-84. doi: 10.1016/j.jad.2012.01.044

Petrovic, P., Carlsson, K., Petersson, K. M., Hansson, P., & Ingvar, M. (2004). Context-dependent deactivation of the amygdala during pain. *J Cogn Neurosci, 16*(7), 1289-1301. doi: 10.1162/0898929041920469

Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: role of the amygdala and vmPFC. *Neuron, 43*(6), 897-905. doi: 10.1016/j.neuron.2004.08.042

Pierce, C. A., & Voss, B. (2010). Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. *Ann Pharmacother, 44*(3), 489-506. doi: aph.1M332 [pii]10.1345/aph.1M332

Pierce, T., Boivin, M., Frenette, E., Forget-Dubois, N., Dionne, G., & Tremblay, R. E. (2010). Maternal self-efficacy and hostile-reactive parenting from infancy to toddlerhood. *Infant Behav Dev, 33*(2), 149-158. doi: S0163-6383(09)00113-1 [pii]10.1016/j.infbeh.2009.12.005

Pine, D. S. (2003). Developmental psychobiology and response to threats: relevance to trauma in children and adolescents. *Biol Psychiatry, 53*(9), 796-808.

Pine, D. S., Helfinstein, S. M., Bar-Haim, Y., Nelson, E., & Fox, N. A. (2009). Challenges in developing novel treatments for childhood disorders: lessons from research on anxiety. *Neuropsychopharmacology, 34*(1), 213-228. doi: 10.1038/npp.2008.113

Pine, D. S., Mogg, K., Bradley, B. P., Montgomery, L., Monk, C. S., McClure, E., . . . Kaufman, J. (2005). Attention bias to threat in maltreated children: implications for vulnerability to stress-related psychopathology. *Am J Psychiatry, 162*(2), 291-296. doi: 10.1176/appi.ajp.162.2.291

Pitkanen, A., Jolkkonen, E., & Kemppainen, S. (2000). Anatomic heterogeneity of the rat amygdaloid complex. *Folia Morphol (Warsz), 59*(1), 1-23.

Pollak, S. D., Cicchetti, D., Hornung, K., & Reed, A. (2000). Recognizing emotion in faces: developmental effects of child abuse and neglect. *Dev Psychol, 36*(5), 679-688.

Pollak, S. D., & Sinha, P. (2002). Effects of early experience on children's recognition of facial displays of emotion. *Dev Psychol, 38*(5), 784-791.

Pollak, S. D., & Tolley-Schell, S. A. (2003). Selective attention to facial emotion in physically abused children. *J Abnorm Psychol, 112*(3), 323-338.

Quirk, G. J., Armony, J. L., & LeDoux, J. E. (1997). Fear conditioning enhances different temporal components of tone-evoked spike trains in auditory cortex and lateral amygdala. *Neuron, 19*(3), 613-624.

Rabinak, C. A., Angstadt, M., Welsh, R. C., Kenndy, A. E., Lyubkin, M., Martis, B., & Phan, K. L. (2011). Altered amygdala resting-state functional connectivity in post-traumatic stress disorder. *Front Psychiatry, 2*, 62. doi: 10.3389/fpsyt.2011.00062

Redlich, R., Stacey, D., Opel, N., Grotegerd, D., Dohm, K., Kugel, H., . . . Dannlowski, U. (2015). Evidence of an IFN-gamma by early life stress interaction in the regulation of amygdala reactivity to emotional stimuli. *Psychoneuroendocrinology, 62*, 166-173. doi: 10.1016/j.psyneuen.2015.08.008

Rotteveel, M., & Phaf, R. H. (2004). Automatic affective evaluation does not automatically predispose for arm flexion and extension. *Emotion, 4*(2), 156-172. doi: 10.1037/1528-3542.4.2.156

Roy, A. K., Fudge, J. L., Kelly, C., Perry, J. S., Daniele, T., Carlisi, C., . . . Ernst, M. (2013). Intrinsic functional connectivity of amygdala-based networks in adolescent generalized

anxiety disorder. *J Am Acad Child Adolesc Psychiatry, 52*(3), 290-299 e292. doi: 10.1016/j.jaac.2012.12.010

Rubin, K. H., & Mills, R. S. (1990). Maternal beliefs about adaptive and maladaptive social behaviors in normal, aggressive, and withdrawn preschoolers. *J Abnorm Child Psychol, 18*(4), 419-435.

Schneider, F., Weiss, U., Kessler, C., Muller-Gartner, H. W., Posse, S., Salloum, J. B., . . . Birbaumer, N. (1999). Subcortical correlates of differential classical conditioning of aversive emotional reactions in social phobia. *Biol Psychiatry, 45*(7), 863-871.

Sehlmeyer, C., Dannlowski, U., Schoning, S., Kugel, H., Pyka, M., Pfleiderer, B., . . . Konrad, C. (2011). Neural correlates of trait anxiety in fear extinction. *Psychol Med, 41*(4), 789-798. doi: 10.1017/S0033291710001248

Sehlmeyer, C., Schoning, S., Zwitserlood, P., Pfleiderer, B., Kircher, T., Arolt, V., & Konrad, C. (2009). Human fear conditioning and extinction in neuroimaging: a systematic review. *PLoS One, 4*(6), e5865. doi: 10.1371/journal.pone.0005865

Seidel, E. M., Habel, U., Kirschner, M., Gur, R. C., & Derntl, B. (2010). The impact of facial emotional expressions on behavioral tendencies in women and men. *J Exp Psychol Hum Percept Perform, 36*(2), 500-507. doi: 2010-06263-017 [pii]10.1037/a0018169

Shackman, A. J., Salomons, T. V., Slagter, H. A., Fox, A. S., Winter, J. J., & Davidson, R. J. (2011). The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci, 12*(3), 154-167. doi: 10.1038/nrn2994

Shay, N. L., & Knutson, J. F. (2008). Maternal depression and trait anger as risk factors for escalated physical discipline. *Child Maltreat, 13*(1), 39-49. doi: 13/1/39 [pii]10.1177/1077559507310611

Silvers, J. A., McRae, K., Gabrieli, J. D., Gross, J. J., Remy, K. A., & Ochsner, K. N. (2012). Age-related differences in emotional reactivity, regulation, and rejection sensitivity in adolescence. *Emotion, 12*(6), 1235-1247. doi: 10.1037/a0028297

Simmons, A. N., Paulus, M. P., Thorp, S. R., Matthews, S. C., Norman, S. B., & Stein, M. B. (2008). Functional activation and neural networks in women with posttraumatic stress disorder related to intimate partner violence. *Biol Psychiatry, 64*(8), 681-690. doi: 10.1016/j.biopsych.2008.05.027

Simmons, W. K., Avery, J. A., Barcalow, J. C., Bodurka, J., Drevets, W. C., & Bellgowan, P. (2013). Keeping the body in mind: insula functional organization and functional connectivity integrate interoceptive, exteroceptive, and emotional awareness. *Hum Brain Mapp, 34*(11), 2944-2958. doi: 10.1002/hbm.22113

Solomon, C. R., & Serres, F. (1999). Effects of parental verbal aggression on children's self-esteem and school marks. *Child Abuse Negl, 23*(4), 339-351. doi: S0145-2134(99)00006-X [pii]

Stein, M. B., Koverola, C., Hanna, C., Torchia, M. G., & McClarty, B. (1997). Hippocampal volume in women victimized by childhood sexual abuse. *Psychol Med, 27*(4), 951-959.

Strange, B. A., & Dolan, R. J. (2006). Anterior medial temporal lobe in human cognition: memory for fear and the unexpected. *Cogn Neuropsychiatry, 11*(3), 198-218. doi: 10.1080/13546800500305096

Straus, M. A. (2000). Corporal punishment and primary prevention of physical abuse. *Child Abuse Negl, 24*(9), 1109-1114. doi: S0145-2134(00)00180-0 [pii]

Straus, M. A., & Stewart, J. H. (1999). Corporal punishment by American parents: national data on prevalence, chronicity, severity, and duration, in relation to child and family characteristics. *Clin Child Fam Psychol Rev, 2*(2), 55-70.

Suyama, N., Hoshiyama, M., Shimizu, H., & Saito, H. (2008). Event-related potentials for gender discrimination: an examination between differences in gender discrimination between males and females. *Int J Neurosci, 118*(9), 1227-1237. doi: 10.1080/00207450601047176

Teicher, M. H., & Samson, J. A. (2013). Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *Am J Psychiatry, 170*(10), 1114-1133. doi: 10.1176/appi.ajp.2013.12070957

Telzer, E. H., Mogg, K., Bradley, B. P., Mai, X., Ernst, M., Pine, D. S., & Monk, C. S. (2008). Relationship between trait anxiety, prefrontal cortex, and attention bias to angry faces in children and adolescents. *Biol Psychol, 79*(2), 216-222. doi: 10.1016/j.biopsycho.2008.05.004

Thomas, K. M., Drevets, W. C., Dahl, R. E., Ryan, N. D., Birmaher, B., Eccard, C. H., . . . Casey, B. J. (2001). Amygdala response to fearful faces in anxious and depressed children. *Arch Gen Psychiatry, 58*(11), 1057-1063.

Thomas, L. A., De Bellis, M. D., Graham, R., & LaBar, K. S. (2007). Development of emotional facial recognition in late childhood and adolescence. *Dev Sci, 10*(5), 547-558. doi: 10.1111/j.1467-7687.2007.00614.x

Thomason, M. E., Marusak, H. A., Tocco, M. A., Vila, A. M., McGarragle, O., & Rosenberg, D. R. (2015). Altered amygdala connectivity in urban youth exposed to trauma. *Soc Cogn Affect Neurosci, 10*(11), 1460-1468. doi: 10.1093/scan/nsv030

Tottenham, N., Hare, T. A., Millner, A., Gilhooly, T., Zevin, J. D., & Casey, B. J. (2011). Elevated amygdala response to faces following early deprivation. *Dev Sci, 14*(2), 190-204. doi: 10.1111/j.1467-7687.2010.00971.x

Tottenham, N., & Sheridan, M. A. (2009). A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. *Front Hum Neurosci, 3*, 68. doi: 10.3389/neuro.09.068.2009

Tremblay, R. E., Desmarais-Gervais, L., Gagnon, C., & Charlebois, P. (1987). The Preschool Behaviour Questionnaire: Stability of its factor structure between cultures, sexes, ages and socioeconomic classes. *International Journal of Behavioral Development,, I*(10), 467-484.

Tremblay, R. E., Nagin, D. S., Seguin, J. R., Zoccolillo, M., Zelazo, P. D., Boivin, M., . . . Japel, C. (2004). Physical aggression during early childhood: trajectories and predictors. *Pediatrics, 114*(1), e43-50.

Tremblay, R. E., Nagin, D. S., Seguin, J. R., Zoccolillo, M., Zelazo, P. D., Boivin, M., . . . Japel, C. (2005). Physical aggression during early childhood: trajectories and predictors. *Can Child Adolesc Psychiatr Rev, 14*(1), 3-9.

Tzschoppe, J., Nees, F., Banaschewski, T., Barker, G. J., Buchel, C., Conrod, P. J., . . . consortium, I. (2014). Aversive learning in adolescents: modulation by amygdala-prefrontal and amygdala-hippocampal connectivity and neuroticism. *Neuropsychopharmacology, 39*(4), 875-884. doi: 10.1038/npp.2013.287

Uematsu, A., Matsui, M., Tanaka, C., Takahashi, T., Noguchi, K., Suzuki, M., & Nishijo, H. (2012). Developmental trajectories of amygdala and hippocampus from infancy to

early adulthood in healthy individuals. *PLoS One, 7*(10), e46970. doi: 10.1371/journal.pone.0046970

van der Schalk, J., Fischer, A., Doosje, B., Wigboldus, D., Hawk, S., Rotteveel, M., & Hess, U. (2011). Convergent and divergent responses to emotional displays of ingroup and outgroup. *Emotion, 11*(2), 286-298. doi: 10.1037/a0022582

van der Werff, S. J., Pannekoek, J. N., Veer, I. M., van Tol, M. J., Aleman, A., Veltman, D. J., . . . van der Wee, N. J. (2013). Resting-state functional connectivity in adults with childhood emotional maltreatment. *Psychol Med, 43*(9), 1825-1836. doi: 10.1017/S0033291712002942

Vicari, S., Reilly, J. S., Pasqualetti, P., Vizzotto, A., & Caltagirone, C. (2000). Recognition of facial expressions of emotions in school-age children: the intersection of perceptual and semantic categories. *Acta Paediatr, 89*(7), 836-845.

Vitaro, F., Barker, E. D., Boivin, M., Brendgen, M., & Tremblay, R. E. (2006). Do early difficult temperament and harsh parenting differentially predict reactive and proactive aggression? *J Abnorm Child Psychol, 34*(5), 685-695. doi: 10.1007/s10802-006-9055-6

Vorria, P., Papaligoura, Z., Sarafidou, J., Kopakaki, M., Dunn, J., Van Ijzendoorn, M. H., & Kontopoulou, A. (2006). The development of adopted children after institutional care: a follow-up study. *J Child Psychol Psychiatry, 47*(12), 1246-1253. doi: 10.1111/j.1469-7610.2006.01666.x

Walkup, J. T., Albano, A. M., Piacentini, J., Birmaher, B., Compton, S. N., Sherrill, J. T., . . . Kendall, P. C. (2008). Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med, 359*(26), 2753-2766. doi: 10.1056/NEJMoa0804633

Waters, A. M., Henry, J., & Neumann, D. L. (2009). Aversive Pavlovian conditioning in childhood anxiety disorders: impaired response inhibition and resistance to extinction. *J Abnorm Psychol, 118*(2), 311-321. doi: 2009-06385-006 [pii]10.1037/a0015635

Waters, A. M., Peters, R. M., Forrest, K. E., & Zimmer-Gembeck, M. (2014). Fear acquisition and extinction in offspring of mothers with anxiety and depressive disorders. *Dev Cogn Neurosci, 7*, 30-42. doi: 10.1016/j.dcn.2013.10.007

Windham, A. M., Rosenberg, L., Fuddy, L., McFarlane, E., Sia, C., & Duggan, A. K. (2004). Risk of mother-reported child abuse in the first 3 years of life. *Child Abuse Negl, 28*(6), 645-667. doi: 10.1016/j.chiabu.2004.01.003S014521340400105X [pii]

Wood, J. J., McLeod, B. D., Sigman, M., Hwang, W. C., & Chu, B. C. (2003). Parenting and childhood anxiety: theory, empirical findings, and future directions. *J Child Psychol Psychiatry, 44*(1), 134-151.

Wood, J. J., Piacentini, J. C., Southam-Gerow, M., Chu, B. C., & Sigman, M. (2006). Family cognitive behavioral therapy for child anxiety disorders. *J Am Acad Child Adolesc Psychiatry, 45*(3), 314-321. doi: 10.1097/01.chi.0000196425.88341.b0

Woods, E. R., Obeidallah-Davis, D., Sherry, M. K., Ettinger, S. L., Simms, E. U., Dixon, R. R., . . . Cox, J. E. (2003). The parenting project for teen mothers: the impact of a nurturing curriculum on adolescent parenting skills and life hassles. *Ambul Pediatr, 3*(5), 240-245.

Zeng, L. L., Shen, H., Liu, L., Wang, L., Li, B., Fang, P., . . . Hu, D. (2012). Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis. *Brain, 135*(Pt 5), 1498-1507. doi: 10.1093/brain/aws05

Annexe 1

Autres contributions

Prefrontal cortex and limbic gray matter volumes in adolescents are associated with chronic harsh parenting practices

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Abstract

Importance: Childhood adversity and anxiety have been associated with increased risk for internalizing disorders during adolescence, and linked to a range of brain structural abnormalities. However, whether childhood adversity, anxiety, or the combination of both sustain these difficulties remains to be investigated in healthy adolescents.

Objective: Investigate anatomy of key emotional brain structures, in relation with chronic harsh parenting and anxiety levels.

Design: Participants were from a representative cohort of 1761 youths of the Quebec Longitudinal Study of Children's Development.

Setting: Developmental trajectory methodology was used to classify healthy adolescents according to the chronicity of harsh parenting and anxiety levels.

Participants: Adolescents (12-16 years, N=88) were divided across four cells of interest: 21 with chronic high levels of harsh parenting and anxiety, 22 with chronic high levels of harsh parenting and low levels of anxiety, 23 with chronic low levels of harsh parenting and high levels of anxiety, and 22 with chronic low levels of harsh parenting and anxiety.

Main Outcome and Measure(s): We used two complementary regions-of-interest-based structural neuroimaging approaches to identify structural differences (volume, cortical thickness and surface area variations) linked to chronic harsh parenting and anxiety levels.

Results: Smaller gray matter volumes of the left and right prefrontal cortex regions, right amygdala and right nucleus accumbens were observed in adolescents with chronic high levels of harsh parenting compared to adolescents with chronic low levels of harsh parenting. In addition, a significant parenting practices-by-anxiety interaction was observed for the left amygdala volume and left rostral anterior cingulate cortical thickness. Specifically, the left amygdala volume was lower, and the left rostral anterior cingulate cortical thickness was higher in adolescents with chronic high levels of harsh parenting and low anxiety levels; and in adolescents with chronic low levels of harsh parenting and high anxiety levels; compared to those with no risk factors (adolescents with chronic low levels of harsh parenting and anxiety).

Conclusions and Relevance: Chronic high levels of harsh parenting during childhood is an important risk factor for reduced gray matter volume during adolescence. Preventive interventions targeting parenting practices should impact gray matter volume.

Introduction

Childhood adversity was associated with a greater risk of developing an internalizing disorder, especially anxiety disorders.[1-3] Harsh parenting, i.e., hostile, cold, critical and coercive child-rearing behaviors, though a milder form of adversity, is closely related to high anxiety levels.[4-6] Chronically elevated levels of both harsh parenting and anxiety levels during childhood may have long-term, pervasive, deleterious influences well into adulthood.[7, 8] Given the ubiquity of harsh parenting and its accompanying anxiety-related difficulties,[6] understanding the neural correlates of this interaction carries considerable public health relevance.

Adversity, as well as anxiety, had been linked to differences in structures of the fear and reward neural circuits (prefrontal cortex (PFC): anterior cingulate cortex (ACC), BA10 and orbito-frontal cortex (OFC), insula, amygdala, hippocampus and striatum), both of which are involved in emotional processing and anxiety-related symptomatology.[9-13]

Many structural neuroanatomical studies had been performed in youths with a history of childhood adversity. However, most of these studies focused on youths who also had a PTSD. In youths with a history of childhood adversity, without PTSD and with only a small proportion of other psychiatric comorbidities, findings generally showed: smaller gray matter volume (GMV) and cortical thickness (CT) in the PFC, OFC, ACC and insula;[14-18] smaller amygdala[16, 19, 20] and striatum[16] volumes, but no difference in the hippocampus,[14, 15, 20] relative to comparison youths.

Between anxiety disorders and comparison youths, PFC/OFC and ACC GMV seemed equivalent.[21-25] Only two studies focus on CT of these structures in anxiety disorders: one showed smaller OFC CT in 12 year old epileptic anxious youths,[26] the other greater rostral middle frontal CT in 14 year old anxious youths,[27] relative to comparison youths. Insula GMV seemed greater[25] or had no differences;[22, 23] amygdala volume findings are mixed, with smaller,[24, 25] greater,[26, 28] or no difference;[22, 23] and hippocampus volume generally did not differ.[22-24, 26, 28] In healthy youths with high anxiety and depression levels on the Child Behavior Checklist questionnaire, vmPFC thickness was reduced before 9 years of age, and increased with anxiety and depression levels between the ages of 15 and 22.[29] In healthy youths, amygdala volume seemed to have increased with anxiety levels.[8, 30] Insula, hippocampus and striatum have never been studied in connection with anxiety symptoms.

Studies on anxiety disorders or symptoms did not report the potential link between childhood adversity and their results. Hence, in order to have a better understanding of how childhood adversity may be associated with the integrity of fear and reward brain regions during adolescence, it thus becomes very important to carefully isolate the influence of adversity and anxiety.

The goal of the present study was to investigate how chronic harsh parenting and anxiety levels, measured yearly from 2.5 to 9 years old, may be associated with the integrity of fear and reward brain structure volumes, thickness and surface areas in 12-16 year old adolescents. To reach this goal, four cells were defined: adolescents with chronic high levels of harsh parenting and chronic high anxiety level (HH/HA), adolescents with chronic high levels of harsh parenting and chronic low anxiety level (HH/LA), adolescents with chronic low levels of harsh parenting and chronic high anxiety level (LH/HA) and adolescents with chronic low levels of harsh parenting and chronic low anxiety level (LH/LA).

Based on the previously reported findings, we hypothesize that chronic high levels of harsh parenting would be linked to smaller PFC/OFC/ACC and insula GMV and CT, smaller amygdala and striatum volumes, and no difference in the hippocampus, compared to youths with low levels of harsh parenting. Adolescents with chronic high anxiety level would show no difference in the GMV, but greater CT in the PFC/OFC/ACC structures (because of lack of studies, we had no a-priori hypothesis regarding insula); greater amygdala volume; and no difference concerning hippocampus and striatum volumes, compared to youths with chronic low anxiety level. Because of lack of studies, we had no a-priori hypothesis about surface areas.

Methods and materials

Participants

The sample. Participants were recruited through a collaboration with the "Institut de la statistique du Québec", in two related cohorts: one headed mainly by Dr. Séguin (in 2001, I was 5 years old), and one headed mainly by Drs. Boivin and Tremblay (The Quebec Longitudinal Study of Children's Development). The total cohort was a sample of 2174 youths born in Quebec, Canada, in 1996 and 1997 (children from the far north, Cree or Inuit regions, and aboriginal reservations excluded). Longitudinal data regarding youths and their parents' socio-demographic profile, psychological development (including anxiety levels), familial

interactions (including harsh parenting practices) and health status were collected yearly from the time youths were 5 months old. We used a developmental trajectory methodology[31] to determine how youths would be distributed across the four cells previously described. Details of this procedure are presented in the eMethods in the Supplement and eFigure 1. Youths with the highest probability of belonging to any of the four cells and who met inclusion criteria were firstly included in the study.

Inclusion/exclusion criteria and measures. Inclusion criteria were defined by the absence of: medical illness; any past or current psychiatric disorders, as determined by a semi-structured psychiatric evaluation conducted with the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS);[32] treatment for psychiatric illness (pharmacological or behavioral); past or current abuse; past head injury or trauma; contraindications for MRI (e.g., braces); IQ score < 70, as assessed by The Peabody Picture Vocabulary Test-Revised (PPVT-R).[33] Current anxiety symptoms were measured through the Screen for Child Anxiety Related Emotional Disorders–Revised (SCARED-R),[34] and the State-Trait Anxiety Inventory for Children (STAI-C).[35] The parenting questionnaire used to evaluate current harsh parenting practices was the same as the one used to determine harsh parenting trajectories from 2.5 to 9 years old.[36-38] Also measured was the socio-economic status (SES) of each participant, assessed using the Hollingshead two-factor index scale;[39, 40] the pubertal stage assessed using the Tanner puberty stage self-administered scale;[41, 42] and the levels of depression symptoms assessed using the Children Depression Inventory (CDI; because of technical difficulties, only the child version was administered).[43, 44]

Scanning session. Structural neuroimaging was performed for 94 youths at the Geriatric University Institute of Montreal (IUGM, Montreal, Canada). The study protocol was approved by the Research Ethics Boards of the CHU Ste-Justine and IUGM, Montreal, Canada. Participants and their parents gave informed assent and consent, respectively, and were compensated for their participation. After removing participants with motion artifacts (ghosting, blurring), a total of 88 youths were included in the analyses: 21 HH/HA; 22 HH/LA; 23 LH/HA and 22 LH/LA. As we can see in Table 1, groups differed significantly on age and SES. Although there were no significant group differences in terms of sex and total brain volume (TBV), these variables were used as covariates of no interest in cerebral analysis, with age and SES, to ensure that they did not account for any of the findings, as these

variables were previously reported to be linked with brain anatomy.[45-48] IQ was not included as a covariate to avoid over-correction because of its significant correlation with SES scores. As expected, the ANOVAs comparing current harsh parenting and anxiety levels revealed that current levels of harsh parenting was significantly higher in the HH relative to the LH adolescents ($p = 0.001$) and that current anxiety levels, as measured by the SCARED (parent ratings), were higher in the HA, compared to LA adolescents ($p < 0.05$). No differences between HA and LA adolescents were observed when analyzing the child scores collected using the SCARED (child ratings) and STAI-C (all $p > 0.05$) (see Table 1).

Insert Table 1

Image acquisition, processing and analysis

All scans were performed on a 3 Tesla MRI scanner (Magnetom Tim Trio, Siemens) equipped with a standard head coil. Whole-brain, high-resolution, T1-weighted anatomical images were acquired using an MPRAGE sequence (TR=2300 ms, TE=2.98 ms, flip angle=9°, matrix size=256 x 256 mm, voxel size=1×1×1 mm^3, FOV=256 mm, 176 slices). The two-dimensional DICOM files of each brain were organized into volumetric three-dimensional files using the MRIcron software package (http://www.mccauslandcenter.sc.edu/mricro/mricron/). Voxel based morphometry (VBM) was used to provide an unbiased, even-handed, voxel-by-voxel assessment. FreeSurfer, a software program for cortical and subcortical surface-based reconstruction and analysis, was then used to extend findings (specific description of image processing is included in the eMethods in the Supplement).

Based on a-priori hypotheses of associations between GMV and CT, and early life adversity and anxiety, in seven regions (prefrontal and orbitofrontal cortices, anterior cingulate cortex, insula, amygdala, hippocampus, striatum), we adopted an independent region of interest (ROI) approach (ROIs are described in the eMethods in the Supplement). For VBM analysis, we corrected for multiple comparisons using small-volume correction (SVC) with a Gaussian random field threshold set at $\alpha = 0.05$, and an extent of at least 10 contiguous voxels,

and significant peak voxels ($p<0.05$, FWE-corrected) were then extracted. For FS analysis, we extracted ROIs GMV, CT and SA.

A 2*2 Analysis of Covariance (ANCOVA) with harsh parenting (high vs. low) and anxiety (high vs. low) levels as the between-subjects factors, and age, sex, SES and TBV as covariates of no interest, were performed in SPSS v.20 (Armonk, NY) on the different extracted measures. When A*H interaction was significant, findings were decomposed using pairwise comparisons with a Bonferroni correction for multiple comparisons.

Finally, with regression analyses, we assessed how significant VBM peak voxels and significant FreeSurfer GMV, CT and SA, were related to the child's current anxiety and depression levels, as specified in the eResults in the Supplement.

Results

Main effect of parenting

Cortical findings. As shown in Figure 1 and Table 2, the ANCOVAs revealed smaller GMV in adolescents with chronic high levels of harsh parenting, relative to adolescents with chronic low levels of harsh parenting, in different regions of the lateral and medial prefrontal cortex. VBM analysis revealed smaller left BA11 ($F_{1,79}$ = 31.53, p < 0.001); left and right BA47 ($F_{1,79}$ = 25.84, p = 0.001; $F_{1,79}$ = 21.25, p = 0.003); left and right BA10 ($F_{1,79}$ = 32.94, p = 0.000; $F_{1,79}$ = 15.37, p = 0.04); and right BA25 ($F_{1,79}$ = 13.06, p = 0.001). FreeSurfer analysis revealed smaller left medial OFC ($F_{1,80}$ = 4.18, p = 0.04) and left lateral parsorbitalis ($F_{1,80}$ = 8.43, p = 0.01) volumes.

Insert Table 2

Insert Figure 1

Subcortical findings. ANCOVAs revealed smaller GMV in adolescents with chronic high levels of harsh parenting, relative to adolescents with chronic low levels of harsh parenting, in the right amygdala from VBM ($F_{1,79}$ = 12.70, p = 0.02, $F_{1,80}$ = 4.48, p = 0.04) and

FreeSurfer ($F_{1,80}$ = 4.48, p = 0.04) analysis; and right nucleus accumbens from VBM analysis ($F_{1,79}$ = 16.27, p = 0.001) (see Table 2 and Figure 2).

Insert Figure 2

Parenting by anxiety interaction

Cortical findings. FreeSurfer Cortical thickness (CT) measurements revealed a parenting by anxiety interaction in the left rostral ACC ($F_{1,80}$ = 6.47, p = 0.01), with greater left rostral ACC thickness in LH/HA ($F_{1,80}$ = 12.26, p = 0.001) and HH/LA ($F_{1,80}$ = 3.9, p = 0.05) adolescents, compared to LH/LA adolescents (see figure 3).

Subcortical findings. In the VBM analysis, a parenting by anxiety interaction emerged in the left amygdala [-28.5, -6, -15] ($F_{1,79}$ = 12.13, p = 0.01, FWE-corrected), with smaller amygdala volume in the LH/HA ($F_{1,84}$ = 4.72, p = 0.03) and HH/LA ($F_{1,84}$ = 6.48, p = 0.01) adolescents, compared to LH/LA adolescents (see figure 3).

Insert Figure 3

Discussion

This study is the first to compare gray matter volume, cortical thickness and surface area in healthy adolescents who experienced chronic high or low levels of harsh parenting and chronic high or low anxiety levels during childhood. The first key finding from this study is the observed smaller volumes of the PFC, OFC, ACC, amygdala and nucleus accumbens among adolescents who have experienced chronic high levels of harsh parenting during childhood, compared to those who have not. A second important finding is the greater ACC thickness and smaller amygdala volume in adolescents with one of these two risk factors, compared to those with no risk factors.

The results linked to chronic high levels of harsh parenting (regardless anxiety levels) are in agreement with the literature on child adversity. It has been suggested that the smaller amygdala and PFC volumes in maltreated children (implicated in emotional processing and regulation, respectively), could be associated with a variety of behavioral problems (e.g.

impulsive, anxious and depressive behaviors) and poorer social functioning,, and may be related to increased psychiatric vulnerability.[15-18, 20] Similarly, decreased nucleus accumbens volume is in line with a study showing decreased striatum volume in maltreated children, a key component in the neural circuitry that underlies impulse control and reward processing.[16]

The results in adolescents with one of the two risk factors are particularly interesting. Greater ACC thickness linked to chronic high anxiety level is consistent with our hypothesis and the literature in adolescence.[29] The first hypothesis to explain this result is that this increased medial PFC thickness with anxiety level in healthy adolescents could be a biological compensatory mechanism for an overly active limbic system, potentially preventing the onset of mood and anxiety disorders.[29] Knowing that the normal development of the PFC/OFC/ACC thickness is to decrease during adolescence,[49-51] the second hypothesis is that this increase would be related to a delayed maturation of that structure with anxiety symptoms. This maturational delay could be a precursor to a pathological decrease in CT associated with the risk or onset of a disorder.[29] Greater ACC thickness linked to chronic high levels of harsh parenting is contrary to our hypothesis and the literature showing smaller PFC regions thickness linked to childhood adversity.[18, 20] It could be because our participants did not experience serious adversity, unlike most of the literature on severe maltreatment. A recent longitudinal study in 120 adolescents has also demonstrated a link between negative maternal behavior and attenuated cortical thinning in the PFC regions,[52] which is consistent with the second hypothesis advanced by Ducharme et al. (2012). Of course, as for anxiety, it could also be a compensatory mechanism to protect against psychopathology. The absence of thicker ACC in adolescents who have the two risk factors (i.e. who have a more severe condition) in this study could be the result of an absence of compensatory mechanism and/or of the beginning of a decrease in the thickness of that structure. Indeed, ACC CT decreases with current anxiety symptoms in this group specifically, which could make them more at risk of developing a disorder.

The smaller amygdala volume in the HH/LA, relative to comparison group, is consistent with our hypothesis and supports the fact that the smaller amygdala volume is linked to adversity even when the teenager has few anxiety symptoms. On the contrary, smaller amygdala volume in the LH/HA, relative to comparison group, is contrary to our hypothesis and the literature showing increased amygdala volume with anxiety levels in

children.[8, 30] However, in these two studies, children were 8 years old at the time of testing. Given the hypothesis that exposure to a stressor,[53] low maternal positive behaviors[52] and psychopathology development in at risk youths[54] are linked to an acceleration of the amygdala's development, followed by atrophy or cell death resulting in a larger than normal decrease in amygdala volume later,[53] the observed smaller amygdala volume here could be explained by a greater than normal atrophy of the gray matter of this structure once measured during the mid-adolescence of our participants. This is particularly interesting when examining the results of a study showing greater amygdala volume, linked to the presence of depression in the mother, in the same population as ours but when the children were 10 years old.[55] The smaller amygdala would be a risk factor for the development of disorders in adolescence, but not in childhood. Amygdala in the two risk factors group is smaller compared to controls (even if non-significant). Perhaps the appearance of a disorder or the risk for it requires the reduction of ACC thickness and amygdala volume together. It seems important to follow these youths in the coming years in order to answer this question.

It is important to keep in mind that we cannot infer causality here, because of the correlational and cross-sectional design of this study. Even if structural abnormalities could be the result of early-life stress, it could also be a pre-existing risk factor for vulnerability to adversity exposure, psychological trauma and stress-related disorders that would be induced by genetics.[56, 57] Even if animal literature tends to confirm that some structural abnormalities follow stress exposure,[8, 58] future studies in humans should try to extend longitudinal studies across the human lifespan.

To conclude, this study has replicated and extended the relation between adversity (chronic high levels of harsh parenting here), and smaller volumes of the PFC, OFC, amygdala and nucleus accumbens, in adolescents without comorbidity and medication. More interestingly, this study established the relation between, on one hand, chronic high levels of harsh parenting and low anxiety levels and, on the other hand, chronic high levels of anxiety and low levels of harsh parenting, and greater ACC thickness and smaller amygdala volume. It is likely that the smaller amygdala volume and ACC thickness represent vulnerability factors to psychopathology, and that the greater ACC thickness in groups with only one risk factor may act as a compensatory mechanism to avoid psychopathology. Since we know that these structural abnormalities can contribute to an increase in psychiatric vulnerability later in life,[59]

following these youth in the coming years may help identify brain markers of risk and resilience to psychopathology in adulthood. In addition, this study demonstrates the importance of establishing preventive interventions targeting parenting early in the child's development.

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References

1. Caspi A, Houts RM, Belsky DW, et al. The p Factor: one general psychopathology factor in the structure of psychiatric disorders? *Clinical Psychological Science.* 2014;2(2):119-137.

2. Pine DS, Cohen JA. Trauma in children and adolescents: risk and treatment of psychiatric sequelae. *Biological Psychiatry.* 2002;51(7):519-531.

3. Teicher MH, Samson JA. Childhood maltreatment and psychopathology: a case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *American Journal of Psychiatry.* 2013;170(10):1114-1133.

4. Arrindell WA, Kwee MG, Methorst GJ, van der Ende J, Pol E, Moritz BJ. Perceived parental rearing styles of agoraphobic and socially phobic in-patients. *The British Journal of Psychiatry.* October 1, 1989 1989;155(4):526-535.

5. McLeod BD, Wood JJ, Weisz JR. Examining the association between parenting and childhood anxiety: A meta-analysis. *Clinical Psychology Review.* 2007;27(2):155-172.

6. Wood JJ, McLeod BD, Sigman M, Hwang W-C, Chu BC. Parenting and childhood anxiety: theory, empirical findings, and future directions. *Journal of Child Psychology and Psychiatry.* 2003;44(1):134-151.

7. Pine DS, Cohen P, Gurley D, Brook J, Ma Y. THe risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Archives of General Psychiatry.* 1998;55(1):56-64.

8. Qin S, Young CB, Duan X, Chen T, Supekar K, Menon V. Amygdala subregional structure and intrinsic functional connectivity predicts individual differences in anxiety during early childhood. *Biological Psychiatry.* 2014;75(11):892-900.

9. Fareri DS, Martin LN, Delgado MR. Reward-related processing in the human brain: Developmental considerations. *Development and Psychopathology.* 2008;20(Special Issue 04):1191-1211.

10. Milad MR, Quirk GJ. Fear Extinction as a Model for Translational Neuroscience: Ten Years of Progress. *Annual Review of Psychology.* 2012;63(1):129-151.

11. Milad MR, Rauch SL, Pitman RK, Quirk GJ. Fear extinction in rats: Implications for human brain imaging and anxiety disorders. *Biological Psychology.* 2006;73(1):61-71.

12. Hirshfeld-Becker DR, Micco JA, Simoes NA, Henin A. High risk studies and developmental antecedents of anxiety disorders. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics.* 2008;148C(2):99-117.

13. Pine DS. Research review: A neuroscience framework for pediatric anxiety disorders. *Journal of Child Psychology and Psychiatry.* 2007;48(7):631-648.

14. Baker L, Williams L, Korgaonkar M, Cohen R, Heaps J, Paul R. Impact of early vs. late childhood early life stress on brain morphometrics. *Brain Imaging and Behavior.* 2012/12/01 2012:1-8.

15. De Brito SA, Viding E, Sebastian CL, et al. Reduced orbitofrontal and temporal grey matter in a community sample of maltreated children. *Journal of Child Psychology and Psychiatry.* 2013;54(1):105-112.

16. Edmiston EE, Wang F, Mazure CM, et al. Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. *Archives of Pediatrics & Adolescent Medicine.* 2011;165(12):1069-1077.

17. Hanson JL, Chung MK, Avants BB, et al. Early stress is associated with alterations in the orbitofrontal cortex: a tensor-based morphometry investigation of brain structure and behavioral risk. *The Journal of Neuroscience.* June 2, 2010 2010;30(22):7466-7472.
18. Kelly PA, Viding E, Wallace GL, et al. Cortical thickness, surface area, and gyrification abnormalities in children exposed to maltreatment: Neural markers of vulnerability? *Biological Psychiatry.* 2013;74(11):845-852.
19. Hanson JL, Nacewicz BM, Sutterer MJ, et al. Behavioral problems after early life stress: contributions of the hippocampus and amygdala. *Biological Psychiatry.* 2015;77(4):314-323.
20. Korgaonkar MS, Antees C, Williams LM, et al. Early exposure to traumatic stressors impairs emotional brain circuitry. *PLoS ONE.* 2013;8(9):e75524.
21. De Bellis MD, Keshavan MS, Shifflett H, et al. Superior temporal gyrus volumes in pediatric generalized anxiety disorder. *Biological Psychiatry.* 2002;51(7):553-562.
22. Liao M, Yang F, Zhang Y, et al. Childhood maltreatment is associated with larger left thalamic gray matter volume in adolescents with generalized anxiety disorder. *PLoS ONE.* 2013;8(8).
23. Liao M, Yang F, Zhang Y, He Z, Su L, Li L. Lack of gender effects on gray matter volumes in adolescent generalized anxiety disorder. *Journal of Affective Disorders.* 2014;155(0):278-282.
24. Milham MP, Nugent AC, Drevets WC, et al. Selective reduction in amygdala volume in pediatric anxiety disorders: A voxel-based morphometry investigation. *Biological Psychiatry.* 2005;57(9):961-966.
25. Mueller SC, Aouidad A, Gorodetsky E, Goldman D, Pine DS, Ernst M. Gray matter volume in adolescent anxiety: An impact of the brain-derived neurotrophic factor Val66Met polymorphism? *Journal of the American Academy of Child & Adolescent Psychiatry.* 2013;52(2):184-195.
26. Jones JE, Jackson DC, Chambers KL, et al. Children with epilepsy and anxiety: Subcortical and cortical differences. *Epilepsia.* 2015;56(2):283-290.
27. Strawn JR, John Wegman C, Dominick KC, et al. Cortical surface anatomy in pediatric patients with generalized anxiety disorder. *Journal of Anxiety Disorders.* 2014;28(7):717-723.
28. De Bellis MD, Casey BJ, Dahl RE, et al. A pilot study of amygdala volumes in pediatric generalized anxiety disorder. *Biological Psychiatry.* 2000;48(1):51-57.
29. Ducharme S, Albaugh MD, Hudziak JJ, et al. Anxious/depressed symptoms are linked to right ventromedial prefrontal cortical thickness maturation in healthy children and young adults. *Cerebral Cortex.* 2013:bht151.
30. Juranek J, Filipek PA, Berenji GR, Modahl C, Osann K, Spence MA. Association between amygdala volume and anxiety level: magnetic resonance imaging (MRI) study in autistic children. *Journal of child neurology.* 2006;21(12):1051-1058.
31. Nagin DS. *Group-based modeling of development over the life course*. Cambridge, MA: Havard university press; 2005.
32. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial Reliability and Validity Data. *Journal of the American Academy of Child and Adolescent Psychiatry.* 1997;36(7):980-988.

33. Dunn L, Dunn L. *Peabody Picture Vocabulary Test-Revised (PPVT): Manual for Forms L and M*. Circle Pines, MN: American Guidance Service; 1981.
34. Martin A, Gosselin P. Propriétés psychométriques de l'adaptation francophone d'une mesure de symptômes des troubles anxieux auprès d'enfants et d'adolescents (SCARED-R). [Psychometric properties of the French adaptation of a measure for symptoms of anxiety disorders among children and adolescents (SCARED-R).]. *Canadian Journal of Behavioural Science/Revue canadienne des sciences du comportement.* 2012;44(1):70-76.
35. Turgeon L, Chartrand É. Psychometric Properties of the French Canadian Version of the State-Trait Anxiety Inventory for Children. *Educational and Psychological Measurement.* 2003;63(1):174-185.
36. Boivin M, Pérusse D, Dionne G, et al. The genetic-environmental etiology of parents' perceptions and self-assessed behaviours toward their 5-month-old infants in a large twin and singleton sample. *Journal of Child Psychology and Psychiatry.* 2005;46(6):612-630.
37. Boyle MH, Jenkins JM, Georgiades K, Cairney J, Duku E, Racine Y. Differential-maternal parenting behavior: estimating within-and between-family effects on children. *Child Development.* 2004;75(5):1457-1476.
38. Pierce T, Boivin M, Frenette É, Forget-Dubois N, Dionne G, Tremblay RE. Maternal self-efficacy and hostile-reactive parenting from infancy to toddlerhood. *Infant Behavior and Development.* 2010;33(2):149-158.
39. Hollingshead AB, Redlich FC. *Social class and mental illness: Community study*. Hoboken, NJ, US: John Wiley & Sons Inc; 1958.
40. Miller DC, Salkind NJ. *Handbook of research design and social measurement*. 6th ed. Thousand Oaks: Sage; 2002.
41. Duke PM, Litt IF, Gross RT. Adolescents' self-assessment of sexual maturation. *Pediatrics.* 1980;66(6):918-920.
42. Morris N, Udry JR. Validation of a self-administered instrument to assess stage of adolescent development. *Journal of Youth and Adolescence.* 1980/06/01 1980;9(3):271-280.
43. Kovacs M. The Children's Depression, Inventory (CDI). *Psychopharmacology bulletin.* 1984;21(4):995-998.
44. Saint-Laurent L. Étude psychométrique de l'Inventaire de dépression pour enfants de Kovacs auprès d'un échantillon francophone. [Psychometric study of Kovacs's Children's Depression Inventory with a French-speaking sample.]. *Canadian Journal of Behavioural Science/Revue canadienne des sciences du comportement.* 1990;22(4):377-384.
45. Burgaleta M, Johnson W, Waber DP, Colom R, Karama S. Cognitive ability changes and dynamics of cortical thickness development in healthy children and adolescents. *NeuroImage.* 2014;84:810-819.
46. Casey BJ, Jones RM, Somerville LH. Braking and accelerating of the adolescent brain. *Journal of Research on Adolescence.* 2011;21(1):21-33.
47. Hanson JL, Hair N, Shen DG, et al. Family poverty affects the rate of human infant brain growth. *PLoS ONE.* 2013;8(12):e80954.

48. Welborn BL, Papademetris X, Reis DL, Rajeevan N, Bloise SM, Gray JR. Variation in orbitofrontal cortex volume: relation to sex, emotion regulation and affect. *Social Cognitive and Affective Neuroscience.* December 17, 2009 2009.

49. Koolschijn P, Crone EA. Sex differences and structural brain maturation from childhood to early adulthood. *Developmental Cognitive Neuroscience.* 2013;5:106-118.

50. Mills KL, Goddings AL, Clasen LS, Giedd JN, Blakemore SJ. The developmental mismatch in structural brain maturation during adolescence. *Developmental Neuroscience.* 2014;36(3-4):147-160.

51. Taki Y, Hashizume H, Thyreau B, et al. Linear and curvilinear correlations of brain gray matter volume and density with age using voxel-based morphometry with the Akaike information criterion in 291 healthy children. *Human Brain Mapping.* 2013;34(8):1857-1871.

52. Whittle S, Simmons JG, Dennison M, et al. Positive parenting predicts the development of adolescent brain structure: A longitudinal study. *Developmental Cognitive Neuroscience.* 2014;8(0):7-17.

53. Tottenham N, Sheridan MA. A Review of Adversity, The Amygdala and the Hippocampus: A Consideration of Developmental Timing. *Frontiers in Human Neuroscience.* 2010;3:1-18.

54. Whittle S, Dennison M, Vijayakumar N, et al. Childhood maltreatment and psychopathology affect brain development during adolescence. *J Am Acad Child Adolesc Psychiatry.* 2013;52(9):940-951.

55. Lupien SJ, Parent S, Evans AC, et al. Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. *Proceedings of the National Academy of Sciences.* August 23, 2011 2011;108(34):14324-14329.

56. Gilbertson MW, Shenton ME, Ciszewski A, et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature neuroscience.* 2002;5(11):1242-1247.

57. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience.* 2009;10(6):434-445.

58. Yan X. Amygdala, Childhood Adversity and Psychiatric Disorders. *The amygdala-A discrete multitasking manager. Available from:* http://www. *intechopen. com/books/the-amygdala-a-discrete-multitasking-manager/amygdala-childhood-adversity-and-psychiatric-disorders.* 2012.

59. McCrory E, De Brito SA, Viding E. The link between child abuse and psychopathology: A review of neurobiological and genetic research. *Journal of the Royal Society of Medicine.* April 1, 2012 2012;105(4):151-156.

Tables

Table 1. Demographic and clinical characteristics of the participants, separately for high and low levels of harsh parenting, and high and low anxiety levels[a]

Chronic levels	High levels of Harsh parenting		Low levels of Harsh parenting		*p*		
	High Anxiety	**Low Anxiety**	**High Anxiety**	**Low Anxiety**	**A**	**H**	**A*H**
N	21	22	23	22			
Sex (female/male)[b]	11/10	11/11	14/9	10/12	0.40	0.84	0.77
Age[c]	13.81 (0.14)	13.36 (0.14)	13.35 (0.14)	13.64 (0.14)	0.58	0.50	**0.01**[f]
Tanner stage[b]	4.05 (0.16)	4.00 (0.16)	3.85 (0.15)	3.75 (0.16)	0.56	0.12	0.41
Verbal IQ (PPVT-R)[c]	105 (2.82)	108 (2.76)	109 (2.70)	111 (2.76)	0.31	0.18	0.68
SES[c d]	44.43 (2.46)	38.21 (2.40)	35.59 (2.40)	34.75 (2.40)	0.15	**0.01**	0.27
Current anxiety							
SCARED-R							
SCARED-R (child)[c]	19.96 (2.03)	19.30 (1.99)	19.85 (1.94)	17.00 (1.99)	0.38	0.55	0.59
SCARED-R (parent)[c]	15.46 (1.94)	10.74 (1.84)	12.75 (1.76)	8.16 (1.89)	**0.07**	0.11	0.70
STAI-C[c]	105.65 (2.78)	103.43 (2.72)	101.32 (2.65)	98.18 (2.65)	0.32	0.80	0.87
Current H (mean)[c]	2.06 (0.11)	2.10 (0.11)	1.53 (0.11)	1.73 (0.11)	0.30	**0.00**	0.50
Current depression							
CDI (child)[c]	46.98 (1.38)	44.86 (1.32)	43.70 (1.29)	44.00 (1.32)	0.50	0.12	0.37
TBV[c e]	1189261 (20106)	1198173 (19644)	1215514 (19212)	1188470 (19644)	0.65	0.68	0.36

Abbreviations. N, number of participants; PPVT-R, Peabody Picture Vocabulary Test-Revised; SES, socio-economic status; SCARED-R, Screen for Child Anxiety Related Emotional Disorders-Revised; STAI-C, State Trait Anxiety Inventory for Children; CDI, Child Depression Inventory; TBV, Total Brain Volume; A, Main effect of anxiety; H, Maine effect of Harsh parenting; A*H, interaction between anxiety and harsh parenting levels.

[a]Means and standard deviations are reported.

[b]Chi-squares for quantitative measures.

[c]Two-way ANOVAs with harsh parenting (high vs. low) and anxiety (high vs. low) levels as the between-subjects factors.

[d]Higher score corresponds to lower SES

[e]TBV was calculated as the sum of the volumes of gray matter and white matter.

[f]Participants HH/HA were significantly older than the HH/LA ($F_{1,84}$= 5.37, p = 0.023) and LH/HA participants ($F_{1,84}$= 4.90, p = 0.03).

Table 2. Significant main effects of harsh parenting in cortical and subcortical gray matter volumes

Cortical Regions	Side	Cluster size (mm3)	Peak	MNI cordinates[a]		
			F[b]	x	y	z
Voxel Based Morphometry						
BA11	L	1956	31.53	-42	52.5	-10.5
			17.24	-43.5	42	-15
BA47	L	1646	25.84	-48	52.5	-9
			19.53	-54	31.5	-15
			18.13	-51	43.5	-15
			17.09	-52.5	39	-15
			16.89	-21	16.5	-18
	R	667	21.25	19.5	15	-16.5
			18.97	24	10.5	-18
BA10	L	2446	32.96	-43.5	54	-9
			17.05	-34.5	57	-7.5
	R	1689	15.37	36	63	18
BA25	R	299	13.06	13.5	16.5	-18
FreeSurfer[c]						
Pars Orbitalis	L					
Medial OFC	L					

Subcortical Regions	Side	Cluster size (mm3)	Peak	MNI cordinates[a]		
			F[b]	x	y	z
Voxel Based Morphometry						
Amygdala	R	105	12.72	21	4.5	-18
N.acc	R	128	16.27	16.5	12	-15
FreeSurfer[c]						
Amygdala	R					

Abbreviations. BA, Brodmann areas; OFC, orbitofrontal cortex; N.acc, nucleus accumbens; R, right; L, left.

[a]coordinates are reported in the Montreal Neurological Institute (MNI) space in millimeters [x,y,z]

[b]all $p < 0.05$, FWE-corrected

[c]all $p < 0.05$, Bonferroni corrected

Figures

Figure 1.

Title: Smaller prefrontal cortex volumes in adolescents with high levels of harsh parenting, compared to those with low levels of harsh parenting.

Legend: Main effect of parenting from VBM (on the left) and FreeSurfer (on the right) analysis, for (a) the left BA11, BA47 and BA10, (b) the right BA10, (c) the right BA47 and BA25, (d) the left pars orbitalis, and (e) the left medial orbitofrontal cortex. All $p <$ 0.05, FWE or Bonferroni corrected. The color bar shows F statistics. The results are displayed on an MNI T1 brain template, at a threshold of $p < 0.005$ for VBM results.

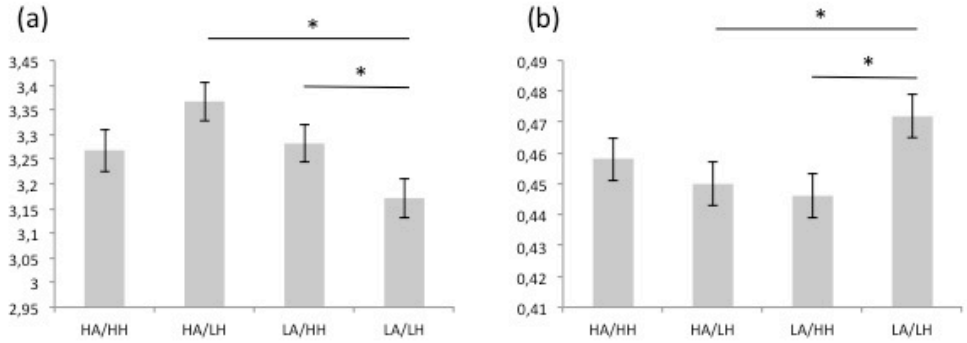


Figure 2.

Title: Smaller subcortical volumes in adolescents with high levels of harsh parenting, compared to those with low levels of harsh parenting.

Legend: Main effect of parenting from VBM (on the left) and FreeSurfer (on the right) analysis, for (a and b) the right amygdala, and (c) the right nucleus accumbens. All $p <$ 0.05, FWE or Bonferroni corrected. The color bar shows F statistics. The results are displayed on an MNI T1 brain template, at a threshold of $p < 0.005$ for VBM analysis.

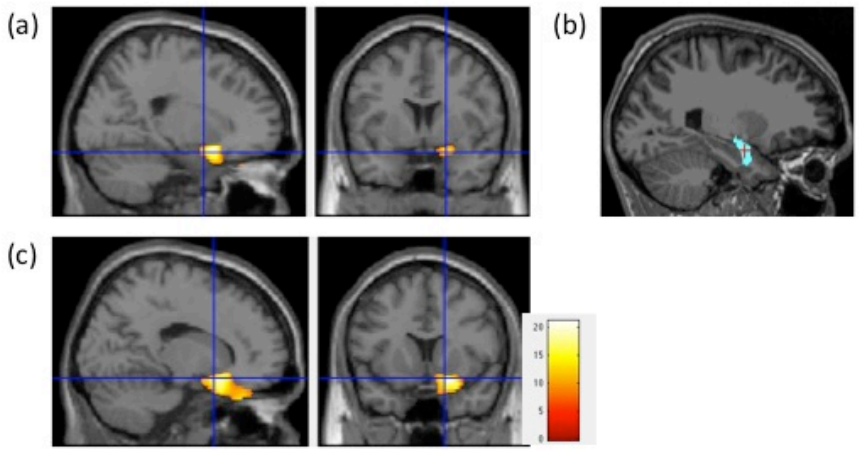
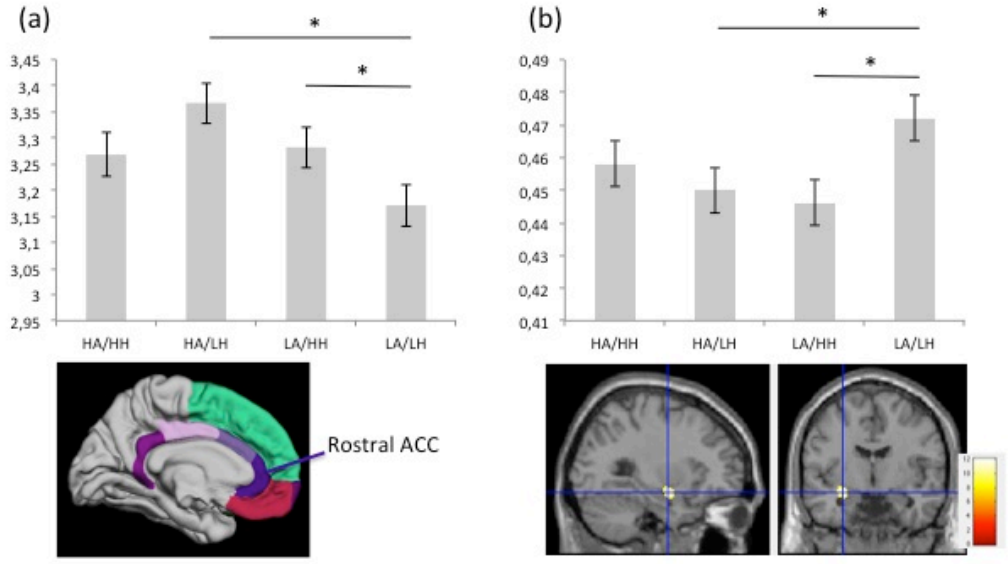


Figure 3.

Title: Significant parenting-by-anxiety interactions

Legend: Significant parenting-by-anxiety interactions for (a) the left rostral ACC thickness from FreeSurfer analysis and (b) the left amygdala volume from VBM analysis, * $p < 0.05$, Bonferroni corrected. The color bar shows F statistics. The results are displayed on an MNI T1 brain template, at a threshold of $p < 0.005$ for VBM results.



Increased odor detection speed in highly anxious healthy adults

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Abstract

Anxiety can either impair or enhance performance depending on the context. Increased sensitivity to threat seems to be an important feature of sensory processing in anxiety since anxious individuals tend to be more attentive to threatening visual stimuli. Evidence of anxiety effects in olfaction is rare; though alterations of olfactory performance in psychiatric patients and some effects of trait and state anxiety on olfactory performance have been reported. Our main objective was thus to investigate whether olfactory processing speed varies as a function of trait anxiety levels. We additionally investigated a possible preferential bias for unpleasant odors in highly anxious participants.

Thirty-eight healthy adults participated in a simple odor detection task, where response times and anxiety levels were measured. We compared response times to a pleasant and an unpleasant food odor between high and low trait anxiety participants. We found that high trait anxiety participants detected both odors faster than low trait anxiety, independently of odor pleasantness. Moreover, trait anxiety levels significantly correlated with reaction times to both odors, indicating that trait anxiety but not odor pleasantness influences olfactory detection speed.

Introduction

Anxiety is an unpleasant and sometimes pervasive emotional state, which may impact several spheres of an individual's life. From milder manifestations of anxiety, like moderate perfectionism, to serious disorders such as agoraphobia or post-traumatic-stress disorder (PTSD), anxiety often influences performance in tasks involving various sensory modalities and cognitive functions. Whether anxiety impairs or enhances performance depends in part on the difficulty level and the nature of the task (Eysenck and Calvo 1992), as well as the participants themselves (Bresin *et al.* 2011). At the participants' level, self-conscious experiences like self-awareness, self-criticism, worries and rumination are commonly encountered in anxious individuals and may interfere with task demands, leading to poorer performances (Bresin *et al.* 2011; Eysenck and Calvo 1992; Eysenck *et al.* 2007). On the other hand, in certain circumstances higher vigilance, arousal and desire to perform in highly anxious people may lead to enhanced performances (Bresin *et al.* 2011; Calvo and Alamo 1987). Participants' performance appears to be more impaired by high levels of anxiety when the task is highly difficult and/or requires an important short-term memory component (Eysenck and Calvo 1992). On the other hand, relatively easy tasks requiring little cognitive load such as fine motor tasks, do not usually seem to be affected by increasing anxiety levels (Eysenck and Calvo 1992).

One key feature inherent to anxious individuals is an enhanced sensitivity to environmental threats, with anxious persons being more prone to detect and being more distracted by threats in the environment than their non-anxious counterparts (Frewen *et al.* 2008; Mathews and McLeod 1994). Accordingly, both clinically anxious and high trait or state anxious individuals display enhanced selective visual attention to threats, which is reflected by faster reaction times to threatening and/or ambiguous than to nonthreatening visual stimuli, and by slower reaction times to neutral targets in the presence of threatening visual distracters (Fox *et al.* 2001; Frewen *et al.* 2008; Garner 2010). Despite the indubitable evolutionary utility of the normal awareness to potential dangers shown by the common person, an excessive sensitivity to threats can be problematic, especially when the presumed threats do not represent real danger.

Although the existence of a cognitive bias for threatening visual material in anxious people now seems to be clearly established, evidence of such bias in olfaction is scarce, as only a few studies have investigated the influence of mental state and/or health on olfactory processing. For instance, patients suffering from major depression were shown to exhibit reduced general olfactory function (Pause *et al.* 2001). With regard to anxiety disorders, patients suffering from post-traumatic-stress disorder tend to perform better in odor identification tests and respond faster to CO_2, an unpleasant stinging gas that acts on the trigeminal system (Croy *et al.* 2009). Furthermore, patients suffering from different anxiety disorders have been shown to be less accurate at discriminating odors and showed higher intensity estimates and increased valence rating ranges to odors from the Sniffin' sticks test than control participants, while their olfactory threshold and ability to identify odors were generally not affected (Clepce *et al.* 2012).

Overall, these findings strongly suggest that psychiatric disorders can significantly affect olfactory function. Concerning non-clinical populations, a more limited literature suggests that trait and state anxiety can also affect olfactory performance; however the nature and direction of this effect has not been clearly established. Although they are closely related, trait and state anxiety represent two fundamentally different concepts; state anxiety refers to a transitory emotional state characterized by subjective perceived feelings of tension and apprehension that fluctuate over time (Spielberger *et al.* 1983), while trait anxiety refers to individual differences in anxiety proneness that are relatively stable over time (Spielberger *et al.* 1983). Recent findings suggested state anxiety effects on olfactory processing, with young healthy adults exhibiting a positive correlation between state anxiety levels and unpleasant odor discrimination accuracy (Krusemark and Li 2012). These behavioral observations were paralleled by the finding of higher skin conductance rate changes, higher BOLD signal changes in the piriform cortex and increased functional connectivity between this cerebral region and emotion-related brain areas (amygdala and hippocampus) in response to negative odors during odor detection in high state anxiety individuals (Krusemark and Li 2012).

A first sign that trait anxiety can effect olfaction was provided when high-trait anxious individuals were shown to exhibit lower sensitivity to n-butanol, a relatively neutral odorant (Rovee *et al.* 1973). More recent studies reported contradictory findings regarding trait anxiety effects on olfactory perception. Havlicek and collaborators (Havlicek *et al.* 2012) found a

positive correlation between trait anxiety (here measured as a subscale of the neuroticism dimension of the Big Five personality model (McCrae and Costa 1997)), and olfactory sensitivity, as well as olfactory discrimination accuracy (both measured by using the Sniffin' sticks test). Karnekull et al (Karnekull *et al.* 2011), on the other side, did not find such a link between neuroticism levels and olfactory thresholds, neither between neuroticism scores and odor ratings. Still, highly neurotic individuals reported increased environmental chemosensory reactivity. In these studies, however, odor valence was not taken into account, hence there was no evidence for attention or perceptual bias to unpleasant odors. In another study, women high in trait anxiety perceived emotionally valenced (pleasant and unpleasant) odorants to be stronger than neutral odorants. They also displayed faster reaction times to pleasant vs. neutral stimuli, while high trait anxious men presented faster reaction times to both pleasant and unpleasant stimuli (Chen and Dalton 2005).

These previous studies suggest olfactory processing may be influenced by trait anxiety levels. However, they do not suggest the existence of a bias for negative olfactory stimuli in high trait anxiety persons. Nevertheless, this could potentially be due to the nature of the odorants employed in these studies (e.g. a lemon/orange scent for the pleasant and a fecal odor for the unpleasant stimuli (Chen and Dalton 2005)), as it has been shown that both pleasantness and edibility can separately affect reaction times and response accuracy to olfactory stimuli, with unpleasant food odors being detected faster than other combinations of edibility and valence (Boesveldt *et al.* 2010). Boesveldt et al., interpreted their results from the viewpoint that food odors in particular might warn of potential dangers in the real life, such as the ingestion of rotten food (Boesveldt *et al.* 2010).

In the current study we aimed to explore the association between trait anxiety and olfactory processing. We investigated whether olfactory perception varies as a function of odor pleasantness and as a function of different levels of trait anxiety. Specifically, we compared response times and subjective evaluations during the detection of two food odors (pleasant and unpleasant) between high and low trait anxiety individuals. We used response times instead of detection accuracy to assess performance to avoid ceiling effects due to the relative easiness of the task employed. We hypothesized that the presence of anxiety affects the olfactory system as it has been shown for the visual system (Frewen *et al.* 2008; Mathews and McLeod 1994). Specifically, we expected lower reaction times in high anxiety people

reflecting increased olfactory processing in these persons, and we expected this effect to be more pronounced for the unpleasant odor, reflecting the increased sensitivity to ecologically relevant stimuli in high anxiety individuals. This would indicate that anxiety has a generalized effect on sensory perception rather than a specific effect on the visual system. Moreover, we hypothesized that participants would generally respond faster to unpleasant odors, in accordance to previous findings (Boesveldt *et al.* 2010). We controlled for state anxiety effects, as potential impacts of this factor on olfactory processing have been recently suggested (Krusemark and Li 2012). Because depression may decrease olfactory perception (Pause *et al.* 2001), and because of the high comorbidity between anxious and depressive symptoms, we also controlled for potential depression effects on olfactory performance in our participants.

Material and methods

Participants

In total, 38 participants (18 women) aged between 18 and 35 years (Mean age 24.3 years, SD= 4.5) participated in the study. Because mean response times (RTs) in two participants were more than two standard deviations above the global mean, their data were discarded. No participant suffered of any medical condition at the time of the testing and did not report any olfactory problem. Participants were asked not to eat, drink and/or smoke one hour prior to the testing session. All participants provided written informed consent prior to testing. The protocol was approved by the Ethics Board of the University of Montreal.

Stimuli

Two olfactory stimuli were employed: a pleasant food odor (strawberry odor; Frey&Lau, Hamburg, Germany) and an unpleasant food odor (fish odor; Givaudan, Geneva, Switzerland), diluted in propylene glycole (Galenova, St. Hyacinth, QC) to concentrations of 10% and 25% respectively. These concentrations remained the same across trials and were selected based on a pretest in which participants rated them as falling well above perception threshold and as being equally intense. To ensure participants would respond only to the perceived odors and not to the tactile stimulation produced by the air puffs, odor-free air puffs

were also presented as a control condition. Stimuli were delivered birhinally in a pseudorandomized order.

Setting

We used customized olfactometer (Institute for Biomagnetism and Biosignalanalysis, University of Münster, Germany), which allows for the presentation of air pulses of well-defined duration to deliver the olfactory stimuli (La Buissonniere-Ariza *et al.* 2012). We connected the outlet channels to odor chambers (50 mL glass bottles, filled with 4 mL of odorant) via polyurethane tubing with 8mm outer diameter and an inner diameter of 4.8 mm (Fre-Thane 85A, Freelin-Wade, McMinnville, OR). The same polyurethane tubing of approximately 50 cm length were connected to the odor chambers at one end, and inserted into the participants' nostrils at the other end. All tubings were separated to avoid cross-contamination of odors. During odor presentation, air with a flow of 3 L/min was switched into the respective channel. All nasal stimuli lasted 500ms. We controlled stimulus delivery and response recording using the "Presentation" software (Neurobs) on a PC (AMD Phenom X3 processor) with Windows XP.

Procedure

Participants were tested in one session of approximately 45 minutes. Before the experimental task, they completed the Spielberg State-Trait Anxiety Inventory (STAI-Y; (Spielberger *et al.* 1983)) and the Beck Depression Inventory (BDI; (Beck *et al.* 1961)). Furthermore, we confirmed normal olfactory ability to identify odors by means of a custom-made 4 choice odor identification test with eight items (pear, cola, rose, peach, eucalyptus, strawberry, cloves and lemon) contained in bottles of 50mL. Odors were presented to the participants one at a time and participants were allowed to smell each bottle as long as they needed to indentify the odor. All participants identified correctly at least 7 out of 8 odors.

Participants were tested in 3 blocks of 7.5 minutes each; they were allowed to rest between the blocks. During the whole procedure, participants were asked to fixate a white cross, presented in the middle of a computer screen. Prior to every nasal stimulation, the white cross was replaced by a red cross, as a signal for the participants to breathe-in. Participants were instructed to detect the presence of the odorants as fast as possible by pressing one button, and were told not to press the button if an odor-free air puff was presented. On

average, participants received a nasal stimulus every 30 seconds (25 – 35s). Each nasal stimulus (pleasant odor, unpleasant odor, odor-free puff) was presented 5 times per block.

Variables of interest

Anxiety and depression levels

Trait and state anxiety were measured with the STAI-Y, a widely used standardized questionnaire for measuring anxiety with good psychometric properties (Spielberger *et al.* 1983). We further measured depression levels in participants using the BDI which also possesses good psychometric properties (Beck *et al.* 1961).

Odor detection

We recorded response accuracy and response times (RT) as dependent variables, with higher accuracy and shorter RT indicative of a better performance.

Odor intensity and pleasantness

After each stimulation block, we assessed odor intensity and pleasantness via a visual analogue scale ranging from 0 (not intense / very unpleasant) to 10 (very intense / very pleasant). Participants were asked to draw a bar across the scale for both ratings for the two odors separately after each block according to their subjective experience of the odors during the entire block. We measured the distance in mm.

Statistical analysis

Participants were divided in two groups according to their trait anxiety levels using the median (30 points) of the overall sample. We removed participants scoring at the median (n=3). Hence, 17 of them were in the Low trait anxiety group, whereas the remaining 18 were in the High trait anxiety group. High and low trait anxiety groups did not differ in terms of age ($T [1,33] = 1.61$, $p = .116$) or sex ($X2 [1, 35] = .274$, $p = .738$) (see Table 1).

Only trials with button-press responses were considered for further analysis (in total, 1129 trials). Participants' performance was evaluated in terms of hit rates (proportion of correct responses) and response times (RT; only for correct responses in the range 100-2000 ms post stimuli). We also compared false positive rates (detection of an odor during the presentation of an odor-free puff) between groups. To ensure that the RT distribution was normal, and in accordance with the literature (Olofsson *et al.* 2012), we performed a log

transformation on the RTs. However, for the sake of clarity, we report the non-transformed values (in ms) for the descriptive statistics.

To assess potential differences in terms of depression levels between anxiety groups, we first performed one-way ANOVAs on BDI scores, as well as state anxiety scores as the dependent variables and trait anxiety group as between subject factor. We then performed repeated measures ANCOVAs on log transformed RT as the dependent variable with odorant (pleasant = strawberry, unpleasant = fish) as within subject factor and trait anxiety group (high anxiety, low anxiety) as between subject factor, and depression levels (BDI scores) and state anxiety scores as covariates. To further investigate potential perceptual differences, we also performed repeated measures ANCOVAs with odorant as within subject factor, anxiety group as between subject factor, intensity and pleasantness as dependent variables, and depression and state anxiety levels as covariates. We calculated partial eta-square to estimate effect sizes and considered them to be small, medium and large if eta=.01, eta=.06, and eta=.14, respectively, in accordance with Cohen (Cohen 1988).

Finally, we performed exploratory analyses on the whole sample to investigate potential sex differences in terms of RT and ratings of intensity and pleasantness. We computed repeated measures ANOVAs with odorant as within subject factor, sex as between subject factor and RT, odor intensity and odor pleasantness ratings as dependent variables.

Following the finding of a significant effect of trait anxiety on RT, we decided to further investigate whether trait anxiety levels were correlated to RTs for both odorants in all participants from the complete sample (n=38). Therefore, we computed Pearson's partial correlation coefficient between trait anxiety levels and RT to both odors, with depression and state anxiety levels as covariates.

Results

Performance was first assessed via hit rates in the detection of both odors. On average, participants detected the presence of both odors with very high accuracy, succeeding in more than 90 % of the trials. Trait anxiety groups did not differ significantly in terms of hit rates for strawberry odor detection (respectively 94.4 % (9.2) for high anxiety and 95.4% (11.2) for low anxiety; $F [1,33] = .066$, $p = .8$), neither for fish odor detection (respectively 98.8% (4.7) for high anxiety and 90.6 % (16.0) for low anxiety; $F [1,33] = 2.35$, $p = .1$). No differences

immerged either in terms of false positive rates (respectively 11.5 % (11.2) for high anxiety and 12.9% (16.8) for low anxiety; F [1,33] = .006, p = .9). Therefore to avoid ceiling effects due to the high accuracy of our participants, we decided to perform all subsequent analyses on the RT only.

On average, participants responded to the strawberry odor after 1003.78 (standard deviation: 298.89) ms and to the fish odor after 1006.91 (264.31) ms. The strawberry odor (M= 5.6 (SD= 1.8)) seemed to be rated as more intense than the fish odor (7.1 (2.1)), but this difference was not statistically significant when controlling for state anxiety and depression levels (F[1,31] = 1.51, p = .228). We did not find anxiety group effects on odor intensity ratings (F[1,31] = 1.20, p = .281). We observed a significant effect of odorant on pleasantness, with the fish odor being rated significantly more unpleasant than the strawberry odor (fish: M=2.0 (1.9); strawberry: 7.8 (1.4); F[1,31]=9.09, p=.005). No effect of anxiety was observed for pleasantness ratings (F[1,31] = .40, p = .53).

----- Insert Figure 1 approximately here------

We observed a significant effect of trait anxiety (F[1,31]=7.86; p=0.009, eta=0.20) on RT (values in log ms) where high trait anxiety participants reacted after 2.92 (.09; corresponding to 851.90 (182.70) ms) to the strawberry odor and 2.94 (.0.10; 894.23 (211) ms) to the fish odor, while low trait anxiety participants reacted more slowly after 3.05 (0.11; 1164.60 (299.47) ms) and 3.04 (.10; 1126.23 (267) ms) for strawberry and fish odors, respectively. No effects of odorant were found (F [1,31] = .01, p = .907) (see Figure 1). We observed significant state anxiety differences between high (M= 34.8. (SD= 7.3)) and low (25.4 (4.6)) trait anxiety participants (F [1,33]= 20.33, p < .0001). We also observed significant group differences in terms of BDI scores between high (M=8.2 (7.7)) and low (3.5 (3.0)) trait anxiety (F[1,33]=5.35, p=.027). Nevertheless, as the ANCOVA showed, neither state anxiety (F [1,31] = .066, p = .799) nor depression levels (F[1,31] = .312, p = .580) played a significant contribution to trait anxiety effects on RT. There was no significant group x odorant interaction.

On average, women responded after 936.39 (322.26) ms to the strawberry odor and after 953.56 (247.94) ms to the fish odor. Men responded after 1032.33 (264.26) ms to the

strawberry odor and 1039.11 (281.94) ms to the fish odor. We did not observe significant sex effects on RT ($F[1, 36] = 1.11$, $p = .229$). Women made average odor intensity ratings of f 5.6 (1.7) for the strawberry odor and of 6.9 (2.3) for the fish odor, while men rated the strawberry odor with a mean intensity of 5.6 (1.7) and the fish odor with a mean intensity of 7.1 (1.9). No sex differences were found for odor intensity ratings ($F[1, 36] = 0.08$, $p = .785$). Finally, women made average pleasantness ratings of 7.6 (1.6) for the strawberry and 1.5 (1.7) for the fish odor. Men rated the strawberry odor with an average pleasantness of 7.6 (1.5) and of 2.3 (1.9) for the fish odor. Again, we did not find significant sex effects on odor pleasantness ratings ($F [1, 36] = 0.75$, $p = .393$).

-----Insert Figure 2 approximately here ------

We identified significant and moderate negative correlations between trait anxiety scores and the log transformed RTs to strawberry ($r[38]=-0.40$, $p=.012$) and fish ($r[38]=-0.40$, $p=.013$) odors (Figure 2).

Discussion

The goal of the present study was to investigate anxiety effects on olfactory processing and a potential bias for unpleasant odors in highly anxious individuals. To address this we compared RT between participants with high and low trait anxiety levels performing an odor detection task using a pleasant and an unpleasant food odor, while controlling for potential state anxiety and depression-related confounds and discarding sex effects on RT, intensity and pleasantness ratings.

As hypothesized, high trait anxiety participants reacted faster to both odorants compared to low anxiety individuals. In several tasks involving other sensory modalities, impaired and slowed performances were often reported in anxious people. This has been explained, in parts, by the detrimental effects that worries may have on the attention capacities in affected people (Bresin *et al.* 2011; Calvo and Alamo 1987; Eysenck and Calvo 1992). However, these impairing effects tend to be greater during complex cognitive tasks with high attention and working memory loads, and comparatively appear to have less impact on simple tasks (Eysenck and Calvo 1992) like odor detection. On the other hand, worries about task

performance in highly anxious people may lead to an increase in motivation regarding the task, and therefore to the allocation of additional processing resources (Eysenck and Calvo 1992). Moreover, anxious people appear to be more sensitive to failure feed-back and are more prone to detect mismatches between performance and expectation, leading them to increase efforts in an effort to increase task performance (Eysenck and Calvo 1992). This may in part explain the faster detection speed encountered in our highly anxious participants. It may also be possible that trait anxiety levels had an influence not only on olfactory processing, but also on motor speed and/or a proneness to respond since the task we used required pressing a button as fast as possible in order to indicate the presence of an odor. However, high and low trait anxiety participants did not differ in terms of false positive rates, which reduces the possibility of a higher proneness to respond in our high anxiety subjects. Macaulay (2010) investigated mouse-click speed while participants performed a stressing 4-choice computer task as a function of state anxiety levels and found no evidence of a correlation between anxiety levels and motor speed, such that high anxiety participants did not tend to respond faster than low anxiety participants (Macaulay 2010). Still, to verify the specificity of trait anxiety effects on olfactory processing, future studies should use visual or auditory control tasks to discard potential effects of anxiety on answering speed in general. Lastly, higher arousal levels, that is, higher state anxiety levels, could also contribute to faster responses in high trait anxiety individuals (Bresin *et al.* 2011; Calvo and Alamo 1987). Indeed, our high trait anxiety participants displayed also higher state anxiety levels when compared to their low trait anxiety counterparts. This is not surprising, since trait anxiety is a relatively stable measure of anxiety which may be considered as an indication of participants' susceptibility to experience state anxiety (Spielberger *et al.* 1983). However, state anxiety levels did not affect trait anxiety effects on RT and did not have a significant effect on RT to any of the two odors, suggesting anxiety effects on odor detection speed are specific to trait anxiety.

Our results do not support the finding that participants detect unpleasant food odors with higher speed (Boesveldt *et al.* 2010). Furthermore, we did not find any evidence for a preferential bias for aversive stimuli in high anxiety individuals (Frewen *et al.* 2008; Mathews and McLeod 1994). Several factors could potentially explain the absence of pleasantness effects in our study. First, it may be possible that some participants did not consider the fish odor to be unpleasant and the strawberry odor to be pleasant, or that differences between the

two odors in terms of perceived pleasantness were too small to differentiate the odors. However, participants on average classified the fish odor as unpleasant and the strawberry odor as pleasant, with pleasantness ratings of similar means and standard deviations as the ones reported by Boesveldt et al. (Boesveldt *et al.* 2010); not to mention that the two odors significantly differed in terms of pleasantness. Differences in terms of odor intensity could also have influenced RT, since more intense odors could be perceived faster, masking potential pleasantness effects if the pleasant odor was more intense. However, no differences in terms of perceived intensity were found between the odors. At the same, it is possible that the two odors did not differ in terms of perceived dangerousness or ecological relevance, although they differed in terms of pleasantness. This should be investigated in future studies using different odors warning of potential dangers such as smoke or gas. Still, Boesveldt employed the same odors and found odor pleasantness effects on detection speed. A potential explanation for the discrepancy between our results (obtained from a French Canadian sample) and Boesveldt's (obtained from an American sample) might be that cultural differences between the samples could lead to distinct subjective experiences, since perceptual judgments such as odor intensity, pleasantness, saliency and edibility may differ between cultures (Chrea *et al.* 2004). Further studies may elucidate whether any of these factors could have had any significant impact on our findings.

The more anxious the participants were, the faster they were at detecting odors, regardless of whether of they were pleasant odors or not, suggesting some defensive and/or motivational mechanisms are possibly enhanced in anxiety. While other researchers have also found participants to be faster in detecting both pleasant and unpleasant vs. neutral olfactory stimuli, with no difference between pleasant and unpleasant stimuli (Chen and Dalton 2005), more recent work has reported altered odor discrimination in high trait anxious participants (Krusemark and Li 2012) and in clinically anxious participants (Clepce *et al.* 2012) for unpleasant odors only, thus supporting the hypothesis of a negative bias in anxious participants in the olfactory modality. Olfactory discrimination however, is a complex task that requires different cognitive processes such as working memory and decision making. Odor detection, in turn, is a much simpler task, where participants only have to detect the presence of an odor, independently of the odor properties (Hedner *et al.* 2010). Hence, it is

possible that odor emotional valence plays a role in odor processing in anxious people, but that the negative bias found in visual tasks is not necessarily present in olfaction, at least for simple tasks like odor detection. Furthermore, anxiety effects seem to be restricted to odor processing and do not apply to odor perception, as subjective ratings did not differ between anxiety groups.

These findings suggest that anxiety levels in healthy participants do modulate olfactory detection speed, and that this influence is independent of odor pleasantness or participants' subjective experience. This may reflect a general effect of anxiety features such as increased awareness and motivation, as previously demonstrated for other sensory modalities (Eysenck and Calvo 1992). However, specific effects of anxiety on the olfactory system may also exist. The olfactory system comprises of several distinct brain regions such as the orbitofrontal cortex, amygdala and hippocampus (Zald and Pardo 2000), which are also implicated in emotional processing and regulation (Gottfried and Dolan 2004; Milad *et al.* 2006; Sehlmeyer *et al.* 2009), underlying the close relationship between the olfactory and the limbic systems. The amygdala and the hippocampus have been shown to be structurally and/or functionally altered in anxious individuals (Bremner 2004; Milad *et al.* 2006); these neural alterations in anxiety could in turn have implications on odor processing. Recent findings suggested that primary olfactory cortex activity could also be modulated by anxiety, with anxious adults showing increased preferential responses in the piriform cortex during the detection of emotionally valenced odors (negative in this case) (Krusemark and Li 2012). Thus, it is possible that highly anxious participants exhibit altered functioning of particular brain regions which in turn lead to decreased RT during odor detection. Future neuroimaging studies comparing high and low trait anxiety participants during olfactory and non-olfactory tasks may clarify the exact location, if any, of the effect of trait anxiety on the olfactory system.

Other factors may also have contributed to our findings. First, we did not control for menstrual cycle and oral contraception usage in our female participants. Although there were no sex differences between anxiety groups, and even though potential sex effects on RTs, intensity or pleasantness ratings were discarded, differences in menstrual cycle phases and/or oral contraception usage between our female participants may have led to differences in their ability to detect the odors, as these factors were shown to modulate olfactory processing in

several contexts such as olfactory sensitivity assessment, odor intensity ratings and odor identification tasks (Derntl *et al.* 2013). Other between-group hormonal differences could also influence our findings. For example, serum leptin levels, which were not measured in the present study, have been associated with modulations in odor identification performance and this effect varied according depending on the sex of the participant (Karlsson *et al.* 2002). Despite the potential influence hormonal levels may have had on our participants' performance, we believe this should not affect between-group comparisons, as it seems unlikely that there was a systematic inclusion of participants in one specific menstrual cycle phase, with higher oral contraception usage and/or with higher leptin levels in one of the experimental groups. Differences in smoking habits could have influenced odor perception and intensity ratings in our participants, as a reduction in olfactory sensitivity in smokers has been previously reported (Ishimaru and Fujii 2007)(Katotomichelakis *et al.* 2007)(Hayes and Jinks 2012). Still, all of our participants reported normal olfactory function and successfully passed a preliminary odor identification task prior to testing, indicating preserved olfactory abilities. Finally, other individual differences such as hunger/satiety levels and circadian phases may have also modulated olfactory processing in our participants', as these factors were not systematically controlled and have been shown to have some effects on olfaction (O'Doherty *et al.* 2000)(Goel and Grasso 2004).

Despite these limitations, we demonstrate here that trait anxiety levels in healthy adults are negatively correlated with odor detection response times. In other words, we found highly anxious participants to be faster at detecting odors than low anxiety individuals, regardless of odor valence, subjective experiences and/or depression and state anxiety levels. Therefore, even though we did not find evidence for a preferential bias for negative olfactory stimuli in anxious people as demonstrated in the visual modality, and suggested by a few recent studies with more complex paradigms in the olfactory modality (Clepce *et al.* 2012; Krusemark and Li 2012), we show that anxiety does influence processing speed in simple olfactory tasks such as odor detection. We believe that specific neural mechanisms, possibly implicating the piriform cortex and/or medial temporal lobe structures, could underlie the enhanced odor detection speeds displayed observed in anxious participants.

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References

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. 1961. An inventory for measuring depression. Arch Gen Psychiatry 4: 561-571.

Boesveldt S, Frasnelli J, Gordon AR, Lundstrom JN. 2010. The fish is bad: Negative food odors elicit faster and more accurate reactions than other odors. Biol Psychol 84: 313-317.

Bremner JD. 2004. Brain imaging in anxiety disorders. Expert review of neurotherapeutics 4: 275-284.

Bresin K, Robinson MD, Ode S, Leth-Steensen C. 2011. Driven, distracted, or both? A performance-based ex-Gaussian analysis of individual differences in anxiety. Journal of personality 79: 875-904.

Calvo MG, Alamo L. 1987. Test anxiety and motor performance: The role of muscular and attentional demands. International journal of psychology 22: 165-177.

Chen D, Dalton P. 2005. The effect of emotion and personality on olfactory perception. Chemical senses 30: 345-351.

Chrea C, Valentin D, Sulmont-Rossé C, Ly Mai H, Hoang Nguyen D, Abdi H. 2004. Culture and odor categorization: agreement between cultures depends upon the odors. Food Quality and Preference 15: 669-679.

Clepce M, Reich K, Gossler A, Kornhuber J, Thuerauf N. 2012. Olfactory abnormalities in anxiety disorders. Neuroscience letters 511: 43-46.

Cohen J. 1988. Statistical power analysis for the behavioral sciences. New Jersey: Lawrence Erlbaum.

Croy I, Schellong J, Joraschky P. 2009. Olfactory Function in Childhood Maltreatment and Post-Traumatic Stress Disorder. Chemical Senses 34: A20-A21.

Derntl B, Schopf V, Kollndorfer K, Lanzenberger R. 2013. Menstrual cycle phase and duration of oral contraception intake affect olfactory perception. Chemical senses 38: 67-75.

Eysenck MW, Calvo MG. 1992. Anxiety and performance: The processing efficiency theory. Cognition & Emotion 6: 409-434.

Eysenck MW, Derakshan N, Santos R, Calvo MG. 2007. Anxiety and cognitive performance: attentional control theory. Emotion 7: 336-353.

Fox E, Russo R, Bowles R, Dutton K. 2001. Do threatening stimuli draw or hold visual attention in subclinical anxiety? Journal of experimental psychology. General 130: 681-700.

Frewen PA, Dozois DJ, Joanisse MF, Neufeld RW. 2008. Selective attention to threat versus reward: meta-analysis and neural-network modeling of the dot-probe task. Clin Psychol Rev 28: 307-337.

Garner M. 2010. Selective attention to threat in childhood anxiety: evidence from visual probe paradigms. In: John Wiley & Sons L, (ed.), Information processing biases and anxiety: A developmental perspective. West Sussex, UK. p. 77-108.

Goel N, Grasso DJ. 2004. Olfactory discrimination and transient mood change in young men and women: variation by season, mood state, and time of day. Chronobiology international 21: 691-719.

Gottfried JA, Dolan RJ. 2004. Human orbitofrontal cortex mediates extinction learning while accessing conditioned representations of value. Nature neuroscience 7: 1144-1152.

Havlicek J, Novakova L, Vondrova M, Kubena AA, Valentova J, Roberts SC. 2012. Olfactory perception is positively linked to anxiety in young adults. Perception 41: 1246-1261.
Hayes JE, Jinks AL. 2012. Evaluation of smoking on olfactory thresholds of phenyl ethyl alcohol and n-butanol. Physiology & behavior 107: 177-180.
Hedner M, Larsson M, Arnold N, Zucco GM, Hummel T. 2010. Cognitive factors in odor detection, odor discrimination, and odor identification tasks. J Clin Exp Neuropsychol 32: 1062-1067.
Ishimaru T, Fujii M. 2007. Effects of smoking on odour identification in Japanese subjects. Rhinology 45: 224-228.
Karlsson AC, Lindroos AK, Lissner L, Torgerson JS, Carlsson B, Carlsson LM, Sjostrom L. 2002. Evidence for gender-specific associations between leptin and olfaction. J Gend Specif Med 5: 25-32.
Karnekull SC, Jonsson FU, Larsson M, Olofsson JK. 2011. Affected by smells? Environmental chemical responsivity predicts odor perception. Chemical senses 36: 641-648.
Katotomichelakis M, Balatsouras D, Tripsianis G, Davris S, Maroudias N, Danielides V, Simopoulos C. 2007. The effect of smoking on the olfactory function. Rhinology 45: 273-280.
Krusemark EA, Li W. 2012. Enhanced olfactory sensory perception of threat in anxiety: An event-related fMRI study. Chemical Perception.
La Buissonniere-Ariza V, Frasnelli J, Collignon O, Lepore F. 2012. Olfactory priming leads to faster sound localization. Neuroscience letters 506: 188-192.
Macaulay M. 2010. The speed of mouse-click as a measure of anxiety during human-computer interaction. Behaviour & Information Technology 23: 427-433.
Mathews A, McLeod CB. 1994. Cognitive approaches to emotion and emotional disorders. Annual Review of Psychology 45: 25-50.
McCrae RR, Costa PT, Jr. 1997. Personality trait structure as a human universal. Am Psychol 52: 509-516.
Milad MR, Rauch SL, Pitman RK, Quirk GJ. 2006. Fear extinction in rats: implications for human brain imaging and anxiety disorders. Biological psychology 73: 61-71.
O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F, Kobal G, Renner B, Ahne G. 2000. Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. Neuroreport 11: 893-897.
Olofsson JK, Bowman NE, Khatibi K, Gottfried JA. 2012. A time-based account of the perception of odor objects and valences. Psychol Sci 23: 1224-1232.
Pause BM, Miranda A, Goder R, Aldenhoff JB, Ferstl R. 2001. Reduced olfactory performance in patients with major depression. J Psychiat Res 35: 271-277.
Rovee CK, Harris SL, Yopp R. 1973. Olfactory thresholds and level of anxiety. Bull Psychonom Soc 2: 76-78.
Sehlmeyer C, Schoning S, Zwitserlood P, Pfleiderer B, Kircher T, Arolt V, Konrad C. 2009. Human fear conditioning and extinction in neuroimaging: a systematic review. PloS one 4: e5865.
Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. 1983. Manual for the State–Trait Anxiety Inventory. Palo Alto, CA: Consultant Psychologists Press.

Zald DH, Pardo JV. 2000. Functional neuroimaging of the olfactory system in humans. International journal of psychophysiology : official journal of the International Organization of Psychophysiology 36: 165-181.

Tables

Table 1. Demographic characteristics of trait anxiety groups

Anxiety group	**Mean age and SD**	**Gender**			
		F		M	
		N	%	N	%
Low trait anxiety	25.5 (5.6)	7	41.2	10	58.8
High trait anxiety	23.0 (3.43)	9	50	9	50

Figures

Figure 1: Average response times (ms) to strawberry and fish odors for Low trait and High trait anxiety participants. Error bars indicate standard deviations. The * indicates p <.01.

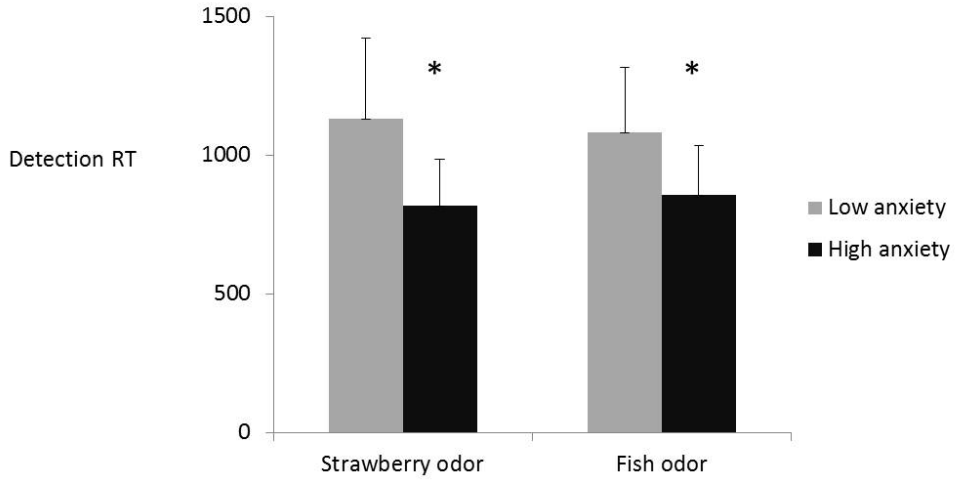

Figure 1

Figure 2: Correlation between response times (ms) to strawberry and fish odorant and trait anxiety levels. both r=-.40, both p <.05.

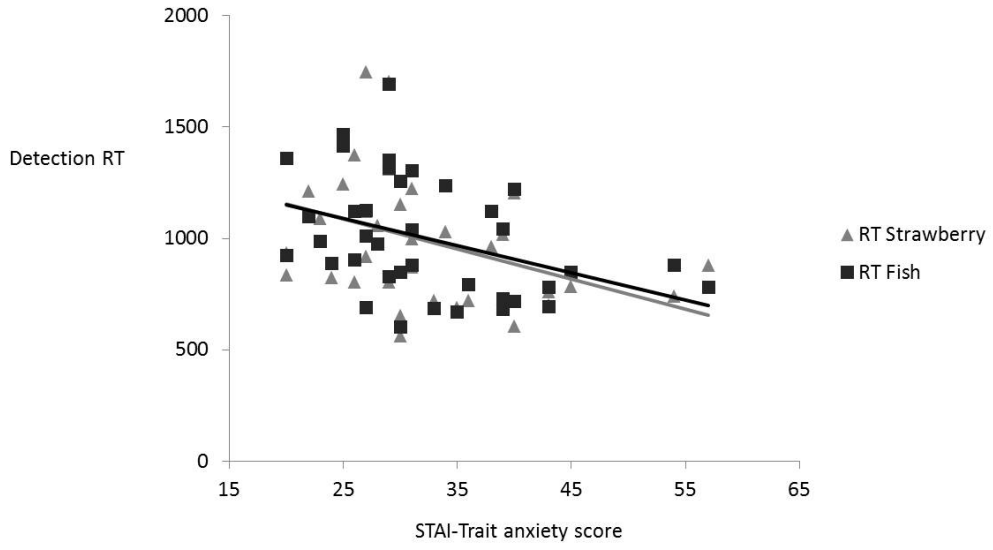

Figure 2

Olfactory priming leads to faster sound localization

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Abstract

Cross-modal interactions between vision, audition and touch have been extensively studied in the last decade. However, our understanding of how the chemical senses interact with other sensory modalities remains relatively scarce.

We therefore performed a cued auditory localization paradigm in healthy young adults by measuring reaction times to monaural auditory stimuli after subjects had been cued by unilateral olfactory stimuli, mixed olfactory/trigeminal stimuli or nasal somatosensory stimuli. We also used a control condition without cuing. As expected, all cuing conditions led to enhanced performances in auditory localization. Further, both odors led to significantly shorter reaction times when compared to the somatosensory stimuli. We did not observe any effect of side-congruency between the cues and the targets. These results suggest facilitative effects of odorous cues independent of a possible trigeminal component in the interaction between olfaction and audition.

Introduction

Environmental stimuli usually activate several sensory systems simultaneously. We know from a rapidly growing literature that the different senses, such as audition, vision, and touch, interact with each other in our perception of the environment [21, 34]. A well-known example of such interactions is the ventriloquism effect [41], a perceptual illusion in which the voice of the puppeteer is shifted to a congruent visual source, that is, the puppet, therefore seeming to emanate from it [21]. At the cortical level, evidence of multisensory integration illustrated by higher neuronal responses to bimodal vs unimodal stimuli has also been shown in previous studies [25, 40]. Interactions between the senses can also lead to changes in terms of performance during the execution of perceptual tasks. Hence, auditory cues have been shown to improve the detection of a visual target when presented simultaneously with it [24, 42]. Similar findings have been reported for vision and touch [43]. Cross-modal interactions have also been reported for the chemical senses, i.e., smell, taste and the trigeminal chemosensory system. Most studies focused on flavor perception and thus the interactions between the chemical senses (e.g., olfactory/ gustatory: [11, 38, 44]; gustatory/ trigeminal: [6, 8]; olfactory/trigeminal [5, 22, 23]).

We know that most of the odors activate the trigeminal system in addition to the olfactory system [12, 15]; thus most odors are mixed olfactory /trigeminal stimuli. Hence, it is difficult to isolate the effect of odors from their trigeminal component, and vice versa. Both systems seem to specifically influence the processing of visual stimuli, by either increasing or decreasing reaction times [26, 27]. However, only a few studies have investigated cross-modal interactions between the olfactory and/or trigeminal systems on one hand and other sensory modalities on the other hand, most of them focusing on vision, and even fewer have compared pure odors with mixed olfactory/trigeminal odorants. The effect of ambient odors on simple reaction times to auditory and visual stimuli was investigated in a series of studies [26-28]. In one study, the unpleasant odor of pyridine or the pleasant odor of lavender were sprayed into a testing room prior to the examination, resulting in a background odor throughout the experiment [28]. Subjects who were exposed to the odors reacted faster to both visual and auditory stimuli than control subjects who performed the test in an odor free environment. The authors interpreted these results as both odors to cause increased arousal levels, leading to

shorter reaction times. Unfortunately, authors did not apply any control condition with continuous stimulation of another sensory modality; thus one cannot conclude that the observed effects to be specific to olfaction. Moreover, both odors likely also activate the trigeminal nerve and are therefore considered mixed olfactory-trigeminal stimuli [1, 30]. The same group investigated olfactory modulation of visual reaction times in two other studies [26, 27]. In the first, subjects' task was to indicate as quickly as possible on which side of a circle a gap appeared on a computer screen. In this study, subjects were exposed to either allyl-thioisocyanate (mustard oil) –, a mixed olfactory/ trigeminal stimulus [4, 13] – or phenyl ethanol – a pure olfactory stimulus [12]. In partial contrast to the findings of the first study, when the pure olfactory ambient stimulus was applied, subjects reacted even slower than in the no ambient odor baseline condition; when the mixed olfactory/trigeminal ambient odor was applied reaction times were not different from baseline. In the second study, the authors distracted the subjects: when a luminance change during the task occurred, subjects reacted slower to the task than in the no ambient odor baseline condition, and even more so in the mixed olfactory/trigeminal ambient odor condition. In the pure odor condition, however, subjects became significantly faster when they were distracted [26, 27]. The authors speculated that odor exposure led to two distinct mechanisms, i.e., a non-specific slowing of processing and an eventual ignorance of the distracter on one hand (pure odorant), and an increase of arousal levels due to the irritant properties of the stimuli, leading to an enhanced sensitivity to distracters on the other hand (mixed olfactory/trigeminal odor). In addition to these studies, we know that pure odorant cues (such as vanillin or H_2S) induce priming effects during the presentation of emotionally-valenced visual stimuli, illustrated by faster reaction times to disgusted faces after the presentation of odor cues vs ambient air [37]. A specialized area for integration of olfactory-visual information, located in the anterior insula, and top-down modulation processes of this area by higher-order structures (prefrontal and cingulate cortices) maybe the neural correlates underlying this priming effect [36]. In summary, odors have an effect on reaction times to heteromodal stimuli, suggesting cross-modal interactions between olfaction and other senses. Ambient odors exhibit an unspecific effect on simple reaction times to visual and auditory stimuli [28]. Pure odors and mixed olfactory/trigeminal stimuli affect reaction times to visual stimuli and visual attentional capture differentially [26,

27]. Finally, pure odorant cues have specific behavioral and functional priming effects on the identification of emotional visual stimuli [36, 37].

In addition to temporal contiguity, spatial proximity is a critical feature of multisensory integration. That is, in order to integrate two stimuli from two different sensory modalities and therefore enhance performance, both stimuli usually need not only to co-occur in time, but also in space [21, 32]. This is particularly salient in spatial localization tasks, where spatially congruent cues from a different modality enhance the detection of a stimulus, whereas incongruent cues may have no influence or even impair performance [17, 21].

In the present study, we planned to elucidate the impact of olfactory and trigeminal co-stimulation on auditory processing. More specifically, we investigated the effect of lateralized chemosensory cuing on sound localization. By doing so we investigated possible interactions between the olfactory and trigeminal systems and the auditory system. Moreover, our paradigm allowed us to separate the effects of the trigeminal and the olfactory components of odorants, which usually occur simultaneously.

We applied an odor localization task, which is one way of dissociating between the olfactory and the trigeminal component of an odor. It is based on the fact that humans cannot detect to which nostril an odorous stimulus has been presented to in a monorhinal stimulation paradigm, unless the stimulus also activates the trigeminal system [14, 16, 20].

We performed a cued auditory localization paradigm by measuring reaction times to monaural auditory stimuli after subjects had been cued by chemosensory stimuli. Shortly before each auditory stimulus, subjects received an alerting chemosensory signal (the cue) delivered to one nostril, either ipsilateral or contralateral to the auditory stimulus. Olfactory cues consisted of (a) a pure odor and (b) a mixed olfactory/trigeminal stimulus. These stimuli were delivered in an air puff, which creates somatosensory stimulation; we thus added (c) odorless air puffs as a somatosensory control condition. All stimuli were delivered very shortly before the target stimuli. In addition, we measured a (d) baseline condition without cuing.

We expected all cuing stimuli to induce shorter reaction times than in the no cue condition. In addition, we had a series of specific hypotheses. First, we hypothesized (1) the facilitative processing induced by cuing to be enhanced by both kinds of olfactory stimuli (the pure olfactory stimulus and the mixed olfactory /trigeminal stimulus) when compared to

simple somatosensory stimulation [24]. Next we hypothesized (2) spatial congruency between cue and target to lead to a larger gain than incongruent stimulation [39]. Consequently, cues which are side congruent with the target stimulus were expected to lead to a stronger reduction of reaction times whereas cues that are side incongruent would serve as distracters and lead to a weaker reduction of reaction times (or not at all). This however would only be true for stimuli which we are able to localize in a monorhinal stimulation design namely the mixed olfactory/trigeminal (b) and somatosensory (c) conditions. Pure olfactory stimuli, which cannot be localized, [16, 20], should not have any effect of olfactory (a) side-congruent stimulation.

Material and Methods

The protocol was approved by the Ethics Board of the University of Montreal and subjects gave informed written consent prior to testing.

Subjects

Thirty-one subjects (14 women) aged between 18 and 35 years (Mean age 23+/-3 years) participated in the study. Two subjects were removed from analysis because their mean reaction times were more than two standard deviations from global mean reaction times, so the final sample consisted of 29 healthy adults (14 women). No participant suffered of any medical condition at the time of the testing and did not report any olfactory or auditory problem.

Stimuli

Olfactory stimuli

We used eucalyptol (eucalyptus odor; Galenova, St.-Hyacinth, QC) and phenyl ethyl alcohol (rose odor; SAFC, St. Louis, MO) as chemosensory stimuli, and air puffs as somatosensory stimuli. Eucalyptol is considered a mixed olfactory trigeminal stimulus [12, 13], which activates both olfactory and chemosensory trigeminal receptors, whereas phenyl ethyl alcohol is considered a relatively pure olfactory stimus [12] which activates the olfactory nerve exclusively. Air puffs, on the other hand, activate only somatosensory trigeminal fibers.

We used the same adapted stimulation device (Institute for Biomagnetism and Biosignalanalysis, University of Münster, Germany) as in an earlier study [16] to deliver the

nasal stimuli. In short, this computer controlled device delivers air pulses of well-defined duration. We connected the outlet channels to odor chambers (50 mL glass bottles, filled with 4 mL of odorant) via polyurethane tubing with 8mm outer diameter and an inner diameter of 4.8 mm (Fre-Thane 85A, Freelin-Wade, McMinnville, OR). The odor chambers were then connected to the subjects' nose by means of the same polyurethane tubing of approximately 50 cm length. Since all tubings were separated we could avoid cross contamination of odors. During odor presentation, air with a flow of 2 L/min was switched into the respective channel. All nasal stimuli lasted 750ms. Therefore, subjects were stimulated with 25mL of air per stimulated nostril.

Auditory stimuli

Unilateral white noise was presented either to the right or to the left ear through headphones. Each presentation lasted 150ms (5ms rise/fall time). Sounds were delivered at a comfortable hearing volume.

Procedure

Subjects were tested in one session of approximately 1.5 hour and were blindfolded during the whole experiment. Subjects were instructed to localize left or right unilateral auditory stimuli (target stimulus) by pressing one of two buttons. Auditory stimulation was preceded by (1.) air puffs (somatosensory stimulation), (2.) phenyl ethanol stimuli (olfactory stimulation), (3.) eucalyptol stimuli (olfactory-trigeminal stimulation). Nasal stimuli were delivered to one nostril (monorhinal stimulation) either ipsilaterally or contralaterally to the auditory target, 600ms before it's presentation. Subjects received a nasal-auditory stimulation each 15 seconds. When pure odor (phenyl ethyl alcohol) and mixed olfactory trigeminal (eucalyptol) stimuli were presented to one nostril, an odor free air puff, equivalent in terms of pressure and duration, was simultaneously delivered to the other nostril in order to isolate the effects of chemosensory stimuli from the effects of somatosensory cues on auditory localization. An alerting high-pitched sound (150ms) was delivered via headphones to announce the arrival of the next stimulation that could arise from 2000 to 4600ms after the alerting sound. In order to standardize the exploration of the nasal stimuli, subjects were asked to breathe in when hearing the alerting acoustic signal, hold the breath during nasal and auditory stimuli presentation, and breathe again after they had given their answer.

After auditory stimulus presentation, subjects' task was to press one of two buttons as fast as they could in order to indicate if they had perceived the auditory stimulus in the left or the right ear. The next stimulus cycle started after a resting period of 8000ms.

Each combination of auditory and nasal stimulus was presented 20 times. Testing was done in 10 blocks of 28 stimuli (2 of each combination per block). Subjects were instructed to rest between the blocks.

See figure 1 for experimental design.

Stimulus delivery and responses recording were controlled by the "Presentation" software (Neurobs) running on a HP PC (AMD Phenom X3 processor) with Windows XP.

Statistical analysis

Subjects' performance was evaluated in terms of hit rates (proportion of correct responses) and reaction times (only for correct responses in the range 100-1500 ms post stimuli). In order to evaluate the effect of a cuing stimulus, we performed paired t-tests (cued stimulation vs. uncued stimulation). Next, we performed a repeated measures ANOVA with side of the auditory stimulus (left, right), modality of the cuing stimulus (somatosensory, olfactory-trigeminal, olfactory), and side congruency of the cuing stimulus (congruent, incongruent) as within subject factors and reaction time as the dependent variable. We performed posthoc paired t-tests with Bonferroni correction.

Results

On average, subjects were able to indicate the side of the auditory stimulation with very high accuracy; in all conditions they were correct in more than 93% of the trials (see Table 2). They responded after 500 (standard deviation: 97) and 489 (115) ms, for the left and the right auditory stimulus, respectively. Independent of its nature, preceding co-stimulation reduced reaction time significantly (all ps<0.001) to the auditory stimulus by over 100 ms (see Table 1).

In the rm-ANOVA we observed a significant effect of cuing stimulus ($F[2,27]=6.26$; $p=0.006$), in that both chemosensory stimuli led to shorter reaction times than the somatosensory air puffs. In fact, post hoc comparisons showed that when alerted by the somatosensory air puff, subjects reacted after 394 (SEM: 88) ms, whereas they were

significantly faster when they had been alerted by either a mixed olfactory-trigeminal stimulus (382 (92) ms; p=.027) or a pure olfactory stimulus (381 (82); p=.026) (Figure 2.).

There was no significant difference between the two chemosensory alerting stimuli (p=1.0). Congruency of the alerting stimulus failed to reach significance (F[1,28] 1.06; p=0.31). In order to further investigate a possible effect of stimulus congruency, we performed planned comparison between reaction times following congruent and incongruent alerting stimuli. There was, however, no significant difference between congruent and incongruent in any condition (F[1,28]=1.06; p=0.31). No other factor or interaction reached significance (Figure 3).

Control experiment

In the somatosensory condition (c), subjects received one air puff, either to the right or to the left nostril. However, when an odorant air puff was delivered (a, b), a simultaneous odorless air puff was presented to the contralateral nostril, so that the subjects would not be influenced by the side of the air puff but by the odorants. Thus, the potential observed effects could be due not to the chemosensory property of the co-stimulation, but to the amount of stimulation available (two air puffs vs one air puff in the somatosensory condition). We then decided to do a second experiment to ensure the effect would be specific to the chemosensory property of the costimulation, by comparing reaction times following the presentation of 1 vs 2 odor-free air puffs. If no difference between the two conditions was found, than we could assume the enhanced facilitative effect of auditory localization by chemosensory stimuli would not be caused by the bilateral character of the stimulation.

Methods

Thirty-two (32) additional subjects (14 women) within the same age range (Mean age 25 +/- 4 years) were included in experiment 2. One subject was excluded from the final analysis because his mean reaction times were more than two standard deviations from global mean reaction times. Auditory and somatosensory stimuli were the same as the ones employed in Experiment 1. Testing session for Experiment 2 lasted approximately 25 minutes. As for the main experiment, subjects were blindfolded during the whole testing session; their task was to localize unilateral auditory stimuli (target stimulus) by pressing one of two buttons. Auditory stimulation was preceded by (1.) one unilateral air puff presented either to the right or the left nostril or (2.) bilateral air puffs presented simultaneously to both nostrils, in a pseudo-

randomized counterbalanced order. Unilateral nasal simuli were presented either ipsilaterally or contralaterally to the auditory target. The rest of the procedure and all other parameters were the same as in main experiment. We performed a repeated measures ANOVA with side of the auditory stimulus (left, right) and type of costimulation (unilateral, bilateral), as within subject factors and reaction time as the dependent variable.

Results

There was no significant difference in mean reaction times between unilateral (465 ms (146)) and bilateral (481 ms (149)) costimulations ($F[1,30]=1.10$; $p=0.302$). No significant effect of side of the auditory stimulus (left= M: 468(128) ms; right= M: 483 (170) ms;) for unilateral costimulations was either found (Figure 4.).

Discussion

Here we show that odorous cues, independent of a possible trigeminal component, lead to shorter reaction times to auditory stimuli. This corroborates an earlier report, where ambient odors induced shorter reaction times to both auditory and visual stimuli [28]. Two conditions of our experiment allowed us to establish the effect to be specific for olfactory stimulation. Firstly, cuing with a somatosensory stimulus (puffs of unodorized air), although leading to shorter reaction times than no cuing at all, did have a significantly weaker effect on reaction times than chemosensory cuing. We excluded a possible effect of bilateral cuing in the control experiment which did not reveal any difference between unilateral and bilateral somatosensory cuing on reaction times to auditory stimuli. This suggests that chemosensory stimulation, whether pure olfactory of mixed olfactory-trigeminal, induces a specific reduction of reaction times. Since no difference was found between pure olfactory and mixed olfactory-trigeminal costimulations, one can speculate that the observed facilitating effects of chemosensory stimuli are attributable to their olfactory properties. These results may seem contradictory to the findings reported by Michael and collaborators (2003), in which a pure odor sprayed into the testing room, in this case phenyl ethyl alcohol, increased reaction times to visual targets, possibly by reducing subjects' arousal levels. However, differences in experimental design may account for the discrepancy between these results and ours. In contrast to Michael's team, we used a priming paradigm similar to the one employed by Seubert’s (2010), who used odorant cues prior to the presentation of visual targets and also found facilitative effects of odors on sensory processing. In the present study, as in Seubert's, the odorants were not

constantly present in the environment as the three nasal stimuli (pure and mixed olfactory/trigeminal odorants and somatosensory cues) and the control condition (without cuing) were alternatively presented before each auditory stimulation. By proceeding this way, we were able to avoid the potential effects of a constant presentation of the odorants, i.e. , habituation and/or a modulation of the arousal levels.

Secondly, side congruency of the cues and the target had no effect on reaction times. In audiovisual cross-modal cueing paradigms, space congruency has been shown to influence performance on localization tasks. For example, an auditory congruent cue usually enhances detection time of a visual target, whereas incongruent cues have no influence or impair performance [21]. While auditory and visual localization tasks are relatively easy, we know that humans are not able to distinguish between an olfactory stimulation of the left and the right nostril [15, 19, 45]. Thus, the absence of an effect of side congruency again suggests that indeed the olfactory component of both chemosensory stimuli was responsible for the observed effects.

It may seem surprising that we did not observe any effect of side congruency for the somatosensory cues. This is in contrast to previous findings of enhanced performances in detection of visual or auditory targets after the presentation of tactile cues [7, 17]. However, in these previous studies, temporal contingency between the two stimuli was maximal, or, in other words, tactile and visual/auditory stimuli were presented simultaneously. In contrast, in the present study, a 600 ms delay separated the presentation of the auditory stimuli from the presentation of the nasal cues in order to ensure the subjects had enough time to perceive the odors. We know that chemosensory processing is relatively slow compared to other sensory systems. Evidence for this comes from the recording of event related potentials. In example, the P3 component – which in the visual system typically occurs after approximately 300ms – of chemosensory event related potentials can be observed after 600-1200 ms [19, 29, 31]. Thus this delay was necessary for the subjects to perceive the olfactory components of the stimuli, therefore allowing for priming effects to occur, it may be possible that it was too long to observe facilitating effects of spatial congruency of the somatosensory cues, as temporal contingency is a primordial feature in multisensory integration [10, 21, 42].

As mentioned above, compared to other sensory systems, the olfactory system reacts relatively slow. When subjects were asked to detect one of four odors as quickly as possible

without any alerting signal, they did so after, on average, more than 1500ms [3]. Similarly, when subjects were asked to evaluate either intensity or pleasantness of odors, they responded after 1500ms [2]. In another study, subjects were asked to discriminate between two odors, and were able to do so after more than 1100ms [9]. The speed of processing in the olfactory system as a whole therefore appears to be significantly lower than in other sensory systems, where reaction times ranging between 200 and 800 ms have been reported in several discrimination tasks [7, 17, 33, 35]. In fact, in our study, subjects reacted to an auditory stimulus after 500ms. Similar to the behavioral findings, peaks of olfactory event related potentials also appear with a delay when compared to corresponding response waves in other sensory systems [18, 29]. Thus, it may be possible that our subjects did not perceive the odor cues before they perceived the auditory stimulus, although they perceived the air puffs which were present in all cuing stimuli. Still, they reacted faster when they received an olfactory stimulus as compared to the pure air puff, we can therefore assume that the air puff per se was not responsible for the increased reaction speed after the presentation of the olfactory cue. These findings may be interpreted as suggesting the existence of a lower order olfactory processing mechanism, which seems to increase attention to auditory cues. Further, this attentional feature seems to be independent from higher order processes such as odor identity or localization since identical between trigeminal and pure odorant.

In summary, in the present study, odorous cues presented shortly before auditory stimuli had a facilitative effect on the localization of the sounds, independently of a trigeminal component and/or lateral congruency of the cues, suggesting the priming effects to be due to the olfactory properties (and not the trigeminal one) of the odors. Importantly, the speeding effects displayed here were superior to the ones observed when using only somatosensory cues, demonstrating the specificity of the effects of the olfactory stimuli. These results therefore intimate the existence of interactions between olfaction and audition and suggest there is an integration of information from both sensory modalities, resulting in behavioral changes, i.e. an enhancement of performance in auditory localization. Spatial congruency, which is a critical factor for cross-modal interactions between other sensory modalities when subjects are involved in spatial discrimination tasks [17], does not seem to play a mandatory role in the integration of olfactory-auditory information. Further studies will be needed in

order to better understand the psychophysical and neural correlates underlying these cross-modal mechanisms.

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References

[1] A. Arzi, L. Sela, A. Green, G. Givaty, Y. Dagan, N. Sobel, The Influence of Odorants on Respiratory Patterns in Sleep, Chemical Senses 35 (2010) 31-40.

[2] M. Bensafi, C. Rouby, V. Farget, M. Vigouroux, A. Holley, Asymmetry of pleasant vs. unpleasant odor processing during affective judgment in humans, Neurosci Lett 328 (2002) 309-313.

[3] S. Boesveldt, J. Frasnelli, A.R. Gordon, J.N. Lundstrom, The fish is bad: Negative food odors elicit faster and more accurate reactions than other odors, Biol Psychol 84 (2010) 313-317.

[4] G. Brand, L. Jacquot, Sensitization and desensitization to allyl isothiocyanate (mustard oil) in the nasal cavity, Chem Senses 27 (2002) 593-598.

[5] W.S. Cain, C.L. Murphy, Interaction between chemoreceptive modalities of odour and irritation, Nature 284 (1980) 255-257.

[6] B. Cerf-Ducastel, P.F. Van de Moortele, P. MacLeod, D. Le Bihan, A. Faurion, Interaction of gustatory and lingual somatosensory perceptions at the cortical level in the human: a functional magnetic resonance imaging study, Chem Senses 26 (2001) 371-383.

[7] O. Collignon, G. Charbonneau, M. Lassonde, F. Lepore, Early visual deprivation alters multisensory processing in peripersonal space, Neuropsychologia 47 (2009) 3236-3243.

[8] J.E. Cometto-Muniz, M.R. Garcia-Medina, A.M. Calvino, G. Noriega, Interactions between CO2 oral pungency and taste, Perception 16 (1987) 629-640.

[9] M.L. Dematte, D. Sanabria, C. Spence, Olfactory discrimination: when vision matters?, Chem Senses 34 (2009) 103-109.

[10] A. Diederich, H. Colonius, Crossmodal interaction in speeded responses: time window of integration model, Prog Brain Res 174 (2009) 119-135.

[11] J. Djordjevic, R.J. Zatorre, M. Jones-Gotman, Odor-induced changes in taste perception, Experimental Brain Research 159 (2004) 405-408.

[12] R.L. Doty, W.P.E. Brugger, P.C. Jurs, M.A. Orndorff, P.J. Snyder, L.D. Lowry, Intranasal trigeminal stimulation from odorous volatiles: psychometric responses from anosmic and normal humans, Physiol Behav 20 (1978) 175-185.

[13] J. Frasnelli, J. Albrecht, B. Bryant, J.N. Lundstrom, Perception of specific trigeminal chemosensory agonists, Neuroscience 189 (2011) 377-383.

[14] J. Frasnelli, G. Charbonneau, O. Collignon, F. Lepore, Odor localization and sniffing, Chem Senses 34 (2009) 139-144.

[15] J. Frasnelli, T. Hummel, J. Berg, G. Huang, R.L. Doty, Intranasal localizability of odorants: influence of stimulus volume, Chem Senses 36 (2011) 405-410.

[16] J. Frasnelli, V.A. La Buissonniere Ariza, O. Collignon, F. Lepore, Localisation of unilateral nasal stimuli across sensory systems, Neurosci Lett 478 (2010) 102-106.

[17] S. Girard, O. Collignon, F. Lepore, Multisensory gain within and across hemispaces in simple and choice reaction time paradigms, Exp Brain Res (2010).

[18] T. Hummel, G. Kobal, Olfactory event related potentials. In: S. Simon, M. Nicolelis (Eds.), Methods in chemosensory research, CRC press, Boca Raton, 2002.

[19] G. Kobal, T. Hummel, S. Van Toller, Differences in chemosensory evoked potentials to olfactory and somatosensory chemical stimuli presented to left and right nostrils, Chemical Senses 17 (1992) 233-244.
[20] G. Kobal, S. Van Toller, T. Hummel, Is there directional smelling?, Experientia 45 (1989) 130-132.
[21] T. Koelewijn, A. Bronkhorst, J. Theeuwes, Attention and the multiple stages of multisensory integration: A review of audiovisual studies, Acta Psychol (Amst) 134 (2010) 372-384.
[22] A. Livermore, T. Hummel, The influence of training on chemosensory event-related potentials and interactions between the olfactory and trigeminal systems, Chem Senses 29 (2004) 41-51.
[23] A. Livermore, T. Hummel, G. Kobal, Chemosensory event-related potentials in the investigation of interactions between the olfactory and the somatosensory (trigeminal) systems, Electroencephalogr Clin Neurophysiol 83 (1992) 201-210.
[24] J.J. McDonald, W.A. Teder-Salejarvi, S.A. Hillyard, Involuntary orienting to sound improves visual perception, Nature 407 (2000) 906-908.
[25] J.J. McDonald, W.A. Teder-Salejarvi, L.M. Ward, Multisensory integration and crossmodal attention effects in the human brain, Science 292 (2001) 1791.
[26] G.A. Michael, L. Jacquot, J.L. Millot, G. Brand, Ambient odors influence the amplitude and time course of visual distraction, Behav Neurosci 119 (2005) 708-715.
[27] G.A. Michael, L. Jacquot, J.L. Millot, G. Brand, Ambient odors modulate visual attentional capture, Neurosci Lett 352 (2003) 221-225.
[28] J.L. Millot, G. Brand, N. Morand, Effects of ambient odors on reaction time in humans, Neuroscience Letters 322 (2002) 79-82.
[29] C. Murphy, C.D. Morgan, M.W. Geisler, S. Wetter, J.W. Covington, M.D. Madowitz, S. Nordin, J.M. Polich, Olfactory event-related potentials and aging: normative data, Int. J. Psychophysiol. 36 (2000) 133-145.
[30] S. Nordin, M. Martinkauppi, J. Olofsson, T. Hummel, E. Millqvist, M. Bende, Chemosensory perception and event-related potentials in self-reported chemical hypersensitivity, Int J Psychophysiol 55 (2005) 243-255.
[31] B.M. Pause, B. Sojka, R. Ferstl, Central processing of odor concentration is a temporal phenomenon as revealed by chemosensory event-related potentials (CSERP), Chemical Senses 22 (1997) 9-26.
[32] D.J. Prime, J.J. McDonald, J. Green, L.M. Ward, When cross-modal spatial attention fails, Can J Exp Psychol 62 (2008) 192-197.
[33] J. Rimmele, H. Jolsvai, E. Sussman, Auditory target detection is affected by implicit temporal and spatial expectations, J Cogn Neurosci 23 (2011) 1136-1147.
[34] M. Schurmann, G. Caetano, Y. Hlushchuk, V. Jousmaki, R. Hari, Touch activates human auditory cortex, Neuroimage 30 (2006) 1325-1331.
[35] D. Senkowski, S. Molholm, M. Gomez-Ramirez, J.J. Foxe, Oscillatory beta activity predicts response speed during a multisensory audiovisual reaction time task: a high-density electrical mapping study, Cereb Cortex 16 (2006) 1556-1565.
[36] J. Seubert, T. Kellermann, J. Loughead, F. Boers, C. Brensinger, F. Schneider, U. Habel, Processing of disgusted faces is facilitated by odor primes: a functional MRI study, Neuroimage 53 (2010) 746-756.

[37] J. Seubert, J. Loughead, T. Kellermann, F. Boers, C.M. Brensinger, U. Habel, Multisensory integration of emotionally valenced olfactory-visual information in patients with schizophrenia and healthy controls, J Psychiatry Neurosci 35 (2010) 185-194.
[38] D.M. Small, M. Jones-Gotman, R.J. Zatorre, M. Petrides, A.C. Evans, Flavor processing: more than the sum of its parts, Neuroreport 8 (1997) 3913-3917.
[39] C. Spence, J. Driver (Eds.), Crossmodal space and crossmodal attention, Oxford University Press, Oxford, 2004.
[40] V.S. Stormer, J.J. McDonald, S.A. Hillyard, Cross-modal cueing of attention alters appearance and early cortical processing of visual stimuli, Proc Natl Acad Sci U S A 106 (2009) 22456-22461.
[41] W.R. Thurlow, C.E. Jack, Certain determinants of the "ventriloquism effect", Percept Mot Skills 36 (1973) 1171-1184.
[42] E. Van der Burg, C.N. Olivers, A.W. Bronkhorst, J. Theeuwes, Pip and pop: nonspatial auditory signals improve spatial visual search, J Exp Psychol Hum Percept Perform 34 (2008) 1053-1065.
[43] Y. Wada, Multisensory integration of vision and touch in nonspatial feature discrimination tasks, Japanese Psychol Res 52 (2010) 12–22.
[44] A. Welge-Lussen, J. Drago, M. Wolfensberger, T. Hummel, Gustatory stimulation influences the processing of intranasal stimuli, Brain Research 1038 (2005) 69-75.
[45] C.J. Wysocki, B.G. Green, T.P. Malia, Monorhinal stimulation as a method for differentiating between thresholds for irritation and odor, Chemical Senses 17 (1992) 722.

Tables

Table 1: Average reaction times with and without alerting stimulus

Modality of alerting stimulus	Side of auditory stimulus	congruent costimulation		incongruent costimulation	
		Average reaction time [ms]	standard deviation	Average reaction time [ms]	standard deviation
Somatosensory	Left	401	94	402	96
	Right	381	77	391	110
Olfactory - trigeminal	Left	387	94	390	89
	Right	369	81	383	121
Olfactory	Left	387	83	382	77
	Right	373	82	383	103
none	Left	500	97		
	Right	489	115		

Table 2: Percentage of correct responses

Modality of alerting stimulus	Side of auditory stimulus	congruent costimulation		incongruent costimulation	
		% correct	SD	% correct	SD
Somatosensory	Left	96.1	4.2	95.0	4.5
	Right	94.1	4.8	94.8	6.9
Olfactory - trigeminal	Left	94.7	4.9	95.6	5.6
	Right	93.8	6.1	96.7	3.7
Olfactory	Left	96.1	4.2	95.5	4.3
	Right	95.7	4.0	96.8	4.2
none	Left	96.0	4.1		
	Right	96.6	4.1		

Figures

Figure 1. Experimental design

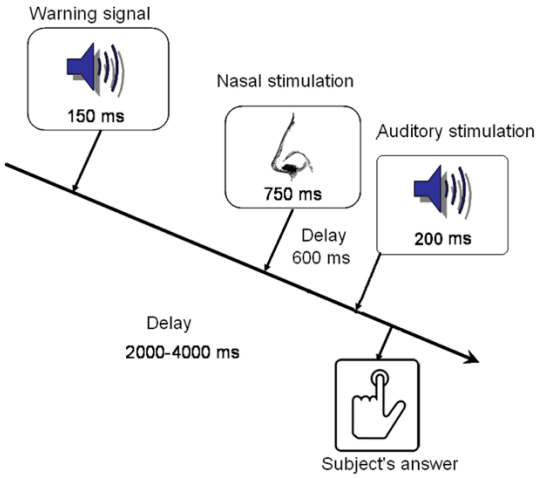


Figure 2.: Average reaction times with and without alerting stimulus

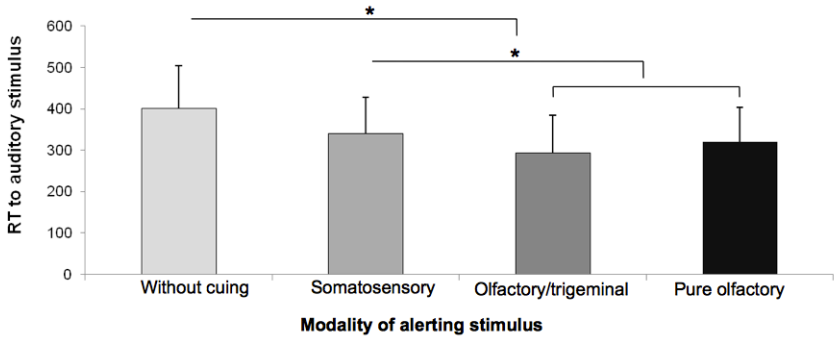


Figure 3.: Average reaction times with alerting congruent and incongruent stimuli

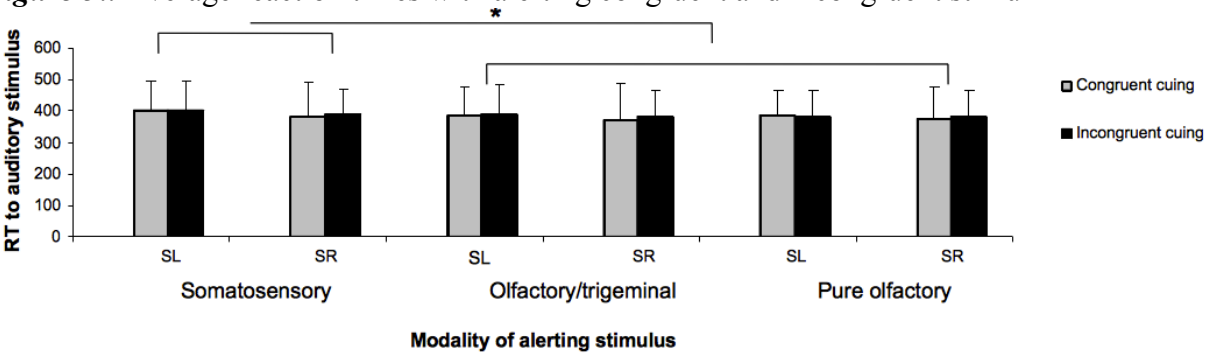
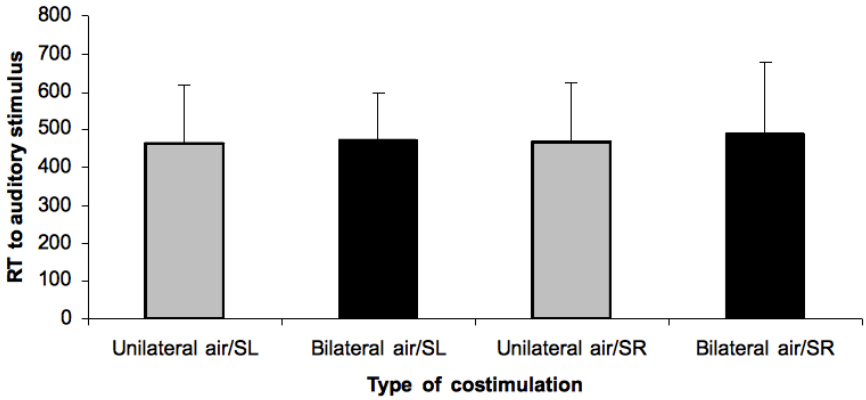


Figure 4. Average reaction times with alerting unilateral and bilateral somatosensory stimuli



Localisation of unilateral nasal stimuli across sensory systems.

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Abstract

It is currently thought that odor stimuli presented to one nostril can only be localized if they additionally activate the trigeminal nerve's chemosensitive fibers. In this study we aimed to investigate characteristics in the localisation of unilateral trigeminal, olfactory and somatosensory nasal stimuli. We compared subjects' ability to localise monorhinally presented a) pure olfactory stimuli (phenyl ethyl alcohol), b) mixed olfactory trigeminal stimuli (eucalyptol), and c) somatosensory stimuli (air puffs). As expected, the subjects could localize the air puffs and eucalyptol, but could not localize phenyl ethyl alcohol. Interestingly, we observed a significant correlation between localization performance for eucalyptol and phenyl ethyl alcohol but not between the ability to localize somatosensory and trigeminal or olfactory stimuli. The present study provides further support for the intimate connection between the chemosensory trigeminal and olfactory systems.

Introduction

The trigeminal system represents a third chemical sense, next to smell and taste. Amongst other it allows for perceiving the burning of chilli, the cooling of mint, or the sparkling of carbonated water. In fact, most odorous substances also activate the trigeminal system, at least in higher concentrations (Doty et al., 1978). One interesting aspect of the intranasal trigeminal system is that it allows for localisation of monorhinally presented stimuli. Thus, we are able to correctly localise odorous stimuli which have been presented to one nostril, only if the substance also activates the trigeminal system (Hummel et al., 2003, Kobal et al., 1989). So, we can localise mixed olfactory trigeminal stimulus, such as eucalyptol, but we cannot localize pure odors, such as the rose odor phenyl ethyl alcohol (Frasnelli et al., 2009a, Kobal et al., 1989). Moreover, active sniffing does not change our inability to localise pure odors (Frasnelli et al., 2009a).

The olfactory and the trigeminal system are closely interconnected. As mentioned above, in higher concentrations, most odors also stimulate the trigeminal system. Furthermore, simultaneous stimulation with a trigeminal stimulus decreases the intensity of an odor (Livermore et al., 1992, Cain & Murphy, 1980), due to a central interaction between both sensory systems (Cain & Murphy, 1980). In addition, subjects with a loss of olfactory function also exhibit a decreased trigeminal sensitivity (Frasnelli et al., 2007, Hummel et al., 2003, Hummel et al., 1996). Interestingly, this decreased sensitivity seems to be limited to the chemosensory portions of the trigeminal system only. When chemosensory trigeminal thresholds were compared between healthy controls and patients with olfactory dysfunction, the latter exhibited higher thresholds indicating lower sensitivity. When however somatosensory trigeminal thresholds were compared, no difference between both groups could be observed (Frasnelli et al., 2006). This suggests that the close connection between olfactory system and trigeminal system is limited to the chemosensory portions of the latter. In other words, the two sensory portions of the trigeminal nerve, i.e., the chemosensory and the somatosensory system seem to be relatively independent from each other.

Because of these close connections between trigeminal and olfactory functions and the relative independence between trigeminal and somatosensory functions, we designed a study to further understand the relations between these sensory systems in our ability to localize odors. We

thus monorhinally presented our subjects with (1) a pure odor, (2) a mixed olfactory trigeminal stimulus, and (3) a somatosensory stimulus.

We hypothesized that subjects could localise both stimuli which activate the trigeminal nerve, i.e., the mixed olfactory trigeminal stimulus and the somatosensory stimulus, but not the pure odor. As a consequence of the relative independence of the different trigeminal fibre subtypes, we hypothesized the results for the somatosensory and the mixed olfactory trigeminal stimulus not to be correlated. In contrast, we expected the results for the pure odorant and the mixed olfactory trigeminal stimulus to be correlated, as an expression of the intimate connection between both chemosensory systems.

Material and Methods

The study was conducted in agreement with the Declaration of Helsinki. Subjects gave informed written consent prior to testing. The protocol was approved by the Ethics Board of the University of Montreal.

Subjects

We included 32 subjects (14 women) aged between 18 and 35 years (Mean age 23 years +- 3). No participant suffered of any medical conditions at the time of the testing and did not report any olfactory problems.

Stimuli

We used eucalyptol (eucalyptus odor; Galenova, St.-Hyacinth, QC) and phenyl ethyl alcohol (rose odor; SAFC, St. Louis, MO) as chemosensory stimuli, and air puffs as somatosensory stimuli.

Eucalyptol is considered a mixed olfactory trigeminal stimulus, and will therefore activate olfactory and chemosensory trigeminal receptors, whereas phenyl ethyl alcohol is considered a pure odorant which activates the olfactory nerve exclusively. The air puffs, on the other hand, will activate only somatosensory trigeminal fibers.

Odor presentation

We adapted an fMRI compatible tactile stimulator (Institute for Biomagnetism and Biosignalanalysis, University of Münster, Germany) in order to present stimuli in an automated fashion. This portable multi-channel stimulator is designed for generation and delivery of constant air puffs for somatosensory stimulation during MEG and fMRI acquisition (Elbert et al., 1994). The stimulator provides air pressure pulses of well defined

duration. Instead of connecting the outlets to balloon diaphragms, as it is done for tactile stimulation, we connected them to odor chambers via polyurethane tubing with 8mm outer diameter and an inner diameter of 4.8 mm (Fre-Thane 85A, Freelin-Wade, McMinnville, OR). The odor chambers were glass bottles with a volume of 50mL and were filled with 4 mL of odorant. The outlet of the odor chambers was then connected to the subjects' nose by means of the same polyurethane tubing of approximately 50 cm length. By keeping all tubings separated we could avoid cross contamination of odors. During odor presentation, air with a flow of 2 L/min was switched into the respective channel. All stimuli lasted 750ms. Therefore, subjects were stimulated with 25mL of air per stimulated nostril.

Procedure

Subjects were blindfolded during the whole experiment. Stimuli were delivered to one nostril (monorhinal stimulation). When pure odor (phenyl ethyl alcohol) and mixed olfactory trigeminal (eucalyptol) stimuli were presented to one nostril, an odor free air puff, equivalent in terms of pressure and duration, was simultaneously delivered to the other nostril, so that the subjects could not use somatosensory cues to localise the stimuli. An alerting high-pitched sound (150ms) was delivered via headphones to announce the arrival of the next stimulation that could arise from 2000 to 4000ms after the alerting sound. In order to standardise the exploration of the stimuli, subjects were asked to breathe when hearing the alerting acoustic signal, hold the breath during stimulus presentation, and breathe again after they had given their answer. After stimulus presentation, subjects' task was to press one of two buttons as fast as they could in order to indicate if they had perceived the stimulus in the left or the right nostril. The next stimulus cycle started after a resting period of 8000ms.

Subjects carried out 2 blocs of 48 pseudo-randomized stimuli (8 times the 6 different stimuli) and thus received a total of 96 stimuli for the whole experiment (32 each for air puffs, eucalyptol and phenyl ethyl alcohol).

Stimulus delivery and responses recording were controlled by the "Presentation" software (Neurobs) running on a HP PC (AMD Phenom X3 processor) with Windows XP. Performances of the subjects were evaluated in terms of Hit rates (proportion of correct responses) and reaction times (only for correct responses in the range 150-3000ms post stimuli).

Statistical analysis

The statistical analysis was performed by means of SPSS 16.0 (SPSS Inc., Chicago IL). First, we compared the performance against chance level using binomial statistics. Then, we calculated repeated measures ANOVA on the variables of interest (accuracy, response times) with "sex" (women, men) as between subject factor, and "stimulus" (phenyl ethyl alcohol, eucalyptol, air puff), "nostril" (left, right) as within subject factors. We calculated post-hoc t-tests when the ANOVA indicated significant main effects. Furthermore, we calculated Pearson's correlation coefficient between scores obtained for the different stimuli as well as scores for the left and right nostril. In order to estimate task accuracy we computed the sensitivity index d' and response bias criterion C, according to the signal detection theory (Snodgrass & Corwin, 1988). Criterion c can range from –1 to +1. A c of 0 denotes no tendency; negative values signify a tendency to the right, positive values signify a tendency to the left. Significance level was set at 0.05.

Results

Air puffs and eucalyptol were localized above chance (binomial; air puffs: $p<0.001$; eucalyptol: $p=0.03$) while phenyl ethyl alcohol was localized at chance.

When computing a repeated measures ANOVA, we observed a significant effect of stimulus ($F[2,58]=110$; $p<0.001$), indicating that air puffs were better localized than eucalyptol (air puffs: 91.3 [SEM: 1.9]%; eucalyptol: 68.1 [3.2]%; $p<0.001$) and that eucalyptol was better localized than phenyl ethyl alcohol stimuli (41.8 [3.2]%; $p=0.001$).

The factor "side" failed to reach significance ($F[1,30]=3.1$; $p=0.088$). Since a side difference has been reported earlier, we decided to compare further the results for both nostrils for the different stimuli. In fact, when we used the mixed trigeminal-olfactory stimulus eucalyptol, subjects performed significantly better on the right nostril (75.4 [3.6]%) than on the left nostril (60.9[4.8]%, $p=0.017$). Although we also observed higher scores on the right nostril for the other stimuli, these differences were not significant (Figure 1).

We did not observe sex differences and no significant interactions between factors.

We then computed Pearson's correlations between the scores obtained for the different stimuli. Here, we observed the results for eucalyptol and phenyl ethyl alcohol to be correlated ($r[32]=0.458$; $p=0.008$). In contrast, scores for air puffs were not correlated neither to eucalyptol nor phenyl ethyl alcohol scores (Figure 2).

When looking at the single nostrils, we observed a significant correlation for the results on the left and the right nostril, when air puffs were used as stimuli ($r[32]=0.67$; $p<0.001$), indicating that subjects who performed well when localizing air puffs on the right nostril, were good in doing so with left sided stimulation, too. No such correlation between left and right nostril was observed for eucalyptol or phenyl ethyl alcohol. In contrast, we observed a significant correlation between results for eucalyptol and phenyl ethyl alcohol stimulation in the left nostril ($r[32]=0.482$; $p=0.005$) and in the right nostril ($r[32]=0.492$; $p=0.004$). This indicates that subjects that had a high score for eucalyptol in a given nostril also performed better for phenyl ethyl alcohol in the same nostril. We did not observe such a correlation between air puffs and both chemosensory stimulations.

On average, we observed a rightward tendency in all conditions, which was smallest for the air puffs (-0.034), larger for phenyl ethyl alcohol (-0.13), and largest for eucalyptol (-0.24). We observed the rightward tendency to be significantly correlated for eucalyptol and phenyl ethyl alcohol ($r[32]=0.57$; $p=0.001$). There was no such correlation for air puffs.

The repeated measures ANOVA computed on the response times revealed a significant effect of "stimulus" ($F[2,58]=5.05$; $p=0.014$). Post hoc tests revealed that subjects responded fastest to the air puffs (1098 [69] ms), then to eucalyptol (1165 [76] ms) and slowest to phenyl ethyl alcohol stimuli (1261 [88] ms). The difference between response times to air puffs and phenyl ethyl alcohol stimuli was significant ($p<0.001$), the other comparisons did not reveal any significant differences in response times between the stimuli.

In addition, we observed a significant effect of "sex" on the response times ($F[1,29]=5.0$; $p=0.032$). Women (1012 [107] ms) responded faster to all stimuli than men (1337 [97] ms). We did not observe any other significant main effects or interactions.

Discussion

For the present study, we were able to design a fully automated delivery system to carry out an olfactory localization task. Compared to the usually used manual devices (Wysocki et al., 2003, Hummel et al., 2003), an automated delivery system has the advantage to not be influenced by subject-tester interactions and to ensure perfect time-control.

The first main result of the present study is that participants were able to localise eucalyptol stimuli and air puffs, but not phenyl ethyl alcohol stimuli. This is in line with previous reports on the ability of humans to localise chemosensory stimuli. In contrast to, e.g., rats (Rajan et

al., 2006), we are able to localise odorous stimuli only if they additionally stimulate the trigeminal nerve (Kobal et al., 1989, Frasnelli et al., 2009a, Frasnelli et al., 2007). Interestingly, we observed the results for both chemosensory stimuli (phenyl ethyl alcohol and eucalyptol) to be correlated, but no correlation between the results for eucalyptol and air puffs was observed. This correlation between scores obtained with eucalyptol and phenyl ethyl alcohol is surprising if one considers the fact that, on average, subjects' performance when localising the pure olfactory stimulus phenyl ethyl alcohol was slightly below chance, in line with earlier reports (Schneider & Schmidt, 1967, Frasnelli et al., 2008, Frasnelli et al., 2009a). In order to explore the correlation closer, we looked at subsets of subjects. We observed the ten subjects performing above chance with phenyl ethyl alcohol as stimulus, with an average score of 62%, to also have a superior average performance of 80% with eucalyptol as the stimulus. Thus it appears as if the most sensitive subjects may also be able to localise phenyl ethyl alcohol. The ten subjects with the lowest scores for phenyl ethyl alcohol (average score: 21%) on the other hand could localise eucalyptol in only 58% of the trials. It would be interesting to know if any of these subject groups could be trained to localise phenyl ethyl alcohol (Wysocki et al., 2003), e.g., if they receive feedback. Mainly subjects having difficulties in correctly localizing eucalyptol localised phenyl ethyl alcohol towards the wrong side. We know that the olfactory and the trigeminal system suppress and enhance each other mutually (Cain & Murphy, 1980, Livermore et al., 1992). One could speculate that, in analogy, the olfactory input may reduce also the somatosensory sensation. In this scenario, on the stimulated side, the olfactory stimulation would lead to a reduced somatosensory sensation as compared to the other nostril, where only an air puff was delivered. In the absence of trigeminal input this may then lead the subject to localise the sensation to the wrong side. Further research is needed to clarify this observation.

We observed a rightward response tendency, in line with research from other sensory areas such as audition (Lewald, 2004, Lewald et al., 2002, Dufour et al., 2007). In the visual domain when subject bisect horizontal lines, they generally lateralize the vertical center to the left. This is thought to represent a rightward shift in the perceived location of this central point (Bowers & Heilman, 1980, Bradshaw et al., 1983, Bradshaw et al., 1985), reflecting a structural specialization of the right cerebral hemisphere for spatial attention (Mesulam, 2000), which induces a tendency to localize uncertain spatial percept to the weaker right hemifield.

However we observed the tendency to the right to be only minimal for the somatosensory stimulus and most prominent for the mixed olfactory trigeminal chemosensory stimulus. Again, we observed a significant correlation between the response bias (rightward tendency) for both chemosensory stimuli, but not for the somatosensory stimuli. A right-sided advantage/tendency in the olfactory system has been found with regards to olfactory discrimination (Zatorre & Jones-Gotman, 1990, Savic & Berglund, 2000), olfactory thresholds (Cain & Gent, 1991), and odor memory (Jones-Gotman & Zatorre, 1993). In addition, there is a right hemispheric predominance in olfactory processing (Zatorre et al., 1992, Savic & Gulyas, 2000, Frasnelli et al., 2009b). In addition to these olfactory tasks, there is also a rightward tendency in tasks involving the trigeminal chemosensory system as we have shown in a localisation paradigm (Frasnelli et al., 2009a). We know that even pure trigeminal chemosensory stimuli in addition to somatosensory brain areas activate brain regions which are usually involved in the processing of olfactory stimuli, including orbitofrontal, piriform and insular cortex (Hummel et al., 2005, Boyle et al., 2007, Albrecht et al., 2010), mainly in the right hemisphere (Boyle et al., 2007, Hummel et al., 2009). An intimate connection between olfactory and chemosensory has also been shown functionally. If the sense of smell is impaired, trigeminal chemosensory sensitivity is also reduced. This has been shown by means of psychophysical methods (Hummel et al., 2003, Frasnelli et al., 2007), electrophysiological measures (Frasnelli et al., 2007, Hummel et al., 1996), and brain imaging techniques (Iannilli et al., 2007). From our results one could therefore conclude that side effects are another common feature of the trigeminal chemosensory system and the olfactory system.

It is unquestionable that a successful localisation of eucalyptol is based on the activation of intranasal trigeminal fibers. Nevertheless, we did not observe a correlation in subjects' ability to localise air puffs and chemosensory stimuli, although in both cases the necessary information is conveyed via the same cranial nerve. This is however in line with a number of reports on dissociations between the chemosensory and the somatosensory portions of the trigeminal nerve. We know, for example, that different regions of the nasal mucosa respond differently to chemosensory and somatosensory trigeminal stimulation. After stimulation with carbon dioxide (chemosensory stimulation) larger ERP responses and greater intensity ratings were obtained after stimulation of the anterior portion of the nasal cavity, when compared to the posterior one. For air puffs (somatosensory stimulation), this was the other way round

(Frasnelli et al., 2004). A similar dissociation between somatosensory and chemosensory sensitivity has been observed in patients with anosmia, who are known to also exhibit reduced chemosensory trigeminal sensitivity (Hummel et al., 1996, Hummel et al., 2003, Stevens et al., 1982, Stevens & Cain, 1986). As expected, patients with anosmia had higher chemosensory thresholds when compared to controls. However, patients and controls had similar thresholds to electrical cutaneous stimulation (somatosensory) (Frasnelli et al., 2006). Finally, differences between chemosensory and somatosensory trigeminal perception have been described with regards to brain activation patterns. Intranasal trigeminal chemosensory stimulation leads to activations of brain regions which are usually activated after olfactory and/ or gustatory stimulation, such as the orbitofrontal cortex, piriform cortex and insula (Albrecht et al., 2010, Boyle et al., 2007). This is usually not observed after somatosensory stimulation (DaSilva et al., 2002). In fact, a direct comparison between chemical (carbon dioxide) and mechanical (air puffs) trigeminal stimulation revealed that the former led to a significantly higher activation in the left insula and the right frontal lobe (Iannilli et al., 2008).

In summary, we show that the ability to correctly localise a monorhinally presented trigeminal chemosensory stimulus is not related to the ability to localise a somatosensory stimulus but rather to the localisation of an olfactory stimulus. Both the localisation of trigeminal chemosensory stimuli and olfactory stimuli share a tendency for a right-sided bias. From the literature we know that the chemosensory trigeminal and the olfactory system exhibit similar characteristics at neuroanatomical (Albrecht et al., 2010, Boyle et al., 2007) and functional (Hummel et al., 1996, Hummel et al., 2003, Stevens et al., 1982, Stevens & Cain, 1986) levels. On the other hand, the somatosensory and the chemosensory portions of the trigeminal nerve have been shown to exhibit different characteristics on neuroanatomical (Iannilli et al., 2008) and functional (Frasnelli et al., 2006) levels. The results of the present study provide thus further support for the notion of an intimate connection between the chemosensory trigeminal and olfactory.

Figures

Figure 1. Mean results (in %) when localising presented air puffs, eucalyptol stimuli and phenyl ethyl alcohol (PEA) stimuli to the left and the right nostril. The dotted line represents chance performance.

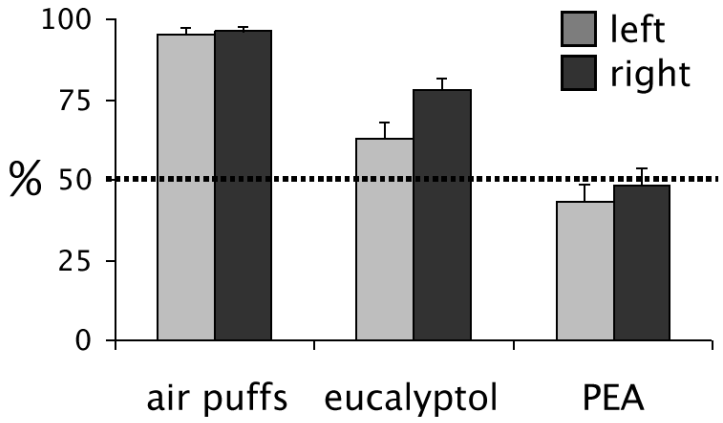
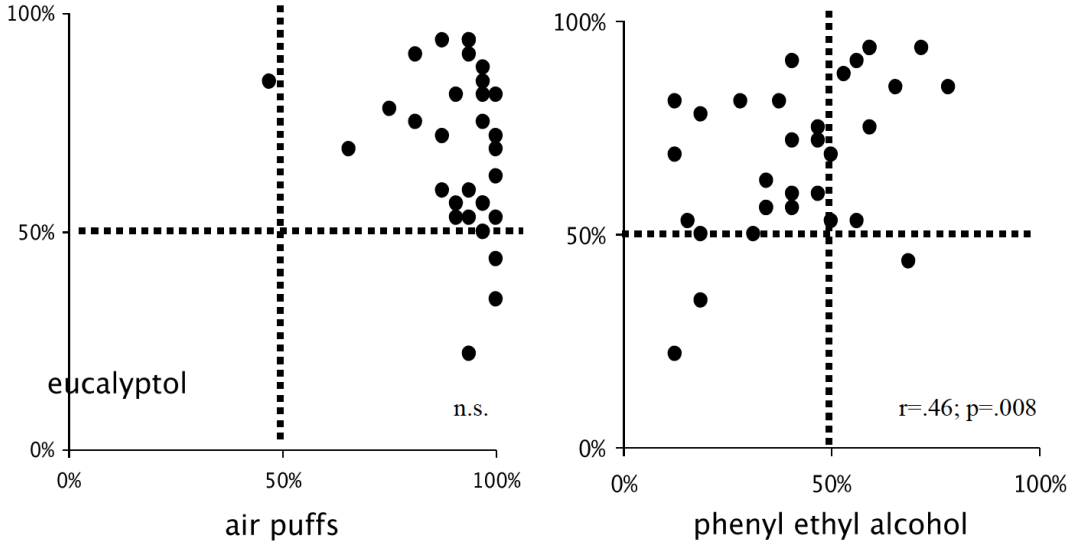


Figure 2. Individual scores when localising monorhinally presented stimuli. On the y-axis, the scores for eucalyptol are represented. On the x-axis scores for air puffs (left diagram) and phenyl ethyl alcohol (right diagram) are depicted. Dotted lines represent chance performance.



References

ALBRECHT, J., KOPIETZ, R., FRASNELLI, J., WIESMANN, M., HUMMEL, T. & LUNDSTRÖM, J. N. (2010) The neuronal correlates of intranasal trigeminal function – An ALE metaanalysis of human functional brain imaging data. *Brain Res Rev,* in press.

BOWERS, D. & HEILMAN, K. M. (1980) Pseudoneglect: effects of hemispace on a tactile line bisection task. *Neuropsychologia,* 18**,** 491-8.

BOYLE, J. A., HEINKE, M., GERBER, J., FRASNELLI, J. & HUMMEL, T. (2007) Cerebral activation to intranasal chemosensory trigeminal stimulation. *Chem Senses,* 32**,** 343-53.

BRADSHAW, J. L., NETTLETON, N. C., NATHAN, G. & WILSON, L. (1983) Head and body space to left and right, front and rear--II. Visuotactual and kinesthetic studies and left-side underestimation. *Neuropsychologia,* 21**,** 475-86.

BRADSHAW, J. L., NETTLETON, N. C., NATHAN, G. & WILSON, L. (1985) Bisecting rods and lines: effects of horizontal and vertical posture on left-side underestimation by normal subjects. *Neuropsychologia,* 23**,** 421-5.

CAIN, W. S. & GENT, J. F. (1991) Olfactory sensitivity: reliability, generality, and association with aging. *J Exp Psychol,* 17**,** 382-91.

CAIN, W. S. & MURPHY, C. L. (1980) Interaction between chemoreceptive modalities of odour and irritation. *Nature,* 284**,** 255-7.

DASILVA, A. F., BECERRA, L., MAKRIS, N., STRASSMAN, A. M., GONZALEZ, R. G., GEATRAKIS, N. & BORSOOK, D. (2002) Somatotopic activation in the human trigeminal pain pathway. *J Neurosci,* 22**,** 8183-92.

DOTY, R. L., BRUGGER, W. P. E., JURS, P. C., ORNDORFF, M. A., SNYDER, P. J. & LOWRY, L. D. (1978) Intranasal trigeminal stimulation from odorous volatiles: psychometric responses from anosmic and normal humans. *Physiol Behav,* 20**,** 175-85.

DUFOUR, A., TOUZALIN, P. & CANDAS, V. (2007) Rightward shift of the auditory subjective straight ahead in right- and left-handed subjects. *Neuropsychologia,* 45**,** 447-53.

ELBERT, T., FLOR, H., BIRBAUMER, N., KNECHT, S., HAMPSON, S., LARBIG, W. & TAUB, E. (1994) Extensive reorganization of the somatosensory cortex in adult humans after nervous system injury. *Neuroreport,* 5**,** 2593-7.

FRASNELLI, J., CHARBONNEAU, G., COLLIGNON, O. & LEPORE, F. (2009a) Odor localization and sniffing. *Chem Senses,* 34**,** 139-44.

FRASNELLI, J., HEILMANN, S. & HUMMEL, T. (2004) Responsiveness of human nasal mucosa to trigeminal stimuli depends on the site of stimulation. *Neurosci Lett,* 362**,** 65-9.

FRASNELLI, J., LUNDSTROM, J. N., BOYLE, J. A., DJORDJEVIC, J., ZATORRE, R. J. & JONES-GOTMAN, M. (2009b) Neuroanatomical correlates of olfactory performance. *Exp Brain Res*.

FRASNELLI, J., SCHUSTER, B. & HUMMEL, T. (2007) Interactions between olfaction and the trigeminal system: what can be learned from olfactory loss. *Cereb Cortex,* 17**,** 2268-75.

FRASNELLI, J., SCHUSTER, B., ZAHNERT, T. & HUMMEL, T. (2006) Chemosensory specific reduction of trigeminal sensitivity in subjects with olfactory dysfunction. *Neuroscience,* 142**,** 541-6.

FRASNELLI, J., UNGERMANN, M. & HUMMEL, T. (2008) Ortho- and retronasal presentation of olfactory stimuli modulates odor percepts. *Chemosens Percept,* 1**,** 9-15.

HUMMEL, T., BARZ, S., LOTSCH, J., ROSCHER, S., KETTENMANN, B. & KOBAL, G. (1996) Loss of olfactory function leads to a decrease of trigeminal sensitivity. *Chem Senses,* 21**,** 75-9.

HUMMEL, T., DOTY, R. L. & YOUSEM, D. M. (2005) Functional MRI of intranasal chemosensory trigeminal activation. *Chem Senses,* 30**,** i205-i6.

HUMMEL, T., FUTSCHIK, T., FRASNELLI, J. & HUTTENBRINK, K. B. (2003) Effects of olfactory function, age, and gender on trigeminally mediated sensations: a study based on the lateralization of chemosensory stimuli. *Toxicol Lett,* 140-141**,** 273-80.

HUMMEL, T., IANNILLI, E., FRASNELLI, J., BOYLE, J. & GERBER, J. (2009) Central processing of trigeminal activation in humans. *Ann N Y Acad Sci,* 1170**,** 190-5.

IANNILLI, E., DEL GRATTA, C., GERBER, J. C., ROMANI, G. L. & HUMMEL, T. (2008) Trigeminal activation using chemical, electrical, and mechanical stimuli. *Pain*.

IANNILLI, E., GERBER, J., FRASNELLI, J. & HUMMEL, T. (2007) Intranasal trigeminal function in subjects with and without an intact sense of smell. *Brain Res,* 1139**,** 235-44.

JONES-GOTMAN, M. & ZATORRE, R. J. (1993) Odor recognition memory in humans: role of right temporal and orbitofrontal regions. *Brain Cogn,* 22**,** 182-98.

KOBAL, G., VAN TOLLER, S. & HUMMEL, T. (1989) Is there directional smelling? *Experientia,* 45**,** 130-2.

LEWALD, J. (2004) Gender-specific hemispheric asymmetry in auditory space perception. *Brain Res Cogn Brain Res,* 19**,** 92-9.

LEWALD, J., FOLTYS, H. & TOPPER, R. (2002) Role of the posterior parietal cortex in spatial hearing. *J Neurosci,* 22**,** RC207.

LIVERMORE, A., HUMMEL, T. & KOBAL, G. (1992) Chemosensory event-related potentials in the investigation of interactions between the olfactory and the somatosensory (trigeminal) systems. *Electroencephalogr Clin Neurophysiol,* 83**,** 201-10.

RAJAN, R., CLEMENT, J. P. & BHALLA, U. S. (2006) Rats smell in stereo. *Science,* 311**,** 666-70.

SAVIC, I. & BERGLUND, H. (2000) Right-nostril dominance in discrimination of unfamiliar, but not familiar, odours. *Chem Senses,* 25**,** 517-23.

SAVIC, I. & GULYAS, B. (2000) PET shows that odors are processed both ipsilaterally and contralaterally to the stimulated nostril. *Neuroreport,* 11**,** 2861-6.

SCHNEIDER, R. A. & SCHMIDT, C. E. (1967) Dependency of olfactory localization on non-olfactory cues. *Physiol Behav,* 2**,** 305-9.

SNODGRASS, J. G. & CORWIN, J. (1988) Pragmatics of measuring recognition memory: Applications to dementia and amnesia. *Journal of Experimental Psychology* 117**,** 34–50.

STEVENS, J. C. & CAIN, W. S. (1986) Smelling via the mouth: effect of aging. *Percept. Psychophys.,* 40**,** 142-6.

STEVENS, J. C., PLANTINGA, A. & CAIN, W. S. (1982) Reduction of odor and nasal pungency associated with aging. *Neurobiol Aging,* 3**,** 125-32.

WYSOCKI, C. J., COWART, B. J. & RADIL, T. (2003) Nasal trigeminal chemosensitivity across the adult life span. *Percept Psychophys,* 65**,** 115-22.
ZATORRE, R. J. & JONES-GOTMAN, M. (1990) Right-nostril advantage for discrimination of odors. *Percept Psychophys,* 47**,** 526-31.
ZATORRE, R. J., JONES-GOTMAN, M., EVANS, A. C. & MEYER, E. (1992) Functional localization and lateralization of human olfactory cortex. *Nature,* 360**,** 339-40.

BOWERS, D. & HEILMAN, K. M. (1980) Pseudoneglect: effects of hemispace on a tactile line bisection task. *Neuropsychologia,* 18**,** 491-8.
BRADSHAW, J. L., NETTLETON, N. C., NATHAN, G. & WILSON, L. (1983) Head and body space to left and right, front and rear--II. Visuotactual and kinesthetic studies and left-side underestimation. *Neuropsychologia,* 21**,** 475-86.
BRADSHAW, J. L., NETTLETON, N. C., NATHAN, G. & WILSON, L. (1985) Bisecting rods and lines: effects of horizontal and vertical posture on left-side underestimation by normal subjects. *Neuropsychologia,* 23**,** 421-5.
CAIN, W. S. & MURPHY, C. L. (1980) Interaction between chemoreceptive modalities of odour and irritation. *Nature,* 284**,** 255-7.
LIVERMORE, A., HUMMEL, T. & KOBAL, G. (1992) Chemosensory event-related potentials in the investigation of interactions between the olfactory and the somatosensory (trigeminal) systems. *Electroencephalogr Clin Neurophysiol,* 83**,** 201-10.
MESULAM, M.-M. (2000) Attentional networks, confusional states, and neglect syndromes. IN MESULAM, M.-M. (Ed.) *Principles of behavioral and cognitive neurology* 2ed. Oxford, UK, Oxford University Press. pp. 174–256
WYSOCKI, C. J., COWART, B. J. & RADIL, T. (2003) Nasal trigeminal chemosensitivity across the adult life span. *Percept Psychophys,* 65**,** 115-22.