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Neuroanatomie fonctionnelle sous-tendant la régulation consciente et volontaire de la tristesse chez l'enfant et l'adulte sains

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Résumé

La capacité d'autoréguler volontairement les émotions négatives est essentielle à une saine psyché. En effet, l'incapacité à supprimer ce type d'émotions peut être un facteur clé dans la genèse de la dépression majeure et des troubles anxieux. En ce qui a trait au substrat neuroanatomique fonctionnel de l'autorégulation des émotions, il a été récemment proposé qu'un circuit préfronto-limbique sous-tend cette capacité.

Par ailleurs, il est clairement démontré que, d'un point de vue comportemental, les émotions et l'autorégulation émotionnelle se développent tout au long de la vie en étroite relation avec le développement cognitif et social. En regard de l'autorégulation émotionnelle, il a été proposé que le développement de cette capacité soit également relié à celui du cortex préfrontal. À ce sujet, très peu d'informations ont été recueillies au sujet des soubassements neuroanatomiques fonctionnels de l'autorégulation émotionnelle chez l'enfant. En fait, aucune étude d'imagerie cérébrale fonctionnelle n'a, à ce jour, examiner les corrélats neuronaux des émotions primaires au cours de l'enfance.

Dans ce contexte, nous avons réalisé deux études d'imagerie par résonance magnétique fonctionnelle afin : 1) d'explorer les soubassements neuroanatomiques de la tristesse chez des jeunes filles (Article #2); et, 2) d'identifier et de comparer le substrat neuroanatomique fonctionnel sous-tendant la suppression volontaire de la tristesse chez les jeunes filles et les femmes (Article #1 et Article #3).

Dans l'Article #1, les résultats ont montré que la suppression volontaire de la tristesse chez les femmes était associée à l'activité d'un circuit préfronto-limbique. En particulier, il a été noté que les cortex préfrontal latéral et orbitofrontal jouent un rôle capital dans cette tâche.

Dans l'Article #2, les résultats ont révélé que le substrat neuroanatomique fonctionnel de la tristesse chez les jeunes filles était très similaire à celui observé lors d'études précédentes chez les adultes, incluant celle présentée dans l'Article #1. De tels résultats supportent la théorie différentielle des émotions voulant que les émotions aient une assise biologique.

Dans l'Article #3, les résultats ont démontré que, comme chez les adultes, la suppression volontaire de la tristesse chez les enfants était supportée par un circuit préfronto-limbique. Cependant, comparé aux résultats obtenus chez l'adulte, ce circuit comprend un volume plus important du cortex préfrontal chez l'enfant.

Globalement, les résultats de ces études pavent la voie à une meilleure compréhension des troubles qui découlent du mauvais fonctionnement du circuit préfronto-limbique sous-tendant la régulation volontaire des émotions, tels que la dépression majeure et les troubles anxieux.

Summary

The ability to voluntarily self-regulate negative emotion is essential to a healthy psyche. Indeed, a chronic incapacity to suppress negative emotion might be a key factor in the genesis of depression and anxiety. Regarding the neural underpinnings of emotional self-regulation, it has been recently hypothesized that a prefronto-limbic circuit underlies the voluntary regulation of emotion.

It is well established that behaviorally, emotions as well as emotional self-regulation develop throughout life in close relationship with cognitive and social development. With respect to emotional self-regulation, it has been proposed that its development critically depends on the maturation of the prefrontal cortex (PFC). Regarding this issue, nothing is known yet concerning the neural substrate underlying emotional self-regulation in children. In fact, to date, no functional brain imaging study has been undertaken in order to circumscribe the neural substrate of basic emotions in children.

In this context, we conducted two functional magnetic resonance imaging studies in order to: 1) investigate the neural substrate underlying the subjective experience of sadness in girls (Article #2); and, 2) identify and compare the neural underpinnings of sadness suppression in girls and women (Article #1 and #3).

In Article #1, results have demonstrated that the voluntary suppression of sadness in women was correlated with the activity of a prefronto-limbic circuit. In particular, these results have shown that the lateral prefrontal and orbitofrontal cortices play a pivotal role in this function.

In Article # 2, results have revealed that the neural substrate of sadness in girls was very similar to that found in previous functional neuroimaging studies in adults, including the study presented in Article #1. Such results lend some support to the differential emotion theory (DET), which claims that emotions are biologically based.

In Article #3, results have shown that, as in adults, the voluntary suppression of sadness in children was supported by a prefrontal-limbic circuit. However, this circuit encompassed a much larger portion of the PFC in children than in adults. Based on those results, it seems reasonable to affirm that neurobiologically, it is harder for children than adults to voluntarily regulate their emotions.

Taken together, the results of these studies pave the way for a better understanding of disorders rooted in the dysfunction of the prefronto-limbic circuit underlying emotional self-regulation, such as major depression and anxiety disorders.

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Liste des abréviations

1H : Atome d'hydrogène

AB : Aire de Brodmann

ACC: Anterior cingulate cortex

Acg: Anterior cingulate gyrus

AC-PC: Anterior commissure-Posterior commissure

BA: Brodmann area

BOLD: Blood-oxygenation-level-dependent

CHUM: Centre hospitalier de l'Université de Montréal

DÉSOXY-Hb : Désoxyhémoglobine

DET: Differential emotions theory

DLPFC: Dorsolateral prefrontal cortex

EPI: Echoplanar images

fMRI: Functional magnetic resonance imaging

FOV: Field of view

FWHM: Full width half maximum

HAM-D: Hamilton Depression Rating Scale

Hb : Hémoglobine

IAPS: International Affective Picture System

IRM : Imagerie par résonance magnétique

IRMf: Imagerie par résonance magnétique fonctionnelle

LPFC: Lateral prefrontal cortex

MNI: Montreal Neurological Institute

MPFC: Medial prefrontal cortex

MR: Magnetic resonance

MRI: Magnetic resonance imaging

NARSAD: National Alliance for Research in Schizophrenia and Depression

NSERC: National Sciences and Engineering Research Council of Canada

OFC: Orbitofrontal cortex

OXY-Hb : Oxyhémoglobine

PET: Positrons emission tomography

PFC: Prefrontal cortex

rCBF: Regional cerebral blood flow

RMN : Résonance magnétique nucléaire

ROI: Region of interest

SD : Standard deviation

SPM: Statistical parametric map

SVC: Small volume correction

TDE: Théorie différentielle des émotions

TE: Time-Echo

TEP : Tomographie par émission de positons

TR: Time repetition

VLPFC: Ventrolateral prefrontal cortex

Dédicace

À Audrey et Marc Antoine, mes enfants bien-aimés, pour leur Patience infinie et leur Amour inconditionnel.

À toi, mon Amour éternel. En ta présence, seul le domaine du possible est réel.

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Chapitre1

INTRODUCTION GÉNÉRALE

1. Définition des émotions

Pour la psychologie évolutionniste, les émotions ont une assise biologique et représentent des modes d'adaptation aux demandes environnementales changeantes (Tooby & Cosmides, 1990; Levenson, 1994). Selon cette discipline, les émotions sont apparues au cours de l'évolution parce qu'elle permettaient de coordonner adéquatement les divers systèmes de réponses émotionnelles (cognitif, subjectif ou expérientiel, physiologique et comportemental) de l'être humain. Dans la même foulée, Oatley & Johnson-Laird (1987) soutiennent que les émotions facilitent la prise de décision tandis que Frijda (1986) met l'emphase sur le fait qu'elles préparent l'individu à une réponse motrice rapide. Par ailleurs, Cahill et *al.* (1994) affirment que les émotions favorisent les apprentissages. D'un point de vue social, les émotions jouent également un rôle important. Par exemple, elles nous informent quant à savoir si quelque chose est bon ou mauvais (Walden, 1991) et permettent de décoder les intentions comportementales des individus (Ekman et *al.* 1972; Fridlund, 1994). Toutefois, Gross (1999) note avec justesse que les émotions ne sont pas toujours la réponse la plus appropriée aux diverses situations rencontrées quotidiennement. Gross souligne aussi que malgré les innombrables bénéfices possibles associés aux émotions, il est important d'évaluer correctement les dangers qui peuvent survenir si l'on suit aveuglément chacune de nos impulsions émotionnelles. En accord avec cette position, il est manifeste que l'incapacité à bien gérer les émotions négatives constitue l'une des causes principales de la souffrance humaine. Ce constat nous amène directement au concept d'autorégulation émotionnelle.

2. Bref historique du concept d'autorégulation émotionnelle

Bien que récent d'un point de vue scientifique, le concept d'autorégulation émotionnelle est apparue en Occident au début du troisième siècle avant Jésus-Christ avec le stoïcisme, doctrine philosophique principalement élaborée par Zénon de Citium (Tarnas, 1993, p.76). Celui-ci fût le premier penseur à proposer que non seulement il était possible mais aussi nécessaire pour les êtres humains d'utiliser leur intellect afin de maîtriser les passions. Depuis, plusieurs philosophes (ex. : les Épicuriens, Spinoza, Smith, Hume etc.) ont argumenté vigoureusement au sujet de l'importance et de l'influence relatives de la raison sur les émotions (pour une revue, voir Tarnas, 1993). Malgré les différences idéologiques qui ont opposé ces philosophes au cours de l'histoire de la civilisation occidentale, ceux-ci ont conclu à l'unanimité qu'il est impératif pour les êtres humains d'apprendre à maîtriser de façon consciente et volontaire leurs émotions.

2.a. Histoire contemporaine : La tradition psychanalytique

Un des précurseurs importants de l'étude contemporaine de l'autorégulation émotionnelle fût Sigmund Freud. Avec l'élaboration de l'approche psychanalytique, celui-ci mit en évidence les conflits qui existent entre les pulsions biologiques internes et les facteurs restrictifs internes et externes (Gross, 1999). De plus, vers la fin de sa carrière, Freud mit davantage l'emphase sur la notion de régulation de l'anxiété (Freud, 1926/1959). Il semble que ce dernier utilisa le terme anxiété comme un concept fourre-tout référant de manière globale aux émotions négatives (Erdelyi, 1993). Sans entrer dans les détails du modèle freudien de la régulation émotionnelle, disons tout de même que la

régulation de l'anxiété est un concept central et que sa réalisation s'opère grâce à différents mécanismes de défenses (Freud, 1926/1959). De façon générale, ces mécanismes sont inconscients mais peuvent aussi être conscients (Freud, 1926/1959).

Aujourd'hui, certains aspects de la recherche sur l'autorégulation émotionnelle sont en continuité avec le modèle proposé par Freud. Ainsi, la recherche contemporaine portant sur l'autorégulation émotionnelle continue d'être préoccupée par la diminution des expériences comportant des émotions négatives, à l'aide de diverses stratégies comportementales et cognitives. Ce courant de recherche s'intéresse également à la capacité de moduler (i.e. augmenter, diminuer ou maintenir) – et de manière consciente ou non (Mayer & Salovey, 1995) - l'expérience et de l'expression des émotions positives ou négatives (Parrott, 1993). Par ailleurs, on retrouve également une certaine discontinuité entre les travaux freudiens et la recherche contemporaine portant sur l'autorégulation émotionnelle. En effet, bien que le style de régulation émotionnelle soit vu comme étant un concept central de la psychopathologie (Cicchetti, Ackerman & Izard, 1995; Gross & Munoz, 1995), on observe un intérêt grandissant pour l'étude de l'autorégulation émotionnelle dans le fonctionnement psychologique normal. De plus, ce type de recherche repose maintenant davantage sur les méthodes corrélationnelles expérimentales plutôt que sur les rapports cliniques comme à l'époque de Freud.

2.b. La tradition du stress et du " coping"

Le deuxième précurseur important de l'étude contemporaine de l'autorégulation émotionnelle est Cannon (1914) avec ses travaux portant sur la réponse de stress. En

effet, Cannon (1914) nota que même confrontés à différents défis, les individus produisaient une réponse de stress similaire. Selye poursuivit l'examen de cette notion et conclu que le profil de la réponse de stress dépendait de la durée d'exposition de l'individu à l'élément stressant (Selye, 1956, 1974). Quoique les recherches portèrent d'abord sur les réponses produites par des agents physiques de stress, rapidement on en vint à étudier les réponses engendrées par des agents psychologiques de stress. Ce faisant, on distingua trois processus distincts impliqués dans la gestion du stress psychologique : a) comment l'individu évalue la situation (évaluation primaire); b) comment l'individu évalue ses propres capacités à répondre à cette situation (évaluation secondaire); et, c) comment l'individu gère la relation individu-environnement occasionnant le stress ("coping ") (Lazarus, 1966).Cette analyse plus fine des processus à l'œuvre dans la gestion du stress psychologique mena du même coup Lazarus (1966) à faire la distinction entre : a) la gestion du stress centré sur le problème (régler le problème); et, b) la gestion du stress centré sur l'émotion (diminuer l'occurrence de l'expérience comportant une émotion négative). C'est ce dernier construit qui constitua la contribution la plus importante de cette approche à l'étude contemporaine de l'autorégulation émotionnelle (Gross, 1999).

Aujourd'hui les chercheurs qui étudient cette question se concentrent davantage sur des processus précis d'autorégulation émotionnelle tels que la rumination (Nolan-Hoeksema, 1993) et la suppression (Gross, 1998a) plutôt que de considérer dans son ensemble la capacité à affronter une situation telle que décrite dans la littérature portant sur la gestion du stress.

3. Modèle de Gross et définition du concept d'autorégulation émotionnelle

Avec en arrière plan les traditions psychanalytique et de gestion du stress, les vingt dernières années ont vu émerger l'autorégulation émotionnelle comme domaine de recherche distinct (Gross, 1998b). Gross définit l'autorégulation émotionnelle comme étant l'ensemble des processus par lesquels l'individu influence quelles émotions il expérimente, à quel moment il expérimente les émotions et comment il expérimente et exprime ces dernières (Gross, 1999). Étant donné que les processus cognitifs impliqués dans l'autorégulation émotionnelle sont étroitement liés à ceux sous-tendant la génération d'une émotion, il a été avancé que l'autorégulation émotionnelle faisait partie intégrante de l'émotion (Frijda, 1986), telle que définie par les tenants de l'approche biologique des émotions (les principaux représentants de cette approche étant : Arnold, 1960; Tomkins, 1962; Ekman, 1972; Izard, 1977; Plutchik, 1980; Scherer, 1984; Buck 1985; Frijda, 1986; Lazarus, 1991). Selon cette approche, la génération d'une émotion débute par l'évaluation d'indices émotionnels internes ou externes. L'évaluation de ces indices déclenche ensuite un ensemble de réponses physiologiques, subjectives et comportementales. Ces réponses peuvent par la suite être modulées, donnant ainsi la teinte finale aux réponses émotionnelles ressenties et exprimées par l'individu.

Dans cette perspective, le modèle d'autorégulation émotionnelle proposé par Gross suggère que l'on peut agir sur un ou plusieurs des divers aspects impliqués dans la génération et l'expression d'une émotion (Gross, 1998b). Premièrement, on peut agir sur la situation elle-même. C'est ce que Gross appelle la *sélection de la situation*. Ainsi,

l'individu peut choisir d'approcher ou d'éviter une situation ou une personne, selon l'impact émotionnel qu'elles déclenchent. Advenant le cas où l'on se retrouve tout de même dans une situation provoquant une réaction émotionnelle, il demeure possible de la modifier. Gross réfère à cet aspect comme étant la *modification de la situation*. Il s'agit alors de modifier l'environnement immédiat de façon à altérer son impact émotionnel.

Il est également possible d'autoréguler ses émotions sans agir sur la situation elle-même. Ainsi, pour une situation donnée, on doit diriger son attention sélectivement de façon à moduler l'émotion ressentie. Il s'agit du *déploiement attentionnel*. Par exemple, la distraction est l'une des stratégies attentionnelles appartenant à cette catégorie. Elle consiste à porter son attention sur des aspects non émotionnels de la situation (Derryberry & Rothbart, 1988). Et même une fois que la situation a été choisie, modifiée et que l'individu porte une attention sélective à cette situation, il est encore possible d'en altérer l'impact émotionnel. Pour ce faire, on utilise le *changement cognitif*, qui réfère à la capacité d'évaluer la situation dans laquelle un individu se trouve de sorte d'en altérer la signification émotionnelle. Ce changement cognitif implique soit de modifier ce que l'individu pense de la situation elle-même, soit de modifier la perception de sa capacité à gérer cette situation. En dernier lieu, l'individu peut également agir sur la réponse émotionnelle directement, au fur et à mesure qu'elle surgit. Gross réfère à cette dernière possibilité comme étant la *modulation de la réponse.* Ainsi donc, tandis que les quatre premiers types de stratégies d'autorégulation sont centrés sur les antécédents de la réponse émotionnelle, le cinquième type de stratégies est centré sur la réponse émotionnelle elle-même (Gross, 2001).

Les changements produits au niveau de l'une ou l'autre des composantes (énumérées ci-haut) associées à la génération d'une émotion impliquent nécessairement des modifications dans ce que Thompson (1990) nomme la « dynamique émotionnelle ». Ce concept inclut l'intensité, le temps de mise en place, la durée de même que la fin des réponses produites dans les diverses composantes de l'émotion (Gross, 1999). L'autorégulation émotionnelle se rapporte tant à la génération ou au maintien qu'à l'augmentation ou la diminution d'émotions positives ou négatives (Masters, 1991; Parrott, 1993; Cole, et *al.* 1994; Langston, 1994). Cette capacité regroupe plusieurs types d'ajustements qui favorisent l'adaptation de l'individu aux circonstances rencontrées dans la vie de tous les jours (Cole et *al.* 1994) et lui permettent d'atteindre ses objectifs (Thompson, 1990).

4. Soubassements neurobiologiques de l'autorégulation émotionnelle

Malgré l'importance indéniable de la capacité à autoréguler nos émotions dans la conduite de nos activités quotidiennes, les soubassements neurobiologiques sous-tendant les processus psychologiques à l'œuvre en regard de cette capacité demeurent méconnus. En rapport avec cette question, Nauta (1971) puis Tucker et collaborateurs (1995) avancèrent l'hypothèse voulant que le cortex préfrontal de même que des structures limbiques et para-limbiques constituaient un circuit impliqué dans l'autorégulation émotionnelle. Plus récemment, se basant sur une série de données provenant d'études lésionnelles chez l'animal ainsi que d'études psychophysiologiques, de neuropsychologie clinique et d'imagerie cérébrale fonctionnelle chez l'humain, Davidson et *al.* (2000) ont suggéré que l'autorégulation émotionnelle est sous-tendue par un circuit neuronal

comprenant différentes régions du cortex préfrontal (par exemple, les cortex orbitofrontal, dorsolatéral et cingulaire antérieur) ainsi que différentes régions limbiques et para-limbiques (par exemple, l'amygdale et l'hypothalamus).

Ce sont Beauregard, Lévesque et Bourgouin (2001) qui les premiers étudièrent les soubassements neurobiologiques de l'autorégulation consciente des émotions. Pour ce faire, ils réalisèrent une étude d'imagerie par résonance magnétique fonctionnelle (IRMf) chez des sujets masculins normaux (droitiers, caucasiens, universitaires) (âgés entre 20 et 42 ans) qui furent soumis à deux conditions expérimentales : une condition *Excitation sexuelle* et une condition *Suppression*. Lors de la condition *Excitation sexuelle*, les sujets devaient regarder des extraits de films érotiques et des extraits de films neutres. Ils avaient comme instruction de réagir normalement lors du visionnement des deux types d'extraits (i.e. de se laisser vivre l'excitation sexuelle ou tout autre émotion associée aux deux types d'extraits de films). Lors de la condition *Suppression*, on présenta aux sujets des extraits neutres et érotiques équivalents à ceux présentés lors de la condition *Excitation sexuelle* mais, cette fois, ils devaient tenter d'inhiber toute émotion induite par le visionnement des extraits de films neutres et érotiques. Pour ce faire, on demanda aux sujets de devenir des observateurs détachés des extraits de films. Une telle stratégie métacognitive s'inspire du concept de « mindfullness », état mental central de la tradition bouddhiste qui consiste à prendre une distance par rapport à ses pensées et ses émotions.

D'un point de vue expérientiel, le visionnement des extraits de films érotiques, tant dans la condition *Excitation sexuelle* que dans la condition *Suppression*, a induit une

excitation sexuelle chez tous les sujets. De plus, dans la condition *Suppression*, la majorité des sujets ont rapporté avoir réussi à prendre une distance par rapport à l'excitation sexuelle ressentie lors du visionnement des extraits de films érotiques. Ceci s'est d'ailleurs traduit par un niveau d'excitation sexuelle moyen significativement plus élevé dans la condition *Excitation sexuelle* (moyenne = 5; étendue = 3-8) que dans la condition *Suppression* (moyenne = 2; étendue = 1-4) ($p < 0.005$).

D'un point de vue neurobiologique, les résultats obtenus furent très révélateurs. D'abord dans la condition *Excitation sexuelle*, le visionnement d'extraits de films érotiques a produit une activation significative de régions limbiques et para-limbiques telles que l'amygdale, le pôle temporal antérieur et l'hypothalamus, régions normalement associées à l'excitation sexuelle (Karama et al. 2002). Dans la condition *Suppression*, les résultats ont révélé que la suppression volontaire de l'excitation sexuelle était corrélée positivement à l'activation du cortex préfrontal latéral (aire de Brodmann – AB- 10) et du cortex cingulaire antérieur (AB 32). Plus intéressant encore, les activations notées dans les régions limbiques et para-limbiques lors de la condition *Excitation sexuelle* avaient complètement disparues lors de la condition *Suppression* (ceci même en utilisant un seuil statistique très permissif de $p < 0.10$, non corrigé).

Ces résultats, obtenus grâce à une technique d'imagerie cérébrale fonctionnelle de pointe, appuient les hypothèses proposées par Nauta, (1971), Tucker et *al.* (1995) et Davidson et *al.* (2000) voulant que l'autorégulation consciente des émotions soit sous-

tendue par un circuit préfronto-limbique dans lequel certaines régions du cortex préfrontal modulent les réponses émotionnelles générées à un niveau sous-cortical.

Dans le même esprit, Schaefer et ses collègues (2002) vérifièrent, lors d'une étude subséquente d'IRMf, si la régulation volontaire d'une émotion négative était associée à la modulation de l'activité neuronale de l'amygdale, une structure clé dans la perception émotionnelle. Au cours de cette étude, on présenta à sept sujets normaux (femmes droitières, âgées entre 19 et 37 ans), des images à valence négative et des images neutres provenant de l'*International Affective Picture System* (IAPS) (Lang et al. 1998). Au cours du visionnement de ces images, on leur demanda soit de *Maintenir* la réponse émotionnelle ainsi générée, soit de *Regarder* ces images passivement sans moduler leurs réponses émotionnelles. L'expérience subjective des sujets fût également notée sur échelle de type Likert numérotée de un (état affectif neutre) à quatre (état affectif très négatif).

Tel qu'anticipé, les sujets rapportèrent avoir ressenti un état négatif significativement plus intense lors du visionnement des images négatives que lors des images neutres ($p < 0.0001$). De plus, les sujets affirmèrent avoir expérimenté un état significativement plus négatif lors de la condition expérimentale *Maintien* que lors de la condition *Regarder* ($p < 0.0005$). En accord avec les études précédentes ayant montré une augmentation de l'activité de l'amygdale en réponse à des stimuli négatifs, une activation significativement plus grande fût notée durant la présentation des images négatives comparé au visionnement des images neutres ($p < 0.01$). Mais ce qu'il faut surtout retenir

de cette étude, c'est qu'une augmentation de l'activité de l'amygdale fût observée dans la condition expérimentale *Maintien* en comparaison avec celle notée lors de la condition *Regarder* ($p < 0.05$). De plus, une prolongation de l'augmentation de cette activité fût observée pendant que les sujets maintenaient leur état émotionnel négatif en réponse à la présentation des images négatives, et cette augmentation s'est avérée corrélée à l'intensité de l'état émotionnel négatif ressenti par les sujets.

Ces résultats suggèrent que les processus cognitifs conscients qui modulent les réponses émotionnelles des sujets suite au visionnement des images négatives sont associés à une modification de la réponse de l'amygdale, i.e. qu'il est possible de moduler consciemment et volontairement l'activité neuronale de l'amygdale.

Dans un effort afin d'identifier les soubassements neurobiologiques des différents processus cognitifs à l'œuvre dans l'autorégulation émotionnelle, Ochsner et ses collaborateurs (2002) ont récemment réalisé une autre étude d'IRMf. Ils ont prédit que les circuits neuronaux de même que les processus impliqués dans l'autorégulation émotionnelle seraient les mêmes que ceux impliqués dans d'autres formes de contrôle cognitif. De façon plus spécifique, Ochsner et *al.* (2002) ont fait l'hypothèse que la réévaluation (stratégie d'autorégulation utilisée par leurs sujets) pouvait être subdivisée en trois processus distincts impliquant le cortex préfrontal latéral, le cortex préfrontal médian, et le cortex cingulaire postérieur. Le premier processus impliqué est l'auto-génération d'une stratégie cognitive permettant de recadrer un événement émotionnel en termes non émotionnel. Cette stratégie doit demeurer en mémoire tant et aussi longtemps

que les conditions produisant l'émotion sont présentes. Les études de neuropsychologie clinique (Barcelo & Knight 2002; Stuss et *al.* 1994) et de neuroimagerie fonctionnelle (Cabeza & Nyberg, 2000; Smith & Jonides, 1999; Barch et *al.* 1997) indiquent que cette habileté est implémentée par les processus impliqués dans la mémoire de travail qui dépendent du cortex latéral préfrontal. Le deuxième processus proposé par Ochsner et *al.* (2002) est celui permettant de monitorer, d'une part, l'interaction entre les processus du haut vers le bas ("top-down") (réévaluation de la situation permettant de contrecarrer l'émotion) et, d'autre part, les processus du bas vers le haut ("bottom-up") (évaluation de la situation qui génère une réponse émotionnelle), indiquant la nécessité de poursuivre le processus de réévaluation. Cette fonction serait associée à la partie postérieure du cortex cingulaire antérieur (pour une revue, voir Botvnick et *al.* 2001; Bush et *al.* 2000). Il a en effet été montré que cette région cérébrale serait impliquée dans diverses tâches telles que le monitorage de processus continus et l'évaluation du besoin de régulation cognitive (van Veen et *al.* 2001). En dernier lieu, le troisième processus implique la réévaluation de la relation entre l'état interne ressenti par l'individu (subjectif ou physiologique) et les stimuli externes générant une émotion. Une telle réévaluation serait utilisée pour monitorer les changements dans l'état émotionnel de l'individu. Ochsner et *al.* (2002) prédirent que cette fonction serait associée à l'activité neuronale du cortex préfrontal médian, étant donnée que cette région cérébrale est impliquée dans la conscience de l'état émotionnel ressenti (Lane 2000; Lane et *al.* 1997), dans les processus reliés à soi (Gusnard et *al.* 2001) ainsi qu'à l'attribution d'un état émotionnel pour soi (Paradiso et *al.* 1999) ou pour autrui (Happe et *al.* 1996). Ochsner et ses collègues ont de plus fait l'hypothèse que ce processus de réévaluation influencerait les processus cognitifs

impliqués dans l'évaluation de la signification émotionnelle des stimuli. À ce sujet, il a été postulé qu'il existait deux types de processus évaluatifs associés à la génération d'une émotion (Lazarus, 1991). Le premier, relativement inconscient et non intentionnel, est activé pour déterminer si un stimulus a une signification émotionnelle. Le second est quant à lui activé consciemment et intentionnellement pour évaluer la signification du contexte et la pertinence d'une réponse comportementale possible (Lazarus, 1991). À cet effet, il semble que l'amygdale joue un rôle primordial dans la détection pré-attentive et la reconnaissance de stimuli ayant une signification émotionnelle (Anderson & Phelps 2001; Whalen et al. 1998) tandis que le cortex orbitofrontal médian joue un rôle clé dans la représentation de la valence émotionnelle d'un stimulus (Kawasaki et al. 2001; O'Doherty et al. 2001; Davidson & Irwin, 1999; Elliott et al. 1997).

Afin de vérifier la validité de leurs hypothèses, Ochsner et *al.* (2002) demandèrent à leurs sujets (15 femmes saines âgées entre 18 et 30 ans) de se soumettre à deux conditions expérimentales : *Regarder* ou *Réévaluer* les images négatives ou neutres (choisies à partir de l'IAPS) qui leurs étaient présentées. Dans la condition *Regarder*, les sujets devaient regarder les images sans tenter de modifier l'état émotionnel qu'elles généraient alors que dans la condition *Réévaluer*, elles devaient réinterpréter les images négatives de sorte qu'elles ne génèrent plus d'émotions négatives. Les sujets devaient, après chaque image, indiquer l'intensité de l'émotion ressentie sur une échelle allant de un (faible) à quatre (forte). Finalement une période de cinq secondes de relaxation leur était accordée entre chaque image.

Les résultats obtenus confirmèrent les hypothèses de Ochsner et *al.* (2002). D'abord, sur le plan comportemental, tel que prévu la réévaluation des images négatives diminua les émotions négatives ressenties. Sur le plan de la neuroanatomie fonctionnelle, la réévaluation fût associée à une activation significative des régions ventrales et dorsales du cortex préfrontal latéral ainsi que de la partie dorsale du cortex préfrontal médian. De plus, l'activation de l'amygdale fût significativement plus intense dans la condition *Regarder* que dans la condition *Réévaluer*. Également, le cortex préfrontal médian montra une activation plus intense pour la majorité des images négatives dans la condition *Regarder* que dans la condition *Réévaluer* alors que les régions activées du cortex préfrontal latéral montrèrent la tendance inverse. En dernier lieu, l'augmentation de l'activité neuronale de l'une de ces régions – la partie ventrale du cortex préfrontal latéral – lors de la condition *Réévaluer* fût corrélée avec une diminution de l'activation de l'amygdale pour l'ensemble des sujets.

Pris dans leur ensemble, ces résultats vont dans le même sens que ceux obtenus précédemment par Beauregard et *al.* (2001) puis Schaefer et *al.* (2002). Les conclusions de ces trois études, bien qu'utilisant des stratégies différentes d'autorégulation émotionnelle pour moduler soit un état émotionnel positif ou négatif, appuient la notion mise de l'avant par Nauta (1971), Tucker et *al.* (1995) et Davidson et *al.* (2000) voulant que différents processus métacognitifs conscients et volontaires utilisés pour altérer l'impact d'une émotion induite de façon externe peuvent moduler de façon significative l'activité neuronale de structures corticales et sous-corticales impliquées dans divers aspects du traitement des émotions.

5. Développement de l'autorégulation émotionnelle

Les enfants débutent très tôt à réguler le stress généré par les émotions qu'ils ressentent ou les situations qui génèrent ces émotions. Toutefois, pour avoir la capacité de réguler consciemment et volontairement ses émotions, l'enfant doit d'abord avoir conscience de vivre une expérience émotionnelle, i.e. qu'il doit interpréter et évaluer l'état émotionnel qu'il perçoit en lui (Lewis, 1998). Pour vivre une expérience émotionnelle – un ensemble d'événements internes – l'enfant doit être en mesure cognitivement de référer au fait qu'il est le « Je » à qui ces événements internes arrivent (Lewis, 1998). Il doit également pouvoir interpréter ces événements en fonction du contexte social qu'il a acquis à travers ses interactions avec autrui. En effet, l'enfant acquiert différentes stratégies de régulation émotionnelle en accord avec les règles sociales qui prévalent dans sa culture. Ces capacités implique le développement de la conscience de soi, une habileté métacognitive centrale dans l'idée d'autoréférence (« l'idée de moi », en tant qu'individu distinct) (Lewis, 1995). Certaines évidences permettent d'affirmer que la conscience de soi émerge entre 12 et 18 mois. C'est avec l'apparition de cette forme de conscience autoréférencielle que l'enfant arrive à monitorer et réagir à l'état émotionnel qu'il expérimente, i.e. à réfléchir sur ses propres pensées, ses émotions et son comportement. Le développement cognitif et le développement social de l'enfant jouent donc un rôle clé dans l'évolution de la capacité de réguler ses émotions (Cole et *al.* 1994).

L'autorégulation émotionnelle débute avec le contrôle de la détresse psychologique. Les enfants entre 8 et 18 mois réagissent avec détresse lors de brèves périodes de séparation d'avec la mère. Entre 19 et 24 mois, il y a une réduction significative d'un état

émotionnel négatif engendré par cette même brève période de séparation maternelle. Fox et ses collaborateurs (2001) ont avancé l'idée selon laquelle les changements observés en rapport avec cette expérience au cours de la deuxième année de la vie de l'enfant pourraient être le résultat : 1) d'une meilleure capacité de l'enfant à reconnaître, définir et se représenter la cause de cette détresse; 2) de son habileté à identifier les caractéristiques contextuelles qui déclenchent l'émotion; 3) de sa capacité à maintenir une représentation cognitive de sa mère pendant son absence; 4) de son habileté à générer un plan d'actions séquentielles lui permettant de modifier la situation et, ainsi, de faire diminuer la détresse ressentie. Les résultats obtenus à l'aide de l'électroencéphalographe (EEG) lors d'une étude réalisée par Fox et *al.* (2001) ont montré le rôle important joué par le cortex préfrontal – le substrat des fonctions les plus « civilisées » du cerveau (Filley, 1995, p. 5) – dans la régulation d'émotions négatives. Par ailleurs, Fox et Bell (1990) ont fait l'hypothèse que la maturation du cortex préfrontal, combinée à certains apprentissages sociaux, sous-tendent l'émergence de l'autorégulation émotionnelle. À ce sujet, au cours des six premiers mois de l'enfant, la capacité de régulation du jeune enfant passe essentiellement d'une réponse réflexe à des stimuli physiologiques (par exemple, la soif, la faim, la peur, la douleur) à une conscience naissante d'un état interne de même qu'à la possibilité d'associer temporairement des états émotionnels à des stimuli externes précis (Kopp, 1989). Entre 6 et 8 mois, la régulation émotionnelle repose déjà sur des fonctions typiques du cortex préfrontal, telles que porter une attention sélective à certains stimuli ainsi que la capacité de percevoir un séquence temporelle impliquant les propres actions de l'enfant et des stimuli externes, ce qui permet à l'enfant de réguler ses émotions, en indiquant par exemple à la gardienne d'agir en regard de son état émotionnel. Avec

l'émergence de la conscience de soi et de l'intentionnalité (agir en fonction d'un objectif), les capacités d'autorégulation de l'enfant augmentent dramatiquement durant la seconde moitié de la première année. À ce moment, la régulation émotionnelle devient réellement de l'autorégulation émotionnelle, i.e. plus consciente et autodirigée. À cette période de sa vie, l'enfant acquiert de nouvelles capacités cognitives exécutives (idée représentationnelle, monitorage de soi, mémoire de travail, formation d'un but, internalisation de règles guidant son comportement, inhibition de la réponse, contrôle attentionnel, planification) qui dépendent directement du développement du cortex préfrontal (Dawson et *al.* 1992).

Phylogénétiquement de même qu'ontogénétiquement, le cortex préfrontal est une des dernières régions du néocortex à se développer. Dans une perspective évolutionniste, c'est dans le cerveau humain que le cortex préfrontal atteint sa dimension la plus grande, occupant plus du tiers du volume total du néocortex. Chez l'être humain normal, son développement s'achève à la fin de l'adolescence et même au début de l'âge adulte (Yakovlev & Lecours, 1967). Sachant que l'autorégulation émotionnelle est étroitement liée au développement du cortex préfrontal, il est normal d'observer un développement quasi continu de cette capacité jusqu'au début de l'âge adulte.

6. Problématique, question générale et objectifs spécifiques

Les résultats des quelques études de neuroimagerie fonctionnelle récemment réalisées au sujet des soubassements neurobiologiques de l'autorégulation émotionnelle suggèrent qu'un circuit neuroanatomique fonctionnel impliquant diverses régions du cortex

préfrontal (cortex préfrontal latéral et cortex cingulaire antérieur) ainsi que des structures limbiques/para-limbiques (hypothalamus, amygdale, pôle temporal antérieur) sous-tendrait la modulation volontaire de l'excitation sexuelle (Beauregard et *al.* 2001) et d'un affect négatif (Ochsner et *al.* 2002; Schaefer et *al.* 2002).

Jusqu'à présent, aucune étude de neuroimagerie fonctionnelle n'a examiné les soubassements neurobiologiques de la suppression d'une émotion primaire négative comme la tristesse. Par ailleurs, même si d'un point de vue comportemental il est clairement documenté que l'autorégulation émotionnelle se développe pratiquement de la naissance jusqu'au début de l'âge adulte via le développement cognitif et social, et que ce développement semble étroitement lié à la maturation du lobe préfrontal, aucune donnée expérimentale n'a été recueillie jusqu'à maintenant en ce qui a trait au substrat neurobiologique de l'autorégulation émotionnelle chez l'enfant sain. En fait, aucune étude d'imagerie cérébrale fonctionnelle n'a été à date menée en ce qui concerne les soubassements neurobiologiques des émotions primaires chez l'enfant sain. À ce sujet, différentes théories des émotions – y compris la théorie différentielle des émotions (Izard, 1991) à caractère plus biologique – s'entendent pour dire que divers aspects des émotions, dont l'expérience subjective, se développent jusqu'à l'âge adulte, légitimant du même coup la question du développement du substrat neurobiologique sous-tendant les émotions primaires.

Dans ce contexte, la présente thèse visait à : 1) identifier les soubassements neurobiologiques de la tristesse chez l'enfant sain; et, 2) comparer les soubassements

neurobiologiques de l'autorégulation volontaire de la tristesse chez l'adulte et l'enfant sains. Afin d'atteindre ces objectifs, nous avons mené deux études d'IRMf qui sont décrites dans les chapitres suivants. Ainsi, le chapitre 2 présente une étude intitulée *Neural circuitry underlying voluntary suppression of sadness* [2003, *Biological Psychiatry*, 53, 502-510], visant à identifier le substrat neurobiologique de la suppression de la tristesse chez l'adulte sain. Le chapitre 3 présente la première partie d'une seconde étude intitulée *Neural correlates of sad feelings in healthy girls,* [*Neuroscience*, 121, 545-551], portant cette fois sur l'identification du substrat neuroanatomique fonctionnel sous-tendant l'expérience subjective de la tristesse chez l'enfant sain. Enfin, le chapitre 4 présente la deuxième partie de la seconde étude intitulée *Neural bases of emotional self-regulation in childhood* [soumis à *Neuroscience*]. Cette partie de la deuxième étude cherchait à circonscrire les soubassements neurobiologiques de la suppression de la tristesse chez l'enfant sain.

7. Aspect méthodologique : la résonance magnétique fonctionnelle

L'IRMf représente aujourd'hui un outil absolument incontournable pour explorer le cerveau normal ou pathologique. C'est une technique sans danger si l'on tient compte comme il se doit des contre-indications (régulateur cardiaque, clips vasculaires intracrâniens ferromagnétiques et corps étrangers ferromagnétiques intra-oculaires) associées aux puissants champs magnétiques (des milliers de fois supérieurs au champ magnétique terrestre!) générés par les appareils d'IRMf. Cette technique d'imagerie cérébrale s'appuie sur le signal de résonance magnétique nucléaire (RMN) découvert en 1946 par deux groupes de chercheurs indépendants. En effet, Bloch, Hanse et Packard de

l'Université Stanford et Purcell, Torrey et Pound de l'Université Harvard ont réussit à détecter le signal 1H de l'eau et de la cire paraffine respectivement. Bloch et Purcell ont reçu conjointement le prix Nobel de physique en 1952 pour leur découverte. D'abord utilisée dans le cadre d'examens anatomiques, y compris d'examens du tissu cérébral au début des années soixante-dix, il fallu attendre les années 1980 pour que cette technique d'imagerie prenne un réel essor. Au cours de cette décennie, l'imagerie par résonance magnétique (IRM) s'imposa de plus en plus en tant que méthode non invasive de choix pour effectuer divers examens radiologiques cliniques.

Au début des années 1990, une nouvelle percée technologique permit au Dr Belliveau et à son équipe du Massachussetts General Hospital de Boston de réaliser et de publier la première étude d'IRMf (Belliveau et *al.* 1991). Cette nouvelle approche permit dès lors d'explorer de façon non traumatique le fonctionnement cérébral dans sa globalité, lors du traitement d'une information sensorielle ou de la réalisation d'une tâche motrice, cognitive ou émotionnelle. Contrairement à la tomographie par émission de positons (TEP), cette technique ne nécessite pas l'injection d'un agent de contraste radioactif et s'appuie plutôt sur la détection des modifications locales de débit sanguin cérébral liées à l'activité neuronale, aussi connu sous le nom de signal BOLD (pour *Blood-level-oxygen-dependent*).

Cette technique non invasive utilise la désoxyhémoglobine comme agent de contraste endogène. En effet, l'activation neuronale s'accompagne d'une augmentation du débit sanguin cérébral d'environ 30% (Fox & Raichle, 1986), non compensée par une augmentation équivalente de la consommation en oxygène qui est d'environ 5%. Il en

résulte une augmentation de la saturation capillaire et veineuse en oxygène dans le territoire cérébral drainé et, donc, une diminution de la concentration relative en désoxyhémoglobine (Stehling et *al.* 1991; Le Bars et *al.* 2000). La désoxyhémoglobine est une molécule paramagnétique qui diminue le signal local par un effet de susceptibilité magnétique (propension pour une substance à être aimantée). La diminution de concentration en désoxyhémoglobine pendant l'activation cérébrale diminue ces effets de susceptibilité magnétique et on observe donc une augmentation localisée et faible (1 à 5 %) du signal dans la zone activée par rapport à l'état de repos (voir Figures 1 et 2).

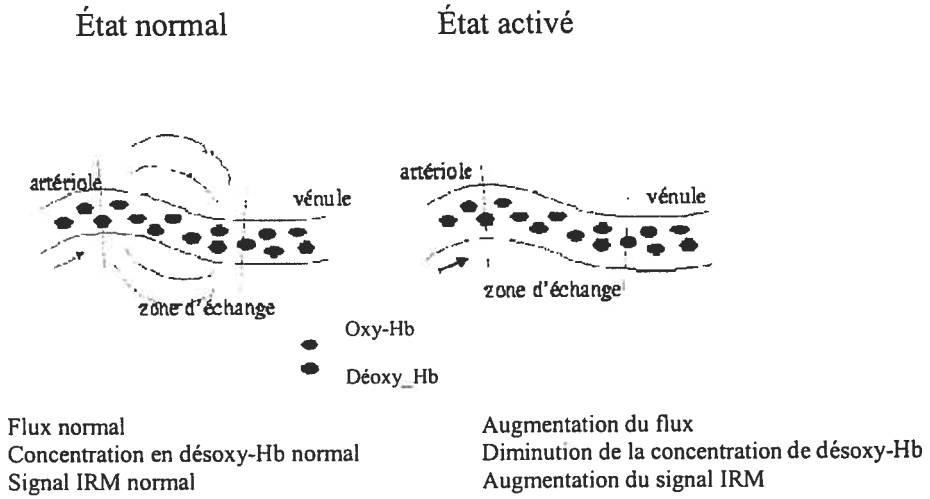

Figure 1. Concentration en oxy et désoxyhémoglobine suivant l'activité cérébrale.

Les variations de signal observées sont faibles et augmentent avec l'intensité du champ magnétique, ce qui en étude clinique requiert un « imageur » de 1.5-3 Teslas. En recherche chez l'humain, l'intensité du champ magnétique de l' « imageur » varie maintenant de 1.5 à 8 Teslas.

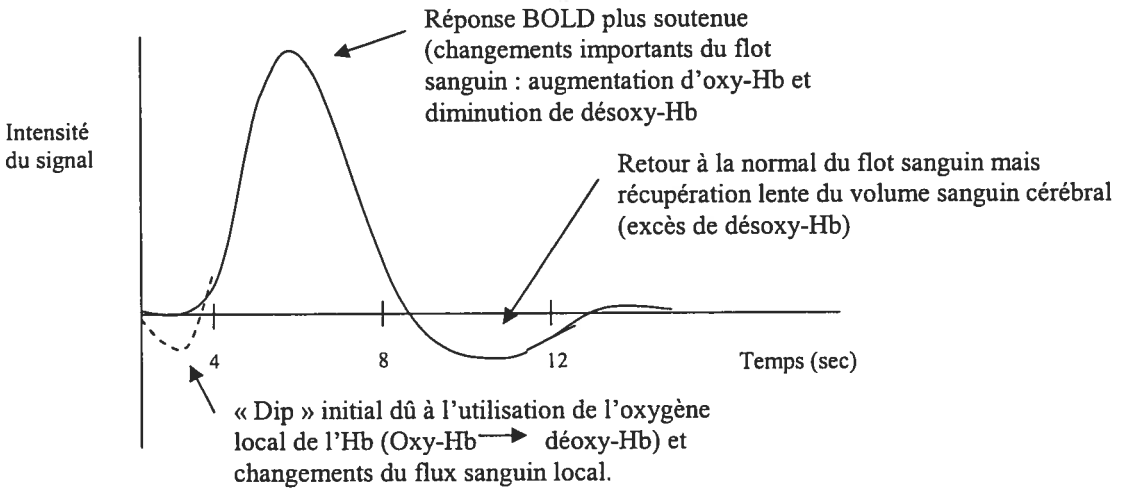

Figure 2. Enregistrement du signal BOLD dans le temps, suite à la présentation d'un bref stimuli. (Traduit de P. Jezzard, http://www.fmrib.ox.ac.uk/physics).

Références

1. Anderson, AK & Phelps, EA. (2001). Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature* 17, 305-309.

2. Arnold, MA. (1960). *Emotion and personality*. New York: Columbia University Press.

3. Barcelo, F & Knight, RT. (2002). Both random and perseverative errors underlie WCST deficits in prefrontal patients. *Neuropsychologia* 40, 349-56.

4. Barch, DM, Braver, TS, Nystrom, LE, Forman, SD, Noll, DC, & Cohen, JD. (1997). Dissociating working memory from task difficulty in human prefrontal cortex. *Neuropsychologia* 35, 1373-80.

5. Beauregard, M, Lévesque, J, & Bourgouin, P. (2001). Neural correlates of the conscious self-regulation of emotion. *Journal of Neuroscience* 21, 1-6.

6. Belliveau, JW, Kennedy, DN Jr, McKinstry, RC, Buchbinder, BR, Weisskoff, RM, Cohen, MS, Vevea, JM, Brady, TJ, & Rosen, BR. (1991). Functional mapping of the human visual cortex by magnetic resonance imaging. *Science* 254, 716-9.

7. Botvinick, MM, Braver, TS, Barch, DM, Carter, CS, & Cohen, JD. (2001). Conflict monitoring and cognitive control. *Psychological Review* 108, 624-52.

8. Buck, R. (1985). Prime theory: An integrated view of motivation and emotion. *Psychological Review* 92, 389-413.

9. Bush, G, Luu, P, & Posner, MI. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Science* 4, 215-222.

10. Cabeza, R & Nyberg, L. (2000). Neural bases of learning and memory: functional neuroimaging evidence. *Current Opinion in Neurology* 13, 415-421.

11. Cahill, L, Prins, B, Weber, M, & McGaugh, JL. (1994). β-Adrenergic activation and memory for emotional events. *Nature* 371, 702-704.

12. Cannon, W. (1914). The interrelations of emotions as suggested by recent physiological researches. *American Journal of Psychology* 25, 256-282.

13. Cicchetti, D, Ackerman, BP. & Izard, CE. (1995). Emotions and emotion regulation in developmental psychopathology. *Development and Psychopathology* 7, 1-10.

14. Cole, PM, Michel, MK, & Teti, LO. (1994). The development of emotion regulation and dysregulation: a clinical perspective. *Monograph of the Society for Research on Child Development* 59, 73-100.

15. Davidson, RJ, Putnam, KM, & Larson, CL. (2000). Dysfunction in the neural circuitry of emotion regulation-A possible prelude to violence. *Science* 289, 591-594.

16. Davidson, RJ & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends in Cognitive Science* 3, 11-21.

17. Dawson, G, Panagiotides, H, Grofer, K, & Hill, D. (1992). The role of frontal lobe functioning in the development of infant self-regulatory behavior. *Brain and Cognition* 20, 152-175.

18. Derryberry, D & Rothbart, MK. (1988). Arousal, affect, and attention as components of temperament. *Journal of Personality and Social Psychology* 55, 958-966.

19. Ekman, P. (1972). Universals and cultural differences in facial expression of emotion. In : J. Cole (Ed.), *Nebraska symposium on motivation* (pp. 207-283). Lincoln, NE: University of Nebraska Press.

20. Ekman, P, Friesen, WV & Ellsworth, P. (1972). *Emotion in the human face: Guidelines for research and integration of findings*. New York: Pergamon.

21. Elliott, R, Frith, CD, & Dolan, RJ. (1997). Differential neural response to positive and negative feedback in planning and guessing tasks. *Neuropsychologia* 35, 1395-404.

22. Erdelyi, MH. (1993). Repression: The mechanism and the defense. In: DM. Wegner & JW Pennebaker (Eds.), *Handbook of mental control* (pp. 126-148). Englewood Cliffs, NJ: Prentice-Hall.

23. Filley, CM. (1995). *Neurobehavioral anatomy*. Niwot, CO: University Press of Colorado.

24. Fox, NA & Bell, MA. (1990). Electrophysiological indices of frontal lobe development. *Annals of the New York Academy of Sciences* 608, 677-704.

25. Fox, NA, Henderson, HA, & Marshall, PJ. (2001). The biology of temperament: An integrative approach. In: CA. Nelson & M. Luciana, (Eds.), *Handbook of Developmental Cognitive Neuroscience* (631-645). Cambridge, Mass.: MIT Press.

26. Fox, PT & Raichle, ME. (1986). Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proceedings of the National Academy of Sciences U S A* 83, 1140-4.

27. Freud, S. (1959). *Inhibitions, symptoms, anxiety*. New York: Norton. (Original work published in 1926).

28. Fridlund, A. (1994). *Human facial expression*. San Diego, CA: Academic Press.

29. Frijda, NH. (1986). *The emotions*. Cambridge, UK: Cambridge University Press.

30. Gross, JJ. (2001). Emotion regulation in adulthood: timing is everything. *Current Diretions in Psychological Science* 10, 214-219.

31. Gross, JJ. (1999): Emotion regulation: Past, Present, Future. *Cognition and Emotion* 13, 551-573.

32. Gross, JJ. (1998a). Antecedent- and response-focused emotion regulation: Divergent consequences for experience, expression, and physiology. *Journal of Personality and Social Psychology* 74, 224-237.

33. Gross, JJ. (1998b). The emerging field of emotion regulation: An integrative review. *Review of General Psychology* 2, 271-299.

34. Gross, JJ. & Munoz, RF. (1995). Emotion elicitation using films. *Cognition and Emotion* 9, 87-108.

35. Gusnard, DA, Akbudak, E, Shulman, GL, & Raichle, ME. (2001). Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proceedings of the National Academy of Sciences of the USA* 98, 4259-64.

36. Happe, F, Ehlers, S, Fletcher, P, Frith, U, Johansson, M, Gillberg, C, Dolan, R, Frackowiak, R, & Frith, C. (1996). 'Theory of mind' in the brain. Evidence from a PET scan study of Asperger syndrome. *Neuroreport* 8, 197-201.

37. Izard, CE. (1992). Basic emotions, relations among emotions, and emotion-cognition relations. *Psychological Review* 99, 561-5.

38. Izard, CE. (1977). *Human emotions.* New York: Plenum.

39. Karama, S, Lecours, AR, Leroux, JM, Bourgouin, P, Beaudoin, G, Joubert, S, & Beauregard, M. (2002). Areas of brain activation in males and females during viewing of erotic film excerpts. *Human Brain Mapping* 16, 1-13.

40. Kawasaki, H, Kaufman, O, Damasio, H, Damasio, AR, Granner, M, Bakken, H, Hori, T, Howard, MA 3rd, & Adolphs, R. (2001). Single-neuron responses to emotional visual stimuli recorded in human ventral prefrontal cortex. *Nature Neuroscience* 4, 15-16.

41. Kopp, CB. (1989). Regulation of distress and negative emotions: A developmental view. *Developmental Psychology* 25, 343-354.

42. Lane, RD & Nadel, L. (2000). *Cognitive neuroscience of emotion.* New York: Oxford UP.

43. Lane, RD, Fink, GR, Chau, PML, & Dolan, RJ. (1997). Neural activation during selective attention to subjective emotional responses. *NeuroReport* 8, 3969-3972.

44. Lang, PJ, Bradley, MM, & Cuthbert, BN. (1998). Emotion and motivation: measuring affective perception. *Journal of Clinical Neurophysiology* 15, 397-408.

45. Langston, CA. (1994). Capitalizing on and coping with daily-life events: Expressive responses to positive events. *Journal of Personality and Social Psychology* 67, 1112-1125.

46. Lazarus, RS. (1966). *Psychological stress and the coping process*. New York: McGraw-Hill.

47. Lazarus, RS. (1991). *Emotion and adaptation.* Oxford, UK: Oxford University Press.

48. Le Bars, E, Gondry-Jouet, C, Deramond, H, Le Gars, D, Idy-Peretty, I. (2000). Imagerie par résonance magnétique de diffusion et de perfusion en pratique clinique. *Journal of neuroradiology* 27, 39-51.

49. Levenson, CA. (1994). Human emotion: a functional view. In: P. Ekman & RJ Davidson, (Eds.), *Fundamental questions about the nature of emotion*, Oxford University Press, New York, pp. 123-126.

50. Lewis, M. (1998). The development and structure of emotions. In: MF Mascolo & S. Griffin (Eds.), *What develops in emotional development?* Plenum Press, New York, pp. 29-50.

51. Lewis, M. (1995). Aspects of self: From systems to ideas. In: P. Rochat (Ed.), *The self in infancy: Theory and research*. Advances in psychology (95-115). North Holland: Elsevier Science Publishers.

52. Masters, JC. (1991). Strategies and mechanisms for the personal and social control of emotion. In: J. Garber, & KA Dodge (Eds.), *The development of emotion regulation and dysregulation* (182-207). Cambridge, U.K.: University Press.

53. Mayer, JD & Salovey, P. (1995). Emotional intelligence and the construction and regulation of feelings. *Applied and Preventive Psychology*, 4, 197-208.

54. Nauta, WJH. (1971). The problem of the frontal lobe: a reinterpretation. J. *Psychiatry Research.* 8, 167-187.

55. Nolan-Hoeksema, S. (1993). Sex differences in control of depression. In: DM Wegner & JW Pennebaker (Eds.), *Handbook of mental control* (pp. 306-324). Prentice-Hall Englewood Cliffs.

56. Oatley, K & Johnson-Laird, PN. (1987). Towards a cognitive theory of emotion. *Cognition and Emotion* 1, 29-50.

57. Ochsner, KN, Bunge, SA, Gross, JJ, & Gabrieli, JD. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience* 14, 1215-29.

58. O'Doherty, J, Kringelbach, ML, Rolls, ET, Hornak, J, & Andrews, C. (2001). Abstract reward and punishment representations in the human orbitofrontal cortex. *Nature Neuroscience* 4, 95-102.

59. Paradiso, S, Johnson, DL, Andreasen, NC, O'Leary, DS, Watkins, GL, Ponto, LL, & Hichwa, RD. (1999). Cerebral blood flow changes associated with attribution of emotional valence to pleasant, unpleasant, and neutral visual stimuli in a PET study of normal subjects. *American Journal of Psychiatry* 156, 1618-29.

60. Parrott, WG. (1993). Beyond hedonism: Motives for inhibiting good moods and for maintaining bad moods. In: DM Wegner & JW Pennebaker (Eds.), *Handbook of mental control (*pp. 278-308). Prentice-Hall, Englewood Cliffs.

61. Plutchik, R. (1980). *Emotion: A psychoevolutionary synthesis*. New York: Harper & Row.

62. Schaefer, SM, Jackson, DC, Davidson, RJ, Aguirre, GK, Kimberg, DY, & Thompson-Schill, SL. (2002). Modulation of amygdalar activity by the conscious regulation of negative emotion. *Journal of Cognitive Neuroscience* 14, 913-21.

63. Scherer, K. (1984). On the nature and function of emotion: A component process approach. In: KR Scherer & PE Ekman (Eds.), *Approaches to emotion* (pp. 293-317). Hillsdale, NJ: Erlbaum.

64. Selye, H. (1956). *The stress of life*. New York: McGraw-Hill.

65. Selye, H. (1974). *Stress without distress*. Philadelphia, PA: Lippincott.

67. Smith, EE & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science* 283, 1657-61.

68. Stehling, MK, Turner, R, & Mansfield, P. (1991). Echo-planar imaging: Magnetic resonance imaging in a fraction of second. *Science* 254: 43-50.

69. Stuss, DT, Alexander, MP, Palumbo, CL, Buckle, L, Sayer, L, & Pogue, J. (1994). Organizational strategies of patients with unilateral or bilateral frontal lobe injury in word list learning tasks. *Neuropsychology* 8, 355-373.

70. Tarnas, R, (1993). Crosscurrents of the Hellenistic Matrix In: *The passion of the western mind* (pp. 75-88). New York, Ballantine Books.

71. Thompson, RA. (1990). Emotion and self-regulation, In: Thompson, RA (Ed.), *Socioemotional Development: Nebraska Symposium on Motivation*. University of Nebraska Press, Lincoln, Neb, pp. 367-467.

72. Tomkins, S, (1962). *Affect, imagery, and consciousness: Vol. 1. The positive affects.* New York, Springer.

73. Tooby, J & Cosmides, L. (1990). On the universality of human nature and the uniqueness of the individual: the role of genetics and adaptation. *Journal of Personality* 58, 17-67.

74. Tucker, DM, Luu, P, & Pribram, KH. (1995). Social and emotional self-regulation. Annual New York Academy of Science. 769, 213-39.

75. van Veen, V, Cohen, JD, Botvinick, MM, Stenger, VA, & Carter, CS. (2001). Anterior cingulate cortex, conflict monitoring, and levels of processing. *Neuroimage* 14, 1302-8.

76. Walden, TA. (1991). Infant social referencing, In: J Garber & KA Dodge (Eds.), *The development of emotion regulation and dysregulation* (pp. 69-88). Cambridge, UK: Cambridge University Press.

77. Whalen, PJ, Rauch, SL, Etcoff, NL, McInerney, SC, Lee, MB, & Jenike, MA. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *Journal of Neuroscience* 18, 411-8.

78. Yakovlev, PI & Lecours, AR. (1967). The myelogenetic cycles of regional maturation of the brain. In: A. Mankowsi (Ed.), *Regional Development of the Brain in Early Life* (pp. 3-69). Davis, Philadelphia.

Chapitre 2

ARTICLE #1

Neural circuitry underlying voluntary suppression of sadness

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Abstract

Background: The ability to voluntarily self-regulate negative emotion is essential to a healthy psyche. Indeed, a chronic incapacity to suppress negative emotion might be a key factor in the genesis of depression and anxiety (Jackson et al., 2000). Regarding the neural underpinnings of emotional self-regulation, a recent functional neuroimaging study carried out by our group (Beauregard et al., 2001) has revealed that the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex are involved in voluntary suppression of sexual arousal. As few things are known, still, with respect to the neural substrate underlying volitional self-regulation of basic emotions, here we used functional magnetic resonance imaging (fMRI) to identify the neural circuitry associated with the voluntary suppression of sadness.

Methods: Healthy female subjects were scanned during a Sad condition and a Suppression condition. In the Sad condition, subjects were instructed to react normally to sad film excerpts whereas, in the Suppression condition, they were asked to voluntarily suppress any emotional reaction in response to comparable stimuli.

Results: Transient sadness was associated with significant loci of activation in the anterior temporal pole and the midbrain, bilaterally, as well as in the left amygdala, left insula, and right ventrolateral prefrontal cortex (VLPFC) (Brodmann area – BA – 47). Correlational analyses carried out between self-report ratings of sadness and regional blood-oxygen level dependent (BOLD) signal changes revealed the existence of positive correlations in the right VLPFC (BA 47), bilaterally, as well as in the left insula and the affective division of the left anterior cingulate gyrus (Acg) (BA24/32). In the Suppression condition, significant loci of activation were noted in the right DLPFC (BA 9) and the

right orbitofrontal cortex (OFC) (BA 11), and positive correlations were found between the self-report ratings of sadness and BOLD signal changes in the right OFC (BA 11) and right DLPFC (BA 9).

Conclusions: These results confirm the key role played by the DLPFC in emotional self-regulation. They also indicate that the right DLPFC and right OFC are components of a neural circuit implicated in voluntary suppression of sadness.

Key words: suppression, volition, metacognition, prefrontal cortex, functional magnetic resonance imaging.

Introduction

Emotional self-regulation has been defined as "the extrinsic and intrinsic processes responsible for monitoring, evaluating, and modifying emotional reaction, especially their intensive and temporal features, to accomplish one's goal" (Thompson, 1994). In a colloquial usage, emotional self-regulation often refers to either suppression, maintenance, or enhancement of the subjective emotional experience, but it also applies to the modulation of the behavioral and physiological dimensions of emotion (Gross, 1999). Rationalization and reappraisal are amongst some of the most prevalent cognitive strategies used in order to self-regulate emotion (Gross, 1999; Hariri et al., 2000).

Conscious and voluntary self-regulation of emotion represents indisputably one of the most remarkable mental faculties having emerged throughout the course of human evolution. In our view, this metacognitive capacity constitutes one of the cornerstones on which human societal systems are built. Supportive of such a view, there is mounting evidence that a chronic incapacity to suppress negative emotion may be a key factor in the genesis of depression, anxiety, and aggressive or violent behaviors (Davidson et al., 2000; Jackson et al., 2000). With respect to major depression, this dysregulation of negative affect may be related to the cognitive/executive inhibitory deficit that characterizes depressed patients. This impairment is manifested by increased choice reaction-time on a Stroop-Color-Word test, and increased effect of interference on the Visuo-Spatial Interference Test, when compared to normal control subjects (Lemelin et al, 1996, 1997).

Regarding the neural bases of such capacity, it has been postulated, several decades ago, that a fronto-limbic network is involved in emotional suppression (Nauta, 1971). More recently, evidence from lesion studies in animals, and clinical neuropsychological, psychophysiological, and functional neuroimaging studies in humans, have led to the view that a neural circuit comprising several prefrontal cortex (PFC) regions (e.g., orbitofrontal, anterior cingulate) underlies emotional suppression (Davidson, 2000). The results of a functional magnetic resonance imaging (fMRI) study recently carried out by our group, to test the validity of this view (Beauregard et al., 2001), demonstrated the involvement of the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex in voluntary suppression of sexual arousal, a positive emotional state.

In the present study, we used whole-brain fMRI to delineate the neural circuitry associated with the voluntary suppression of sadness, a basic emotion with a negative valence (Plutchik, 1994). We predicted *a priori* that various subdivisions of the prefrontal cortex (DLPFC, orbitofrontal cortex - OFC, medial PFC, anterior cingulate cortex) would be associated with voluntary suppression of sadness.

Methods and materials

Subjects

Twenty healthy female volunteers (right-handed Caucasian university students) (age range: 20 - 30, mean age: 24.3) took part in the study. They had no history of psychiatric or neurological disorder. These subjects all gave written informed consent and the study

was approved by the ethics committee of Centre hospitalier de l'Université de Montréal (CHUM), Hôpital Notre-Dame.

Behavioral procedures

Blood oxygen level dependent (BOLD) signal changes were measured during two experimental conditions, i.e., a Sad condition and an Suppression condition. In the Sad condition, subjects first viewed four blocks of emotionally neutral film excerpts and then, four blocks of sad film excerpts. On the basis of evidence gathered previously by our group, this design was adopted to avoid contamination of the neutral stimuli by the sad stimuli (unpublished data). Each block lasted 48 sec and was separated by resting periods of 15 sec during which subjects viewed a blue cyan screen. Subjects were instructed to react normally to the sad film excerpts, that is, to allow themselves to become sad in response to these stimuli. In the Suppression condition, they were also presented with, first, four blocks of emotionally neutral film excerpts and, then, four blocks of sad film excerpts. In this condition, subjects were instructed to suppress any emotional reaction to the sad stimuli. That is, they had to voluntarily decrease the intensity of the sad feelings felt in response to the sad film excerpts. In order to accomplish that goal, subjects were encouraged to distance themselves from those stimuli, i.e., to become a detached observer. Subjects were instructed to look at the stimuli directly during both experimental conditions. Overall, a total of eight different sad film excerpts and eight different neutral film excerpts were used. Their utilization was counterbalanced across conditions and subjects, that is, the sad and neutral film excerpts appeared as equally often in both conditions, and subjects saw each film excerpt (sad or neutral) only once. The order of

presentation of the experimental conditions was counterbalanced across subjects. Sad film excerpts depicted the death of a beloved person, either a father, a mother, or a friend. Each scene contained either a child or two children, or a child and one or more adults. The emotionally neutral film excerpts were matched to the sad film excerpts with respect to the number and the gender of the individuals involved. Emotionally neutral film excerpts depicted various human activities (e.g., interviews, carpentry, etc). To assess the subjective responses of the subjects to the stimuli, immediately at the end of each run, they were asked to rate verbally - on a visual analog rating scale ranging from 0 (absence of any emotional reaction) to 8 (strongest emotion ever felt in one's lifetime) - the average intensity of sadness or of any other primary emotions (e.g., happiness, disgust, fear, anger, surprise - Plutchik, 1994) felt during the viewing of both categories of film excerpts. For each run, an average rating score was computed for the four blocks of sad film excerpts and the four blocks of emotionally neutral film excerpts. At the end of the scanning session, subjects were also asked to complete a "strategy questionnaire" in which they described the emotion regulation strategies they used to inhibit the sad feelings generated by the sad stimuli. In this questionnaire, subjects were also asked to evaluate (in percentage) the degree to which they thought having succeeded in suppressing sad feelings during the Suppression condition.

Image acquisition and analysis

Echoplanar images (EPI) were acquired on a 1.5 Tesla system (Magnetom Vision, Siemens Electric, Erlangen, Germany). Twenty-eight slices (5 mm thick) were acquired every 2.65 s in an inclined axial plane, aligned with the AC-PC axis. These T2* weighted

functional images were acquired using an EPI pulse sequence (TR = 0.8 ms, TE = 54 ms, Flip = 90°, FOV = 215 mm, Matrix = 64 x 64). Following functional scanning, high-resolution data were acquired via a Tl-weighted three-dimensional volume acquisition obtained using a gradient echo pulse sequence (TR = 9.7 ms, TE = 4 ms, Flip = 12° FOV = 250 mm, Matrix = 256 x 256).

Data were analyzed using Statistical Parametric Mapping software (SPM99, Wellcome Department of Cognitive Neurology, London, UK). Images for all subjects were realigned to correct for artifacts due to small head movements. The gradient-recalled echo-planar sequence that we used is associated with large static magnetic field inhomogeneities commonly found near air/tissue interfaces (Cordes et al., 2000). These inhomogeneities can create artifacts like signal loss and voxel shifts in the ventral frontal, medial temporal, and inferior temporal regions (Song, 2001). To correct for such artifacts, a mask was applied to the slices of the mean EPI image which presented signal loss. This procedure was implemented for every subject. The images for all subjects were then spatially normalized (voxel size: 3 mm x 3 mm x 5 mm) into an MRI stereotactic space (Talairach and Tournoux, 1988) using this masked mean image. Images were then convolved in space with a three-dimensional isotropic gaussian kernel (12 mm FWHM) to improve the signal-to-noise ratio and to accommodate for residual variations in functional neuroanatomy that usually persist between subjects after spatial normalization.

For the statistical analysis, the time series of the images were convolved with the delayed box-car function which approximates the activation patterns. Effects at each and

every voxel were estimated using the general linear model. Voxel values for the contrasts of interest yielded a statistical parametric map of the t statistic (SPM *t*), subsequently transformed to the unit normal distribution, (SPM Z). For the Sad condition, a "fixed-effects model" was implemented to contrast the brain activity associated with the viewing of the sad film excerpts and that associated with the viewing of the emotionally neutral film excerpts (Sad - Neutral). To delineate the brain regions associated with voluntary suppression of sad feelings, a "fixed-effects model" was also implemented to compare the brain activity associated with the Sad condition and that associated with the Suppression condition. To do so, the brain activity associated with viewing the sad film excerpts in the Sad condition was directly subtracted from the brain activity associated with viewing the sad film excerpts in the Suppression condition. These "fixed-effects model" produced individual contrast images, which were used as raw data for the implementation of a "random-effects model" (Friston and Frackowiack, 1997). An *a priori* search strategy was used and a small volume correction was performed in the brain regions (ROIs) defined *a priori.* The search volume corresponding to the ROIs was defined *a priori* by tracing the neuroanatomical boundaries of these regions on the MR reference image (MNI template), using SVC and box volume function in SPM99. For this *a priori* search, a corrected probability threshold for multiple comparisons of $p < 0.05$ corrected was used. Only clusters showing a spatial extent of at least 5 contiguous voxels were kept for image analysis.

In the Sad condition, the *a priori* search strategy encompassed the ventrolateral prefrontal cortex (VLPFC) PFC (BA 47), medial PFC (BA 9 and 10), anterior cingulate

cortex (affective division: rostral areas of BA 24a-c and 32, ventral areas of BA 25 and 33) (Bush et al., 2000), anterior temporal pole (BA21 and 38), insula, amygdala, hypothalamus, pons, and midbrain. These brain regions have been found activated on a more or less consistent basis in previous functional neuroimaging studies of sadness (Pardo et al., 1993; George et al., 1995; Lane et al., 1997a; Beauregard et al., 1998; Damasio et al., 2000). In the Suppression condition, the *a priori* search strategy included the DLPFC (BA10), the anterior cingulate cortex (cognitive division) (BA 24b'-c' and 32') (Bush et al., 2000), the OFC (BA 11), and the medial PFC (BA 9 and 10), based on the hypothesis made by Davidson and colleagues (Davidson et al., 2000), and on the results of a previous study recently carried out by our group (Beauregard et al., 2001).

Results

Self-report data

Phenomenologically, the viewing of the sad film excerpts, in both the Sad and the Suppression conditions, induced a transient state of sadness in all subjects. As expected, the mean level of reported sadness was significantly higher in the Sad condition (mean = 5.15; SD = 1.30; range: 2 - 7) than in the Suppression condition (mean = 1.85; SD = 1.42; range: 0 - 4) ($p < 0.0001$). During both experimental conditions, the viewing of the sad film excerpts did not practically produce other marked changes in the emotional state than sadness (Mean levels - Sad condition: fear = 1.0; anger = 1.4; surprise = 0.3; happiness = 0; disgust = 0.2; Suppression condition: fear = 0; anger = 0.1; surprise = 0; happiness = 0; disgust = 0.33) and viewing the emotionally neutral film excerpts did not generate any basic emotion. In addition, the strategy questionnaire completed at the end

of the scanning session revealed that, in the Suppression condition, all subjects reported having succeeded in distancing themselves from the sad film excerpts, i.e., in becoming a detached observer. The mean suppression percentage reflecting the degree to which subjects thought having succeeded in suppressing sad feelings was 84% (range: 50 - 100; SD: ± 11).

fMRI data

Subtraction approach

Sad condition: The 'random-effects model' revealed significant bilateral loci of activation in the anterior temporal pole (BA 38 and BA 21) and the midbrain. Significant loci of activations were also seen in the right VLPFC (BA 47), the left amygdala, and the left insula (Fig. 1, Table 1).

Suppression condition: Significant loci of activation were noted in the right OFC (BA 11) and right DLPFC (BA 9) (Fig 2. Table 2). Additionally, when using a liberal threshold of $p < 0.05$, uncorrected for multiple comparisons, activated voxels were found in the right VLPFC (BA 47).

A posteriori correlational analyses

Sad condition: correlational analyses were conducted betweeen self-report ratings of sadness and BOLD signal increases found in the ROIs. These analyses revealed the existence of positive correlations in the right VLPFC (BA 47; coordinates of maximum = [27, 20, -11]; $z = 2.80$; $p < 0.05$, uncorrected), the affective division of the left anterior

cingulate cortex (BA24/32; coordinates of maximum = [-3, 38, 1]; $z = 3.69$; $p < 0.05$, uncorrected), and the left insula (coordinates of maximum = [-42, 9, -2]; $z = 2.01$; $p < 0.05$, uncorrected).

Suppression condition: positive correlations were found between the self-report ratings of sadness and BOLD signal increases in the right OFC (BA 11; coordinates of maximum = [27, 34, -19]; $z = 2.50$; $p < 0.05$, uncorrected) and right DLPFC (BA 9; coordinates of maximum = [36, 34, 28]; $z = 3.13$; $p < 0.05$, uncorrected).

[Insert Figure 1 about here]

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[Insert Table 1 about here]

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Discussion

The main goal of the present study was to identify the neural substrate associated with voluntary suppression of sadness. This study comprised two experimental conditions, a Sad condition and an Suppression condition. In the Sad condition, significant loci of activation were noted, bilaterally, in the anterior temporal pole (BA 21 and 38) and the midbrain. Significant loci of activation were also seen in the right VLPFC (BA 47), left amygdala, and left insula. In the Suppression condition, significant loci of activation were detected in the right OFC (BA 11) and right DLPFC (BA 9).

Brain regions activated in the Sad condition

In regard to the activations noted in the anterior temporopolar cortex, activity of this cortical region have been reported, in healthy subjects, during memory-driven sadness (Lane et al., 1997a), script-generated anger and anxiety (Dougherty et al., 1999; Damasio et al., 2000; Kimbrell et al., 1999), normal anticipatory anxiety (Reiman et al., 1989; Chua et al.,. 1999), and film-induced sexual arousal (Beauregard et al., 2001). This paralimbic region receives inputs from unimodal and heteromodal sensory regions as well as limbic inputs. As Mesulam (1985) proposed, and in light of the previous functional brain imaging studies of emotion, it seems conceivable that the anterior temporopolar activations found here, during the viewing of the sad films excerpts, was associated with imparting affective tone to the subjects' experience.

In other respects, the activations seen in the midbrain is not surprising since this brain region has been found activated in several functional neuroimaging studies of various emotional states (e.g., disgust, sadness, anger, fear, happiness, pain and anxiety) (Fredrikson et al., 1995; Lane et al., 1997a; Rauch et al., 1997; Tölle et al., 1999; Damasio et al., 2000). It has been shown that this brain region mediates, at least in part, autonomic responses such as skin conductance responses (Sequeira & Roy, 1993) and body temperature changes (Nagashima, et al., 2000). Given the close relationship between autonomic responses and the subjective experience of emotion (Damasio et al. 2000), the mesencephalic activations seen in this study likely reflected the autonomic responses accompanying subjects' sad feelings.

The VLPFC has been seen activated – in healthy subjects - during external (e.g., looking at human faces) and/or internal (e.g., recalling appropriate life events) induction of sadness (Pardo et al 1993; George et al 1995; Beauregard et al., 1998; Damasio et al., 2000), anxiety (Fredrikson et al 1997; Kimbrell et al 1999), and anger (Dougherty et al 1999; Kimbrell et al 1999). Taken together with the present results, these findings suggest that this prefrontal cortical region participates in aspects of emotion processing that are not exclusively related to a discrete emotion in particular. Given the sensory inputs (olfactory, gustatory, visceral afferent, somatic sensory, and visual) as well as the limbic inputs that this cortical region receives from the amygdala, entorhinal and perirhinal cortex, and subiculum, it seems conceivable that the VLPFC may be implicated in the integration of viscerosensory information with affective signals (Price, 1999). The fact that ventromedial prefrontal lesions are correlated with the absence of autonomic responses to emotionally-laden (positive or negative) pictures (Damasio et al., 1990) appears to support such a view. In addition, the positive correlation found here between self-report ratings of sadness and BOLD signals increases in the right VLPFC suggests that this paralimbic area is also involved in the subjective dimension of the sad experience. Interestingly, increased VLPFC activity has been reported in association with sad thoughts/sadness in subjects with major depressive disorder (Brody et al., 2001). It thus appears that this brain region is associated with the processing of normal as well as pathological aspects of sadness.

The amygdaloid activation noted here is consistent with the results obtained in previous PET (Schneider et al., 1995; Lane et al., 1997a; Reiman et al., 1997; Blair et al., 1999)

and fMRI (Schneider et al., 1997; Whalen et al., 1998; Beauregard et al., 2001; Karama et al. 2002) studies on positive and negative emotions. The appraisal function of the amygdala is well documented at this point in the literature (for a review, see Lane and Nadel, 2000), and it seems possible that the amygdala activation seen in this study reflects the appraisal process of the stimuli through which significance was attributed to the sad film excerpts.

Concerning the activation of the insula, this region has been reported to be activated, in healthy subjects, during recall-induced sadness (Lane et al., 1997a; Damasio et al., 2000; Liotti et al., 2000), happiness (Damasio et al., 2000), fear (Damasio et al., 2000), and anger (Damasio et al., 2000), as well as in normal anticipatory anxiety (Chua et al 1999; Reiman 1997). In view of the rich interconnection of the insula with regions involved in autonomic regulation (Cechetto, 1994), the insular activation noted here may be a neural correlate of the autonomic changes associated with the subjective experience of sadness. This conclusion appears even more plausible when considering the positive correlation we found between self-report ratings of sadness and activated voxels in the left insula.

The positive correlation found between average ratings of sadness and BOLD signal increases in the affective division of the anterior cingulate cortex fits rather nicely with the results of a recent PET study by Lane and colleagues (1997b). Indeed, the results of this PET investigation suggested that the rostral portion of the anterior cingulate gyrus plays a pivotal role in the interoceptive or exteroceptive detection of emotional signals, and, hence, in emotional awareness.

Brain regions activated in the Suppression condition

In the Suppression condition, significant loci of activation were noted in the right OFC (BA 11) and right DLPFC (BA 9). When using a liberal threshold of $p < 0.05$, uncorrected for multiple comparisons, activated voxels were also found in the right VLPFC (BA 47). This VLPFC activation was probably related to the residual sad feelings experienced by the subjects during the Suppression task. With respect to the right DLPFC activation, the present results demonstrate that, in addition to being involved in the voluntary suppression of a positive emotional reaction such as sexual arousal (Beauregard, et al., 2001), the lateral portion of the right DLPFC is also associated with the voluntary suppression of a negative emotion such as sadness. These results, and the positive correlation found between the self-report ratings of sadness and the significant loci of activation in the right DLPFC, are consistent with a variety of evidence from experimental lesion studies in animals, and clinical neuropsychological and functional brain mapping studies in humans, indicating that the DLPFC is a key structure involved in willed actions (Frith and Dolan, 1996) and with the holding in mind of information on which an action is to be based (Goldman-Rakic, 1987; Fuster, 1999; Roberts and Wallis, 2000). In our previous study, BA 10 of the right DLPFC BA was associated with the suppression of sexual arousal. In this study, the group analysis revealed activation only in BA 9 of the DLPFC. However, careful examination of the individual statistical parametric maps revealed that 5 subjects were also showing activation in BA 10 of the DLPFC ($p < 0.001$, uncorrected). At this point, few things are known about the respective roles of the DLPFC's BA 9 and BA 10 in emotional suppression. Regarding this issue,

Dias and colleagues (1996) have shown that, in monkeys, BA 9 of the DLPFC is involved in inhibitory control, namely, in attentional set-shifting capacity. In humans, further studies are needed to delineate the functional specificity of these two prefrontal subregions with respect to emotional self-regulation.

Human and animal neuropsychological studies suggest that the OFC exerts an inhibitory control to protect goal-directed behaviour from interference (Casey et al., 1997; Fuster, 1999; Roberts and Wallis, 2000). Also, by virtue of his anatomic projections into autonomic centers, it has been proposed that the OFC initiates or controls the autonomic responses that are associated with emotional experience (Öngür et al., 1998; Rempel-Clower and Barbas, 1998). Furthermore, the OFC is the prefrontal area that has the strongest links with the anterior temporal pole (Cavada et al. 2000; Morecraft et al. 1992). It is also heavily connected with the amygdala and the insular cortex (Cavada et al., 2000). The connections between the OFC, the insula, and the anterior temporal pole have been studied carefully by Mesulam and colleagues who proposed that these three cortical regions form an integrated unit on the basis of similarities in cytoarchitectonic trends and connections (Mesulam and Mufson, 1982; Morán et al., 1987). It is also well demonstrated, in non-human primates, that the OFC has heavy connections with several intraprefrontal regions such as BA 9 of the DLPFC (Cavada et al., 2000). The positive correlation found, in the Suppression condition, between the self-report ratings of sadness and the BOLD signal increases in the right OFC (BA 11), lend some more support to the view that the OFC, through its anatomic projections to limbic and paralimbic structures, is a key structure involved in behavioral inhibition and voluntary suppression of emotion.

With regard to the neuroanatomical and neuropsychological findings presented above, and the paradigm used in the Suppression condition, we submit that, first, the right DLPFC holds in mind the instruction "to become a detached observer" and then, sends an executive command to the right OFC, which is charged to inhibit, through the integrated unit proposed by Mesulam and Mufson (1982) as well as through the amygdala and the midbrain, the various dimensions (e.g., cognitive, behavioral, physiological, feeling) associated with the experience of sadness. The positive correlations found between the self-report ratings of sadness and BOLD signal increases in the right DLPFC (BA 9) and right OFC (BA 11) suggest that higher residual levels of sadness, during the Suppression task, led to greater activation/work in these two prefrontal regions.

Contrary to our *a priori* hypothesis, as well as to the results of our recent fMRI study regarding the neural substrate of volitional suppression of sexual arousal (Beauregard et al., 2001), no significant activation was noted in the anterior cingulate cortex during voluntary suppression of sad feelings. In order to interpret this negative result, we decided to examine the individual statistical parametric maps produced in the Suppression condition. These maps revealed that the cognitive division of the anterior cingulate cortex was activated in seventy-five percent of the subjects while they attempted to voluntarily suppress sadness. These maps also showed an important degree of interindividual variability. That is, the activated voxels in the cognitive division of the anterior cingulate cortex were not consistently localized, across subjects, in the same sub-areas of this cortical region. Thus, it appears that interindividual variability, in terms of

functional neuroanatomy, may account for the apparent absence of anterior cingulate activation during the Suppression condition.

Clinical implications of the present findings

From a clinical perspective, our results are particularly important given the notion that a permanent inability to suppress a negative emotion, such as sadness, may be crucially related to the etiology of major depression (Davidson et al., 2000). Such inability may result from a dysfunction in the neural circuit identified here. Indeed, as recently reviewed by Brody and colleagues (2001), depressed patients often show decreased activity in DLPFC (BA 9) and increased activity in VLPFC (BA 47). Brody et al. (2001) also reported that, in several studies, a negative correlation has been found between the scores of depressed patients on the Hamilton Depression Rating Scale (HAM-D) and either metabolism or regional cerebral blood flow (rCBF) in the prefrontal cortex. In view of these findings, Brody and colleagues (2001) have proposed that, in major depression, ventral prefrontal and limbic circuits (originating in the VLPFC and ventral anterior cingulate cortex) override the relatively hypoactive dorsal circuit (originating in the DLPFC and dorsal anterior cingulate cortex) and may allow the content of depressive/sad thoughts to be prominent.

Regarding the OFC, a recent study conducted with elderly depressed patients has shown that, compared to normal control subjects, these patients had an increased density of medial OFC white matter lesions (MacFall et al., 2001). Furthermore, a correlation analysis revealed that this prefrontal cortical region was significantly correlated with the

severity of depression of these patients (MacFall et al., 2001). These results contribute to the growing evidence that the OFC is critically involved in affective disorders.

Limitations of the present study

Last, we would like to acknowledge some of the limitations of this study. First, no objective measures were performed before and immediately after the two experimental conditions to characterize the subjects' emotional state. Instead, self-report ratings were used. Self-report data are extremely susceptible to bias: the subjects knew that their task was to suppress sadness (Suppression condition), and it should not be terribly surprising that their sadness ratings were lower in the Suppression condition than in the Sad condition. A more objective measure would have definitely bolster the results of this study, even though the results in the Suppression condition are in keeping with our predictions and the literature. Second, we could not verify that the subjects have indeed performed the suppression task the way they were requested to. At the end of the Suppression condition, subjects were asked to report if they have had difficulty performing the suppression task, what strategy they used to suppress sadness, and if they were witnessing internal speech while doing this task. Nobody reported performing another task or being distracted during the Suppression condition. Again, as we had no objective means to verify subjects' assertions, we relied on their honesty to interpret the results.

Conclusion

In conclusion, the present fMRI study shows that, in normal female subjects, the right DLPFC and right OFC cortex are associated with voluntary suppression of sadness. These results confirm the involvement of the DLPFC in emotional self-regulation. They also support the view that various subdivisions of the PFC are components of a neural circuit that underlies this metacognitive capacity. From a clinical perspective, our findings highlight the fact that a "good functioning" of the DLPFC and OFC is essential to the volitional regulation of emotional impulses mediated by limbic/paralimbic structures. Indeed, a defect in the neural circuit evidenced here may lead to an inability to suppress a negative emotion such as sadness. Such defect may be intimately linked to the etiology of major depression.

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References

1. Beauregard M, Leroux J-M, Bergman S, Arzoumanian S, Beaudoin G, Bourgouin P, Stip E (1998): The functional neuroanatomy of major depression: an fMRI study using an emotional activation paradigm. NeuroReport 9: 3253-3258.

2. Beauregard M, Lévesque J, Bourgouin P (2001) : Neural correlates of the conscious self-regulation of emotion. J Neurosci 21: 1-6.

3. Blair RJ, Morris JS, Frith CD, Perrett DI, Dolan RJ (1999): Dissociable neural responses to facial expressions of sadness and anger. Brain122:883-93.

4. Brody AL, Barsom MW, Bota RG, Saxena S (2001): Prefrontal-subcortical and limbic circuit mediation of major depressive disorder. Semin Clin Neuropsychiatry 6:102-12.

5. Bush, G., Luu, P., and Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. Trends in Cog. Sci. 4: 215-222.

6. Casey BJ, Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Schubert AB et al. (1997) : Implication of right frontostriatal circuitry in response suppression and attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 36:374-83.

7. Cavada C, Company T, Tejedor J, Cruz-Rizzolo RJ, Reinoso-Suarez F (2000): The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb Cortex 10: 220-42.

8. Cechetto DF (1994): Identification of a cortical site for stress-induced cardiovascular dysfunction. Integr Physiol Behav Sci 29:362-73.

9. Cordes D, Turski PA, Sorenson JA (2000): Compensation of susceptibility-induced signal loss in echo-planar imaging for functional applications. Mag Res Imaging 18: 1055-1068.

10. Chua P, Krams M, Toni I, Passingham R, Dolan R (1999): A functional anatomy of anticipatory anxiety. Neuroimage 9: 563-71.

11. Damasio, A. R., Tranel D., and Damasio, H. (1990). Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. Behav. Brain. Res. 41, 81-94.

12. Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LL, Parvizi J, Hichwa RD (2000): Subcortical and cortical brain activity during the feeling of self-generated emotions. Nature Neurosci 3: 1049-56.

13. Davidson RJ, Putnam KM, Larson CL (2000): Dysfunction in the neural circuitry of emotion regulation-A possible prelude to violence. Science 289: 591-594.

14. Dias R, Robbins TW, Roberts AC (1996): Dissociation in prefrontal cortex of affective and attentional shifts. Nature 380:69-72.

15. Dougherty DD, Shin LM, Alpert NM, Pitman RK, Orr SP, Lasko M, Macklin ML, Fischman AJ, Rauch SL (1999): Anger in healthy men: a PET study using script-driven imagery. Biol Psychiatry 46:466-72.

16. Fredrikson M, Wik G, Fischer H, Anderson J (1995): Affective and attentive neural networks in human: A PET study of Pavlovian conditioning. NeuroReport 7: 97-101.

17. Friston K. J. and Frackowiak, R. S. J. 1997. Images of the future: a philosophical coda. In *Human Brain Function* (R. S. J. Frackowiak, K. J. Friston, R. J. Dolan and J. C. Mazziotta, Eds.), pp. 487-517. Academic Press, San Diego.

18. Frith C, Dolan R (1996): The prefrontal cortex in higher cognitive functions. Cogn Brain Res 5:175-181.

19. Fuster JM (1999): Synopsis of function and dysfunction of the frontal lobe. Acta Psychiatr Scand 99: 51-57.

20. George MS, Ketter TA, Parekh PI, Horwitz B, Herscovitch P, Post RM (1995): Brain activity during transient sadness and happiness in healthy women. Am J Psychiatry 152: 341-51.

21. Goldman-Rakic PS (1987): Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: F Plum, editor. Handbook Physiology, The Nervous System, Higher Functions of the brain.

22. Gross JJ (1999): Emotion regulation: Past, Present, Future. Cogn. Emot 13: 551-573.

23. Hariri AR, Bookheimer SY, Mazziotta JC (2000): Modulating emotional responses: effects of a neocortical network on the limbic system. NeuroReport 11:43-8.

24. Jackson DC, Malmstadt JR, Larson CL, Davidson RJ (2000): Suppression and enhancement of emotional responses to unpleasant pictures. Psychophysiology 37: 512-522.

25. Karama S, Lecours AR, Leroux JM, Bourgouin P, Beaudoin G, Joubert S, et al. (2002): Areas of brain activation in males and females during viewing of erotic film excerpts. Hum Brain Mapp 16:1-13

26. Kimbrell TA, George MS, Parekh PI, Ketter TA, Podell DM, Danielson AL et al. (1999): Regional brain activity during transient self-induced anxiety and anger in healthy adults. Biol Psychiatry 46:454-65.

27. Lane RD, Nadel L (2000): Cognitive neuroscience of emotion. New York: Oxford UP.

28. Lane RD, Reiman EM, Ahern GL, Schwartz GE, Davidson RJ (1997a): Neuroanatomical correlates of happiness, sadness, and disgust. Am J Psychiatry 154: 926-33.

29. Lane RD, Fink GR, Chau PML, Dolan RJ (1997b): Neural activation during selective attention to subjective emotional responses. NeuroReport 8: 3969-3972.

30. Lemelin S, Baruch P, Vincent A, Laplante L, Everett S, Vincent P (1996): Attention disturbance in clinical depression. Deficient distractor inhibition or processing resource deficit? J Nerv Ment Dis 184: 114-121.

31. Lemelin S, Baruch P, Vincent A, Everett S, Vincent P (1997): Distractibility and processing resource deficit in major depression. Evidence for two deficient attentional processing models. J Nerv Ment Dis 185: 542-548.

32. Liotti M, Mayberg HS, Brannan SK, McGinnis S, Jerabek P, Fox PT (2000): Differential limbic--cortical correlates of sadness and anxiety in healthy subjects: implications for affective disorders. Biol Psychiatry 48:30-42.

33. MacFall JR, Payne ME, Provenzale JE, Krishnan KRR (2001): Medial orbiral frontal lesions in late-onset depression. Biol Psychiatry 49: 803-806.

34. Mesulam M-M (1985): Patterns in behavioural neuroanatomy: Association areas, the limbic system, and hemispheric specialization. In: Principles of behavioral neurology (Mesulam M-M, ed), pp 1-70. Philadelphia: F.A. Davis Company.

35. Mesulam M-M, Mufson EJ (1982): Insula of the old world monkey: Architectonics in the insulo-orbital temporal component of the paralimbic brain. J Comp Neurol 212:1–22.

36. Morán MA, Mufson EJ, Mesulam M-M (1987) Neural inputs into the temporopolar cortex of the rhesus monkey. J Comp Neurol 256:88–103.

37. Morecraft RJ, Geula C, Mesulam MM (1992): Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. J Comp Neurol 323, 341-58.

38. Nagashima K, Nakai S, Tanaka M, Kanosue (2000): Neuronal circuitries involved in thermoregulation. Auton Neurosci 85:18-25.

39. Nauta WJH (1971) : The problem of the frontal lobe: a reinterpretation J. Psychiatr Res. 8:167-187.

40. Öngür D, An X, Price JL (1998): Prefrontal cortical projections to the hypothalamus in macaque monkeys. J Comp Neurol 401:480–505.

41. Pardo JV, Pardo PJ, Raichle ME (1993): Neural correlates of self-induced dysphoria. Am J Psychiatry 150: 713-9.

42. Plutchik R (1994): The psychology and biology of emotion. New York :Harper Collins.

43. Price JL (1999): Prefrontal cortical networks related to visceral function and mood. Ann NY Acad Sci 877: 383-396.

44. Rauch SL, Savage CR, Alpert NM, Fischman AJ, Jenike MA (1997):The functional neuroanatomy of anxiety: A study of three disorders using positron emission tomography and symptom provocation. Biol Psychiatry 42: 446-452.

45. Reiman EM (1997): The application of positron emission tomography to the study of normal and pathologic emotions. J Clin Psychiatry 58: 4-12.

46. Reiman EM, Fusselman MJ, Fox PT, Raichle ME (1989): Neuroanatomical correlates of anticipatory anxiety. Science 243:1071-4

47. Rempel-Clower NL, Barbas H (1998): Topographic organization of connections between the hypothalamus and prefrontal cortex in the rhesus monkey. J Comp Neurol 398:393–419.

48. Roberts AC, Wallis JD (2000): Inhibitory Control and Affective Processing in the prefrontal Cortex: Neuropsychological Studies in the common Marmoset. Cerebral Cortex 10: 252-262.

49. Schneider F, Gur RE, Mozley LH, Smith RJ, Mozley PD, Censits et al. (1995): Mood effects on limbic blood flow correlate with emotional self-rating: a PET study with oxygen-15 labeled water. Psychiatry Res 61:265-83.

50. Schneider F, Grodd W, Weiss U, Klose U, Mayer KR, Nagele T, Gur RC (1997): Functional MRI reveals left amygdala activation during emotion. Psychiatry Res76:75-82.

51. Sequeira H, Roy J-C (1993): Cortical and hypothalamo-limbic control of electrodermal responses. In Roy J-C, Boucsein W, Fowles D, Gruzelier J, Editors. Progress in electrodemal research, New York: Plenum, pp.93-114.

52. Song AW (2001): Single-shot EPI with signal recovery from the susceptibility-induced losses. Mag Reson Med 46: 407-411.

53. Talairach J, Tournoux P (1988) : Co-planar stereotaxic atlas of the human brain, Stuttgart: Thieme Medical.

54. Tölle TR, Kaufmann T, Siessmeier T, Lautenbacher S, Berthele A, Munz F et al. (1999): Region-specific encoding of sensory and affective components of pain in the human brain: A positron emission tomography correlation analysis. Ann of Neurology 45: 40-47.

55. Thompson RA (1994): Emotion regulation: A theme in search of definition. Monographs of the Society for research in Child Development 59:27-28.

56. Whalen PJ, Rauch SL, Etcoff NL, McInerney SC, Lee MB, Jenike MA (1998): Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. J Neurosci18:411-8.

Figure caption

Figure 1. Statistical activation maps for limbic/paralimbic regions defined *a priori.* Images are sagittal sections for the data averaged across subjects. In the Sad condition, greater activation during the viewing of sad film excerpts relative to the viewing of emotionally neutral film excerpts, was noted in the left midbrain (a), the left amygdala (b), the left insula (c), the left anterior temporal pole (uppest arrow BA 38, lowest arrow BA 21) (d), the right midbrain(e), BA 38 of the right anterior temporal pole (f), the right VLPFC (BA 47) (g), and BA 21 of the right anterior temporal pole(h).

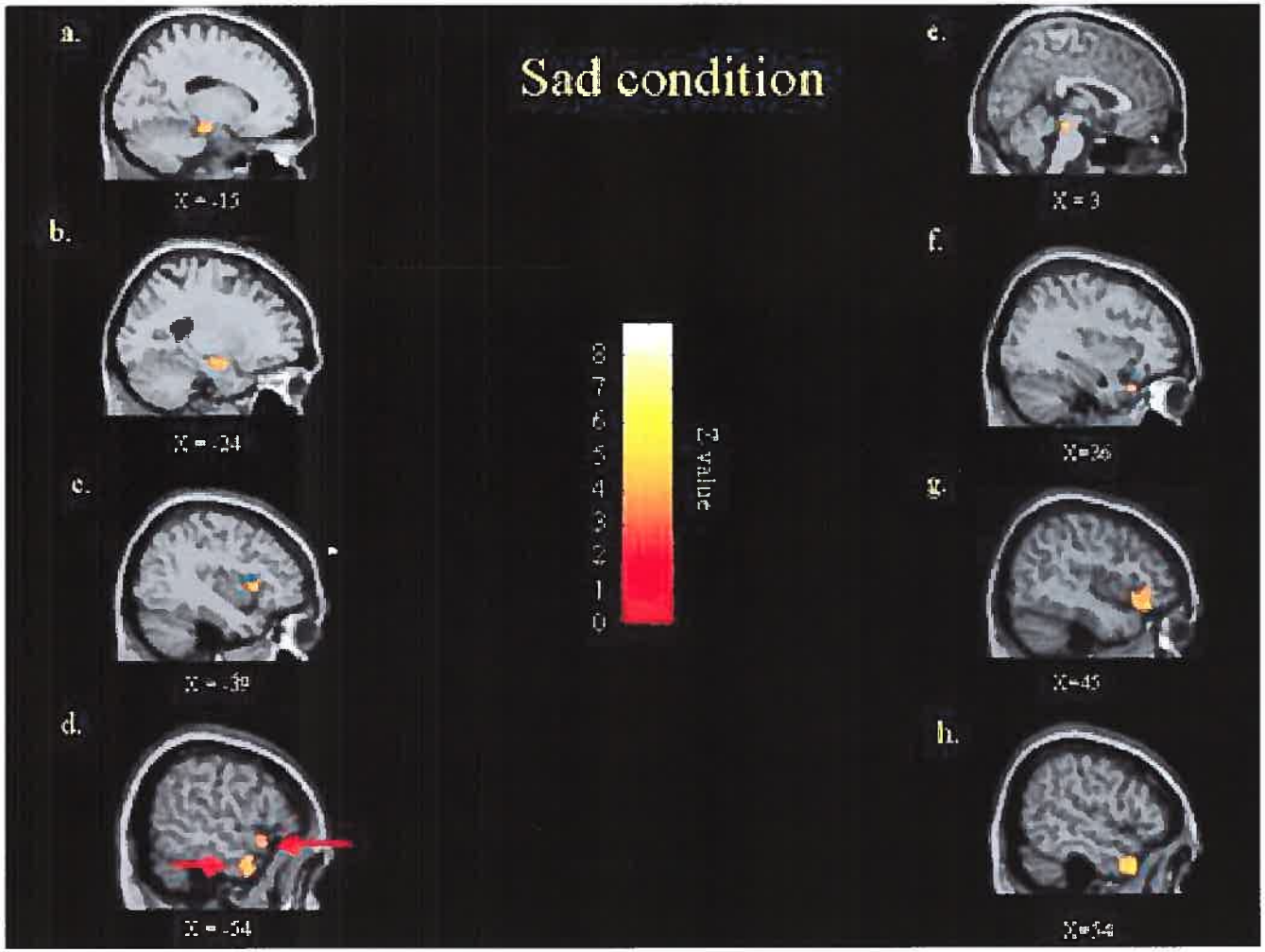
Sad condition
a.
X = -15
b.
X = -24
c.
X = -39
d.
X = -54
e.
X = 3
f.
X=26
g.
X=45
h.
X=54
t-value
0 1 2 3 4 5 6 7 8

Figure caption

Figure 2. Statistical activation maps during the Suppression condition. Images are sagittal sections for the data averaged across subjects. Significant loci of activation were observed in the in the right DLPFC (BA 9) (a) and right OFC (BA 11) (b).

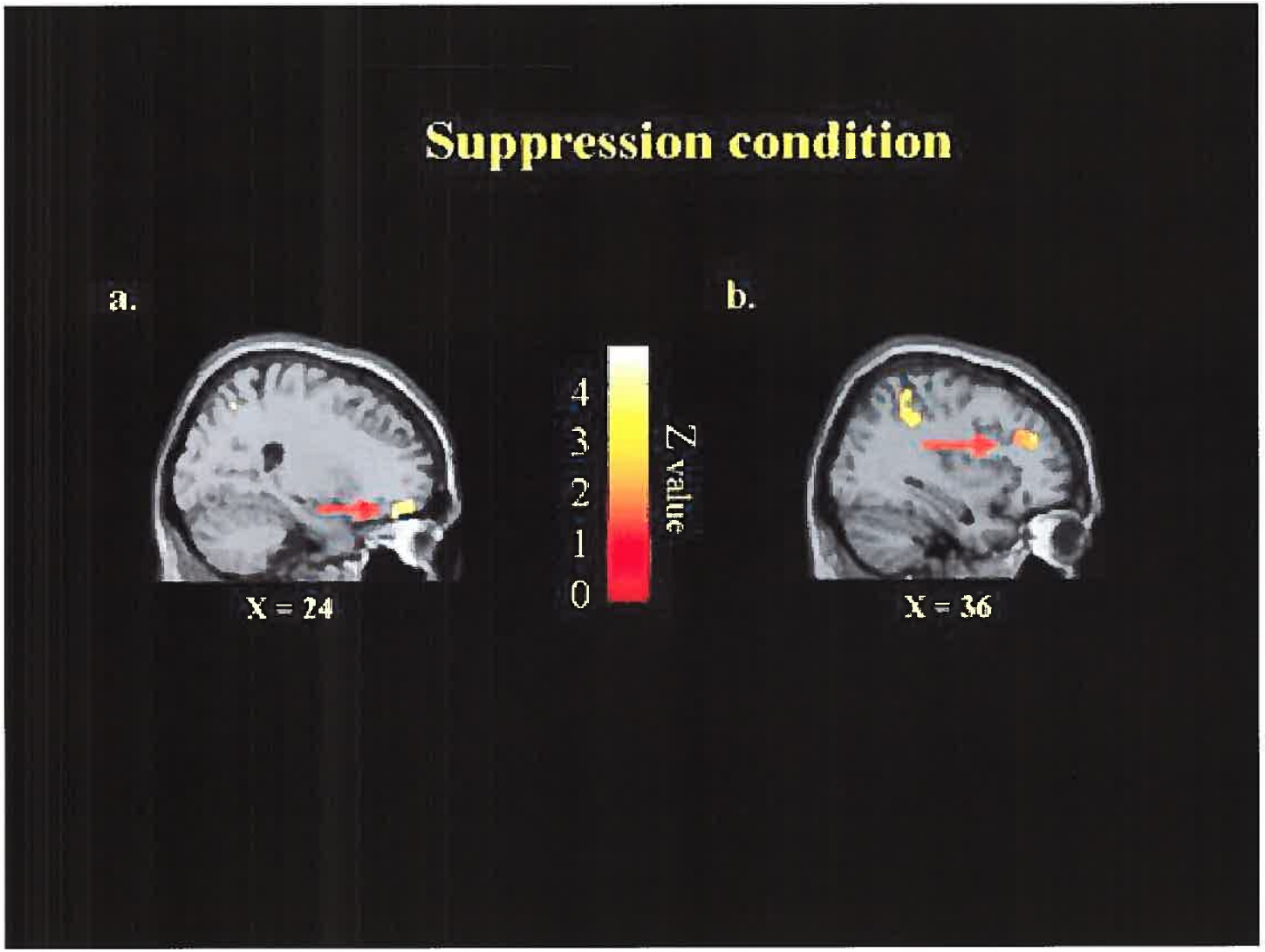
Suppression condition
a.
b.
4
3
2
1
0
Z value
X = 24
X = 36

Table 1. Significant loci of activation in the Sad condition

			Talairach coordinates (mm)				
	Region	Brodmann area	x	y	z	Z - statistic	Corrected p value
Search volume defined a priori	L. Anterior temporal pole	21	-54	2	-24	3.89	$p < 0.002$
	L. Midbrain		-15	-21	-12	3.78	$p < 0.006$
	R. Anterior temporal pole	21	54	5	-15	3.72	$p < 0.004$
	R. Ventrolateral PFC	47	45	26	-11	3.70	$p < 0.031$
	L. Amygdala		-24	-4	-15	3.70	$p < 0.003$
	R. Midbrain		3	-30	-11	3.63	$p < 0.010$
	R. Anterior temporal pole	38	36	13	-26	3.41	$p < 0.036$
	L. Insula		-39	15	-1	3.36	$p < 0.005$
	L. Anterior temporal pole	38	-54	8	-5	3.35	$p < 0.043$

Stereotaxic coordinates are derived from the human atlas of Talairach and Tournoux (1988) and refer to medial - lateral position (x) relative to midline (positive = right), anterior - posterior position (y) relative to the anterior commissure (positive = anterior), and superior – inferior position (z) relative to the commissural line (positive = superior). Designations of Brodmann areas for cortical areas are also based on this atlas. L, left; R, right.

Table 2. Significant loci of activation in the Suppression condition

		Talairach coordinates (mm)					
	Region	Brodmann area	x	y	z	Z - statistic	Corrected p value
Search volume defined a priori	R. OFC	11	24	46	-17	3.29	$p < 0.024$
	R. DLPFC	9	36	25	26	2.84	$p < 0.032$

As in Table 1.

Chapitre 3

ARTICLE #2

Neural correlates of sad feelings in healthy girls

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Abstract

Emotional development is indisputably one of the cornerstones of personality development during infancy. According to the differential emotions theory (DET), primary emotions are constituted of three distinct components: the neural-evaluative, the expressive, and the experiential. The DET further assumes that these three components are biologically based and functional nearly from birth. Such a view entails that the neural substrate of primary emotions must be similar in children and adults. Guided by this assumption of the DET, the present functional magnetic resonance imaging (fMRI) study was conducted to identify the neural correlates of sad feelings in healthy children. Fourteen healthy girls (aged 8 to 10) were scanned while they watched sad film excerpts aimed at externally inducing a transient state of sadness (activation task). Emotionally neutral film excerpts were also presented to the subjects (reference task). The subtraction of the brain activity measured during the viewing of the emotionally neutral film excerpts from that noted during the viewing of the sad film excerpts revealed that sad feelings were associated with significant bilateral activations of the midbrain, the medial prefrontal cortex (Brodmann area – BA - 10), and the anterior temporal pole (BA 21). A significant locus of activation was also noted in the right ventrolateral prefrontal cortex (BA 47). These results are compatible with those of previous functional neuroimaging studies of sadness in adults. They suggest that the neural substrate underlying the subjective experience of sadness is comparable in children and adults. Such a similitude provides empirical support to the DET assumption that the neural substrate of primary emotions is biologically based. However, as our subjects were aged between eight and ten

year old, our results could not confirm or dismissed another DET assumption saying that the neural substrate of primary emotions is functional from birth or nearly after.

Key words: sadness, subjective experience, children, functional magnetic resonance imaging.

Introduction

Emotional maturation indisputably represents one of the cornerstones of personality development during infancy. Regarding this question, Malatesta and colleagues (1989) have found that emotional expressive patterns tend to show stability during infancy across a wide range of primary emotions. This kind of stability extends to the preschool year, as revealed by the work of LaFrenière and Sroufe (1985). These findings have led some researchers to emphasize the importance of "emotional style" for emotional development. This concept refers to the fact that relatively ingrained and stable components of personality modulate the way children express and experience primary emotions (Malatesta et al., 1989; Tomkins, 1962, 1963, 1991). With respect to this issue, it has been well demonstrated that there are marked individual differences regarding the extent to which children may become emotionally aroused by various types of stimuli (Denham, 1998).

One theoretical view that accords with the concept of emotional style is the differential emotions theory (DET) (Izard, 1992). According to the DET, the self and the mental life are based on the early establishment of stable "affective-cognitive" schemas, and emotional development refers to "the processes whereby the emotions system achieves an increasingly complex matrix of functional links with the other subsystems of the individual - the physiological/drive, perceptual, cognitive, and action systems" (Izard, 1994, p. 356). This theory posits that primary emotions are subsystems of the emotion system. Primary emotions are constituted of three distinct components: the neural-evaluative, the expressive, and the experiential (Izard, 1992). The DET further contends

that these three components are biologically based and functional nearly from birth (Izard, 1992). It follows from this assumption that the neural substrate of primary emotions must be comparable in childhood and adulthood.

To date, functional neuroimaging studies of sadness in healthy adults (Pardo et al., 1993; George et al., 1995; Lane et al., 1997; Beauregard et al., 1998; Damasio et al., 2000; Lévesque et al. 2003) have found on a more or less consistent basis that the subjective experience of sadness is associated with activation in several limbic and paralimbic brain regions such as the ventrolateral prefrontal cortex (VLPFC), the medial prefrontal cortex (MPFC), the anterior cingulate cortex (ACC), the anterior temporal pole, the insula, the amygdala, the hypothalamus, the pons, and the midbrain. Guided by this bulk of data and the DET, the present functional magnetic resonance imaging (fMRI) study was conducted to investigate the neural correlates of externally-induced sad feelings in healthy children. We predicted *a priori* that the subjective experience of sadness in healthy children would be associated with significant blood-oxygenation-level-dependent (BOLD) signal changes in the brain regions that have previously been associated with sadness in adults. To our knowledge, this is the first attempt at delineating the neural correlates of the feelings associated with a primary emotion in children.

Experimental procedure

Subjects

Fourteen healthy Caucasian right-handed girls (age range: 8 – 10; mean age: 9.8) took part in this study. Girls were studied to allow qualitative comparisons with the results of our previous study conducted in women using exactly the same protocol (Lévesque et al., 2003). None of these subjects presented a history of neurological or psychiatric disorders. As confirmed by the subjects' mothers, all subjects were prepubescent. The parents of the subjects gave written inform consent and the study was approved by the ethics committee of Centre hospitalier de l'Université de Montréal (CHUM), Hôpital Notre-Dame.

Behavioral protocol

Before scanning. To insure that all subjects would feel at ease with the scanning procedure, they first saw (several days before the actual experiment), with their parents and in the comfort of their homes, a videotape explaining in lay terms what is a MRI scanner and how it works. On the day of the experiment, the experimenter asked if the subjects (and their parents) had any question about this videotape. Afterwards, a detailed step-by-step explanation of the protocol was given to the subjects regarding their installation in the scanner and the equipment (goggles and headphones) that they would wear during scanning. Subjects were also presented with a numerical (analog) rating scale ranging from 0 (absence of any emotional reaction) to 8 (strongest emotion ever felt in one's lifetime) and used to evaluate the emotional state of the subjects during the experiment. To make sure that they understood the various emotional intensities

represented by the numbers of the scale, the experimenter asked the subjects to rate from 0 to 8 five sad events having occurred lately in their life. Finally, in order to avoid as much as possible brain activation patterns due to anxiety or fear, only subjects who appeared and said feeling at ease with the scanning procedure were included in the study.

During scanning. BOLD signal changes were measured while subjects first viewed four blocks of emotionally neutral film excerpts (reference task) and, then, four blocks of sad film excerpts (activation task). Based on evidence gathered previously by our group, this design was adopted to avoid contamination of the neutral stimuli by the sad stimuli (unpublished data). Each block lasted 48 sec and was separated by resting periods of 15 sec during which subjects viewed a blue cyan screen. Subjects were instructed to react normally to the sad film excerpts, that is, to allow themselves to become sad in response to these stimuli. Subjects were also instructed to look directly at both categories of stimuli. Sad film excerpts depicted the death of a beloved person, either a father, a mother, or a friend. Each excerpt depicted either a group of children, or a child and one or more adults. The emotionally neutral film excerpts were matched to the sad film excerpts with respect to the number and gender of the individuals depicted in these excerpts. Emotionally neutral film excerpts depicted various human activities (e.g., interviews, carpentry, etc.). To assess the subjective responses of the subjects to the stimuli, immediately at the end of the run, they were asked to rate verbally using the numerical (analog) rating scale the average intensity of sadness or of any other primary emotions (e.g., happiness, disgust, fear, anger, surprise (Plutchik, 1994) felt during the *viewing of*

both categories of film excerpts. An average rating score was computed for the four blocks of sad film excerpts and the four blocks of emotionally neutral film excerpts.

Image acquisition and analysis

Echoplanar images (EPI) were acquired on a 1.5 Tesla system (Magnetom Vision, Siemens Electric, Erlangen, Germany). Twenty-eight slices (5 mm thick) were acquired every 2.65 sec. in an inclined axial plane, aligned with the AC-PC axis. These T2* weighted functional images were acquired using an EPI pulse sequence (TR = 0.8 msec, TE = 54 msec, Flip = 90°, FOV = 215 mm, Matrix = 64 x 64, Voxel size = 3.36 mm x 3.36 mm x 5 mm). Following functional scanning, high-resolution data were acquired via a Tl-weighted three-dimensional volume acquisition obtained using a gradient echo pulse sequence (TR = 9.7 msec, TE = 4 msec, Flip = 12° FOV = 250 mm, Matrix = 256 x 256, Voxel size = 0.94 mm^3).

Data were analyzed using Statistical Parametric Mapping software (SPM99, Wellcome Department of Cognitive Neurology, London, UK). Images for all subjects were realigned to correct for artifacts due to small head movements. The gradient-recalled echo-planar sequence that we used is associated with large static magnetic field inhomogeneities commonly found near air/tissue interfaces (Cordes et al., 2000). These inhomogeneities can create artifacts like signal loss and voxel shifts in the ventral frontal, medial temporal, and inferior temporal regions (Song, 2001). To correct for such artifacts, a mask was applied to the slices of the mean EPI image which presented signal loss. This procedure was implemented for every subject. The images for all subjects were

then spatially normalized into an MRI stereotactic space (Montreal Neurological Institute – MNI - template) using this masked mean image. Even if the subjects were children, the MNI template (adult's template) was used. Indeed, Burgund and colleagues have shown, in a recent MRI study (2002), that even if there is some small anatomical differences between the brain'structures and sulci of adults (age range: 18 – 30) compare to that of children (age range: 7-8), those differences does not compromise the usefulness of an adult stereotactic space for children's functional images, assuming a functional resolution of 5 mm in images averaged across children. Images were then convolved in space with a three-dimensional isotropic gaussian kernel (12 mm FWHM) to improve the signal-to-noise ratio and to accommodate for residual variations in functional neuroanatomy that usually persist between subjects after spatial normalization.

Statistical analyses

The time series of the images were convolved with the delayed box-car function which approximates the activation patterns. Effects at each and every voxel were estimated using the general linear model. Voxel values for the contrasts of interest yielded a statistical parametric map of the t statistic (SPM *t*), subsequently transformed to the unit normal distribution, (SPM Z). A "fixed-effects model" was implemented to contrast the brain activity associated with the viewing of the sad film excerpts and that associated with the viewing of the emotionally neutral film excerpts (Sad – Neutral). This "fixed-effects model" produced individual contrast images, which were used as raw data for the implementation of a "random-effects model" (Friston and Frackowiak, 1997). An *a priori* search strategy was used and a small volume correction was performed in the

following brain regions of interest (ROIs): VLPFC (BA 47), MPFC (BA 9 and 10), ACC (affective division: rostral areas of BA 24a-c and 32, ventral areas of BA 25 and 33 - Bush et al., 2000), anterior temporal pole (BA 21 and 38), insula, amygdala, hypothalamus, pons, and midbrain. The search volume corresponding to the ROIs was defined by tracing the neuroanatomical boundaries of these regions on the MR reference image (MNI template), using the small volume correction function (SVC) and box volume function in SPM99. For this *a priori* search, a corrected probability threshold for multiple comparisons of $p < 0.05$ corrected was used. Only clusters showing a spatial extent of at least 5 contiguous voxels were kept for image analysis.

Results

Self-report data

From a phenomenological perspective, the viewing of the sad film excerpts induced a transient state of sadness in all subjects. Actually, all subjects reported feeling sad during the viewing of the sad film excerpts and some of them even cried. The mean level of reported sadness was 5/8 (SD = 2; range 2-8). The viewing of the sad film excerpts did not produce other significant change of the emotional state than sadness (Mean levels: happiness: 0; anger: 0; disgust: 0.9; surprise: 0.5; fear: 0.5) Likewise, the viewing of the neutral film excerpts did not generate any marked alteration of the emotional state (Mean levels: sadness: 0.0; happiness: 0.8; anger: 0.1; disgust: 0; surprise: 0.9; fear: 0.3).

fMRI data (Sad minus Neutral)

From a functional neuroanatomical perspective, the subtraction of the brain activity associated with the viewing of the neutral film excerpts from that associated with the viewing of the sad film excerpts revealed significant bilateral activations in the midbrain, anterior temporal pole (BA 21), and MPFC (BA 10). A significant locus of activation was also noted in the right VLPFC (BA 47) (Table 1, Figure 1).

[Insert Figure 1 about here]

[Insert Table 1 about here]

Discussion

This fMRI study was undertaken to identify the neural correlates of sad feelings in healthy children. Results showed that the transient state of sadness, externally induced using sad film excerpts was associated with significant loci of activation in the midbrain, the anterior temporal pole (BA 21), the MPFC (BA 10), and the right VLPFC (BA 47).

Comparison with previous functional neuroimaging studies of sadness in adults

Collectively, the neural correlates of sadness found here in children are comparable to those reported in previous functional neuroimaging studies of sadness in adults. Indeed, significant loci of activation have been previously noted in the midbrain (Lane et al., 1997), the anterior temporal pole (Lane et al., 1997), the MPFC (Beauregard et al., 1998; Lane et al., 1997), and the right VLPFC (Beauregard et al., 1998) when sad feelings were

induced externally (e.g., with sad film excerpts). Significant loci of activation have also been seen in the midbrain (Damasio et al., 2000), the anterior temporal pole (Damasio et al., 2000), and the MPFC (George et al., 1995) while subjects had to recall and/or re-enact sad events.

Our group has recently conducted a fMRI study in healthy women (20 subjects; age range: 20 – 30) using exactly the same protocol and the same film excerpts than in the present investigation (Lévesque et al., 2003). Phenomenologically, the scores on the emotion rating scale were very similar. As mentioned above, the mean level of reported sadness in girls was 5/8 (SD = 2; range 2 - 8) whereas, in women, this level was 5.15/8 (SD = 1.30; range: 2 - 7). Moreover, as it is the case here for girls, women did not report experiencing other primary emotion during the viewing of the sad film excerpts. Thus, based on the self-report data, it appears that in these two studies, both groups of subjects experienced sadness with a relative specificity, and that the intensity of the sad feelings was analogous.

Likewise, the patterns of brain activation associated with sadness were relatively comparable in these two fMRI studies. Indeed, for both girls and women, the viewing of the sad film excerpts was associated with activation of the anterior temporal pole (BA 21) and the midbrain, bilaterally, as well as with activation of the right VLPFC (BA 47). Such a similitude provides empirical support to our *a priori* hypothesis. However, there were also some differences in the patterns of brain activation noted in these two investigations. Actually, significant loci of activation in the amygdala, the insula and the

anterior temporal pole (BA 38) were found only in women, whereas the MPFC (BA 10) was activated only in girls. To account for these differences, we examined the individual statistical parametric maps (SPMs) generated in the two studies. Interestingly, in girls, the amygdala was activated in 40 % of the subjects while the insula was activated in 60 % of the subjects. In addition, the anterior temporal pole (BA 38) was found activated in 80 % of the subjects. These loci of activation barely fell short of statistical significance. In women, activation of the MPFC was noted in 40 % the subjects. Again these BOLD signal increases were just beneath significance. Of note is the fact that, in both groups of subjects, the individual SPMs revealed an important degree of interindividual variability in terms of the functional neuroanatomy underlying sad feelings (as in the case of another fMRI study recently carried out by our group – see Eugène et al., in press). That is, across subjects belonging to the same group (girls vs. women), the activated voxels in a given brain region were not consistently localized within the same regional subdivisions. Therefore, it seems reasonable to assume that individual differences in regional cerebral patterns of activation may be responsible, at least in part, for the differences found between girls and women with respect to the neural correlates of sadness. Differences in what Davidson (1992) has termed "affective style" could be related to the inter-individual variability noted in these two studies. It is conceivable that other personality variables may also underlie such inter-individual variability. With respect to this issue, there is mounting evidence that neural activity in the cerebral cortex may be related to specific dimensions of personality (Sugiura et al., 2000). Alternatively, we cannot rule out the possibility that differences in brain maturation could account for some of the differences in patterns of brain activation found between these two studies (although no clear

relationship has been evidenced yet between brain maturation and emotional development).

Role of the various brain regions activated in children during sadness

Activation of the anterior temporal pole has been reported, in healthy adults, during normal anticipatory anxiety (Reiman et al., 1989; Chua et al.,. 1999), script-generated anger and anxiety (Dougherty et al., 1999; Damasio et al., 2000; Kimbrell et al., 1999), film-induced sexual arousal (Beauregard et al., 2001), and memory-driven sadness (Lane et al., 1997). This paralimbic cortical region receives inputs from unimodal and heteromodal sensory regions as well as limbic inputs. It has been proposed by Mesulam (1985) that the anterior temporopolar region may be associated with imparting affective tone to the individual's experience. In this context, it is possible that the anterior temporopolar activations of the anterior temporal pole seen here reflected the attribution of the emotional (sad) color to the subjective experience externally induced by the sad film excerpts.

The midbrain has been found activated in functional neuroimaging studies of various emotional states (e.g., disgust, sadness, anger, fear, happiness, pain and anxiety) (Fredrikson et al., 1995; Lane et al., 1997; Rauch et al., 1997; Tölle et al., 1999; Damasio et al., 2000; Lévesque et al., 2003). There is some evidence suggesting that this cerebral structure is involved in the mediation of autonomic responses such as skin conductance responses (Sequeira & Roy, 1993) and body temperature changes (Nagashima, et al., 2000). Given that autonomic responses often accompanied the subjective experience of

primary emotions (Damasio et al. 2000), the bilateral midbrain activations noted here may be related to the autonomic responses associated with subjects' sad feelings.

The MPFC has been reported to be activated in several functional neuroimaging studies of sadness conducted in healthy adults (Beauregard et al., 1998; Damasio et al., 2000; George et al., 1995; George et al., 1996; Lane et al., 1997; Reiman et al., 1997). This prefrontal cortical region has also been associated with other positive (e.g., happiness) and negative (e.g., disgust) emotions, regardless of the emotion-induction procedure used (e.g., film, pictures, recall of emotional events) (George et al., 1996; Lane et al., 1997; Reiman et al., 1997; Teasdale et al., 1999). The MPFC, which sends extensive connections to the hypothalamus and brain stem and is the site of convergence for limbic inputs, has been postulated to participate in the integration of cognition and emotion (Mesulam, 1985). In keeping with this, studies of patients with damage to the MPFC suggest that this cortical area is involved in the conscious monitoring of the individual's emotional state (Damasio et al., 1994). The bilateral MPFC activations found here may be related to such a metacognitive process.

Activation of the VLPFC has been reported, in adult subjects, during externally (e.g., looking at human faces) and/or internally (e.g., recalling appropriate life events) induced sadness (Pardo et al 1993; George et al 1995; Beauregard et al., 1998; Damasio et al., 2000), anxiety (Fredrikson et al 1997; Kimbrell et al 1999), and anger (Dougherty et al 1999; Kimbrell et al 1999). These findings suggest that the VLPFC participates in aspects of emotion processing that are not exclusively related to a discrete emotion in particular.

Given the fact that this prefrontal cortical region receives extensive sensory inputs (olfactory, gustatory, visceral afferent, somatic sensory, and visual) as well as limbic inputs from the amygdala, entorhinal and perirhinal cortex, and subiculum, it seems plausible that the VLPFC activation noted here may be associated with the integration of viscerosensory information with information signalling changes in the subjects' emotional state.

Factors influencing the neural processing related to emotion with regard to emotional development

The fact that the neural correlates of sadness found here in children are comparable to those reported in previous functional neuroimaging studies of sadness in adults fits rather nicely with one of the assumptions of the DET. Indeed, this theory postulates that the neural–evaluative component of primary emotions is biologically based and functional from birth or nearly after (Izard, 1992). Such a view entails that the neural substrate of primary emotions is similar in children and adults. Another assumption of the DET is that emotional experience is a direct product of the neural-evaluative component. Therefore, the experiential dimension of emotion does not develop over time (Izard, 1992). With regard to this issue, the DET further contends that the motivational/feeling states associated with primary emotions remain invariant across lifespan (Campos and Barrett, 1984; Emde, 1980), and that only cognitive development and social learning can give rise to secondary emotions such as contempt, guilt or shame (Ackerman et al., 1998). This last assumption has been overtly questioned by Dunn (1994) who argues that, as children grow up, there are important changes in emotion eliciting conditions that necessarily

imply changes in the emotional experience itself. For Dunn and other proponents of the cognitive perspective to emotional development, emotion is a function of cognition inasmuch as it refers to various relations among external incentives, thoughts and detected changes in internal feeling states (Kagan, 1978, 1984, 1994; Mandler, 1984, 1990).

Besides cognitive development, social environment (Dickson et al., 1998) and culture (Mesquita & Frijda, 1992) are two other factors playing a pivotal role in emotional development. According to the social view of emotion, the transaction between the individual and the environment constitutes the core aspect of emotional development (Dickson et al., 1998). Emotions are not encapsulated in the individual, "... but are socially constructed, dynamically created out of the constituents' interaction" (Fogel et al., 1992). In the cultural perspective, emotion "...is an event-elicited response set that involves one's relationship to some object or person (possibly the self), and that involves control precedence" (Frijda and Mesquita, 1998). Within the cultural perspective, the precedence or the context that precedes an emotion is a crucial aspect of emotional development and may vary tremendously from one culture to another. For instance, Iktu Inuits have different words for sadness depending on the eliciting conditions (Briggs, 1970).

Whether or not the neural substrate of primary emotions is present and functional from birth or nearly after, we submit that cognitive development, social environment and culture all contribute to emotional development and influence the nature of the emotional experience across lifespan by modulating neural processing in the brain regions

underlying the various components (e.g., cognitive, experiential, physiological, behavioral) of emotion. For instance, a moral value inculcated in a 6 year old child by her parents may exert a major influence on the way this child will later react emotionally to certain types of situations or events. By definition, such a regulating influence implies a modulation of the neural circuitry related with the diverse aspects of emotion.

Conclusion

In this fMRI study, an externally-induced state of sadness was associated, in healthy girls, with significant loci of activations, bilaterally, in the midbrain, the MPFC (BA 10), and the anterior temporal pole (BA 21). A significant locus of activation was also found in the right VLPFC (BA 47). These results are compatible with those of previous functional neuroimaging studies of sadness in adults. They suggest that the neural substrate underlying the subjective experience of sadness is comparable in children and adults. Such a similitude provides empirical support to the DET assumption that the neural substrate of primary emotions is biologically based. However, as our subjects were aged between eight and ten year old, our results cannot validate the DET assumption saying that the neural substrate of primary emotions is functional from birth or nearly after.

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References

1. Ackerman, B.P., Abe, J.A.A., and Izard, C.E., 1998. In: M.F. Mascolo and S. Griffith (Eds.), What develops in emotional development? Plenum, New York, pp.85-109.

2. Beauregard, M., Lévesque, J., and Bourgouin, P., 2001. Neural correlates of the conscious self-regulation of emotion. J. Neuroscience, 21, RC165, 1-6.

3. Beauregard, M., Leroux, J.-M., Bergman, S., Arzoumanian, S., Beaudoin, G., Bourgouin, P., Stip, E., 1998. The functional neuroanatomy of major depression: an fMRI study using an emotional activation paradigm. NeuroReport, 9, 3253-3258.

4. Briggs, J.L., 1970. Never in anger: Portrait of an Eskimo family. Harvard University Press, Cambridge.

5. Bush, G., Luu, P., and Posner, M.I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends in Cog. Sci. 4, 215-222.

6. Campos, J.J., and Barrett, K.C., 1984. Toward a new understanding of emotions and their development. In: C.E. Izard, J. Kagan, and R.B. Zajonc (Eds.),

Emotions, cognition, and behavior, Cambridge University Press, Cambridge, pp. 229-263.

7. Cordes, D., Turski, P.A., Sorenson, J.A., 2000. Compensation of susceptibility-induced signal loss in echo-planar imaging for functional applications. Mag Res Imaging 18, 1055-1068.

8. Chua, P., Krams, M., Toni, I., Passingham, R., Dolan, R., 1999. A functional anatomy of anticipatory anxiety. Neuroimage 9, 563-71.

9. Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L.L., Parvizi, J., Hichwa, R.D., 2000. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nature Neurosci 3, 1049-56.

10. Damasio, A.R., 1994. Descartes' Error: Emotion, Reason, and the Human Brain. Putnam, New York.

11. Davidson, R.J., 1992. Emotion and affective style: Hemispheric substrates. Psychological Science, 3, 39-43.

12. Denham, S.A., 1998. Emotional development in young children. Guilford Press, New York.

13. Dickson, K.L., Fogel, A., and Messinger, D., 1998. The development of emotion from a social process view. In: M.F. Mascolo and S. Griffith (Eds.), What develops in emotional development? Plenum, New York, pp. 253-271.

14. Dougherty, D.D., Shin, L.M., Alpert, N.M., Pitman, R.K., Orr, S.P., Lasko, M., Macklin, M.L., Fischman, A.J., Rauch, S.L., 1999. Anger in healthy men: a PET study using script-driven imagery. Biol Psychiatry, 46, 466-72.

15. Dunn, J., 1994. Experience and understanding of emotions, relationships, and membership in a particular culture. In: P. Ekman and R.J. Davidson (Eds.), The nature of emotion, Oxford University Press, New York, pp. 352-355.

16. Emde, R.N., 1980. Levels of meaning for infant emotions: A biosocial view. In: W.A. Collins (Ed.), Minnesota symposium on child psychology, Vol. 13, Lawrence Erlbaum, Hillsdale, pp. 1-37.

17. Eugène, F., Lévesque, J., Mensour, B., Leroux, J.-M., Beaudoin, G., Bourgouin, P. and Beauregard, M., in press. The impact of individual differences on the neural circuitry underlying emotion. NeuroImage.

18. Fogel, A., Nwokah, E., Dedo, J.Y., Messinger, D., Dickson, K.L., Matusov, E., and Holt, S.A., 1992. Social process theory of emotion: A dynamic systems approach. Social development, 1, 122-142.

19. Fredrikson, M., Fischer, H., and Wik, G., 1997. Cerebral blood flow during anxiety provocation. Journal of Clinical Psychiatry 58 (suppl. 16), 16-21.

20. Fredrikson, M., Wik, G., Fischer, H., Anderson, J., 1995. Affective and attentive neural networks in human: A PET study of Pavlovian conditioning. NeuroReport, 7, 97-101.

21. Frijda, N.H., and Mesquita, B., 1998. The analysis of emotions. Dimensions of variation. In: M.F. Mascolo and S. Griffith (Eds.), What develops in emotional development? Plenum, New York, pp. 273-295.

22. Friston, K.J,. and Frackowiak, R.S.J., 1997. Images of the future: a philosophical coda. In: R.S.J. Frackowiak, K.J. Friston, R.J. Dolan and J.C. Mazziotta (Eds.), Human Brain Function, Academic Press, San Diego, pp. 487-517.

23. Giedd, J.N., Vaituzis, A.C., Hamburger, S.D., Lange, N., Rajapakse, J.C., Kaysen, D., Vauss, Y.C., Rapoport, J.L., 1996a. Quantitative MRI of the temporal lobe,

amygdala, and hippocampus in normal human development: ages 4-18 years. J Comp Neurol. 4, 366, 223-230.

24. Giedd, J.N., Snell, J.W., Lange, N., Rajapakse, J.C., Casey, B.J., Kozuch, P.L., Vaituzis, A.C., Vauss, Y.C., Hamburger, S.D., Kaysen, D., Rapoport, J.L.,1996b. Quantitative magnetic resonance imaging of human brain development: ages 4-18. Cereb Cortex, 6, 551-560.

25. George, M.S., Ketter, T.A., Parekh, P.I., Herscovitch, P., and Post, R.M., 1996. Gender differences in regional cerebral blood flow during transient self-induced sadness or happiness. Biological Psychiatry, 40, 859-871.

26. George, M.S., Ketter, T.A., Parekh, P.I., Horwitz, B., Herscovitch, P., Post, R.M., 1995. Brain activity during transient sadness and happiness in healthy women. Am J Psychiatry, 152, 341-51.

27. Izard, C.E., 1994. Intersystem connections. In: P. Ekman & R.J. Davidson (Eds.), The nature of emotion. Fundamental questions, Oxford Press, New York, p.356.

28. Izard, C.E., 1992. Basic emotions, relations among emotions, and emotion-cognition relations. Psychological Review, 100, 561-565.

29. Kagan, J., 1994. On the nature of emotion. In: N.A. Fox (Ed.), The development of emotional regulation: Biological and behavioral considerations. Monograph of the Society for Research in Child Development, Serial No. 240, pp.7-24.

30. Kagan, J., 1984. The idea of emotion in human development. In: C.E. Izard, J. Kagan, and R. Zajonc (Eds.), Emotions, cognition, and behavior, Cambridge University Press, New York, pp.38-72.

31. Kagan, J., 1978. On emotion and its development: A working paper. In: M. Lewis & L.A. Rosenblum (Eds.), The development of affect, Plenum Press, New York, pp. 11-42.

32. Kimbrell, T.A., George, M.S., Parekh, P.I., Ketter, T.A., Podell, D.M., Danielson, A.L., Repella, J.D., Benson, B.E., Willis, M.W., Herscovitch, P., Post, R.M., 1999. Regional brain activity during transient self-induced anxiety and anger in healthy adults. Biol Psychiatry, 46, 454-65.

33. LaFrenière, P.J., and Sroufe, L.A., 1985. Profiles of peer competence in the preschool: Interrelations between measures, influence of social ecology, and relation to attachment history. Developmental Psychology, 21, 46-69.

34. Lane, R.D., Reiman, E.M., Ahern, G.L., Schwartz, G.E., Davidson, R.J., 1997. Neuroanatomical correlates of happiness, sadness, and disgust. Am J Psychiatry, 154, 926-933.

35. Lévesque, J., Joanette, Y., Paquette, V., Mensour, B., Beaudoin, G., Leroux, J.-M., Bourgouin, P., & Beauregard, M., 2003. Neural circuitry underlying voluntary suppression of sadness. Biological Psychiatry. 15, 53, 502-510.

36. Malatesta, C.Z., Culver, C., Tesman, J.R., Shepard, B., 1989. The development of emotional expression during the first two years of life. Monographs of the Society for Research in Child Development, 54, 1-2, Serial No. 219.

37. Mandler, G., 1990. A constructivist theory of emotion. In: N.L. Stein, B. Leventhal, and T. Trabasso (Eds.), Psychological and biological approaches to emotion, Erlbaum, Hillsdale, pp.21-44.

38. Mandler, G., 1984. Mind and body. Wiley, New York.

39. Mesquita, B., and Frijda, N.H., 1992. Cultural variations in emotion : A review. Psychological Bulletin, 112, 179-204.

40. Mesulam, M.-M., 1985. Patterns in behavioural neuroanatomy: Association areas, the limbic system, and hemispheric specialization. In: Mesulam M-M, (Ed.), Principles of behavioral neurology, F.A. Davis Company, Philadelphia, pp 1-70.

41. Nagashima, K., Nakai, S., Tanaka, M., Kanosue, 2000. Neuronal circuitries involved in thermoregulation. Auton Neurosci. 85,18-25.

42. Pardo, J.V., Pardo, P.J., Raichle, M.E., 1993. Neural correlates of self-induced dysphoria. Am J Psychiatry, 150, 713-719.

43. Plutchik, R., 1994. The psychology and biology of emotion. Harper Collins, New York.

44. Rauch, S.L., Savage, C.R., Alpert, N.M., Fischman, A.J., Jenike, M.A., 1997. The functional neuroanatomy of anxiety: A study of three disorders using positron emission tomography and symptom provocation. Biol Psychiatry, 42, 446-452.

45. Reiman, E.M., Lane, R.D., Ahern, G.L., Schwartz, G.E., Davidson, R.J., Friston, K.J., Yun, L.-S., and Chen, K., 1997. Neuroanatomical correlates of externally and internally generated human emotion. Am Journal of Psychiatry, 154, 918-925.

46. Reiman, E.M., Fusselmann M.J., Fox, P.T., Raichle, M.E., 1989. Neuroanatomical correlates of anticipatory anxiety. Science, 243, 1071-1074.

47. Sequeira, H., Roy, J.-C., 1993. Cortical and hypothalamo-limbic control of electrodermal responses. In: J.-C. Roy, W. Boucsein, D. Fowles, and J. Gruzelier (Eds.), Progress in electrodemal research, Plenum, New York, pp.93-114.

48. Reiss, A.L., Abrams, M.T., Singer, H.S., Ross, J.L., Denckla, M.B., 1996. Brain development, gender and IQ in children. A volumetric imaging study. Brain, 119, 1763-74.

49. Song, A.W., 2001. Single-shot EPI with signal recovery from the susceptibility-induced losses. Mag Reson Med. 46, 407-411.

50. Sugiura, M., Kawashima, R., Nakagawa, M., Okada, K., Sato, T., Goto, R., Sato, K., Ono, S., Schormann, T., Zilles, K., and Fukuda, H., 2000. Correlation between human personality and neural activity in cerebral cortex. NeuroImage, 11, 541-546.

51. Teasdale, J.D., Howard, R.J., Cox, S.G., Ha, Y., Brammer, M.J., Williams, S.C.R., and Checkley, S.A., 1999. Functional MRI study of the cognitive generation of affect. Am Journal of Psychiatry, 156, 209-215.

52. Tölle, T.R., Kaufmann, T., Siessmeier, T., Lautenbacher, S., Berthele, A., Munz, F., Zieglgansberger, W., Willoch, F., Schwaiger, M., Conrad, B., Bartenstein, P., 1999. Region-specific encoding of sensory and affective components of pain in

the human brain: A positron emission tomography correlation analysis. Ann of Neurology, 45, 40-47.

53. Tomkins, S., 1991. Affect, imagery, and consciousness: Vol. 3. The negative affects: Anger and fear. Springer, New York.

54. Tomkins, S., 1963. Affect, imagery, and consciousness: Vol. 2. The negative affects. Springer, New York.

55. Tomkins, S., 1962. Affect, imagery, and consciousness: Vol. 1. The positive affects. Springer, New York.

Figure caption

Figure 1. Statistical activation maps for the brain regions defined *a priori*. Images are sagittal sections for the data averaged across subjects. During the transient state of sadness, significant loci of activation were noted in a) the right MPFC (BA 10) and the right midbrain, b) the left MPFC (BA 10) and the left midbrain, c) the right VLPFC (BA 47) and the right anterior temporal pole (BA 21), and d) the left anterior temporal pole (BA 21).

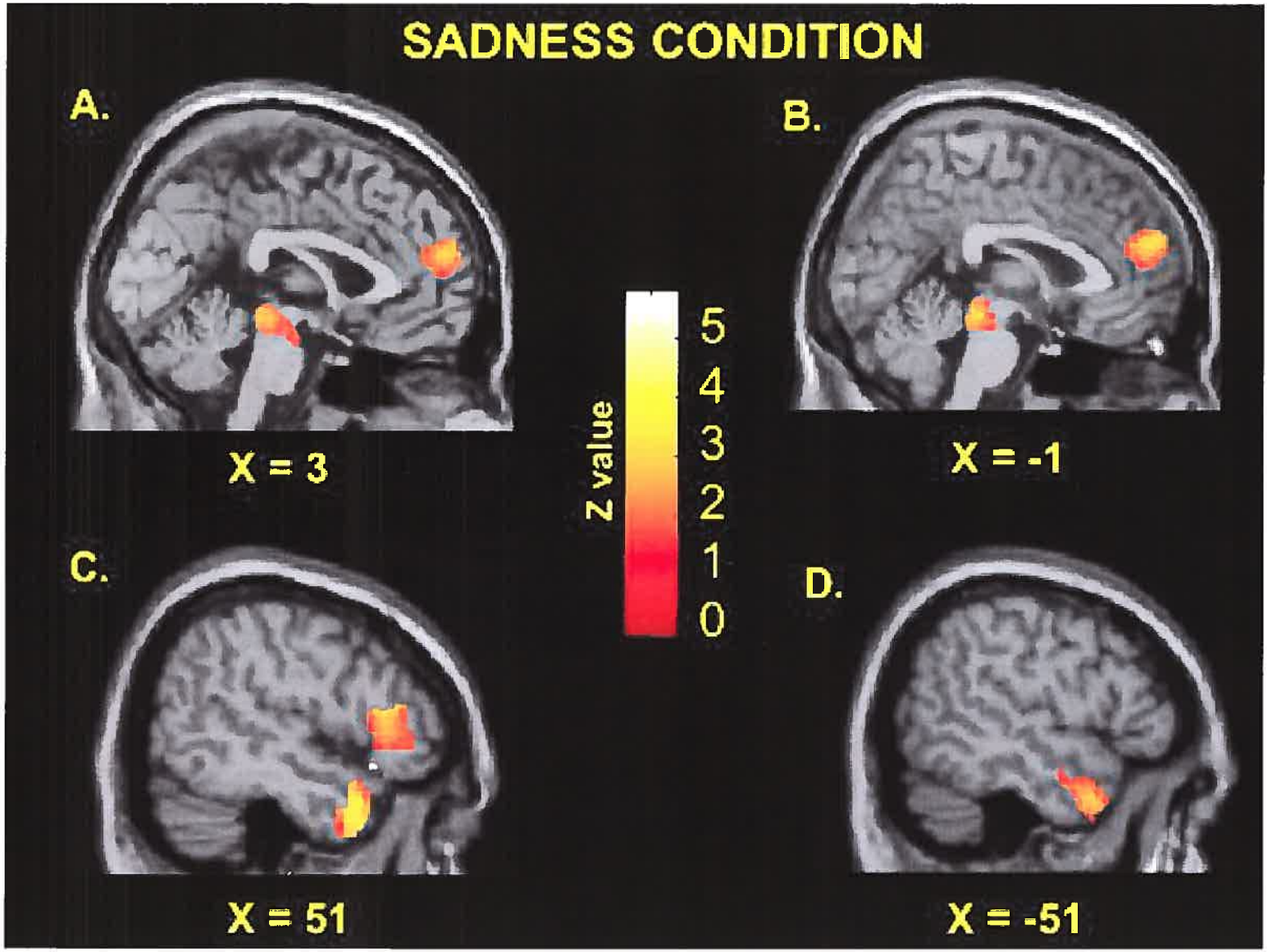
SADNESS CONDITION
A.
B.
X = 3
X = -1
Z value
5
4
3
2
1
0
C.
D.
X = 51
X = -51

Table 1. Significant loci of activation during sadness (Sad minus Neutral)

Region	Talairach coordinates (mm) Brodmann area	x	y	z	Z - statistic	Corrected p value
R Anterior temporal pole	21	50	7	-26	3.65	$p < 0.002$
R MPFC	10	3	56	17	3.13	$p < 0.014$
R Midbrain		3	-30	-9	3.06	$p < 0.019$
L MPFC	10	-1	57	-15	2.96	$p < 0.022$
L Anterior temporal pole	21	-50	4	-28	2.84	$p < 0.023$
L Midbrain		-3	32	-8	2.82	$p < 0.037$
R. VLPFC	47	3	56	17	2.57	$p < 0.002$

Stereotaxic coordinates are derived from the human atlas of Talairach and Tournoux (1988) and refer to medial - lateral position (x) relative to midline (positive = right), anterior - posterior position (y) relative to the anterior commissure (positive = anterior), and superior – inferior position (z) relative to the commissural line (positive = superior). Designation of Brodmann areas for cortical areas is also based on this atlas. L, left; R, right.

Chapitre 4

ARTICLE #3

Neural basis of emotional self-regulation in childhood

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Abstract

Emotional self-regulation plays a pivotal role in socialization and moral development. This capacity critically depends on the development of the prefrontal cortex (PFC). The present functional magnetic resonance imaging (fMRI) study was conducted to identify the neural circuitry underlying voluntary suppression of sadness in healthy girls. Fourteen normal girls aged between 8 and 10 years were scanned during a Sadness condition and a Suppression condition. In the Sadness condition, subjects were instructed to react normally to sad film excerpts whereas, in the Suppression condition, they were asked to voluntarily suppress any emotional reaction in response to comparable stimuli. Results revealed that the Suppression task was associated with bilateral activations of the lateral PFC (LPFC) (Brodmann area – BA - 10), orbitofrontal cortex (OFC) (BA 11), medial MPFC (BA 10), and rostral anterior cingulate cortex (ACC) (BA 24), as well as activation of the left LPFC (BA 9). In an identical study previously conducted by our group in adult women (Lévesque et al., 2003), suppression of sadness was associated with activation of the right OFC (BA 11) and right LPFC (BA 9), and the spatial extent of the right LPFC activation was five-fold smaller in women than in children. These differences indicate that the voluntary suppression of sadness necessitates more prefrontal work in children than in adults. In keeping with this, conscious and voluntary self-regulation of emotion may be more challenging cognitively and emotionally in children than in adults because the maturation of the prefronto-subcortical (limbic) connections is not completed before the end of adolescence.

Key words: suppression, volition, metacognition, prefrontal cortex, functional magnetic resonance imaging children, sadness.

Introduction

According to evolutionary psychology, biologically based emotions represent efficient modes of adaptation to changing environmental demands (Tooby and Cosmides, 1990). From this theoretical perspective, emotions have emerged in the course of evolution by virtue of their capacity to adequately co-ordinate the diverse response systems (e.g., cognitive, subjective, physiological, and behavioral) that characterize emotion's multidimensional nature (Levenson, 1994). However, as noted by Gross (1999), emotions are not always the most pertinent response to the various situations encountered in daily life. Gross further contends that, despite the many possible benefits of emotion, it is paramount to avoid erroneously evaluating the consequences of blindly following all sorts of emotional impulses. Regarding this issue, negative emotions are undoubtedly one of the main causes of human suffering. This is why, at both an individual and a collective level, it is peremptory for human beings to learn how to properly control their emotional reactions using their cognitive capacities. This point leads us directly to the construct of emotional self-regulation.

Emotional self-regulation refers to the heterogeneous set of cognitive processes by which emotions are regulated, i.e., the ways individuals influence which emotions they have, when they have them, and how they experience and express these emotions (Gross, 1999). This instance of self-regulation implicates changes in one or more of the various response systems of emotion (Gross, 1999). Emotional self-regulation involves generating, maintaining, decreasing, or increasing positive or negative emotions (Cole et al., 1994; Langston, 1994; Masters, 1991; Parrott, 1993). This capacity implicates

several types of adjustments that favour the adaptation of the individual to life circumstances (Cole et al., 1994) and allow this individual to accomplish his/her goals (Thompson, 1990). The cognitive strategies used to self-regulate emotion are numerous and include, among others, rationalization, reappraisal, and suppression (Gross, 1999).

Emotional self-regulation constitutes one of the cornerstones of socialization and moral development (Kochanska et al., 1997). To date, much of the research into the development of emotion regulation has focused on infancy and toddlerhood, primarily because a dramatic cognitive maturation is taking place during this developmental period (Calkins, in press). Generally speaking, the development of emotion regulation can be described as one in which the relatively passive and reactive neonate becomes a child capable of self-initiated behaviours that serve a regulatory function (Calkins, 1994; Kopp, 1982; Sroufe, 1996). In fact, the infant progresses from near complete reliance on caregivers for regulation to independent self-regulation. As the infant makes this transition, the use of specific strategies and behaviours becomes organized into the infant's repertoire of emotional regulation that may be used in a variety of contexts and that lead to independent functioning across a variety of skill domains (Calkins, in press).

Stuss (1992) has proposed that the capacity to self-regulate, a crucial executive function, develops in close relationship with the prefrontal cortex (PFC) development. This proposal has received some empirical support from magnetic resonance imaging (MRI) studies of structural and functional changes in the developing human brain during the first few decades of life (for review, see Casey et al., 2000). In particular, a recent

event-related fMRI study comparing interference suppression and response inhibition in children (aged from 8 to 12) and adults has evidenced that children were more prone to interference and had more difficulty to inhibit inappropriate responses than adults (Bunge et al., 2002). In their study, Bunge and colleagues observed that effective interference suppression in children was associated with PFC activation but in the opposite hemisphere compared to adults. Bunge et al. (2002) concluded that the immaturity of the PFC accounted for this difference.

Regarding this issue, it is noteworthy that myelination and dendritic development occur later in the human PFC than in other cortical regions. Synaptogenesis reaches a plateau between the ages of 1 and 7 and declines through adolescence to the adult level (Bourgeois et al., 1994; Huttenlocher, 1994; Rakic et al., 1994). This decrease in synaptic number coincides with the continued development of cognitive capacities (Caviness et al., 1996). In addition, cortical grey matter volume achieved its peak at around 5 years of age and decreases from that time forward, while the white matter volume increases constantly until about the age of 20 years (Pfefferbaum et al., 1994). With respect to myelination, Yakovlev and Lecours (1967) have postulated that it might continue in the PFC well into the third decade of life. Interestingly, Fox et al. (2001) have emphasized the obvious similarities between the disinhibited behaviours of adults following damage to the PFC and the emotional reactions and behaviours of normal infants and young children. The cognitive and emotional changes following PFC damage have been attributed to a disruption in the inhibitory control normally exerted by the PFC on subcortical "limbic" structures. In line with this, Posner and Rothbart (1998) have

postulated that emotional self-regulation likely involves the interaction of the midfrontal anterior cingulate cortex (ACC) with the amygdala. In addition, early-acquired orbitofrontal cortex (OFC) damage has been associated with disruption to social-emotional regulation (Eslinger et al., 1997).

The present functional MRI (fMRI) study was conducted to identify the neural circuitry underlying voluntary suppression of sadness in healthy children. This study represents the continuation of a fMRI study recently carried out by our group (Lévesque et al., 2003) in healthy women. In this recent investigation, we found that voluntary suppression of sadness was associated with significant loci of activation in the right OFC (Brodmann area – BA - 11) and right lateral prefrontal cortex (LPFC) (BA 9). Based on these findings and the corpus of knowledge above-mentioned concerning the neural substrate underlying the development of emotional self-regulation, we hypothesized *a priori* that various subdivisions of the PFC (LPFC, OFC, ACC, and medial PFC - MPFC) would be associated with voluntary suppression of sadness in children.

Methods

Subjects

Fourteen healthy Caucasian right-handed girls (mean age: 9.9; range: 8 - 10) took part in this study. None of these subjects presented a history of neurological or psychiatric disorders. According to the subjects' mothers, none of the subjects were pubescent. Their parents gave written inform consent and the study was approved by the ethics

committee of Centre hospitalier de l'Université de Montréal (CHUM), Hôpital Notre-Dame.

Behavioral procedures

Before the scanning session

To insure that all subjects would feel at ease with the scanning procedure, they first saw (several days before the actual experiment), with their parents and in the comfort of their homes, a videotape explaining in lay terms what is a MRI scanner and how it works. On the day of the experiment, the experimenter asked if the subjects (and their parents) had any question about this videotape. Afterwards, a detailed step-by-step explanation of the protocol was given to the subjects regarding their installation in the scanner and the equipment (goggles and headphones) that they would wear during scanning. Subjects were also presented with a numerical (analogue) rating scale ranging from 0 (absence of any emotional reaction) to 8 (strongest emotion ever felt in one's lifetime) used to evaluate the emotional state of the subjects during the experiment. To make sure that they understood the various emotional intensities represented by the numbers of the scale, the experimenter asked the subjects to rate from 0 to 8 five sad events having occurred lately in their life. Finally, in order to avoid as much as possible brain activation patterns due to anxiety or fear, only subjects who appeared and said feeling at ease with the scanning procedure were included in the study.

During the scanning session

Blood-oxygen level-dependent (BOLD) signal changes were measured during two experimental conditions, i.e., a Sadness condition and a Suppression condition. During both conditions, subjects first viewed four blocks of emotionally neutral film excerpts and, then, four blocks of sad film excerpts. As Garrett and Maddock (2001) have recently shown that the subjective emotional responses persist on average 32 sec after the presentation of aversive pictures before self-reported negative feelings show a 74-80% decline, this design was adopted to avoid contamination of the neutral stimuli by the sad stimuli. Each block lasted 48 sec and was separated by resting periods of 15 sec during which subjects viewed a blue cyan screen. The neutral and the sad film excerpts presented in the Sadness condition were equivalent but not identical to those presented in the Suppression condition. In the Sadness condition, subjects were instructed to react normally to the neutral as well as the sad film excerpts, that is, to allow themselves to feel sadness or any other emotions in response to these stimuli. In the Suppression condition, the subjects were asked to suppress as much as possible any emotion they might have with regard to the neutral or the sad film excerpts. More specifically, subjects were instructed to take a distance from the stimuli, that is, to become a detached observer. To ensure that the suppression strategy was properly understood, subjects were trained prior to the scanning session. Subjects were also instructed to look directly at both categories of stimuli. Sad film excerpts depicted the death of a beloved person, either a father, a mother, or a friend. Each scene contained either a child or two children, or a child and one or more adults. The emotionally neutral film excerpts were matched to the sad film excerpts with respect to the number and the gender of the individuals

involved. Emotionally neutral film excerpts depicted various human activities (e.g., interviews, carpentry, etc). Overall, a total of eight different sad film excerpts and eight different neutral film excerpts were used. Their utilization was counterbalanced across conditions and subjects, i.e., the sad and neutral film excerpts appeared as equally often in both conditions, and subjects saw each film excerpt (sad or neutral) only once. In addition, the order of presentation of the experimental conditions was counterbalanced across subjects. To assess the subjective responses of the subjects to the stimuli, immediately at the end of the run, they were asked to rate verbally - on a visual analog rating scale ranging from 0 (absence of any emotional reaction) to 8 (strongest emotion ever felt in one's lifetime) - the average intensity of sadness or of any other primary emotions (e.g., happiness, disgust, fear, anger, surprise (Plutchik, 1994) felt during the viewing of both categories of film excerpts. An average rating score was computed for the four blocks of sad film excerpts and the four blocks of emotionally neutral film excerpts. At the end of the scanning session, subjects were asked to complete a "strategy questionnaire" in which they described the emotion regulation strategies they used to inhibit the sad feelings generated by the sad stimuli. In this questionnaire, subjects were also asked to evaluate (in percentage) the degree to which they thought having succeeded in suppressing sad feelings during the Suppression condition.

Image acquisition

Echoplanar images (EPI) were acquired on a 1.5 Tesla system (Magnetom Vision, Siemens Electric, Erlangen, Germany). Twenty-eight slices (voxel size: 3.36 mm x 3.36 mm x 5 mm) were acquired every 3 sec (2.65 sec of acquisition time and 0.35 sec of

silence) in an inclined axial plane, aligned with the AC-PC axis. These T2* weighted functional images were acquired using an EPI pulse sequence (echo-spacing time = 0.8 ms, TE = 54 ms, Flip = 90°, FOV = 215 mm, Matrix = 64 x 64). Following functional scanning, high-resolution data were acquired via a Tl-weighted three-dimensional volume acquisition obtained using a gradient echo pulse sequence (TR = 9.7 ms, TE = 4 ms, Flip = 12° FOV = 250 mm, Matrix = 256 x 256).

Data were analyzed using Statistical Parametric Mapping software (SPM99, Wellcome Department of Cognitive Neurology, London, UK). Images for all subjects were realigned to correct for artifacts due to small head movements. The gradient-recalled echo-planar sequence that we used is associated with large static magnetic field inhomogeneities commonly found near air/tissue interfaces (Cordes et al., 2000). These inhomogeneities can create artifacts like signal loss and voxel shifts in the ventral frontal, medial temporal, and inferior temporal regions (Song, 2001). To correct for such artifacts, a mask was applied to the slices of the mean EPI image, which presented signal loss. This procedure was implemented for every subject. The images for all subjects were then spatially normalized into an MRI stereotactic space (Montreal Neurological Institute – MNI - template) using this masked mean image, and convolved in space with a three-dimensional isotropic gaussian kernel (12 mm FWHM) to improve the signal-to-noise ratio and to accommodate for residual variations in functional neuroanatomy that usually persist between subjects after spatial normalization.

The MNI template was used since Burgund and colleagues have recently shown (2002) that even if there are some small anatomical differences between the brain' structures and sulci of adults (age range: 18 – 30) and those of children (age range: 7-8), those differences do not compromise the usefulness of an adult stereotactic space for children's functional images.

Statistical analyses

The time series of the images were convolved with the delayed box-car function which approximates the activation patterns. Effects at each and every voxel were estimated using the general linear model. Voxel values for the contrasts of interest yielded a statistical parametric map of the t statistic (SPM *t*), subsequently transformed to the unit normal distribution, (SPM Z). For the Sadness condition, a "fixed-effects model" was implemented to contrast the brain activity associated with the viewing of the sad film excerpts and that associated with the viewing of the emotionally neutral film excerpts (Sadness - Neutral). To delineate the brain regions associated with voluntary suppression of sad feelings, a "fixed-effects model" was also implemented to compare the brain activity associated with the Sadness condition and that associated with the Suppression condition. To do so, the brain activity associated with viewing the sad film excerpts in the Sadness condition was directly subtracted from the brain activity associated with viewing the sad film excerpts in the Suppression condition. These "fixed-effects models" produced individual contrast images, which were used as raw data for the implementation of "random-effects models" (Friston and Frackowiack, 1997). An *a priori* search strategy was used and a small volume correction was performed in the

brain regions (ROIs) defined *a priori.* The search volume corresponding to the ROIs was defined *a priori* by tracing the neuroanatomical boundaries of these regions on the MR reference image (MNI template), using SVC and box volume function in SPM99. For this *a priori* search, a corrected probability threshold for multiple comparisons of $p < 0.05$ corrected was used (voxel-level statistics). Only clusters showing a spatial extent of at least 5 contiguous voxels were kept for image analysis. A whole-brain search was also carried out using SVC.

In the Sadness condition, the *a priori* search strategy encompassed the ventrolateral PFC (VLPFC) PFC (BA 47), MPFC (BA 9 and 10), ACC (affective division: rostral areas of BA 24a-c and 32, ventral areas of BA 25 and 33) (Bush et al., 2000), anterior temporal pole (BA21 and 38), insula, amygdala, hypothalamus, pons, and midbrain. These brain regions have been found activated on a more or less consistent basis in previous functional neuroimaging studies of sadness (Beauregard et al., 1998; Damasio et al., 2000; George et al., 1995; Lane et al., 1997; Lévesque et al., 2003; Pardo et al., 1993). In the Suppression condition, based on the results of previous studies recently carried out by our group (Beauregard et al., 2001; Lévesque et al., 2003) or by others (Hariri et al., 2003; Ochsner et al., 2002), the *a priori* search strategy included the LPFC (BA10), ACC (cognitive division) (BA 24b'-c' and 32', Bush et al., 2000), OFC (BA 11), and MPFC (BA 9 and 10).

Results

Self-report data

From a subjective perspective, the viewing of the sad film excerpts, in both the Sadness and Suppression conditions, induced a transient state of sadness in all subjects. The mean level of reported sadness was significantly higher in the Sadness condition (mean = 4.9, SD = 2.0, range: 2 - 8) than in the Suppression condition (mean = 3.2; SD = 2.3, range: 1 - 8) ($p < 0.01$). During both conditions, the viewing of the sad film excerpts did not induce other significant changes in the emotional state than sadness (Mean levels - Sadness condition: fear = 0.5 ; anger = 0 ; surprise = 0.5 ; happiness = 0 ; disgust = 0.9 ; Suppression condition: fear = 1.1; anger = 0.1 ; surprise = 0.4 ; happiness = 0.5 ; disgust = 0.6). In addition, viewing the emotionally neutral film excerpts did not generate any basic emotion. Finally, the strategy questionnaire completed at the end of the scanning session revealed that, in the Suppression condition, all subjects reported having succeeded in distancing themselves from the sad film excerpts, i.e., in becoming a detached observer. The mean suppression percentage reflecting the degree to which subjects thought having succeeded in suppressing sad feelings was 84 % (range: 40 - 100; SD: ± 21).

fMRI data

A priori search

Sadness condition: significant loci of activation were noted in the right VLPFC (BA 47) and, bilaterally, in the midbrain, anterior temporal pole (BA 21), and MPFC (BA 10) (Table 1 and Figure 1).

Suppression condition: significant loci of activation were seen, bilaterally, in the LPFC (BA 10), OFC (BA 11), MPFC (BA 10), and rostral ACC (BA 24). Significant loci of activation were also detected in the left LPFC (BA 9) and left VLPFC (BA 47) (Table 2 and Figure 2).

Whole-brain search

Sadness condition: significant loci of activation were observed in the right middle temporal gyrus (BA 21) and the superior temporal gyrus (BA 42), bilaterally (Table 1).

Suppression condition: significant loci of activations were detected in the right middle temporal gyrus (BA 37) (Table 2).

{Insert Table 1 about here}

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{Insert Figure 1 about here}

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Discussion

The goal of this study was to identify the neural circuitry underlying voluntary suppression of sadness in healthy children. This study comprised two experimental conditions: a Sadness condition and a Suppression condition. In the Sadness condition, the subjective experience of sadness was associated with significant loci of activation in the left VLPFC (BA 47), and in the midbrain, anterior temporal pole (BA 21) and MPFC

(BA 10), bilaterally. In the Suppression condition, when the brain activity associated with viewing the sad film excerpts in the Sadness condition was directly subtracted from the brain activity associated with viewing the sad film excerpts in the Suppression condition, significant loci of activation were found, bilaterally, in the LPFC (BA 9 and 10), OFC (BA 11), MPFC (BA 10), and rostral ACC (BA 24). A significant locus of activation was also noted in the left LPFC (BA 9).

Brain regions activated in the Sadness condition

The midbrain has been found activated in functional neuroimaging studies of several emotional states (e.g., disgust, sadness, anger, fear, happiness, pain and anxiety) (Fredrikson et al., 1995; Lane et al., 1997; Rauch et al., 1997; Tölle et al., 1999; Damasio et al., 2000). Various lines of evidence suggest that this cerebral structure is implicated in the mediation of autonomic responses such as skin conductance responses (Sequeira & Roy, 1993) and body temperature changes (Nagashima, et al., 2000). Given this, we propose that the bilateral midbrain activations noted during the Sadness condition reflected the autonomic responses associated with the subjects' sad feelings.

It has been claimed that the anterior temporal pole region is associated with imparting affective tone to the individual's experience (Mesulam, 1985). In the present context, it is possible that the bilateral activations of the anterior temporopolar region measured during the Sadness condition were related to the attribution of the emotional (sad) color to the participants' subjective experience.

An area of the MPFC close to that seen activated here, during the Sadness condition, has been postulated to be implicated in theory-of-mind tasks (Fletcher et al., 1995) and conscious representation of one's own emotional state (Reiman et al., 1997; Lane, 2000). It thus seems plausible that the MPFC activation seen in the Sadness condition reflected the awareness of the sad state from physiological and subjective aspects.

Activation of the VLPFC has been reported in adult subjects during externally and/or internally induced sadness (Pardo et al 1993; George et al 1995; Beauregard et al., 1998; Damasio et al., 2000), anger (Dougherty et al 1999; Kimbrell et al 1999), and anxiety (Fredrikson et al 1997; Kimbrell et al 1999). These findings indicate that the VLPFC participates in aspects of emotion processing that are not exclusively related to a specific primary emotion. Since this prefrontal cortical region receives extensive sensory inputs and limbic inputs from the amygdala, entorhinal/perirhinal cortices, and subiculum, it appears conceivable that the VLPFC activation noted during the Sadness condition was associated with the integration of viscerosensory information with information signalling changes in the subjects' emotional state.

Comparison with previous functional neuroimaging studies of emotional self-regulation

The present results are fairly consistent with those of previous fMRI studies of emotional self-regulation conducted either by our group or other research teams. In the

first of these studies (Beauregard et al., 2001), we found that sexual arousal induced by erotic film excerpts was associated with activation of the right amygdala, right anterior temporal pole, and hypothalamus. In addition, voluntary suppression of sexual arousal was associated with activation of the right LPFC (BA10) and right ACC (BA 32). The cognitive strategy adopted to modulate sexual arousal was identical to that used in the present investigation to regulate sadness. In another of these studies, Ochsner and colleagues (2002) have shown that the reappraisal of negative pictures (selected from the International Affective Picture System – IAPS - , Lang et al., 1998) was associated with activation of the dorsal and ventral regions of the left LPFC, as well as the dorsal MPFC. Of note, the increased activation of the ventral LPFC during reappraisal was correlated across subjects with decreased activation in the amygdala. Along the same lines, Hariri and co-workers (2003) demonstrated that whereas perceptual processing of threatening and fearful non-face (IAPS) stimuli was associated with a bilateral amygdala response, cognitive reappraisal of the same stimuli was associated with a reduction of this amygdala response and a concomitant increase in response of the right PFC and the ACC.

Recently, we have carried out a fMRI study in adult women using the same protocol and film excerpts than those utilized in the current investigation (Lévesque et al., 2003). The comparison of the two studies, from a phenomenological perspective, revealed that the differential between the subjective scores noted for the Sadness and Suppression conditions (Sadness minus Suppression) was significantly greater in women (Sad: 5.15, Suppression: 1.85) than in girls (Sadness: 4.9, Suppression: 3.2) ($p < 0.0001$).

Furthermore, even if the mean percentage reflecting the degree to which subjects estimated having succeeded in suppressing sad feelings was the same in both studies (i.e., 84%), it is of interest to note that the standard deviation was two-fold higher in girls than in women. Based on these self-report data, it is clear that voluntary suppression of sadness was more difficult in children than in adults.

From a functional neuroanatomical point of view, the voluntary suppression of sadness recruited more prefrontal cortical areas in girls than in women. Indeed, in girls, this task was associated with bilateral activation of the LPFC (BA 10), OFC (BA 11), MPFC (BA 10), rostral ACC (BA 24), as well as activation of the left LPFC (BA 9). In contrast, in women voluntary suppression of sadness was associated with activation of the right OFC (BA 11) and right LPFC (BA 9) (Lévesque et al., 2003). In addition, the spatial extent (in terms of the number of voxels) of the right LPFC activation was five-fold greater in children than in adults. Of note, when the brain activity associated with voluntary suppression of sadness in girls was subtracted from the brain activity associated with voluntary suppression of sadness in women, no significant loci of activation were found. In contrast, the converse subtraction revealed significant loci of activation in the LPFC (BA 10), MPFC (BA 10), rostral ACC (BA 24), and left LPFC (BA 9). These findings suggest that the voluntary suppression of a primary emotion, such as sadness, requires more prefrontal work in children than in adults. In agreement with this, it has been demonstrated that children show greater volume of PFC activity than adults when performing tasks requiring active maintenance and/or suppression of different types of information (e.g., Go/NoGo paradigm) (Casey et al., 1995; Cohen, et

al., 1994). Likewise, Tamm et al. (2002) found that children activated more extensively than young adults discrete regions of the PFC during a Go/NoGo task. Casey and colleagues have proposed that such differences may reflect maturational differences with respect to the PFC. In the present context, it appears reasonably fair to assume that conscious and voluntary self-regulation of emotion was more challenging cognitively and emotionally in children than in adults because the maturation of the prefronto-subcortical (limbic) connections is not completed before the end of adolescence.

Brain regions activated in the Suppression condition

The loci of activation noted in the VLPFC and MPFC, during the Suppression condition, were probably related to the residual sad feelings experienced by the subjects while they voluntarily attempted to suppress sadness, given that these "hot spots" were localized very close to those found in these prefrontal regions during the Sadness condition. The remaining brain regions activated in this condition suggest that a neural circuit encompassing the LPFC (BA 9 and 10), OFC (BA 11), and rostral ACC (BA 24) underlies voluntary suppression of sadness in children. The activation of the LPFC (in BA 9 and 10) fits rather nicely with the various lines of evidence suggesting that this prefrontal cortical region plays a pivotal role in the selection and control of behavioral strategies and action (Fuster, 1999), especially in the inhibition of inherent response tendency (Damasio, 1995; Frith and Dolan, 1996; Fuster, 1997; Goldman-Rakic, 1987), as well as in metacognition, i.e., the ability to monitor and control the information processing necessary to produce voluntary action (Flavell, 1979).

From a neural systemic point of view, the OFC is located at the junction of the prefrontal associative cortex and the limbic system. This prefrontal region has strong links with the LPFC, anterior temporal pole and insula, and it sends extensive projections to the amygdala, lateral hypothalamus, diencephalon, brain stem and spinal cord (Cavada, et al., 2000; Morecraft et al., 1992). Neuropsychological studies indicate that damage to the OFC leads to a *frontal lobe syndrome* (Silver & Yudofsky, 1987) or *pseudopsychopathic syndrome* (Stuss & Benson, 1984) that is characterized by distractibility, impulsivity, emotional outbursts, shallowness, argumentativeness, verbal and physical aggressiveness, lack of concern of consequences of behavior, failure to observe social and moral rules, and risky decision-making behavior. Interestingly, individuals with OFC lesions show abnormal autonomic responses to emotional elicitors, difficulty to experience emotion related to situations that would normally evoke emotion, and impaired understanding of the adverse consequences of detrimental social behaviors (Anderson et al., 1999; Damasio et al., 1990). These findings indicate that the OFC is crucially involved in the protection of goal-directed behaviors from interference (Casey et al., 1997; Fuster, 1999; Roberts & Wallis, 2000) and the regulation of socio-emotional behavior (Bechara et al., 1994; Cummings, 1993; Damasio, 1995; Damasio et al., 1990; Dolan, 1999; Elliott, 1990; Eslinger, 1999; Fuster, 1997; Giancola & Zeichner, 1994; Grafman & Litvan, 1999; Grafman et al., 1996; Lapierre et al., 1995; Mesulam, 1986; Zald & Kim, 1996). In the context of the present study, we propose that the OFC areas (BA 11) activated in the Suppression condition were involved in the inhibition of the physiological and subjective aspects of sadness associated with the neural activity in the midbrain, anterior temporal pole, MPFC (BA 10), and right VLPFC (BA 47).

By virtue of its anatomic connections with brain regions implicated in the modulation of autonomic and endocrine functions such as the OFC, the amygdala, hypothalamus, the periacqueductal gray, the dorsal motor nucleus of the vagus, and preganglionic sympathetic neurons in the intermediolateral cell column of the spinal cord (for a review, see Benes, 1997), the rostral-ventral subdivision of the ACC appears to play a key role in the regulation of the autonomic aspect of emotional responses (Bush et al., 2000; Devinsky et al., 1995; Vogt et al., 1992). Given this, we submit that the rostral ACC (BA 24) activation noted in the Suppression condition was related to the suppression of the autonomic and endocrine responses associated with the sad feelings.

Limitations of the present study

Lastly, we would like to mention some of the limitations of this study. First, no objective measures were collected regarding the developmental stage of the subjects from a neuroendocrine perspective. Second, no objective measures have been acquired before and immediately after the two experimental conditions to evaluate the subjects' emotional state. Instead, self-report ratings were used. Since self-report data are extremely susceptible to bias, a more objective measure would have definitely reinforced the results of this study, even though the results in the Suppression condition were in keeping with our predictions and the literature. Third, we could not verify that the subjects have effectively performed the suppression task the way they were requested to. At the end of the Suppression condition, subjects were asked to report if they have had difficulty performing the suppression task, what strategy they used to suppress sadness,

and if they were witnessing internal speech while doing this task. Nobody reported performing another task or being distracted during the Suppression condition. Again, as we had no objective means to verify subjects' assertions, we relied on their honesty to interpret the results.

In conclusion, the present fMRI study demonstrated that conscious and voluntary suppression of sadness in healthy girls was associated with bilateral activation of the LPFC (BA 10), OFC (BA 11), MPFC (BA 10), and rostral ACC (BA 24), as well as activation of the left LPFC (BA 9). In an identical study previously conducted by our group in adult women (Lévesque et al., 2003), the same task was associated with activation of the right OFC (BA 11) and right LPFC (BA 9) In addition, the spatial extent of the right LPFC activation was five-fold greater in children than in adults. These differences indicate that the voluntary suppression of sadness demands more prefrontal work in children than in adults. In line with this, conscious and voluntary self-regulation of emotion may be more challenging cognitively and emotionally in children than in adults because the maturation of the prefronto-subcortical (limbic) connections is not completed before the end of adolescence.

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References

1. Anderson, S.W., Bechara, A., Damasio, H., Tranel, D., and Damasio, A.R., 1999. Impairment of social and moral behavior related to early damage in human prefrontal cortex. Nature Neuroscience, 11, 1032-1037.

2. Beauregard, M., Leroux, J.-M., Bergman, S., Arzoumanian, S., Beaudoin, G., Bourgouin, P., Stip, E., 1998. The functional neuroanatomy of major depression: an fMRI study using an emotional activation paradigm. NeuroReport 9, 3253-3258.

3. Beauregard, M., Lévesque, J., Bourgouin, P., 2001. Neural correlates of the conscious self-regulation of emotion. J Neurosci, RC 21: 1-6.

4. Bechara, A., Damasio, A.R., Damasio, H., and Anderson, S.W., 1994. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition, 50, 7-1

5. Benes, F., 1997. Corticolimbic circuitry and the development of psychopathology during childhood and adolescence, in: N.A. Krasnegor, G. Reid Lyon, and P.S. Goldman-Rakic (Eds.), Development of the Prefrontal Cortex. Paul H. Brookes Publishing Co., Inc., Baltimore, MD pp.211-240.

6. Bourgeois, J.-P., Goldman-Rakic, P.S., and Rakic, P., 1994. Synaptogenesis in the prefrontal cortex of rhesus monkeys. Progress in Brain Research, 102, 227-43.

7. Bunge, S. A., Dudukovic, N.M., Thomason, M.E., Vaidya, C.J., Gabrieli, J.D. 2002. Immature frontal lobe contributions to cognitive control in children: evidence from fMRI. Neuron, 33, 301-11.

8. Burgund, E.D., Kang, H.C., Kelly, J.E., Buckner, R.L., Snyder, A.Z., Petersen, S.E., and Schlaggar, B.L., 2002. The feasibility of a common stereotactic space for children and adults in fMRI studies of development. Neuroimage 17, 184-200.

9. Bush, G., Luu, P., and Posner, M.I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends in Cognitive Science, 4, 215-222.

10. Calkins, S.D. *in press.* Temperament and emotional regulation: Multiple models of early Development in: Beauregard, M. (Ed.), Consciousness, emotional self-regulation and the brain, John Benjamins Publishing Company, Amsterdam/Philadelphia.

11. Calkins, S.D. 1994. Origins and outcomes of individual differences in emotional regulation in Fox, N.A. (Ed.), *Emotion regulation: Behavioral and biological considerations,* Monographs of the Society for Research in Child Development.

12. Casey, B.J., Giedd, J.N., Thomas, K.M. 2000. Structural and functional brain development and its relation to cognitive development. Biol Psychol., 54, 241-57.

13. Casey, B.J., Castellanos, F.X., Giedd, J.N., Marsh, W.L., Hamburger, S.D., Schubert, A.B., Vauss, Y.C., Vaituzis, A.C., Dickstein, D.P., Sarfatti, S.E., and Rapaport, J.L., 1997. Implication of right frontostriatal circuitry in response suppression and attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 36, 374-83.

14. Casey, B.J., Cohen, J.D., Jezzard, P., Turner, R., Noll, D.C., Trainor, R.J., Giedd, J., Kaysen, D., Hertz-Pannier, L., and Rapoport, J.L., 1995. Activation of prefrontal cortex in children during a nonspatial working memory task with functional MRI. Neuroimage 2, 221-9.

15. Cavada, C., Company, T., Tejedor, J., Cruz-Rizzolo, R.J., Reinoso-Suarez, F., 2000. The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb Cortex 10, 220-42.

16. Caviness, V.S. Jr., Kennedy, D.N., Richelme, C., Rademacher, J., and Filipek, P.A., 1996. The human brain age 7-11 years: a volumetric analysis based on magnetic resonance images. Cerebral Cortex 6, 726-36.

17. Cohen, J.D., Forman, S.D., Braver, T.S., Casey, B.J., Servan-Schreiber, D., and Noll, D.C., 1994. Activation of prefrontal cortex in a nonspatial working memory task with functional MRI. Human Brain Mapping 1, 293-304.

18. Cole, P.M., Michel, M.K., and Teti, L.O., 1994. The development of emotion regulation and dysregulation: a clinical perspective. Monograph of the Society for Research on Child Development, 59, 73-100.

19. Cordes, D, Turski, P.A., Sorenson, J.A., 2000. Compensation of susceptibility-induced signal loss in echo-planar imaging for functional applications. Mag Res Imaging 18, 1055-1068.

20. Cummings, J.L., 1993. Frontal-subcortical circuits and human behavior. Archives of Neurology 50, 873-880.

21. Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L.L., Parvizi, J., Hichwa, R.D., 2000. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nature Neurosci 3, 1049-56.

22. Damasio, A.R., 1995. On some functions of the human prefrontal cortex. Annals of the New York Academy of Sciences 769, 241-251.

23. Damasio, A.R., Tranel, D., and Damasio, H., 1990. Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. Behavioural Brain. Research 41, 81-94.

24. Devinsky, O., Morrell, M.J., and Vogt, B.A., 1995. Contributions of anterior cingulate cortex to behaviour. Brain 118, 279-306.

25. Dolan, R.J., 1999. On the neurology of morals. Nature Neuroscience 11, 927-929.

26. Dougherty, D.D., Shin, L.M., Alpert, N.M., Pitman, R.K., Orr, S.P., Lasko, M., Macklin, M.L., Fischman, A.J., Rauch, S.L., 1999. Anger in healthy men: a PET study using script-driven imagery. Biol Psychiatry 4, 466-72.

27. Elliott, F.A., 1990. Neurology of aggression and episodic dyscontrol. Seminars in Neurology 10, 303-312.

28. Eslinger, P.J., 1999. Orbital frontal cortex: behavioral and physiological significance (Part II). Neurocase 5, 299-300.

29. Eslinger, P.J., Biddle, K.R., and Grattan, L.M., 1997. Cognitive and social development in children with prefrontal cortex lesions, in: N.A. Krasnegor, G. Reid Lyon, and P.S. Goldman-Rakic (Eds.), Development of the Prefrontal Cortex. Paul H. Brookes Publishing Co., Inc., Baltimore, MD pp.295-335.

30. Flavell, J.H., 1979. Metacognition and cognitive monitoring: A new area of cognitive development inquiry. American Psychologist 34, 906-911.

31. Fletcher, P.C., Happe, F., Frith, U., Dolan, R.J., Frackowiak, R.S., and Frith, C. D., 1995. Other minds in the brain: a functional imaging study of ''theory of mind'' n story comprehension. Cognition 57, 109-128.

32. Fox, N.A., Henderson, H.A., and Marshall, P.J., 2001. The biology of temperament: An integrative approach, in: C. A. Nelson & Luciana, M. (Eds.), Handbook of Developmental Cognitive Neuroscience. MIT Press, Cambridge, Mass., pp. 631-645.

33. Fredrikson, M., Fischer, H., and Wik, G., 1997. Cerebral blood flow during anxiety provocation. Journal of Clinical Psychiatry 58 (suppl. 16), 16-21.

34. Fredrikson, M., Wik, G., Fischer, H., Anderson, J., (1995). Affective and attentive neural networks in human: A PET study of Pavlovian conditioning. NeuroReport 7, 97-101.

35. Friston, K.J. and Frackowiak, R.S.J., 1997. Images of the future: a philosophical coda, in: Frackowiak, R. S. J., Friston, K. J., Dolan, R. J. and Mazziotta, J. C. (Eds.), uman Brain Function. Academic Press, San Diego, pp. 487-517.

36. Frith, C., Dolan, R. 1996. The prefrontal cortex in higher cognitive functions. Cogn Brain Res *5*,175-181.

37. Fuster, J.M., 1999. Synopsis of function and dysfunction of the frontal lobe. Acta Psychiatrica Scandinava 99, 51-57.

38. Fuster, J.M., 1997. The Prefrontal Cortex: Anatomy, Physiology and Neuropsychology of the Frontal Lobe. 3rd edition. Lippincott-Raven, Philadelphia, PA.

39. Garrett, A.S., and Maddock, R.J. 2001. Time course of the subjective emotional response to aversive pictures: relevance to fMRI study. Psychiatry Research: Neuroimaging section 108, 39-48.

40. George, M.S., Ketter, T.A., Parekh, P.I., Horwitz, B., Herscovitch. P., Post, R.M., 1995. Brain activity during transient sadness and happiness in healthy women. Am J Psychiatry 152, 341-51.

41. Giancola, P. R. and Zeichner, A., 1994. Neuropsychological performance on tests of frontal-lobe functioning and aggressive behavior in men. Journal of Abnormal Psychology 103, 832-835.

42. Goldman-Rakic, P.S., 1987. Circuitry of primate prefrontal cortex and regulation of behavior by representational memory, in: Mountcastle, V. B., Plum, F., and Geiger, S. R. (Eds.), Handbook of Physiology. American Physiological Society, Bethesda, MD, pp. 373-417.

43. Grafman, J. and Litvan, I., 1999. Importance of deficits in executive functions. Lancet 354, 1921-1923.

44. Grafman, J., Schwab, K., Warden, D., Pridgen, A., Brown, H. R., and Salazar, A. M., 1996. Frontal lobe injuries, violence, and aggression: a report of the Vietnam Head Injury Study. Neurology 46, 1231-1238.

45. Gross, J.J., 1999. Emotion regulation: past, present, future. Cognition and Emotion, 13, 551-573.

46. Hariri, A.R., Mattay, V.S., Tessitore, A., Fera, F., and Weinberger, D.R., 2003. Neocortical modulation of the amygdala response to fearful stimuli. Biological Psychiatry 53, 494-501.

47. Huttenlocher, P.R., 1994. Synaptogenesis, synapse elimination, and neural plasticity in human cerebral cortex, in: C. A. Nelson (Ed.), Threats to optimal development: Integrating, biological, psychological, and social risk factors. Lawrence Erlbaum Associates Minnesota Symposia on Child Psychology, Hillsdale, NJ, Vol. 27, pp. 35-54.

48. Kimbrell, T.A., George, M.S., Parekh, P.I., Ketter, T.A., Podell, D.M., Danielson, A.L., Repella, J.D., benson, B.E., Willis, M.W., Herscovitch, P., and Post, R.M., 1999. Regional brain activity during transient self-induced anxiety and anger in healthy adults. Biol Psychiatry 46, 454-65.

49. Kochanska, G., Murray, K., and Coy, K.C., 1997. Inhibitory control as a contributor to conscience in childhood: from toddler to early school age. Child Development, 68, 263-77.

50. Kopp, C. (1982). Antecedents of self-regulation: A developmental perspective. *Developmental Psychology, 18,* 199-214.

51. Lane, R.D., 2000. Neural correlates of conscious emotional experience, in: Lane, R.D. and Nadel, L, (Eds.), Cognitive neuroscience of emotion. Oxford University Press, New York, pp. 345-370.

52. Lane, R.D., Reiman, E.M., Ahern, G.L., Schwartz, G.E., Davidson, R.J., 1997. Neuroanatomical correlates of happiness, sadness, and disgust. Am J Psychiatry 154, 926-33.

53. Lang, P.J., Bradley, M.M., and Cuthbert, B. N., 1998. Emotion and motivation: measuring affective perception. Journal of Clinical Neurophysiology 15, 397-408.

54. Langston, C.A., 1994. Capitalizing on and coping with daily-life events: Expressive responses to positive events. Journal of Personality and Social Psychology 67, 1112-1125.

55. Lapierre, D., Braun, C.M.J., and Hodgings, S., 1995. Ventral frontal deficits in psychopathy: neuropsychological test findings. Neuropsychologia 33, 139-151.

56. Levenson, C., A., 1994. Human emotion: a functional view, in: Ekman, P. & Davidson, R. J. (Eds.), Fundamental questions about the nature of emotion, Oxford University Press, New York, pp. 123-126.

57. Lévesque, J., Eugène, F., Joanette, Y., Paquette, V., Mensour, B., Beaudoin, G., Leroux, J.-M., Bourgouin, P. & Beauregard, M., 2003. Neural circuitry underlying voluntary self-regulation of sadness. Biological Psychiatry 53, 502-510.

58. Masters, J.C., 1991. Strategies and mechanisms for the personal and social control of emotion, in: Garber, J. & Dodge K. A., (Eds.), The development of emotion regulation and dysregulation. University Press, Cambridge, U.K, pp. 182-207.

59. Mesulam, M.-M., 1986. Frontal cortex and behavior. Annals of Neurology 19, 320-325.

60. Mesulam, M.-M., 1985. Patterns in behavioural neuroanatomy: Association areas, the limbic system, and hemispheric specialization, in: Mesulam M-M (ed.), Principles of behavioral neurology. F.A. Davis Company, Philadelphia, pp 1-70.

61. Morecraft, R.J., Geula, C., Mesulam, M.M., 1992. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. J Comp Neurol 323, 341-58.

62. Nagashima, K., Nakai, S., Tanaka, M., Kanosue, K., 2000. Neuronal circuitries involved in thermoregulation. Auton Neurosci 85, 18-25.

63. Ochsner, K.N., Bunge, S. A., Gross, J.J., and Gabrieli, J.D., 2002. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. Journal of Cognitive Neuroscience 14, 1215-29.

64. Pardo, J.V., Pardo, P.J., Raichle, M.E., 1993. Neural correlates of self-induced dysphoria. Am J Psychiatry 150, 713-9.

65. Parrott, W.G., 1993. Beyond hedonism: Motives for inhibiting good moods and for maintaining bad moods, in: Wegner, D. M. & Pennebaker J. W. (Eds.), Handbook of mental control. Prentice-Hall, Englewood Cliffs, pp. 278-308.

66. Pfefferbaum, A., Mathalon, D.H., Sullivan, E.V., Rawles, J.M., Zipursky, R.B., and Lim, K. O., 1994. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. Archives of Neurolog, 51, 874-87.

67. Plutchik, R., 1994. The psychology and biology of emotion (New York: Harper Collins).

68. Posner, M.I., and Rothbart, M.K. 1998. Attention, self-regulation and consciousness. Philos Trans R Soc Lond B Biol Sci., 353, 1915-27.

69. Rakic, P., Bourgeois, J.P., Goldman-Rakic, P.S., 1994. Synaptic development of the cerebral cortex: implications for learning, memory, and mental illness. Progress in Brain Research 102, 227-43.

70. Rauch, S.L., Savage, C.R., Alpert, N.M., Fischman, A.J., and Jenike, M.A., 1997 .The functional neuroanatomy of anxiety: A study of three disorders using positron emission tomography and symptom provocation. Biol Psychiatry 42, 446-452.

71. Reiman, E.M., 1997. The application of positron emission tomography to the study of normal and pathologic emotions. J Clin Psychiatry 58, 4-12.

72. Roberts, A.C., and Wallis, J.D., 2000. Inhibitory Control and Affective Processing in the prefrontal Cortex: Neuropsychological Studies in the common Marmoset. Cerebral Cortex 10, 252-262.

73. Sequeira, H., Roy, J.-C., 1993. Cortical and hypothalamo-limbic control of electrodermal responses, in: Roy J.-C., Boucsein W., Fowles, D., Gruzelier,J. (Eds.), Progress in electrodemal research. Plenum, New York, pp.93-114.

74. Silver, J.M., and Yudofsky, S.C., 1987. Aggressive behavior in patients with neuropsychiatric disorders. Psychiatric Annals 17, 367-370.

75. Song, A.W., 2001. Single-shot EPI with signal recovery from the susceptibility-induced losses. Mag Reson Med 46, 407-411.

76. Sroufe, A. L. (1996). Emotional development: The organization of emotional life in the early years. New York, NY: Cambridge University Press.

77. Stuss, D.T. 1992. Biological and psychological development of executive functions. Brain and Cognition, 20, 8-23.

78. Stuss, D.T., and Benson, D.F. 1986. The frontal lobes. New York: Raven Press.

79. Talairach, J., Tournoux, P., 1988. Co-planar stereotaxic atlas of the human brain. Thieme Medical, Stuttgart.

80. Tamm, L., Menon, V., and Reiss, A., L., 2002. Maturation of Brain Function Associated With Response Inhibition. Journal of the American Academy of Child & Adolescent Psychiatry 41, 1231-1238.

81. Thompson, R.A., 1990. Emotion and self-regulation, in: Thompson, R.A. (Ed.), Socioemotional Development: Nebraska Symposium on Motivation. University of Nebraska Press, Lincoln, Neb, pp. 367-467.

82. Tölle, T.R., Kaufmann, T., Siessmeier, T., Lautenbacher, S., Berthele, A., Munz, F., Zieglgansberger, W., Willoch, F., Schwaiger, M., Conrad, B., and Bartenstein, P., 1999. Region-specific encoding of sensory and affective components of pain in the human brain: A positron emission tomography correlation analysis. Ann of Neurology 45, 40-47.

83. Tooby, J., and Cosmides, L., 1990. On the universality of human nature and the uniqueness of the individual: the role of genetics and adaptation. Journal of Personality, 58, 17-67.

84. Vogt, B.A., Finch, D.M., and Olson, C.R., 1992. Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. Cerebral Cortex 2, 435-43.

85. Yakovlev, P.I. and Lecours, A.R., 1967. The myelogenetic cycles of regional maturation of the brain, in: Mankowsi, A. (Ed.), Regional Development of the Brain in Early Life. Davis, Philadelphia, pp. 3-69.

86. Zald, D.H. and Kim, S.W., 1996. The anatomy and function of the orbito-frontal cortex I: Anatomy, neurocircuitry, and obsessive-compulsive disorder. Journal of Neuropsychiatry and Clinical Neuroscience 8, 125-138.

Figure caption

Figure 1. Statistical activation maps for the brain regions defined *a priori* during the Sadness condition. Images are sagittal sections for the data averaged across subjects. Significant loci of activation were noted in a) the right MPFC (BA 10) and right midbrain, b) the left MPFC (BA 10) and left midbrain, c) the right VLPFC (BA 47) and right anterior temporal pole (BA 21), and d) the left anterior temporal pole (BA 21).

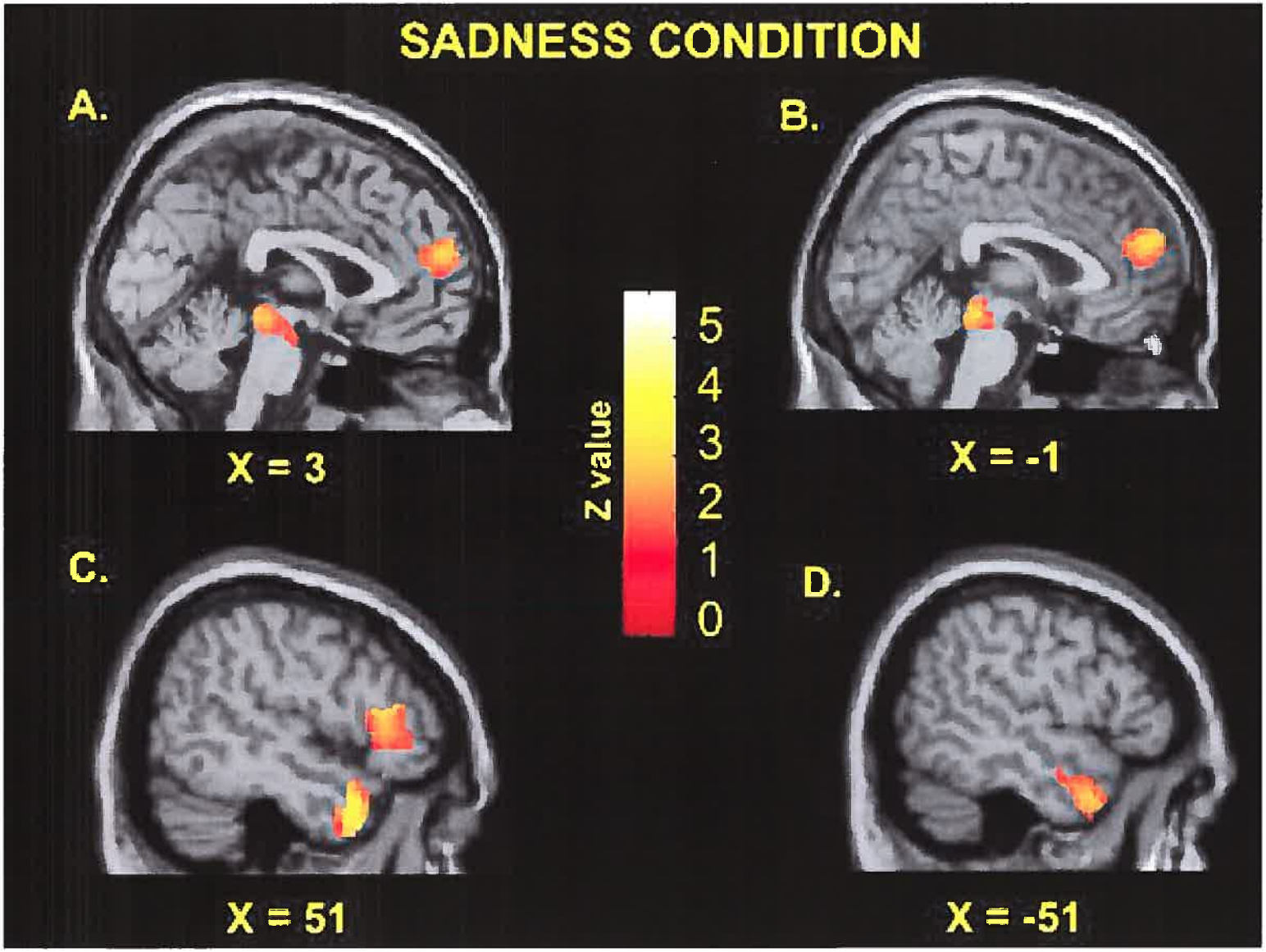
SADNESS CONDITION
A.
B.
X = 3
X = -1
Z value
5
4
3
2
1
0
C.
D.
X = 51
X = -51

Figure caption

Figure 2. Statistical activation maps during the Suppression condition. Significant loci of activation were observed in a) the left OFC (BA 11), left MPFC (BA 10), and left ACC (BA 24), b) the right OFC (BA 11), right MPFC (BA 10), and right ACC (BA 24), c) the left OFC (BA 11) and left LPFC (BA 10), and d) the right OFC (BA 11) and right LPFC (BA 10).

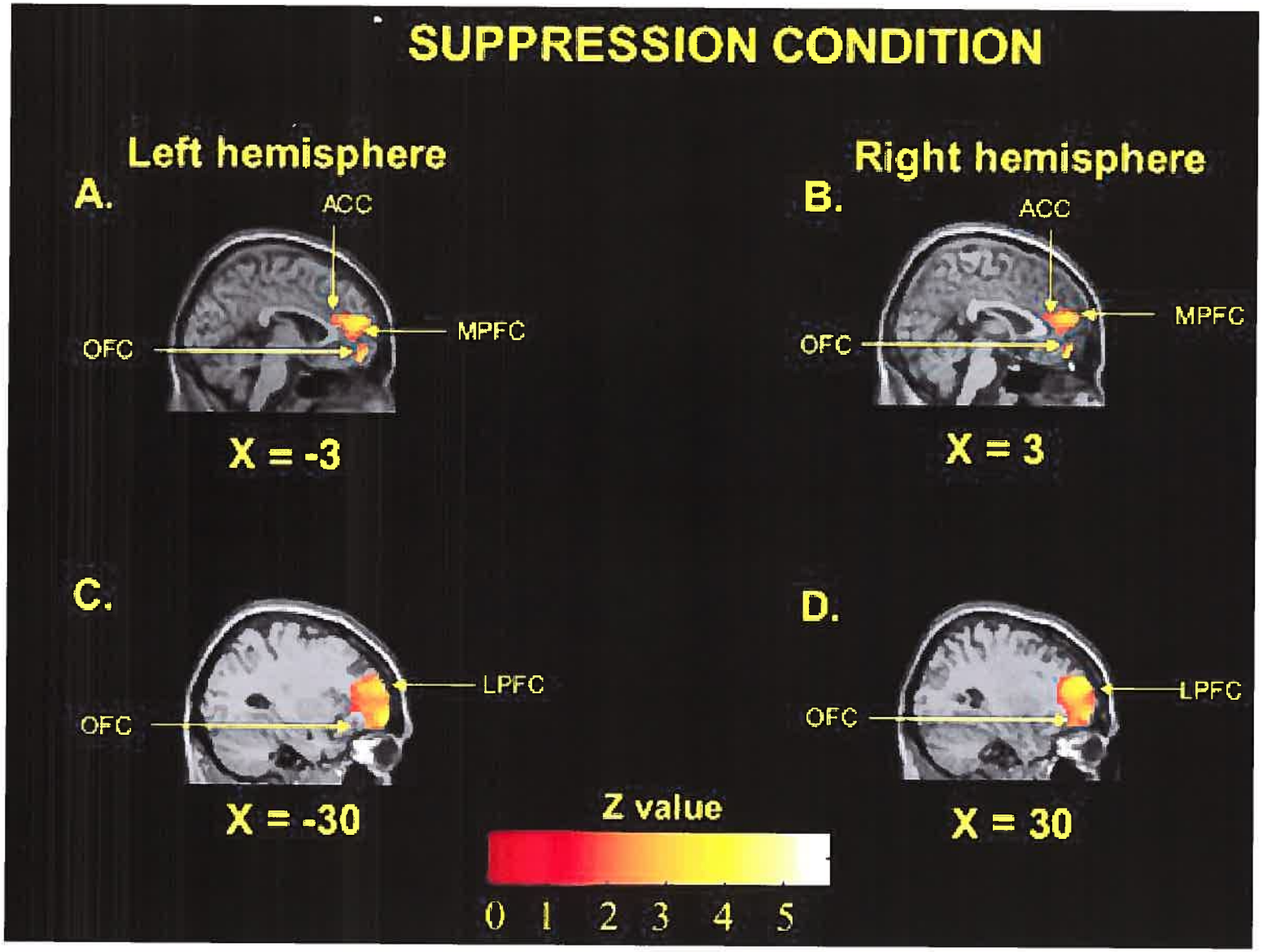
SUPPRESSION CONDITION
Left hemisphere
A.
ACC
OFC
MPFC
X = -3
Right hemisphere
B.
ACC
OFC
MPFC
X = 3
C.
LPFC
OFC
X = -30
D.
LPFC
OFC
X = 30
Z value
0 1 2 3 4 5

Table 1. Significant loci of activation in the Sadness condition

	Talairach coordinates (mm)							
	Region	Brodmann area	x	y	z	Z-statistic	Corrected p value	Voxels #
A priori search	R Anterior temporal pole	21	50	7	-26	3.65	$p < 0.002$	34
	R MPFC	10	3	56	17	3.13	$p < 0.014$	17
	R Midbrain		3	-30	-9	3.06	$p < 0.019$	79
	L MPFC	10	-1	57	-15	2.96	$p < 0.022$	35
	L Anterior temporal pole	21	-50	4	-28	2.84	$p < 0.023$	39
	L Midbrain		-3	32	-8	2.82	$p < 0.037$	75
	R VLPFC	47	3	56	17	2.57	$p < 0.002$	42
Whole-brain search	R Middle temporal gyrus	21	51	-21	-6	4.61	$p < 0.05$	15
	R Superior temporal gyrus	42	51	-39	11	5.73	$p < 0.05$	112
	L Superior temporal gyrus	42	-51	-51	12	4.75	$p < 0.05$	20

Stereotaxic coordinates are derived from the human atlas of Talairach and Tournoux (1988) and refer to medial - lateral position (x) relative to midline (positive = right), anterior - posterior position (y) relative to the anterior commissure (positive = anterior), and superior – inferior position (z) relative to the commissural line (positive = superior). Designation of Brodmann areas for cortical areas is also based on this atlas. L, left; R, right.

Table 2. Significant loci of activation in the Suppression condition

		Talairach coordinates (mm)						
	Region	Brodmann area	x	y	z	Z - statistic	Corrected p value	Voxels #
Search volume defined a priori	R LPFC	10	29	52	13	4.42	$p < 0.001$	101
	L OFC	11	-18	48	-18	4.16	$p < 0.001$	13
	L LPFC	10	-30	57	-10	4.07	$p < 0.001$	98
	L Gyrus rectus	11	-3	54	-15	3.69	$p < 0.001$	5
	L MPFC	10	-3	53	14	3.68	$p < 0.001$	33
	R OFC	11	30	55	-12	3.61	$p < 0.005$	35
	R Gyrus rectus	11	3	54	-18	3.59	$p < 0.001$	5
	R MPFC	10	3	55	13	3.54	$p < 0.004$	22
	L LPFC	9	-42	36	26	3.20	$p < 0.033$	200
	L VLPFC	47	-18	5	-10	3.18	$p < 0.009$	90
	L ACC	24	-3	36	18	2.78	$p < 0.002$	21
	R ACC	24	6	34	14	2.65	$p < 0.004$	14
Whole-brain search	R Middle temporal gyrus	37	54	-54	0	5.82	$p < 0.05$	66

As in Table 1.

Chapitre 5

DISCUSSION GÉNÉRALE

Le principal objectif des travaux présentés dans cette thèse était, d'une part, d'étudier les soubassements neurobiologiques de l'autorégulation émotionnelle chez l'adulte et l'enfant sains et, d'autre part, d'identifier les corrélats neuronaux sous-tendant l'expérience subjective de la tristesse chez l'enfant sain. En ce qui a trait à l'autorégulation émotionnelle, une étude récente d'IRMf (Beauregard et *al.* 2001) a mis en évidence l'implication de certaines structures préfrontales et limbiques/para-limbiques dans la suppression d'un état émotionnel positif (l'excitation sexuelle) chez des sujets masculins, confirmant ainsi l'hypothèse préfronto-limbique proposée antérieurement par divers groupes de chercheurs intéressés par cette question. Puis, une étude subséquente d'IRMf (Ochsner et *al.* 2002) a montré que ce circuit préfronto-limbique était également associé à l'autorégulation (maintien et suppression) d'un affect de valence négative.

Aucune étude n'avait jusqu'à présent tenté d'identifier les régions cérébrales associées à la suppression de l'expérience subjective d'une émotion primaire négative, tant chez l'adulte que chez l'enfant. Dans cette perspective, les études qui composent cette thèse ont été menées dans le but spécifique d'identifier les corrélats neuronaux de la suppression de la tristesse chez les femmes (Article #1) et les jeunes filles (Article #3). Ce faisant, nous avons également examiné les corrélats neuronaux de la tristesse chez ce dernier groupe de sujets (Article #2).

Cette discussion générale se subdivisera en cinq sections. D'abord, un rappel des principaux résultats obtenus au cours de chacune de ces études sera fait. Puis, les résultats concernant le substrat neuroanatomique fonctionnel de la tristesse chez l'enfant seront

présentés et discutés. Par la suite, les résultats ayant trait à l'autorégulation émotionnelle seront comparés aux résultats des études antérieures. Dans la section suivante, nous porterons notre attention sur les aspects différenciant la suppression de la tristesse chez les femmes et les filles. Enfin, la dernière section, davantage spéculative, portera sur la capacité d'autodétermination et l'interaction esprit – cerveau en relation avec l'autorégulation consciente et volontaire des émotions.

1. Bref rappel des résultats

1.a. Soubassements neurobiologiques de la tristesse chez l'enfant sain.

En ce qui a trait aux résultats obtenus chez les enfants, la première partie de la deuxième étude rapportée dans l'article #2 intitulé "***Neural correlates of sad feelings in healthy girls***", a permis de mettre en évidence que, tel que proposé par la TDE, les régions cérébrales associées à l'expérience subjective de la tristesse vécue chez les jeunes filles sont comparables à celles associées à l'expérience subjective de la tristesse chez les femmes. À ce sujet, une augmentation significative du signal BOLD fut notée au niveau de certaines régions limbique (le mésencéphale) et para-limbiques (pôle temporal antérieur - AB 21, cortex préfrontal médian - AB 10, cortex préfrontal ventrolatéral - AB 47). Fait à noter, tandis que toutes ont rapporté avoir vécu la tristesse, certaines d'entre elles ont même versé quelques larmes pendant l'étude. Toutefois, pris dans leur ensemble, les résultats subjectifs ayant trait à l'intensité moyenne de la tristesse ressentie étaient comparables aux résultats observés chez les femmes.

1.b. Neuroanatomie fonctionnelle de la suppression de la tristesse chez l'enfant et l'adulte sains

L'hypothèse voulant qu'un circuit préfronto-limbique sous-tende la suppression volontaire de la tristesse chez des sujets adultes sains a été confirmée, tel que rapporté dans l'article #1 intitulé "***Neural circuitry underlying the voluntary suppression of sadness***". Rappelons d'abord que d'un point de vue phénoménologique, les sujets ont tous vécu l'expérience subjective de la tristesse lors de la Condition *Tristesse*, et que cette expérience était significativement plus intense que lors de la condition *Suppression*. De plus, tel qu'anticipé, des régions du cortex préfrontal, à savoir le cortex orbitofrontal (AB 11) et le cortex préfrontal latéral (AB 9), ont été impliquées dans la suppression de la tristesse tandis que des régions limbiques (amygdale et mésencéphale) et para-limbiques (insula, pôle temporal antérieur, cortex préfrontal ventrolatéral – AB - 47) ont été associées à l'expérience subjective de la tristesse. Comme lors de la première étude réalisée par notre groupe, les activations limbiques présentes dans la condition *Tristesse* avaient complètement disparues lors de la condition Suppression. Toutefois en utilisant un seuil statistique très permissif de $p < 0.05$ non corrigé, une activation résiduelle a été notée au niveau du cortex préfrontal ventrolatéral (AB 47). Aussi, lors d'analyses corrélationnelles effectuées *a posteriori*, une corrélation positive a été établie entre l'intensité de la tristesse ressentie par les sujets lors de la condition *Tristesse* et l'intensité du signal BOLD dans le cortex préfrontal ventrolatéral (AB 47), la partie affective du cortex cingulaire antérieur (AB 24/32) et l'insula. Par ailleurs, au cours de la condition *Suppression*, une corrélation positive a également été trouvée entre l'intensité de la

tristesse ressentie par les sujets et l'intensité du signal BOLD au niveau du cortex orbitofrontal (AB 11) et du cortex préfrontal latéral (AB 9).

En regard de la seconde partie de la deuxième étude présentée dans l'article intitulé "***Neural bases of emotional self-regulation in childhood*** " (Article #3), les résultats ont permis de confirmer qu'un circuit comprenant différentes régions du cortex préfrontal et du système limbique/para-limbique sous-tendait la suppression de la tristesse. Parallèlement à ce qui a été noté chez les adultes, les résultats ont révélé que l'expérience subjective de la tristesse était significativement plus intense lors de la condition *Tristesse* que lors de la condition *Suppression*. Également, les régions activées lors de la condition *Suppression* ont été nombreuses et incluaient le cortex préfrontal latéral (AB 9 et 10), le cortex orbitofrontal (AB 11), le cortex préfrontal médian (AB 10), le cortex cingulaire antérieur (AB 24) ainsi que le cortex préfrontal ventrolatéral (AB 47).

2. Soubassements neurobiologiques de l'expérience subjective de la tristesse chez l'enfant

Mis en relation avec les études précédentes d'imagerie cérébrale visant à identifier le substrat neuroanatomique fonctionnel de la tristesse chez l'adulte (George et *al.* 1995; Lane et *al.* 1997; Beauregard et *al.* 1998; Damasio et *al.* 2000), les résultats de notre étude (Article #2) ont montré que les corrélats neuronaux de la tristesse observés chez les enfants sont comparables à ceux identifiés chez des adultes. Par ailleurs, lorsque comparés aux résultats de notre étude d'IRMf menée chez des femmes en utilisant le même paradigme expérimental (Lévesque et *al.* 2003), les résultats obtenus chez les

jeunes filles ont permit de conclure que les soubassements neurobiologiques sous-tendant l'expérience subjective de la tristesse chez ces sujets étaient passablement similaires, bien que non identiques, chez les femmes et les jeunes filles. À cet égard, nous avons fait valoir que les différences observées pouvaient être attribuées à une certaine variabilité inter-individuelle en terme de neuroanatomie fonctionnelle sous-tendant la tristesse (Eugène et *al.* 2003) ainsi qu'à des différences inter-sujets sur le plan de la personnalité (Sugiura et *al.* 2000).

Cette similitude vient appuyer la TDE qui prétend que les corrélats neuronaux des émotions primaires ont une assise biologique (Izard, 1992). Selon cette théorie, seule la composante « cognition » de l'émotion se développe et permet l'apparition d'émotions secondaires telles que la honte, la fierté et la culpabilité. En ce qui a trait à l'expérience subjective des émotions, la TDE assume qu'elle découle directement du substrat neurobiologique sous-tendant les émotions, que ce substrat est présent et fonctionnel peu après la naissance et que, par conséquent, l'expérience subjective de l'émotion ne se développe pas. Cette dernière assomption ne fait pas l'unanimité dans le domaine du développement des émotions et d'aucuns argumentent que d'autres facteurs tels que la culture (Mesquita & Frijda, 1992; Briggs, 1970) et l'environnement social (Dickson et *al.*1998) influencent le développement des émotions, y compris sa dimension subjective. En tenant compte de ces différentes positions, et sur la base des résultats de notre étude d'IRMf, il nous semble raisonnable de penser que le développement des émotions et la nature de l'expérience émotionnelle sont influencés à la fois par le développement cognitif, l'environnement social et la culture, qui tous influencent l'activité neuronale des

différentes régions cérébrales impliquées dans les divers aspects (cognitifs, physiologiques, expérientiels et comportementaux) de l'émotion.

3. Comparaison neuroanatomique fonctionnelle de la suppression de la tristesse chez les femmes et les jeunes filles

Cette comparaison s'est avérée fort intéressante et révélatrice. Ainsi, tandis que chez les femmes seules deux régions du cortex préfrontal droit furent activées lors de la condition *Suppression* (cortex latéral préfrontal - AB 9 - et cortex orbitofrontal - AB 11), chez les jeunes filles, une augmentation significative du signal BOLD a été observée bilatéralement, lors de la suppression volontaire de la tristesse, dans les régions préfrontales suivantes : le cortex préfrontal latéral (AB 10), le cortex orbitofrontal (AB 11), le cortex préfrontal médian (AB 10) et le cortex cingulaire antérieur (AB 24). De plus, des activations ont été notées au niveau du cortex préfrontal latéral gauche (AB 9) ainsi qu'au niveau du cortex préfrontal ventral gauche (AB 47). Il est également notable que l'étendue spatiale (en terme de nombre de voxels) de l'activation cérébrale observée au niveau du cortex latéral préfrontal, structure clé de l'autorégulation émotionnelle, était cinq fois plus élevée chez les jeunes filles que chez les femmes. Ces résultats sont en accord avec les études de Tamm et *al.* (2002), Casey et *al.* (1995) et Cohen, et *al.* (1994), qui ont montré que les enfants recrutent un plus grand volume du cortex préfrontal que les adultes lors de la réalisation d'une tâche de maintien et /ou de suppression de divers types d'information (ex. : Tâche de Go/NoGo). Ces résultats suggèrent qu'il est cognitivement et neurobiologiquement plus difficile pour un enfant que pour un adulte d'autoréguler ses émotions. Le fait que la différence entre les scores subjectifs de la

tristesse lors de la condition *Suppression* versus la condition *Tristesse* était plus grande chez les femmes que chez les jeunes filles supporte cette idée. Cette plus grande difficulté d'autorégulation chez les enfants découlerait de l'immaturité relative des connexions préfronto-limbiques dans l'enfance (Casey et *al.* 1995).

4. Les soubassements neuroanatomiques fonctionnels de la suppression de la tristesse chez les enfants et les adultes : Comparaison avec les études antérieures

Les résultats obtenus tant chez les femmes que chez les filles lors de la condition *Suppression* sont, de façon générale, en accord avec les résultats des précédentes études d'IRMf réalisées au sujet des soubassements neurobiologiques de l'autorégulation émotionnelle. En effet, Beauregard et *al.* (2001) ont d'abord montré que la suppression de l'excitation sexuelle - un état émotionnel positif - était associée à une augmentation du signal BOLD au niveau du cortex latéral préfrontal droit (AB 10) et du cortex cingulaire antérieur droit (AB 32), et que ces régions du cortex préfrontal modulaient l'activité des régions limbiques corrélées à cet état émotionnel. Il est à noter que la stratégie d'autorégulation utilisée dans cette étude était la même que celle utilisée par les femmes et les jeunes filles. Suite à l'étude de Beauregard et al. (2001), Ochsner et collaborateurs (2002) ont montré que la réévaluation d'images négatives était associée à l'activation des régions ventrales et dorsales du cortex préfrontal gauche ainsi qu'à la partie dorsale du cortex préfrontal médian. De plus, ils ont observé que l'augmentation du signal BOLD au niveau de la partie ventrale du cortex préfrontal latéral était corrélée avec une diminution de l'activité neuronale dans l'amygdale.

Les résultats observés dans nos études portant sur la suppression de la tristesse sont également en accord avec ceux obtenus récemment par Hariri et collaborateurs (2003). En effet, ces derniers ont comparé l'impact d'une tâche perceptuelle et celui d'une tâche cognitive sur l'activité des substrats neurobiologiques associés à la peur et à la colère. Dans cette étude, ils ont demandé aux sujets d'associer correctement l'émotion (peur ou colère) dépeinte par un des deux visages présentés simultanément avec un visage-cible (tâche perceptuelle), et d'identifier l'émotion (peur ou colère) exprimée par un visage-cible (tâche cognitive) en choisissant un des deux visages présentés simultanément. Tel qu'anticipé, l'association d'une expression faciale de peur ou de colère a été corrélée positivement à une augmentation bilatérale du débit sanguin cérébral régional (dscr) de l'amygdale. À l'opposé, l'identification d'une émotion de peur ou de colère a été associée à une diminution du dscr dans l'amygdale ainsi qu'à une augmentation du dscr dans le cortex préfrontal droit.

Considérés dans leur ensemble, ces résultats confirment l'idée avancée précédemment par Nauta (1971), Tucker et *al.* (1995) puis Davidson et *al.* (2000) voulant que l'autorégulation émotionnelle soit associée à l'activité d'un circuit préfronto-limbique dans lequel certaines régions du cortex préfrontal peuvent moduler, via l'activité cognitive, la réponse émotionnelle générée à un niveau sous-cortical. Il est intéressant de noter la constance au niveau des résultats des études citées ci-dessus, ceci en dépit des différences méthodologiques liées aux modes d'induction émotionnelle (images, expression du visage, extraits de films), aux états émotionnels (positif ou négatifs), aux tâches (maintien ou suppression) et stratégies d'autorégulation (" mindfullness ",

réévaluation), ainsi qu'au genre (masculin ou féminin) et à l'âge (8 à 10 ans versus 20 à 42 ans) des sujets.

5. Note théorique sur l'interaction esprit-cerveau et l'autorégulation émotionnelle

Actuellement, le computationalisme demeure le mode d'explication privilégié en psychologie cognitive ainsi qu'en neuroscience cognitive en ce qui a trait au fonctionnement du cerveau et de l'esprit (au sens de *mind*). Selon cette vision, le comportement humain est déterminé par l'activité inconsciente de modules exécutifs et de leurs contreparties neuronales. Cette vision récuse tout attribut humain telles que la subjectivité et l'intentionnalité, et réduit littéralement l'être humain à un ordinateur biologique. Toutefois, comme le fait remarquer Bandura (2001), un problème majeur de cette vision découle du fait que les aspirations, les désirs, les croyances, les buts et les attentes ont une grande valeur explicative et prédictive chez l'humain. Dans cette perspective, les êtres humains sont créatifs, conscients et pourvus de volonté. Ils sont des agents d'expérience et non des objets de cette expérience. En ce sens, la métacognition et les processus d'autorégulation, dont l'autorégulation émotionnelle, sont une des manifestations de cette capacité d'autodétermination. En accord avec cette vision, nous avançons que la conscience de soi et les processus de l'esprit, quoique étroitement liés aux processus cérébraux, ne peuvent être réduits strictement aux processus neuro-électriques et neurochimiques. Aussi, le soi en tant qu'agent, ainsi que la terminologie mentaliste qui y réfère, demeure absolument essentiels comme facteurs explicatifs du comportement humain. À cet égard, Bandura (2001) mentionne avec justesse que la

cartographie du substrat neuronal sous-tendant le célèbre discours de Martin Luther King intitulé « I have a dream » n'aurait pu rendre ni la puissance ni la signification sociale de ce discours.

Depuis de nombreuses décennies, la neuropsychologie et les neurosciences cognitives ont accumulé une pléthore de données montrant comment des fonctions psychologiques telles que la mémoire, l'attention et les émotions sont corrélées à des processus neuronaux dans des régions et circuits spécifiques du cerveau. À l'inverse, les croyances ou les émotions sont aussi capables de significativement moduler les processus neuroélectriques et neurochimiques. À ce sujet, des études d'imagerie cérébrale fonctionnelle ont montré l'influence de la thérapie cognitive behaviorale (TCB) sur le fonctionnement cérébral. La première de ces études, qui utilisait la tomographie par émission de positons (TEP), a montré que la TCB pouvait produire des changements au niveau du métabolisme du glucose dans le noyau caudé d'individus souffrant d'un Trouble Obsessif Compulsif (Schwartz et *al.* 1996). Dans la même veine, une étude d'IRMf réalisée par notre groupe de recherche a montré que la TCB pouvait normaliser le fonctionnement dysfonctionnel du circuit neuronal impliqué dans l'arachnophobie (Paquette et *al.* 2003). De plus, une étude de TEP récemment menée au sein de notre laboratoire chez des acteurs professionnels a révélé qu'il était possible de moduler la synthèse de la sérotonine par l'auto-induction d'une expérience émotionnelle intense (manuscrit en préparation).

Il semble donc qu'avec l'émergence de la conscience de soi et des capacités « agentielles », l'évolution biologique a permis à l'être humain de moduler consciemment et volontairement l'activité de son cerveau. Ces capacités l'empêche d'être complètement asservi par le déterminisme génétique et lui permettent de créer délibérément un nouvel environnement culturel et social. Une telle liberté d'action est responsable du fait que malgré l'homogénéité du génotype humain à travers les diverses sociétés humaines, certaines cultures sont belliqueuses alors que d'autres ne connaissent pas l'agression et désapprouvent la violence (Alland, 1972; Sanday, 1981).

Conclusions

Les travaux présentés dans le cadre de cette thèse ont permis d'enrichir de façon importante nos connaissances ayant trait aux soubassements neurobiologiques d'une émotion primaire – la tristesse - chez l'enfant sain. Ces travaux ont également conduit à une meilleure compréhension des soubassements neuroanatomiques fonctionnels de l'autorégulation émotionnelle chez l'enfant et l'adulte sains. *Primo*, nous avons montré que la suppression de la tristesse chez l'adulte (Article #1) s'effectuait par l'entremise d'un circuit préfronto-limbique, et que les cortex préfrontal latéral et orbitofrontal jouent un rôle crucial dans la régulation volontaire des émotions. *Secundo*, nous avons démontré que l'expérience subjective de la tristesse chez l'enfant était sous-tendue par un substrat neuroanatomique fonctionnel très semblable à celui observé chez l'adulte (Article #2). Ces résultats viennent appuyer l'hypothèse de la TDE voulant que le substrat neuroanatomique fonctionnel des émotions ait une assise biologique. *Tertio*, nous avons examiné la neuroanatomie fonctionnelle de la suppression de la tristesse chez l'enfant

(Article #3). Comme chez l'adulte, nous avons d'abord constaté que cette fonction était desservie par un circuit préfronto-limbique. En particulier, nous avons noté que les enfants recrutaient un volume beaucoup plus important du cortex préfrontal que les adultes pour réaliser cette même fonction. En regard de ces résultats, il semble qu'il soit neurobiologiquement plus difficile pour les enfants que pour les adultes d'autoréguler leurs émotions. Globalement, les résultats de ces études pavent la voie à une meilleure compréhension des troubles qui découlent du mauvais fonctionnement du circuit préfronto-limbique sous-tendant la régulation volontaire des émotions, tels que la dépression majeure et les troubles anxieux.

Références

1. Alland, A Jr. (1972). *The Human Imperative.* New York: Columbia University Press.

2. Bandura, A. (2001). Social cognitive theory: an agentic perspective. *Annual Review of Psychology* 52, 1-26.

3. Beauregard, M, Leroux, J-M, Bergman, S, Arzoumanian, S, Beaudoin, G, Bourgouin, & P, Stip E. (1998). The functional neuroanatomy of major depression: an fMRI study using an emotional activation paradigm. *NeuroReport* 9, 3253-3258.

4. Beauregard, M, Lévesque, J, & Bourgouin, P. (2001). Neural correlates of the conscious self-regulation of emotion. *Journal of Neuroscience* 21, RC165 (1-6).

5. Briggs, JL. (1970). *Never in anger: portrait of an Eskimo family*. Harvard University Press: Cambridge.

6. Cohen, JD, Forman, SD, Braver, TS, Casey, BJ, Servan-Schreiber, D, & Noll, DC. (1994). Activation of prefrontal cortex in a nonspatial working memory task with functional MRI. *Human Brain Mapping* 1, 293-304.

7. Damasio, AR, Grabowski, TJ, Bechara, A, Damasio, H, Ponto, LL, Parvizi, J, & Hichwa, RD. (2000). Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature Neuroscience* 3, 1049-56.

8. Davidson, RJ, Putnam, KM, & Larson, CL. (2000). Dysfunction in the neural circuitry of emotion regulation – A possible prelude to violence. *Science* 289, 591-594.

9. Dickson, KL, Fogel, A, & Messinger, D. (1998). The development of emotion from a social process view. In: M.F. Mascolo and S. Griffith (Eds.), *What develops in emotional development*? Plenum, New York, pp. 253-271.

10. Eugène, F, Lévesque, J, Mensour, B, Leroux, J.-M, Beaudoin, G, Bourgouin, P & Beauregard, M. (2003). The impact of individual differences on the neural circuitry underlying emotion. *NeuroImage* 19, 354-364.

11. George, MS, Ketter, TA, Parekh, PI, Horwitz, B, Herscovitch, P, & Post, RM. (1995). Brain activity during transient sadness and happiness in healthy women. *American Journal of Psychiatry* 152, 341-51.

12. Hariri, AR, Mattay, VS, Tessitore, A, Fera, F, & Weinberger, DR. (2003). Neocortical modulation of the amygdala response to fearful stimuli. *Biological Psychiatry* 53, 494-501.

13. Izard, CE. (1992). Basic emotions, relations among emotions, and emotion-cognition relations. *Psychological Review* 99, 561-5.

14. Lane, RD, Reiman, EM, Ahern, GL, Schwartz, GE, Davidson, RJ. (1997). Neuroanatomical correlates of happiness, sadness, and disgust. *American Journal of Psychiatry* 154, 926-33.

15. Lévesque, J, Eugène, F, Joanette, Y, Paquette, V, Mensour, B, Beaudoin, G, Leroux, J-M, Bourgouin, P, & Beauregard, M. (2003). Neural circuitry underlying voluntary self-regulation of sadness. *Biological Psychiatry* 53, 502-510.

16. Mesquita, B, & Frijda, NH. (1992). Cultural variations in emotion: A review. *Psychological Bulletin* 112, 179-204.

17. Nauta, WJH. (1971). The problem of the frontal lobe: A reinterpretation. *Journal of Psychiatry Research* 8, 167-187.

18. Ochsner, KN, Bunge, SA, Gross, JJ, & Gabrieli, JD. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience,* 14, 1215-29.

19. Paquette, V, Lévesque, J, Mensour, B, Leroux, J-M, Beaudoin, G, Bourgouin, P, & Beauregard, M. (2003). "Change the mind and you change the brain" : Effects of cognitive-behavioral therapy on the neural correlates of spider phobia. *NeuroImage* 18, 401-409.

20. Sanday, PR. (1981). The socio-cultural context of rape: a cross-cultural study. *Journal of Societal Issues* 37, 5-27.

21. Sugiura, M, Kawashima, R, Nakagawa, M, Okada, K, Sato, T, Goto, R, Sato, K, Ono, S, Schormann, T, Zilles, K, & Fukuda, H. (2000). Correlation between human personality and neural activity in cerebral cortex. *NeuroImage* 11, 541-546.

22. Tucker, DM, Luu, P, & Pribram, KH. (1995). Social and emotional self-regulation. *Annals of New York Academy of Sciences* 769, 213-239.