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Impact de la cécité sur le système nociceptif

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Résumé

La vision joue un rôle très important dans la prévention du danger. La douleur a aussi pour fonction de prévenir les lésions corporelles. Nous avons donc testé l'hypothèse qu'une hypersensibilité à la douleur découlerait de la cécité en guise de compensation sensorielle. En effet, une littérature exhaustive indique qu'une plasticité intermodale s'opère chez les non-voyants, ce qui module à la hausse la sensibilité de leurs sens résiduels. De plus, plusieurs études montrent que la douleur peut être modulée par la vision et par une privation visuelle temporaire.

Dans une première étude, nous avons mesuré les seuils de détection thermique et les seuils de douleur chez des aveugles de naissance et des voyants à l'aide d'une thermode qui permet de chauffer ou de refroidir la peau. Les participants ont aussi eu à quantifier la douleur perçue en réponse à des stimuli laser CO_2 et à répondre à des questionnaires mesurant leur attitude face à des situations douloureuses de la vie quotidienne. Les résultats obtenus montrent que les aveugles congénitaux ont des seuils de douleur plus bas et des rapports de douleur plus élevés que leurs congénères voyants. De plus, les résultats psychométriques indiquent que les non-voyants sont plus attentifs à la douleur. Dans une deuxième étude, nous avons mesuré l'impact de l'expérience visuelle sur la perception de la douleur en répliquant la première étude dans un échantillon d'aveugles tardifs. Les résultats montrent que ces derniers sont en tous points similaires aux voyants quant à leur sensibilité à la douleur. Dans une troisième étude, nous avons testé les capacités de discrimination de température des aveugles congénitaux, car la détection de changements rapides de température est cruciale pour éviter les brûlures. Il s'est avéré que les aveugles de naissance ont une discrimination de température plus fine et qu'ils sont plus sensibles à la sommation spatiale de la chaleur. Dans une quatrième étude, nous avons examiné la contribution des fibres A∂ et C au traitement nociceptif des non-voyants, car ces récepteurs signalent la première et la deuxième douleur, respectivement. Nous avons observé que les aveugles congénitaux détectent plus facilement et répondent plus rapidement aux sensations générées par l'activation des fibres C. Dans une cinquième et dernière étude, nous avons sondé les changements potentiels qu'entrainerait la perte de vision dans la modulation descendante des intrants nociceptifs en mesurant les effets

de l'appréhension d'un stimulus nocif sur la perception de la douleur. Les résultats montrent que, contrairement aux voyants, les aveugles congénitaux voient leur douleur exacerbée par l'incertitude face au danger, suggérant ainsi que la modulation centrale de la douleur est facilitée chez ces derniers.

En gros, ces travaux indiquent que l'absence d'expérience visuelle, plutôt que la cécité, entraine une hausse de la sensibilité nociceptive, ce qui apporte une autre dimension au modèle d'intégration multi-sensorielle de la vision et de la douleur.

Mots-clés : Thermoception, Nociception, Douleur, Vision, Cécité, Intégration multi-sensorielle, Compensation sensorielle, Plasticité cérébrale.

Abstract

Vision is important for avoiding encounters with objects in the environment that may imperil physical integrity. Since pain also plays a major role in preventing bodily injury, we tested whether, in the absence of vision, pain hypersensitivity would arise from an adaptive shift to other sensory channels. Indeed, a wealth of literature indicates that blindness leads to sensory compensation and crossmodal plasticity. Furthermore, studies have shown that pain perception can be modulated by vision and by temporary visual deprivation.

In a first study, we measured innocuous and noxious thermal thresholds using a Peltier-based thermotester in congenitally blind and normal sighted participants. We also assessed their suprathreshold pain ratings using a CO_2 laser device and evaluated their attitude towards daily pain encounters using questionnaires on attention and anxiety. Results show that congenitally participants have lower pain thresholds and higher suprathreshold pain ratings. The psychometric data further indicates that they are more attentive to pain compared to their sighted peers. In a second study, we investigated whether visual experience has an impact on pain perception by replicating the first study in late blind participants. Results indicate that individuals who lost sight later in life are similar to the sighted in every aspect of pain perception that we measured. In a third study, we tested whether blind individuals have supranormal skills in detecting small and quick increases in temperature, as these thermal cues of the environment might help identifying and avoiding potentially harmful objects. Results show that congenitally blind participants outperform their sighted peers and that they are more susceptible to spatial summation of heat. In a fourth study, we examined the contribution of A∂ and C-fibres to blind individuals' nociceptive processing, as these fibres are thought to signal the first and second pain, respectively. Our findings indicate that congenital blindness leads to an enhanced detection to C-fibre mediated sensations and to faster reaction times to these nociceptive inputs. In a fifth and final study, we probed the potential changes in the descending modulation of nociceptive inputs following visual deprivation by measuring the effects of psychological factors like anticipation and anxiety on blind individuals' pain perception. Results show that congenitally blind participants are more sensitive to pain in

response to uncertainty about threat, suggesting that they are more susceptible to top-down modulation of pain.

Overall, this work indicates that visual deprivation from birth, but not later in life, causes a leftward shift in the stimulus–response function to nociceptive stimuli and lends new support to a model of sensory integration of vision and pain processing.

Keywords: Thermoception, Nociception, Pain perception, Vision, Blindness, Multisensory integration, Sensory compensation, Brain plasticity.

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OMS : Organisation Mondiale de la Santé

Liste des abréviations

AMT : Fibres A mécano-thermiques

AMT-I : AMT de type I

AMT-II : AMT de type II

CMT : Fibres C mécano-thermiques

CNS : Système nerveux central

IRMf : Imagerie par résonnance magnétique fonctionnelle

m/s : Mètres par seconde

ms : Milliseconde(s)

s : Seconde(s)

SMT : Simulation magnétique transcrânienne

NCF : Nucleus cuneiformis

PAG : Periaqueductal gray (Substance grise périaqueducale)

DLPT : Dorsolateral pontine tegmentum (Tegmentum pontique dorsolatéral)

ACC : Anterior cingulated cortex (Gyrus cingulaire antérieur)

Cécité : point de vue.

– Michel Laclos

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I. INTRODUCTION

La plupart des avancées de la recherche clinique et fondamentale ont été faites en étudiant des processus physiologiques dysfonctionnels. En effet, c'est souvent par l'étude de pathologies ou de lésions que l'on déduit les mécanismes d'action qui œuvrent en conditions physiologiques normales. La découverte des deux grandes voies visuelles corticales en est un bon exemple. C'est en causant des lésions précises dans le cortex de primates non humains ou encore en étudiant des patients qui ont subi des traumatismes crâniens que les chercheurs ont montré qu'il existe la voie occipito-pariétale du « Où? » qui traite l'information visuelle spatiale et la voie occipito-temporale du « Quoi? » qui traite la forme et la couleur des objets (Schneider, 1969; Mishkin & Ungerleider, 1982; Goodale *et al.*, 1991; Goodale & Milner, 1992). De la même manière, la privation sensorielle a permis de comprendre la structure et le fonctionnement du cortex visuel primaire. En effet, Hubel et Wiesel ont observé que la suture temporaire d'un œil tôt dans le développement mène au débalancement de la représentation corticale des yeux et ont ainsi découvert la période critique de la formation des colonnes de dominance oculaire (Wiesel & Hubel, 1965b; a; Hubel *et al.*, 1976). Les études de privation sensorielle ont aussi permis de comprendre que les sens interagissent entre eux, et qu'un sens défaillant a des répercussions majeures sur les autres. Dans les deux dernières décennies, on a accordé beaucoup d'importance à l'étude de la cécité et à ses répercussions sur l'intégration multi-sensorielle et sur les mécanismes de plasticité cérébrale (Kupers & Ptito, 2014). Malgré que les implications de la cécité sur le système somesthésique aient été largement explorées, on ne sait aujourd'hui que très peu sur ses répercussions sur la perception de la douleur. Cet essai a donc pour but d'illustrer mes travaux sur l'impact de la cécité congénitale et tardive sur le système nociceptif.

1. Neuroanatomie et neurophysiologie de la douleur

Le système somesthésique est composé de deux sous-systèmes : un premier dédié à la détection de stimuli mécaniques (e.g. toucher, pression, vibration et distension cutanée) et un deuxième dédié à la perception de stimuli thermiques et nociceptifs. La combinaison de ces deux afférences sensorielles permet aux humains et aux animaux de discriminer les formes et les textures, de ressentir les différentes forces externes et internes que le corps subit, ainsi que de détecter et d'identifier des stimuli dangereux (Purves *et al.*, 2004).

Il existe une grande variété de récepteurs cutanés et sous-cutanés (Figure 1) que l'on peut fonctionnellement diviser en trois groupes : mécanorécepteurs, thermorécepteurs et nocicepteurs. Les premiers se distinguent morphologiquement des deux autres, car ils sont encapsulés. Les thermorécepteurs et les nocicepteurs, quant à eux, sont dits terminaisons nerveuses libres, car leurs branches terminales peu ou non myélinisées se ramifient dans les couches superficielles du derme et dans l'épiderme (Purves *et al.*, 2004). Je discuterai ici de leur rôle dans la perception de la chaleur et de la douleur.

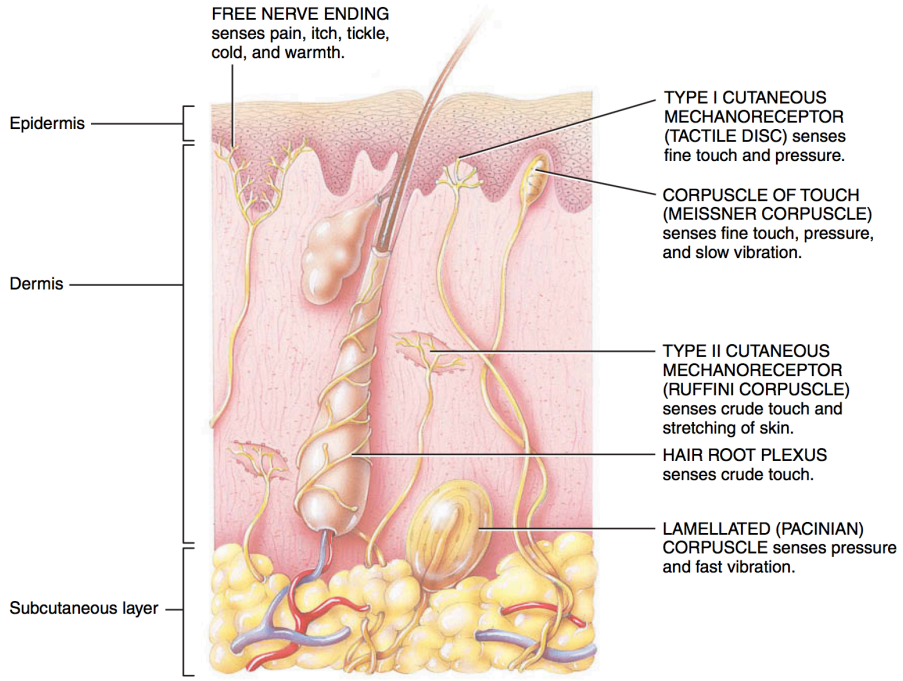

Figure 1. Structure et emplacement des récepteurs cutanés et sous-cutanés. Reproduit à partir de Tortora & Derrickson, 2014.

1.1. Afférences nociceptives

Une des fonctions vitales du système somesthésique est d'informer l'organisme lorsque le corps subit un stimulus nocif. La douleur, étant une sensation aversive par définition, est donc responsable de la fonction protectrice de ce système. Cette sensation agit en effet comme un signal d'alarme qui véhicule les paramètres du stimulus néfaste (nature, intensité, localisation, etc.) au système nerveux central (CNS). Cette communication se fait au travers de fibres sensorielles hautement spécialisées qui informent l'organisme non seulement des stimuli environnementaux, mais aussi de l'état de l'organisme. Celles-ci sont divisées en deux grandes catégories sur la base de leur myélinisation : les fibres C, non myélinisées, et les fibres A, faiblement myélinisées. Il existe plusieurs sous-classes de fibres dont certaines répondent à des stimuli nociceptifs et d'autres à des stimuli thermiques non douloureux. Parmi ces dernières, on compte des fibres C qui encodent exclusivement la qualité de basses intensités de chaleur (Johnson *et al.*, 1979) et des fibres A∂ qui répondent à de légères baisses de température (Darian-Smith *et al.*, 1973).

Les autres récepteurs se distinguent par leur seuil d'activation plus élevé. Ils sont dits « nocicepteurs » (du latin *nocere*, faire du mal), car ils répondent préférentiellement à des stimuli aversifs (Sherrington, 1906). Contrairement à d'autres récepteurs cutanés, les nocicepteurs sont généralement activés par plusieurs types de stimulations (mécaniques, thermiques et chimiques); d'où leur caractérisation comme étant polymodaux. On en décompte deux grandes catégories : Les fibres C mécano-thermiques (CMT) et les fibres A mécano-thermiques (AMT). Les CMT sont généralement actives pour des températures variant entre 38 et 50 ˚C et leur degré d'activation augmente de manière monotone avec l'intensité du stimulus thermique (LaMotte & Campbell, 1978). Dû au fait qu'elles ne soient pas myélinisées, les CMT ont vitesse de conduction de l'influx nerveux lente qui est généralement inférieure à 2 m/s (McMahon & Koltzenburg, 2006). Pour ce qui est des AMT, deux types ont été identifiés à ce jour (Dubner & Hu, 1977; Treede *et al.*, 1998): Les AMT de type I (AMT-I) répondent à des températures supérieures à 53 ˚C pour des stimulations courtes, mais peuvent être activées par des températures plus basses (40 à 50 ˚C) lorsque stimulées plus longuement. Elles sont donc dites à adaptation lente et sont généralement impliquées dans les mécanismes d'hyperalgésie (McMahon & Koltzenburg, 2006). Ceci les

distingue des AMT de type II (AMT-II) qui, tout comme les CMT, sont des fibres à adaptation rapide (Treede *et al.*, 1995). Les AMT-II ont un seuil médian d'environ 46 ˚C, nettement supérieur à celui des CMT qui tourne autour de 41 ˚C (Treede *et al.*, 1995; Plaghki *et al.*, 2010; Churyukanov *et al.*, 2012; Wooten *et al.*, 2014). Contrairement à ces dernières, les AMT sont myélinisées et ont donc une vitesse de conduction de l'influx nerveux nettement plus rapide. Les AMT-I transmettent généralement le signal nociceptif à une vitesse de 25 à 55 m/s, selon la contribution respective des fibres nociceptives A∂ ou des fibres tactiles Aβ. Les AMT-II, quant à elles, sont composées uniquement de fibres A∂; d'où le fait qu'elles conduisent l'information sensorielle à une vitesse de 15 m/s (Treede *et al.*, 1995; McMahon & Koltzenburg, 2006; Plaghki *et al.*, 2010).

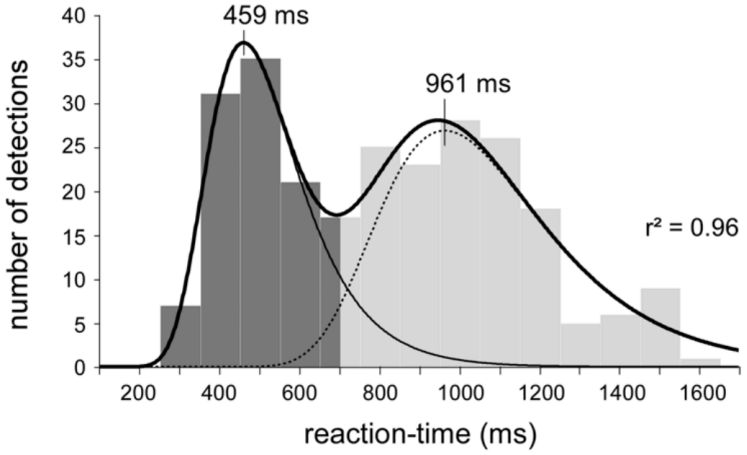

Figure 2. Distribution bimodale des temps de réaction en réponse à des stimulations au laser CO_2. Reproduit à partir de Churyukanov et al.,

Vu leur adaptation rapide les AMT-II (ou fibres A∂) et les CMT (ou fibres C) sont responsables de la douleur aigue en réponse à de courts stimuli nociceptifs (Treede *et al.*, 1995; Plaghki *et al.*, 2010; Churyukanov *et al.*, 2012). Lorsque l'on stimule la peau de la main dorsale avec de la chaleur ponctuelle sans contact, on note une distribution bimodale des temps de réaction avec un point d'inflexion qui tourne autour de 650 ms (Figure 2). En général, les temps de réaction plus rapides (< 650 ms) sont générés à partir de températures plus élevées alors que les temps de réaction plus lents (> 650 ms) sont générés à partir de températures plus basses. Sur la base des propriétés physiologiques des fibres A∂ et C décrites

plus haut, il a été conclu que celles-ci sont responsables des sensations de première et seconde douleur, respectivement (Treede *et al.*, 1995; Plaghki *et al.*, 2010; Churyukanov *et al.*, 2012).

1.2. Aspects cognitifs de la douleur

La douleur a longtemps été vue sous un angle purement biomédical selon laquelle elle constituerait une représentation directe des intrants nociceptifs et, par le fait même, des dommages physiologiques. Cependant, depuis la fin du 20^{e} siècle, ce modèle a été enrichi d'un aspect psychologique qui l'a rendu plus représentatif de la manière dont la douleur est ressentie (Morley & Vlaeyen, 2010). En effet, malgré que cette sensation soit en général un bon indicateur de l'étendue des dommages tissulaires, plusieurs études ont montré que ce n'est pas nécessairement toujours le cas (Gatchel *et al.*, 2007): la douleur peut se produire en l'absence de lésions tissulaires et *vice versa* (Fernandez & Turk, 1992). C'est entre autres l'étude de la douleur chronique qui a permis de mettre en évidence l'importance de l'état psychologique d'un individu dans la manière dont la douleur sera perçue (Gatchel *et al.*, 2007). Par exemple, il y a une plus grande prévalence de problèmes de santé mentale chez les patients souffrant de maux chroniques que chez la population générale (Demyttenaere *et al.*, 2007). La douleur dépend aussi du contexte dans lequel elle est vécue. En effet, pendant la Seconde Guerre mondiale, une étude systématique de l'anesthésiste Henry Beecher et ses collègues de la Harvard Medical School a montré que, contrairement à ceux qui souffraient de blessures mineures, les soldats qui souffraient de graves blessures de guerre ressentaient souvent peu ou pas de douleur (Beecher, 1946). Les chercheurs ont attribué ce phénomène au fait que la douleur d'un soldat blessé sur le champ de bataille était probablement atténuée par les conséquences avantageuses d'être écarté du danger. À l'inverse, une blessure similaire dans un cadre domestique présenterait un ensemble tout à fait différent de circonstances qui pourraient exacerber la douleur (perte d'emploi, dépendance financière, etc.).

Cette évolution de notre compréhension de la douleur a permis de la définir comme « une expérience sensorielle et émotionnelle désagréable associée à une lésion tissulaire réelle ou potentielle ou décrite en termes d'un tel dommage » (Mersky & Bodguk, 1994). Le consensus actuel établit que la composante sensorielle-discriminative de la douleur est responsable de la perception de l'emplacement, l'intensité et la qualité de la stimulation nocive, alors que sa composante affective-motivationnelle joue plutôt un rôle modulateur du signal nociceptif (Purves *et al.*, 2004). Cette dichotomie fonctionnelle prend racine dans les projections anatomiques des fibres nociceptives. En effet, les voies responsables de la composante sensorielle-discriminative de la douleur prennent leur origine dans les ganglions spinaux et pénètrent la moelle épinière par la racine dorsale où elles bifurquent en une branche ascendante et une branche descendante. Ces fibres forment ainsi le faisceau dorsolatéral de Lissauer dont les projections font un relais dans le thalamus et le tronc cérébral avant d'aboutir dans plusieurs structures corticales dont le cortex somesthésique primaire et secondaire (Figure 3). Quant à la composante affective-motivationnelle, elle dépend de voies

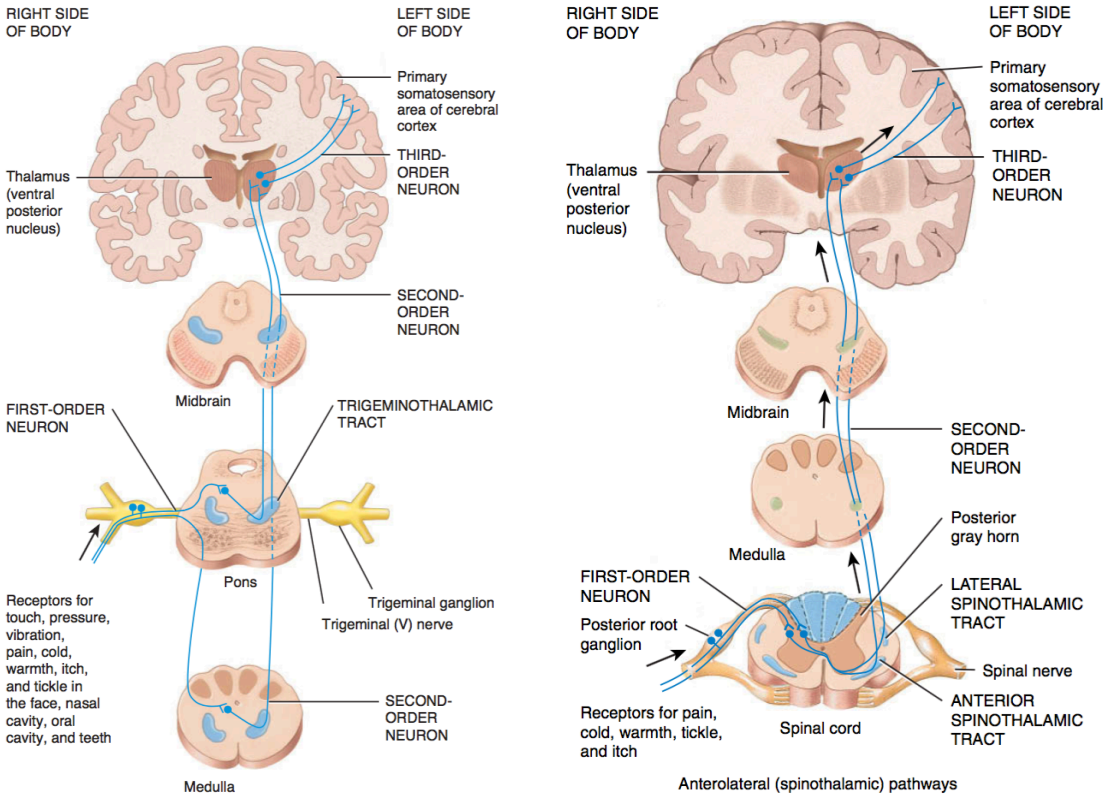

Figure 3. Projections des fibres nociceptives du visage (voie trigéminothalamique, à gauche) et du reste du corps (voie spinothalamique, à droite). Reproduit à partir de Tortora et Derrickson, 2014.

additionnelles qui projettent du système antérolatéral à l'hypothalamus et à l'amygdale en passant par la formation réticulaire du mésencéphale, particulièrement par le noyau parabrachial. Ce dernier constitue aussi une source de projections qui aboutissent dans des structures qui ont pour rôle de moduler les signaux nociceptifs; la substance grise périaqueducale (SGP) entre autres (Purves *et al.*, 2004).

Ces deux aspects combinés activent un vaste réseau cortical qui comprend le cortex somatosensoriel, l'insula, le gyrus cingulaire, ainsi que les zones préfrontales et pariétales. Ce conglomérat de zones cérébrales a été baptisé « matrice de la douleur », car son activité neuronale est associée à la transformation sensorielle et affective de stimuli nociceptifs qui, ultimement, déclenche l'expérience douloureuse (Legrain *et al.*, 2011). Cependant, de récentes études ont montré que les stimuli non nociceptifs, pour autant qu'ils soient saillants, peuvent provoquer des réponses corticales avec une configuration spatiale très similaire à celle de la matrice de la douleur (Mouraux *et al.*, 2011), et que le degré d'activité de celle-ci ne traduit pas nécessairement le degré d'intensité du stimulus douloureux (Clark *et al.*, 2008; Iannetti *et al.*, 2008). Legrain et collaborateurs (2011) suggèrent donc que la matrice de la douleur est plutôt un réseau cortical dont la fonction principale est de détecter les évènements qui menacent l'intégrité du corps, quel que soit l'intrant sensoriel. Ce réseau serait aussi impliqué dans le recrutement des ressources attentionnelles nécessaires au déclenchement d'une réponse comportementale optimale. Quoique controversée (Zhang *et al.*, 2012), cette interprétation renforce l'idée que les signaux nociceptifs sont fortement modulés par des mécanismes cognitifs de haut niveau (Tracey & Mantyh, 2007). Par exemple, des études physiologiques et en imagerie par résonnance magnétique fonctionnelle (IRMf) ont montré que porter attention à un stimulus nocif exacerbe l'expérience douloureuse, alors qu'en être distrait produit l'effet inverse (Peyron *et al.*, 1999; Petrovic *et al.*, 2000; Bantick *et al.*, 2002; Legrain *et al.*, 2002; Ohara *et al.*, 2004a; Ohara *et al.*, 2004b). De la même manière, la peur et l'anxiété ont des effets contraires sur la perception de la douleur (Rhudy & Meagher, 2000). La première a un effet analgésique qui s'explique par le fait que cette émotion est plus saillante que la douleur, réduisant ainsi l'effet potentialisateur de l'attention sur les intrants nociceptifs. De plus, la peur inhibe les réflexes nociceptifs qui pourraient interférer avec les patrons comportementaux de défense, d'évitement et de fuite face au danger (Rhudy & Meagher, 2000). L'anxiété, quant

à elle, a un effet hyperalgésique, car elle est souvent déclenchée par des situations d'incertitude où l'anticipation d'un danger exacerbe l'expérience douloureuse (Tracey & Mantyh, 2007). De plus, l'anticipation et l'anxiété induisent automatiquement le recrutement de ressources attentionnelles supplémentaires, modulant ainsi à la hausse le signal douloureux (Ploghaus *et al.*, 2003).

Les mécanismes énoncés ci-haut s'opèrent sous la gouvernance d'un réseau neuronal qui facilite ou inhibe les signaux nociceptifs afférents : Le système de modulation centrale de la douleur (Figure 4) (Hagbarth & Kerr, 1954). En effet, plusieurs études ont montré que des connections anatomiques existent entre les régions de la matrice de la douleur et certaines structures du tronc cérébral (Hadjipavlou *et al.*, 2006). Parmi celles-ci, on compte un circuit inhibiteur qui est impliqué dans l'analgésie en réponse à des stimuli environnementaux (réaction de fuite ou de lutte) et aux opiacés (Tracey & Mantyh, 2007). La modulation des intrants nociceptifs peut aussi avoir pour effet d'exacerber la douleur. Plusieurs études anatomiques et fonctionnelles ont effectivement mis en évidence l'implication des structures du tronc cérébral dans la facilitation des signaux nociceptifs (Hadjipavlou *et al.*, 2006; Tracey & Mantyh, 2007). Ce circuit est sujet à une grande plasticité, car il a pour rôle de peaufiner notre habileté à éviter des situations qui menacent l'intégrité du corps. En revanche, cette grande capacité d'adaptation des mécanismes de facilitation de la douleur peut avoir des effets néfastes, voire même handicapants. En effet, une activation soutenue du circuit facilitateur peut contribuer au développement de douleur chronique (Porreca *et al.*, 2002; Gebhart, 2004; Suzuki *et al.*, 2004). Chez ces patients, l'anticipation de la douleur et l'anxiété qui en découle mènent souvent à l'exacerbation de la douleur vécue et, ultimement, au développement de comportements pathologiques d'évitement (Tracey & Mantyh, 2007).

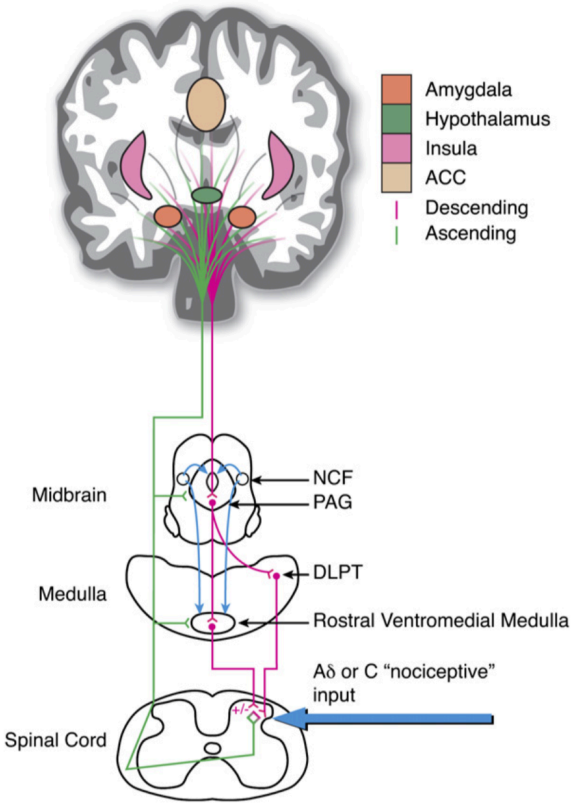

Figure 4. Le système central de modulation de la douleur. NCF (nucleus cuneiformis), PAG (periaqueductal gray), DLPT (dorsolateral pontine tegmentum), ACC (anterior cingulated cortex), +/- indiquent la facilitation ou l'inhibition des signaux nociceptifs, respectivement. Reproduit à partir de Tracey & Mantyh, 2007.

2. Influence de la vision sur la somesthésie

Lorsque l'information sensorielle est transmise au CNS par plusieurs modalités de manière congruente et simultanée, il en résulte le plus souvent une amélioration nette des performances cognitives. Celles-ci se manifestent par une meilleure précision (Stein *et al.*, 1996; Frassinetti *et al.*, 2002) et une plus grande vitesse de traitement (Hershenson, 1962). Ceci est d'autant plus vrai pour les interactions entre le système somesthésique et la vision, vu le rôle dominant de cette dernière dans notre perception du monde extérieur. Nous avons récemment publié un chapitre de livre à ce sujet (voir annexe) dont je vais, ici, exposer les points principaux.

2.1. Interactions vision-toucher

Les bénéfices cognitifs qui découlent de l'intégration visuo-tactile ont été démontrés à maintes reprises. En effet, un stimulus tactile près du seuil de détection est perçu plus facilement lorsqu'il est présenté en même temps qu'un stimulus visuel (Johnson *et al.*, 2006), même si ce dernier n'est pas pertinent pour la tâche à accomplir (Lloyd *et al.*, 2008). Par exemple, Serino et collaborateurs (2008) ont montré que la détection de stimuli tactiles infra-seuil, administrés sur le visage d'un observateur, était nettement améliorée lorsque celui-ci voyait simultanément un visage se faire toucher. Ce genre d'effets n'est par contre pas présent lorsque l'on observe un objet non corporel, suggérant que le stimulus visuel doit représenter le corps humain afin d'améliorer les performances tactiles (Kennett *et al.*, 2001).

L'influence de la vision sur la somesthésie va jusqu'à interférer avec l'image et le sentiment d'appartenance de notre corps. Des études pionnières ont effectivement montré que l'image corporelle est malléable, qu'elle n'est pas nécessairement ancrée à notre corps et qu'elle peut intégrer des objets inanimés (Ramachandran & Hirstein, 1998). Avec des illusions simples impliquant des intrants sensoriels contradictoires, les sensations tactiles peuvent être référées à des objets externes. Le phénomène du *rubber hand illusion* en est un bon exemple (Botvinick & Cohen, 1998). Ce paradigme permet, par la stimulation répétée de la main d'un observateur alors qu'il regarde une main en caoutchouc stimulée simultanément, de référer les

sensations perçues à cette dernière. Plus récemment, des études d'imagerie cérébrale ont renforcé l'idée que ce genre d'illusions soit le fruit d'une intégration multi-sensorielle dans un cadre de référence centré sur le corps (Ehrsson *et al.*, 2007).

2.2. Interactions vision-nociception

Tout comme pour le toucher, la vision module aussi la perception de la douleur. À titre d'exemple, la douleur perçue après avoir cogné une partie de notre corps est généralement minimisée ou exacerbée selon que le membre atteint paraisse intact ou blessé, respectivement. De la même manière, un enfant qui se fait mal en tombant a généralement le réflexe de regarder la réaction des parents. Si ceux-ci esquissent une grimace, l'enfant sera porté à pleurer, alors que s'ils affichent un sourire, l'enfant aura tendance à ignorer sa douleur et à passer rapidement à autre chose.

2.2.1. Analgésie visuelle

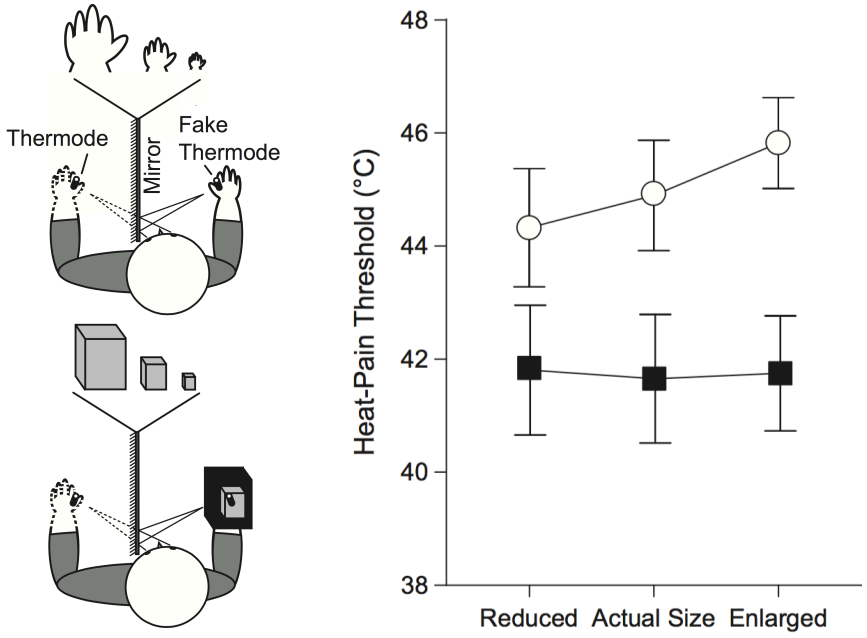

Figure 5. Analgésie visuelle. Reproduit à partir de Mancini et al., 2011.

Les observations anecdotiques énoncées ci-haut ont été confirmées dans plusieurs études récentes qui montrent un effet analgésique au simple fait de voir sa main intacte alors qu'elle est soumise à un stimulus douloureux (Longo *et al.*, 2009). Cet effet a été baptisé « analgésie visuelle », un phénomène qui suggère l'existence d'une interaction entre la matrice de la douleur et le réseau neuronal de la représentation du corps. Mancini et collaborateurs (2011) ont poussé plus loin ce champ de recherche en explorant les effets qu'entrainerait la distorsion virtuelle des membres stimulés. Il s'est avéré que l'intensité de la douleur perçue était inversement proportionnelle à la taille apparente de la main (Figure 5). En d'autres mots, agrandir la main avait un effet analgésique alors que la réduction de sa taille exacerbait la douleur. Cet effet s'observe non seulement dans les rapports subjectifs de la douleur, mais aussi de manière implicite par la réduction de la conductance cutanée lorsque la main est grossie (Romano & Maravita, 2014). Il est aussi intéressant de noter que cet effet analgésique est lié de près à l'appartenance perçue du membre stimulé (Hansel *et al.*, 2011; Mancini *et al.*, 2011).

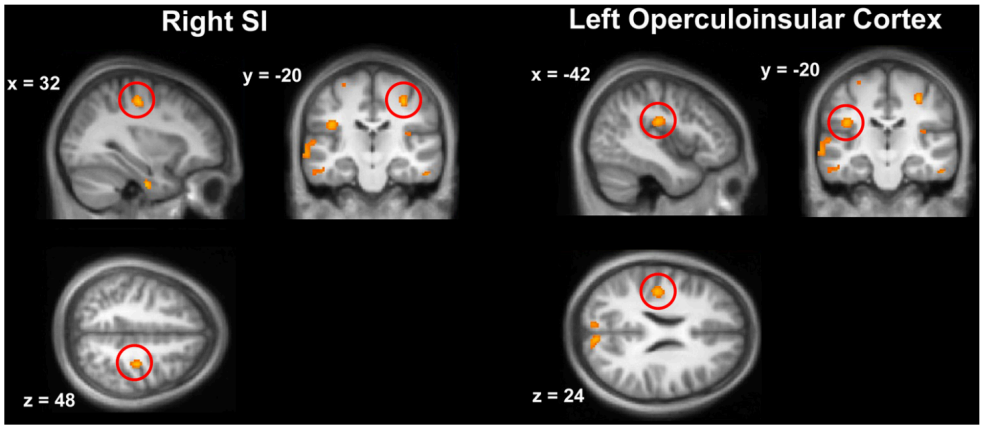

Figure 6. Corrélats neuronaux de l'analgésie visuelle.
Reproduit à partir de Longo et al., 2012.

Les réseaux neuronaux responsables de la représentation du corps chevauchent ceux de la matrice de la douleur, faisant du cortex pariétal postérieur et du cortex somesthésique des candidats possibles pour l'analgésie visuelle (Pandya & Seltzer, 1982; Longo *et al.*, 2012). Des études en imagerie cérébrale ont effectivement montré que le cortex pariétal postérieur et le cortex inféro-temporal sont impliqués dans la représentation du corps, incluant l'aire

corporelle extrastriée « extrastriate body area » (Downing *et al.*, 2001) et l'aire corporelle fusiforme (Peelen & Downing, 2005). Ces études ont aussi révélé une représentation topographique du corps au travers du cortex occipito-temporal (Orlov *et al.*, 2010). De plus, Longo et collaborateurs (2012) ont rapporté une baisse d'activité dans certaines structures de la matrice de la douleur, telles que le cortex somesthésique primaire et le cortex operculo-insulaire lorsque les participants voyaient leur main plutôt qu'un objet (Figure 6). Ceci était accompagné d'un couplage fonctionnel entre les noyaux pariétaux postérieurs du réseau de représentation visuelle du corps et la matrice de la douleur, suggérant que ce sont probablement des interactions multi-sensorielles impliquant la perception du corps qui sous-tendent l'analgésie visuelle (Haggard *et al.*, 2013).

L'analgésie visuelle peut toutefois paraitre paradoxale, car on s'attendrait à ce que diriger son attention sur le stimulus nociceptif exacerbe l'expérience douloureuse plutôt que de la réduire (Peyron *et al.*, 1999). Il s'avère, en effet, que ce phénomène n'a pas encore été intégralement répliqué. Par exemple, dans une étude récente, on a mesuré les potentiels évoqués par un stimulus laser alors que les participants voyaient leur main (Torta *et al.*, 2015). Les résultats obtenus ont confirmé que voir le membre stimulé réduit l'amplitude de l'onde N240 (activée par des stimuli nociceptifs) et augmente celle de l'onde P200 (activée par des stimuli thermiques non douloureux). Par contre, les rapports subjectifs de douleur n'étaient pas affectés par la vision de la main. Les auteurs avancent l'idée que l'intégration multi-sensorielle responsable de l'analgésie visuelle est sûrement influencée par le contexte expérimental (Torta *et al.*, 2015). En effet, Valentini et collaborateurs (2015) n'ont pu mesurer d'effet analgésique que lorsque les mains des participants étaient croisées. Le fait que la douleur perçue n'était réduite que lorsque la main stimulée se trouvait dans l'hémi-champ controlatéral suggère donc que l'information proprioceptive module aussi la douleur. D'autres facteurs, comme couleur de la peau, peuvent aussi contribuer à l'analgésie visuelle. En effet, une peau rouge est généralement indicatrice d'une irritation ou d'une blessure, alors qu'une peau bleutée est généralement perçue comme froide et moins sensible. Une étude récente a d'ailleurs montré que la couleur d'un bras virtuel que les participants s'approprient par transposition influence leurs seuils de douleur (Martini *et al.*, 2013). Lorsque les participants recevaient une stimulation combinée à l'apparition d'une peau rougeâtre sur bras virtuel, leurs seuils de

douleur étaient diminués, alors que ceux-ci n'étaient pas affectés par la couleur bleue. Similairement, lorsque des participants subissent un stimulus douloureux alors qu'ils observent une main virtuelle qu'ils s'approprient par transposition, ils rapportent plus de douleur lorsque la main virtuelle est stimulée avec une aiguille plutôt qu'avec un coton-tige (Höfle *et al.*, 2012). Contrairement à l'analgésie visuelle, cette augmentation de la douleur perçue est associée avec une réduction de l'activité des bandes alpha dans le cortex cingulaire postérieur et le gyrus fusiforme (Höfle *et al.*, 2013).

2.2.2. Empathie

Voir quelqu'un souffrir nous rend plus sensibles à la douleur. Des études ont effectivement montré que de voir un acteur jouer le rôle de quelqu'un qui a mal entraine des rapports subjectifs de douleur plus élevés (Craig & Weiss, 1971; Craig *et al.*, 1975). Plusieurs parents ont été témoin de ce phénomène quand leur enfant se fait mal. Si le parent affiche une grimace signalant de la douleur, l'enfant aura tendance à pleurer. Par contre, s'il affiche un sourire, l'enfant passera généralement à autre chose assez rapidement. L'inverse est aussi vrai, car, dans certains cas, voir une personne endolorie inhibe l'expérience douloureuse de l'observateur. Turkat et collaborateurs (1983) en sont arrivés à cette conclusion en remarquant que le visionnement d'une personne tolérante à la douleur augmente le seuil de tolérance de l'observateur. Dans une étude similaire, des participants étaient exposés soit à des images déplaisantes (situations douloureuses, mutilation, etc.), soit à des objets neutres. Ils étaient ensuite soumis à des stimuli thermiques de différentes intensités. Il en a résulté que les participants qui ont vu les images désagréables étaient plus susceptibles de rapporter de la douleur, même lorsqu'aucun stimulus n'a été administré (Kirwilliam & Derbyshire, 2008).

Cette modulation de la douleur par l'observation d'autrui est gérée par plusieurs facteurs; l'empathie en particulier. Celle-ci est généralement définie comme étant la capacité à comprendre et à répondre aux expériences affectives uniques à une autre personne (Goubert *et al.*, 2005; Decety & Jackson, 2006). Malgré qu'elles soient perçues différemment, la douleur que l'on ressent directement et l'empathie ressentie pour la douleur d'autrui ont des représentations corticales très similaires (Figure 7) (Singer *et al.*, 2004; Jackson *et al.*, 2005;

Valentini *et al.*, 2012). L'étendue du chevauchement des patrons d'activité cérébrale est même corrélée aux niveaux d'empathie ressentie (Singer *et al.*, 2004). L'excitabilité cortico-spinale est aussi réduite sélectivement pour la partie du corps que les participants voient être stimulée chez les autres; un effet qui est en corrélation directe avec l'intensité supposée de la douleur ressentie chez la personne observée (Avenanti *et al.*, 2009).

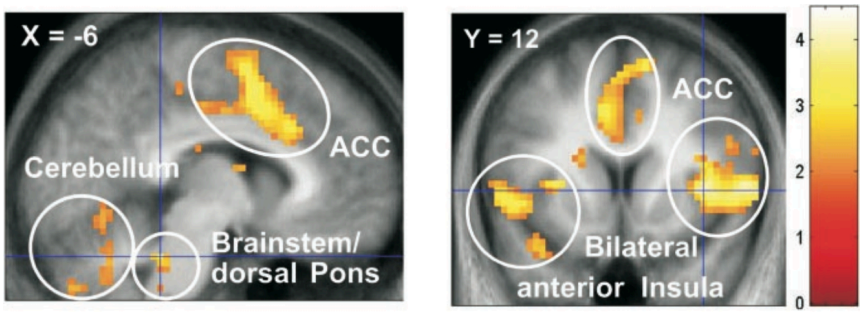

Figure 7. Représentations corticales communes à la douleur ressentie sur soi et à celle perçue chez les autres. Reproduit à partir de Singer et al., 2004.

Le contexte social dans lequel on baigne module aussi notre expérience de la douleur. En grandissant, nous apprenons que notre expérience personnelle est souvent similaire à celle de ceux qui évoluent autour de nous. Par exemple, si les personnes qui partagent la même pièce que nous ont froid, il y a de fortes chances que ressentions la même chose. Afin de concrétiser cette idée de manière contrôlée, Mazzoni et collaborateurs (2010) ont demandé à des participants d'inhaler un gaz qu'ils affichaient comme pouvant causer de la nausée, de la somnolence, des maux de tête et/ou de l'irritation. En manipulant le contexte social, les auteurs ont noté que les participants qui ont côtoyé des personnes exhibant ces symptômes étaient plus susceptibles de les subir eux-mêmes par transposition. D'autres études ont même montré que le degré de transposition sociale est corrélé au degré de similarité physique entre l'observateur et l'acteur (Serino *et al.*, 2008; Serino *et al.*, 2009). À l'inverse, le support social réduit l'expérience douloureuse. Ceci a été illustré dans plusieurs études dans lesquelles les participants qui ont reçu un soutien continu au cours du « cold pressor test » ont rapporté moins de douleur que les participants qui ont accompli cette tâche seuls ou en présence de quelqu'un avec qui ils ont interagi de manière neutre (Brown *et al.*, 2003; Jackson *et al.*, 2005). La familiarité de ceux qui nous apportent le soutient social est aussi un facteur non

négligeable en termes de modulation de signaux nociceptifs. En effet, des études récentes ont montré que tenir la main, ou simplement voir une photo ou une bande vidéo de sa tendre moitié réduit l'expérience douloureuse (Master *et al.*, 2009; Gougeon *et al.*, 2016).

Enfin, l'apprentissage associatif joue aussi un rôle important à savoir si un stimulus est perçu comme douloureux ou non. Au courant de nos vies, nous apprenons, par exemple, à associer l'aspect de nos blessures à la douleur qu'elles causent. C'est donc, en grande partie, par simple observation que nous développons, au travers d'un conditionnement classique, des réponses autonomiques. C'est aussi de cette manière que l'appréhension d'un évènement douloureux est parfois suffisante pour causer la douleur (Schweiger & Parducci, 1981). En effet, les réponses conditionnées aux images désagréables peuvent moduler l'expérience douloureuse (Rainville *et al.*, 2005). Ceci a entre autres été démontré par une étude où le conditionnement aversif à partir de stimuli visuels a augmenté l'intensité perçue et le caractère déplaisant des stimulations thermiques; que celles-ci soient douloureuses ou non (Wunsch *et al.*, 2003).

3. Conséquences de la cécité

À la lumière des éléments décrits jusqu'ici, il n'est pas faux de dire que voir adoucit les maux. Cela dit, le contraire est-il vrai? Comment l'absence de vision affecte-t-elle notre perception de la douleur? Comment un non-voyant apprend-il à gérer cette sensation et comment son système nerveux traite-il les stimuli nociceptifs? On ne sait aujourd'hui que très peu sur le sujet. Par contre, les conséquences de la cécité sur les autres sens ont été largement documentées.

3.1. Conséquences neuronales

3.1.1. Aveugles de naissance

On a longtemps pensé que la cécité engendre une dégradation généralisée des fonctions sensorielles, car la vision, étant le sens dominant, serait nécessaire à la calibration des intrants auditifs et tactiles (Rauschecker, 1995). Malgré que l'idée ne soit pas entièrement erronée – comme illustré par la Figure 8A, on observe une réduction volumétrique de la matière blanche (bleu) et de la matière grise (rouge) chez les gens atteints de cécité congénitale –, nous savons aujourd'hui que le cerveau des aveugles congénitaux subit des changements structurels et fonctionnels majeurs qui permettent à ces individus d'être tout à fait aptes à percevoir le monde extérieur et même, dans certains cas, de surpasser les voyants (Kupers & Ptito, 2014). Plusieurs études animales ont montré que ces changements affectent non seulement le cortex occipital privé de ses afférences visuelles, mais aussi d'aires corticales responsables de l'intégration d'autres afférences sensorielles (Ptito & Desgent, 2006; Desgent & Ptito, 2012). On y observe, par exemple, que le cortex occipital d'animaux privés de vision à la naissance est activé par des stimuli non visuels. Plusieurs études ont confirmé que cette plasticité intermodale se produit aussi chez l'humain (Kupers & Ptito, 2014). En effet, on note une augmentation de l'épaisseur corticale (Figure 8B) et une plus grande activité cérébrale au repos (Figure 8C) au niveau du cortex visuel des aveugles congénitaux (Kupers *et al.*, 2009). Alors que les premières études dans le domaine se sont principalement concentrées sur les

sens du toucher et de l'ouïe, des études plus récentes ont peint un portrait plus global qui montre que le cortex visuel des aveugles congénitaux est multi-sensoriel (Kupers & Ptito, 2014) et qu'il est impliqué dans le traitement de plusieurs processus cognitifs non visuels (Amedi *et al.*, 2003; Burton *et al.*, 2003; Amedi *et al.*, 2004; Raz *et al.*, 2005; Kupers *et al.*, 2007; Stevens *et al.*, 2007; Bonino *et al.*, 2008; Cattaneo *et al.*, 2008; Kupers *et al.*, 2010).

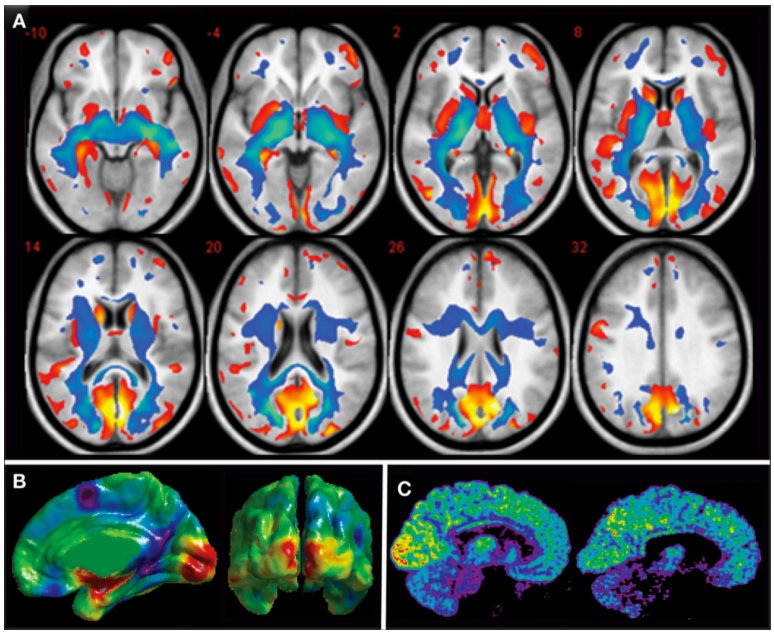

Figure 8. Changements structurels et fonctionnels chez l'aveugle de naissance. Reproduit à partir de Kupers et al., 2011.

3.1.2. Aveugles tardifs

Alors que le consensus actuel établit que la cécité congénitale est généralement synonyme de compensation sensorielle (Kupers *et al.*, 2011; Kupers & Ptito, 2014), le constat n'est pas aussi clair pour ce qui concerne la cécité tardive. Les premières études animales sur la privation sensorielle ont montré que l'étendue de la réorganisation structurelle et fonctionnelle du cortex visuel dépendait du moment de l'occlusion oculaire, plutôt que de sa durée (Wiesel & Hubel, 1965b; a; Hubel *et al.*, 1976). Ces inférences ont été corroborées par plusieurs études qui indiquent que les aveugles tardifs, contrairement aux personnes qui ont perdu la vue à la naissance ou très tôt dans le développement, ne subissent pas de changements corticaux significatifs (Blakemore, 1991; Price *et al.*, 1994; Kujala *et al.*, 1997a; Cohen *et al.*,

1999). Cependant, certaines études montrent le contraire. Par exemple, Burton et collaborateurs (2006) ont observé des activations du cortex visuel chez des aveugles tardifs pour une tâche de reconnaissance tactile de lettres. D'autres ont des résultats plus mitigés qui montrent que les changements structurels et fonctionnels que subissent les aveugles tardifs dépendent de la modalité sensorielle impliquée et surtout de la tâche comportementale à accomplir. Lorsqu'on les soumet à la lecture du Braille, les aveugles tardifs et les aveugles congénitaux ont des patrons d'activité cérébrale différents au niveau du cortex visuel, mais similaires lors de l'écoute de ces mêmes mots (Büchel *et al.*, 1998).

3.2 Conséquences comportementales

3.2.1. Aveugles de naissance

Le sens de l'audition a été l'un des plus explorés chez les aveugles congénitaux. L'exploration de leur capacité à discriminer des tons a montré qu'ils surpassaient les voyants (Niemeyer & Starlinger, 1981; Gougoux *et al.*, 2004; Wan *et al.*, 2010). Hamilton et collaborateurs (2004) ont même montré qu'il y a une plus grande prévalence à avoir l'oreille absolue chez ces individus que chez les voyants. En ce qui a trait à la localisation de sons, la littérature indique que les aveugles congénitaux ont, en général, de meilleures performances que les voyants (Lessard *et al.*, 1998; Röder *et al.*, 1999; Fieger *et al.*, 2006) et que cette performance supranormale est associée à l'activation de leur cortex visuel (Gougoux *et al.*, 2005; Voss *et al.*, 2008). Cependant, il semblerait que cet avantage ne se manifeste que sur le plan horizontal, car les aveugles congénitaux ont plus de difficulté que les voyants à apprécier l'élévation des sons dans des environnements acoustiques multidimensionnels (Zwiers *et al.*, 2001; Lewald, 2002). Ceci ne semble toutefois pas avoir de conséquences néfastes sur leur capacité à utiliser l'écholocation comme moyen compensatoire. En effet, des études montrent que les aveugles de naissance réussissent mieux que les voyants dans des tâches où ils doivent utiliser des indices d'écho pour localiser ou identifier la présence d'objets (Dufour *et al.*, 2005; Schenkman & Nilsson, 2010).

Dans le domaine tactile, le fait que les aveugles congénitaux lisent le Braille a lancé toute une série d'études sur la sensibilité de leurs doigts. Les résultats issus de celles-ci convergent et indiquent que la cécité congénitale a pour conséquence d'augmenter la capacité à discriminer des stimuli tactiles (Van Boven *et al.*, 2000; Goldreich & Kanics, 2003; Legge *et al.*, 2008). Legge et collaborateurs (2008), ont même montré que la sensibilité tactile des voyants décline avec l'âge d'environ 1% par année, alors qu'elle reste stable chez les aveugles. Plus récemment, on s'est intéressé à l'idée que cette sensibilité tactile supranormale des aveugles congénitaux serait peut-être due au fait que ceux-ci, étant obligés de se fier à cette modalité plus souvent que les voyants, cumulent simplement plus d'expérience. C'est notamment ce qu'ont exploré Wong et collaborateurs (2011) qui ont montré que les aveugles ont une performance supérieure aux voyants dans une tâche de discrimination tactile lorsque mesurée sur les doigts, mais pas lorsque mesurée sur les lèvres. De plus, la supra-sensibilité des doigts des aveugles est spécifique au doigt préféré pour la lecture du Braille et corrèle avec l'expérience de lecture. Une corrélation semblable a aussi été notée dans une étude où l'on a appliqué une stimulation magnétique transcrânienne (SMT) sur le cortex visuel de voyants et d'aveugles lecteurs de Braille (Ptito *et al.*, 2008). Les auteurs ont observé que la stimulation du cortex visuel des voyants induit des phosphènes dans leur champ visuel, alors qu'elle induit des picotements dans les doigts des aveugles. De surcroit, plus le lecteur de Braille est expérimenté, plus il y a de sites du cortex visuel qui activent des sensations sur les doigts (Figure 9).

Plus récemment, on s'est intéressé aux sens chimiques. Alors que l'odorat des aveugles congénitaux semble être plus fin que celui des voyants (Murphy & Cain, 1986; Rosenbluth *et al.*, 2000; Cuevas *et al.*, 2009; Beaulieu-Lefebvre *et al.*, 2011), on ne peut pas en dire autant pour leur goût. En effet, Gagnon et collaborateurs (2013) ont montré que les aveugles de naissance ont une sensibilité et des capacités d'identification des goûts de base inférieure à celle des voyants. Les auteurs attribuent ce résultat au fait que les aveugles sont confrontés à plus d'obstacles – l'emballage des aliments limite la quantité d'indices sensoriels, la rareté des menus en Braille dans les restaurants, etc. – dans la vie courante qui diminuent leur exposition à des variétés de goûts différents. Ceci a été corroboré par une étude subséquente qui montre que la supériorité olfactive des aveugles de naissance est spécifique à la voie ortho-nasale, car

ils perdent leur avantage lorsqu'ils sentent des odeurs de manière rétro-nasale (Gagnon *et al.*, 2015).

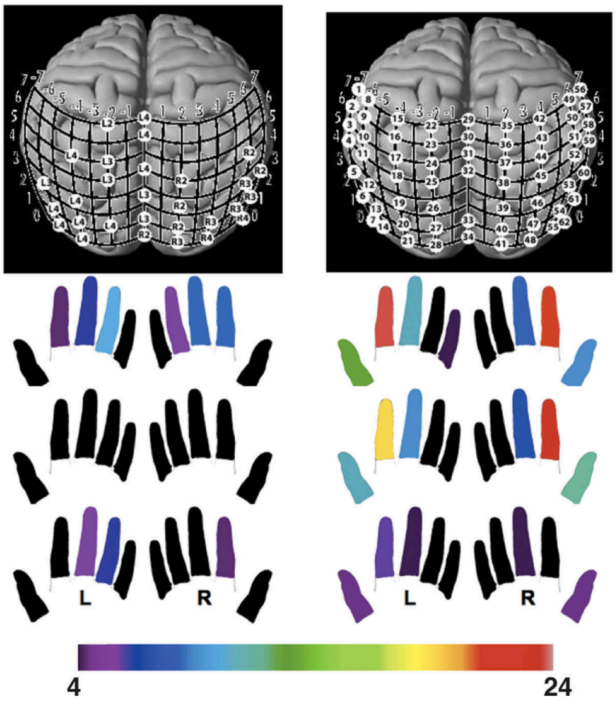

Figure 9. Paresthésies induites sur les doigts de lecteurs de Braille novice (à gauche) et expérimenté (à droite) par SMT du cortex visuel. Reproduit à partir de Kupers et al., 2011.

3.2.2. Aveugles tardifs

Les résultats comportementaux obtenus de l'étude des aveugles tardifs sont à l'image de ce qui a été rapporté sur leur potentiel de plasticité cérébrale et intermodale. En effet, la littérature est ponctuée de rapports contradictoires concernant la performance de ces individus dans différentes tâches cognitives. D'un côté, plusieurs études montrent que les aveugles tardifs surpassent les voyants dans des tâches de discrimination tactile (Goldreich & Kanics, 2003; Voss *et al.*, 2004; Fieger *et al.*, 2006; Legge *et al.*, 2008). Parfois, il arrive même qu'ils atteignent le niveau de performance que l'on observe chez les aveugles congénitaux, comme l'ont montré Dufour et collaborateurs (2005) pour une tâche d'écholocation ou encore Röder et collaborateurs dans une tâche de mémorisation de sons (Röder & Rösler, 2003). D'un autre côté, il y a toute une littérature qui montre que les aveugles tardifs ont une sensibilité et des

performances cognitives similaires à celles des voyants dans des tâches auditives (Wan *et al.*, 2010) et tactiles (Grant *et al.*, 2000; Burton & McLaren, 2006; Alary *et al.*, 2008). Il y a aussi des études qui ont des résultats plus nuancés, indiquant une performance intermédiaire des aveugles tardifs, i.e. à mi-chemin entre celle des voyants et celle des aveugles congénitaux (Collignon *et al.*, 2009).

4. Problématique et hypothèses

4.1. Pertinence du projet et hypothèses générales

Les études énumérées ci-dessus montrent indéniablement que la cécité entraine des changements plastiques dans le cerveau qui se traduisent généralement par une compensation sensorielle (Kupers & Ptito, 2014). L'étendue de cette compensation dans une modalité sensorielle donnée dépend fortement de la pertinence de cette dernière dans le quotidien des non-voyants et de la quantité d'entrainement que les tâches cognitives en question ont subi. Vu l'importance de la nociception dans la prévention du danger et dans le maintien de l'intégrité du corps (Tracey, 2011), nous nous sommes demandé si cette branche du système somesthésique est, elle aussi, propice à une compensation sensorielle. À ce jour, très peu d'études ont étudié de façon systématique l'influence de la cécité sur la nociception. Le but de ce travail est donc d'évaluer l'impact de la privation visuelle sur la perception de la douleur et, plus largement, des stimuli thermiques. Cette thèse tire son originalité non seulement du fait qu'elle traite d'un sujet encore inexploré, mais aussi de la combinaison d'approches méthodologiques sophistiquées et d'équipement à la fine pointe de la technologie que très peu de laboratoires dans le monde possèdent.

4.1.1. Implications comportementales

La vision joue un rôle très important dans la prévention du danger. Tout comme l'ouïe, elle nous permet de percevoir une menace à très grande distance, mais elle permet aussi d'identifier la nature du danger longtemps avant d'y être exposé. Chez les animaux, le comportement en milieu hostile se décrit en un continuum de risque qui se décompose en trois phases : pré-exposition au danger, exposition au danger et confrontation avec le danger (Fanselow, 1994). La première phase décrit les comportements exploratoires adoptés en milieu inconnu. C'est durant cette phase, généralement à faible risque, que l'animal gère le dilemme curiosité-sécurité. La deuxième phase décrit le moment où l'animal détecte un danger; un prédateur, par exemple. Le patron comportemental qui lui est associé est généralement

préprogrammé (inné) et varie selon l'espèce animale (Bolles, 1970). La phase d'exposition au danger comporte un risque élevé et engendre le plus souvent un comportement de pétrification *('freezing behavior')* qui permet à l'animal d'éviter de se faire remarquer et de se donner le temps d'évaluer quelle serait la meilleure manière d'agir afin de s'en sortir indemne. Si l'animal ne réussit pas à éviter la confrontation et que le danger est imminent ou inévitable, c'est le mode lutte ou fuite qui est enclenché (Combe & Fujii, 2011).

En l'absence de vision, les deux premières phases d'évitement du danger sont compromises, surtout si la menace est inaudible et inodore; chose très commune dans le quotidien des non-voyants. Il n'y a qu'à penser aux obstacles sur lesquels ces individus se heurtent lors de la navigation ou encore aux sources de chaleur qui pourraient les brûler. Une étude récente a d'ailleurs décelé une répercussion de l'absence de vision sur les patrons comportementaux des aveugles qui correspondrait à la phase d'exposition au danger (Kunz *et al.*, 2012). En effet, on y montre que les aveugles congénitaux sont incapables de mimer avec précision les expressions faciales correspondant à différentes intensités de douleur, suggérant que la vision est nécessaire au raffinement de la communication de niveaux de détresse. Les non-voyants semblent donc moins outillés en patrons comportementaux précédant la confrontation avec le danger. Cela dit, il est possible que leur système nociceptif prenne le relais. En effet, cet intrant sensoriel est un candidat de choix pour compenser pour cette lacune, car une des fonctions biologiques de la douleur est d'adopter des comportements défensifs pour prévenir les blessures et de protection pour accélérer la guérison (Tracey, 2011). Suivant cette hypothèse, une hypersensibilité nociceptive déclencherait la sensation de douleur à des niveaux d'intensité plus bas que la normale, afin que les non-voyants aient plus de temps pour réagir aux menaces externes.

Les non-voyants ont aussi des lacunes comportementales qui pourraient être reliées à la phase de pré-exposition au danger. En effet, Gagnon et collaborateurs (2010) ont montré que les aveugles congénitaux font plus d'erreurs de navigation lorsqu'ils n'ont pas accès aux indices environnementaux (sonores ou autres) pour compléter la tâche. Est-il alors possible que ces individus aient développé un moyen de compenser pour ces lacunes? Naviguer dans l'obscurité totale est certainement très anxiogène et, sachant que l'appréhension d'un stimulus douloureux exacerbe l'expérience douloureuse (Ploghaus *et al.*, 1999; Ploghaus *et al.*, 2001;

Ploghaus *et al.*, 2003; Wiech *et al.*, 2008; Johnston *et al.*, 2012), une facilitation du traitement nociceptif par le système de modulation centrale de la douleur pourrait constituer une piste de réponse. De la même manière, il ne serait pas surprenant que les aveugles recrutent plus de ressources attentionnelles lorsqu'ils explorent leur environnement, ce qui augmenterait aussi l'intensité de la douleur perçue (Tracey & Mantyh, 2007). Nous postulons donc que l'absence d'indices visuels ait pour conséquence de mettre les non-voyants dans un état permanent d'hyper-vigilance qui modulerait les signaux nociceptifs à la hausse afin de mieux détecter les menaces externes.

4.1.2. Intégration multi-sensorielle

Au terme d'une analyse approfondie de la littérature, nous avons remarqué que tous les systèmes et sous-systèmes sensoriels ont été explorés chez les non-voyants, à l'exception de la douleur. En plus de ce que l'on pourrait comprendre sur la plasticité cérébrale et intermodale suivant la privation d'un sens, l'étude des aveugles dans le cadre de la perception thermique et nociceptive serait un bon moyen de mettre en lumière les mécanismes sous-jacents à l'analgésie visuelle. Jusqu'à ce jour, une seule étude s'est intéressée à cette question et elle montre que bander les yeux à des voyants pendant une semaine augmente leur sensibilité à la chaleur et à la douleur (Zubek *et al.*, 1964). En effet, ceux-ci répondent sentir plus rapidement la chaleur ou encore la douleur induite thermiquement. Curieusement, les auteurs ont remarqué que cet effet persiste quelques jours après que les participants recouvrent la vue (Figure 10). Ceci suggère que cette hypersensibilité à la chaleur et à la douleur n'est pas seulement due à l'absence d'effets analgésiques de la vision pendant la période d'aveuglement, mais aussi à des mécanismes compensatoires qui s'opèrent très vite en réponse à la privation visuelle. L'étude du système nociceptif chez les non-voyants servirait donc à mieux comprendre les effets à long terme de la privation visuelle sur la nociception et ainsi mieux cerner le rôle de la vision dans l'intégration multi-sensorielle et dans l'analgésie visuelle (Haggard *et al.*, 2013).

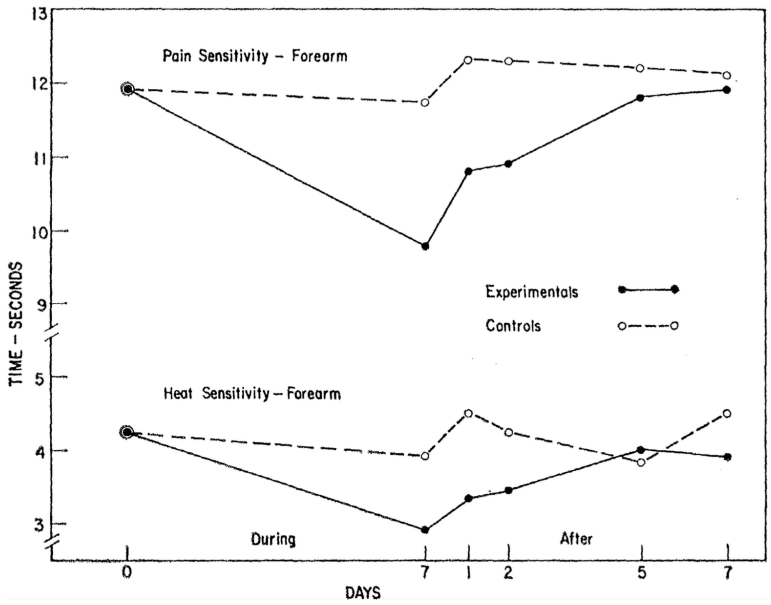

Figure 10. Décours temporel de la sensibilité thermique et nociceptive de voyants privés de vision pendant 1 semaine. Reproduit à partir de Zubek et al., 1964.

4.1.3. Motivation clinique

L'Organisation Mondiale de la Santé (OMS) estime qu'en 2014 près de 285 millions de personnes dans le monde présentent une déficience visuelle et que 39 millions d'entre elles sont totalement aveugles (World Health Organization, 2014). Ces individus vivent souvent dans des conditions précaires, ont une mauvaise qualité de vie et souffrent de troubles du sommeil, d'isolement et parfois même de dépression et d'anxiété (Huurre & Aro, 1998; Tabandeh *et al.*, 1998; Boulton *et al.*, 2006; Jones *et al.*, 2009; Bolat *et al.*, 2011; Nyman *et al.*, 2012). À ce bilan, s'ajoute le fait que plus de 80 % des aveugles sont âgés de 50 ans et plus (World Health Organization, 2014). Cinquante ans, c'est aussi l'âge moyen pour le développement de douleurs chroniques (Breivik *et al.*, 2006). Vu le vieillissement de la population que l'on connait dans plusieurs sociétés occidentales comme le Québec et le Canada (Statistique Canada, 2014; Banque de données des statistiques officielles sur le Québec, 2015), il ne serait pas surprenant que ces deux conditions gagnent du terrain dans les prochaines années. Ceci aurait pour effet de réduire encore plus la qualité de vie de nos ainés déjà très vulnérables. Il est donc primordial d'examiner les effets potentiels à court et à long terme de la cécité sur la perception de la douleur. Mieux comprendre les interactions entre

l'absence de vision et le système nociceptif pourrait aussi constituer le point de départ d'une série d'études qui conduirait ultimement à une réévaluation des traitements antalgiques et des programmes de réadaptation pour les personnes atteintes de cécité.

4.2. Hypothèses et justification des méthodes

Étant donné que l'influence de la cécité sur la perception thermique et nociceptive est un domaine de recherche relativement vierge, les possibilités de pistes d'étude sont nombreuses. Je vais ici détailler les aspects sur lesquels nous avons jugé bon de s'attarder afin d'initier ce champ de recherche.

4.2.1. Article 1

Le but de cette première étude était de tester notre hypothèse de recherche principale, à savoir si l'absence de la vision dès la naissance augmente la sensibilité à la douleur. Pour y arriver, nous avons mesuré les seuils de détection de douleur en réponse au chaud ou au froid chez des aveugles congénitaux et des contrôles voyants. Nous avons aussi recueilli leurs rapports subjectifs de douleur en réponse à différentes intensités de chaleur. Afin de discerner nociception et thermoception, nous avons aussi mesuré les seuils de détection de chaleur et de froid. De plus, nous avons soumis nos participants à des questionnaires mesurant le degré d'attention et d'anxiété en réponse à des situations douloureuses de la vie courante, car, comme décrit plus haut, ces facteurs contribuent grandement à l'exacerbation de la douleur (Tracey & Mantyh, 2007). Finalement, nous avons testé la reproductibilité des nos résultats dans une cohorte indépendante. Nous en avons profité pour aussi déterminer les influences culturelles sur la douleur en cas de cécité. En effet, la douleur est hautement subjective et son expérience est vécue différemment d'une culture à une autre (Pennebaker, 1982; Breivik *et al.*, 2006; Rahim-Williams *et al.*, 2012).

Les seuils de détection ont été mesurés en utilisant la méthode des limites, qui consiste à graduellement augmenter l'intensité du stimulus jusqu'à ce que le participant le détecte. Ceci a été accompli à l'aide d'une thermode qui permet de chauffer ou de refroidir la peau de

manière précise et contrôlée. Quant aux rapports subjectifs de douleur, ils ont été quantifiés sur une échelle de Likert en réponse à des stimuli laser d'intensités variables (Figure 11). Contrairement à la thermode, le laser CO_2 utilisé ici permet de chauffer la peau sans contact, éliminant ainsi la contribution des fibres Aβ à la sensation de douleur.

Figure 11. Thermode TSA-II, Medoc, Haifa, Israel (à gauche) et laser CO_2 LSD, SIFEC, Ferrières, Belgique (à droite). Reproduit à partir des sites web des manufacturiers.

4.2.2. Article 2

Dans cette deuxième étude, nous avons voulu déterminer si le fait d'avoir eu une expérience visuelle affecte la perception de la douleur chez les non-voyants. Pour y arriver, nous avons répliqué l'étude 1, mais en recrutant un groupe d'aveugles tardifs cette fois-ci. Étant donné que la privation prolongée de vision augmente la sensibilité à la douleur (Zubek *et al.*, 1964), nous nous attendions à ce que la cécité tardive module à la hausse les signaux nociceptifs.

4.2.3. Article 3

Cette troisième étude avait pour but de déterminer si les aveugles congénitaux ont une capacité de discrimination de température supranormale. Cette hypothèse est basée sur deux observations documentées dans la littérature. La première montre que les humains peuvent discriminer une grande variété de matériaux en se basant seulement sur les propriétés de diffusivité thermique de ceux-ci (Ho & Jones, 2006; Yang *et al.*, 2008; Kahrimanovic *et al.*, 2009). Il ne serait donc pas surprenant que les non-voyants comptent plus souvent sur ce genre

d'indices environnementaux pour reconnaitre des objets, ce qui, ultimement, raffinerait leur aptitude à détecter les différences subtiles de température. Le deuxième indice de la littérature sur lequel se fonde no`tre hypothèse est que la thermoception participe activement à l'évitement des brulures (Green, 2004). En effet, la chaleur est codée par l'activité combinée de thermorécepteurs et de nocicepteurs, suggérant que les fibres thermiques contribuent à la douleur (Bushnell *et al.*, 1983; Defrin & Urca, 1996; Craig *et al.*, 2001; Defrin *et al.*, 2002; Green, 2004). Par conséquent, une augmentation rapide de la température, même à des intensités inoffensives de chaleur, peut être codée comme étant dangereuse. Si le système nociceptif prend effectivement le relais pour initier plus rapidement les patrons comportementaux d'évitement du danger en cas de cécité, il ne serait donc pas surprenant que les non-voyants aient plus de facilité à percevoir les changements rapides de température.

Dans la thermoception, l'étendue de la surface stimulée est aussi importante que son intensité (Kenshalo *et al.*, 1967; Stevens & Marks, 1979; Stevens, 1991; Yang *et al.*, 2008). Nous avons donc aussi comparé la susceptibilité à la sommation spatiale de la chaleur des aveugles à celle des voyants. Pour y arriver, nous avons eu recours à deux thermodes dont les superficies différaient (Figure 12).

Figure 12. Thermode TSA-II, Medoc, Haifa, Israel de 2,56 cm^2 (à gauche) et de 9,00 cm^2 (à droite). Reproduit à partir du site web du manufacturier.

4.2.4. Article 4

Dans cette quatrième étude, nous avons voulu mettre en lumière les mécanismes sous-jacents à la perception de la douleur chez les gens atteints de cécité. Notre travail s'est fondé sur des études qui ont montré que les aveugles congénitaux ont des réponses plus fortes aux menaces auditives (Klinge *et al.*, 2010) et détectent plus facilement les odeurs à valence négative, telles que la peur et le dégoût (Iversen *et al.*, 2015). Nous sommes donc partis de

l'idée que si les non-voyants sont plus vigilants et attentifs aux dangers environnementaux, ils devraient détecter plus facilement et répondre plus rapidement aux stimuli nociceptifs.

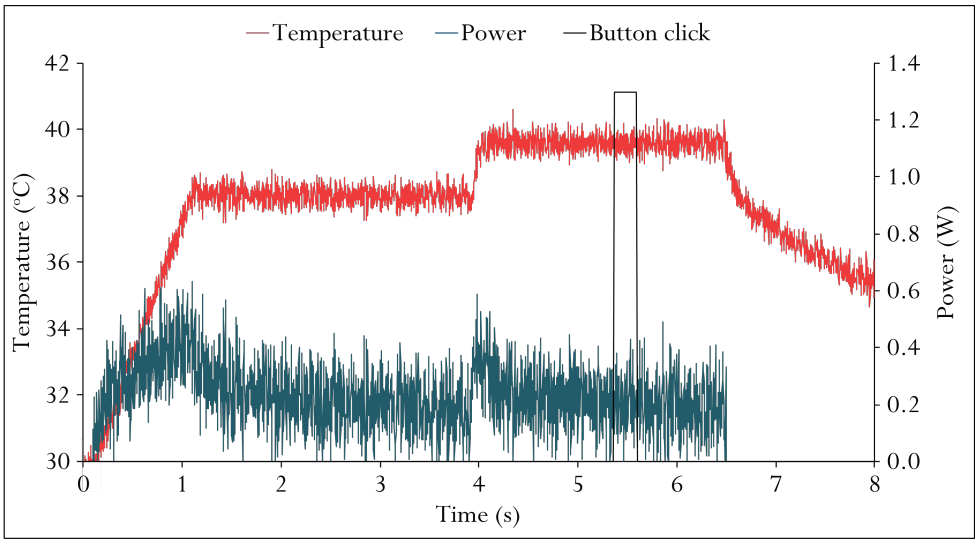

Figure 13. Décours temporel d'une stimulation au laser CO_2. Schéma original.

Pour tester cette hypothèse, nous avons mesuré chez des aveugles et des voyants la fréquence de détection et les temps de réaction à des stimuli nociceptifs administrés à l'aide du laser CO_2 décrit plus haut. En plus de permettre de stimuler la peau thermiquement sans activer les fibres tactiles, cet appareil a des propriétés uniques qui permettent une grande précision de stimulation. En effet, il est équipé d'une unité infrarouge intégrée dans la tête du stimulateur qui permet de mesurer la température de la peau à une fréquence de 0,5 kHz et d'ajuster en temps réel la puissance générée par le système afin de maintenir une température stable. Le laser CO_2 permet aussi de mesurer les temps de réaction des participants avec une précision de ±2 ms (Figure 13). Ces deux propriétés combinées nous ont permis de profiter de l'organisation anatomo-physiologique du système nociceptif afin de discerner la contribution respective des fibres C et A∂ dans la perception de la douleur chez les aveugles congénitaux et tardifs. En effet, comme décrit dans le chapitre d'introduction, ces fibres ont des vélocités de conduction de l'influx nerveux et répondent à des plages de température qui diffèrent grandement, ce qui se traduit en une distribution bimodale de la fréquence de détection de stimuli nociceptifs (Figure 14).

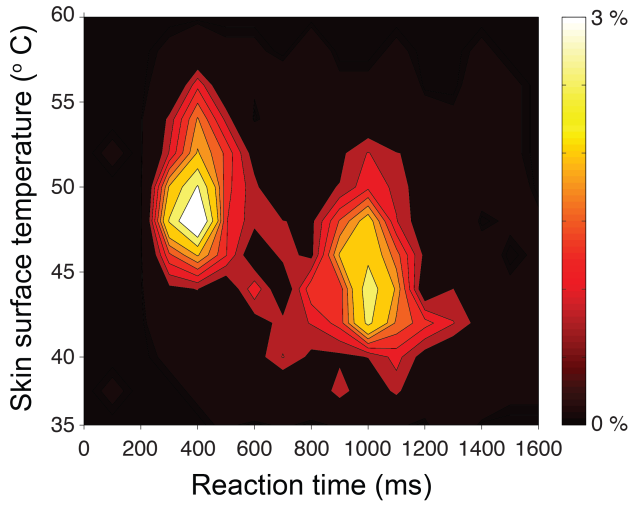

Figure 14. Fréquence de détection de stimuli laser CO_2 chez des voyants aux yeux bandés. La distribution de gauche correspond à l'activité des fibres Aδ et celle de droite à l'activité des fibres C. Reproduit à partir de Slimani et al., 2016.

4.2.5. Article 5

Suivant le postulat énoncé plus haut qui veut que de vivre dans le noir a sûrement des répercussions sur les comportements d'exploration et d'évitement du danger, le but de cette dernière étude a été d'évaluer la contribution de facteurs psychologiques comme l'anticipation et l'anxiété sur la perception de la douleur en cas de cécité. En effet, des études ont montré que perception de la douleur est fortement influencée par l'état psychologique d'une personne, et que l'anxiété exacerbe la douleur induite expérimentalement (Ploghaus *et al.*, 2003; Tang & Gibson, 2005; Tracey & Mantyh, 2007). En nous basant sur des paradigmes expérimentaux existants (Figure 15), nous avons donc manipulé les conditions expérimentales de manière à ce que les participants subissent des stimuli nociceptifs dans une situation normale et dans une situation d'appréhension de la douleur. Cela nous a permis de comparer leurs rapports subjectifs de douleur selon qu'ils soient anxieux ou non (Ploghaus *et al.*, 2001). Suivant notre hypothèse générale, nous nous sommes attendus à ce que, comparés aux voyants, les aveugles congénitaux soient plus susceptibles de voir leur douleur exacerbée par des hausses de niveaux d'anxiété induite expérimentalement.

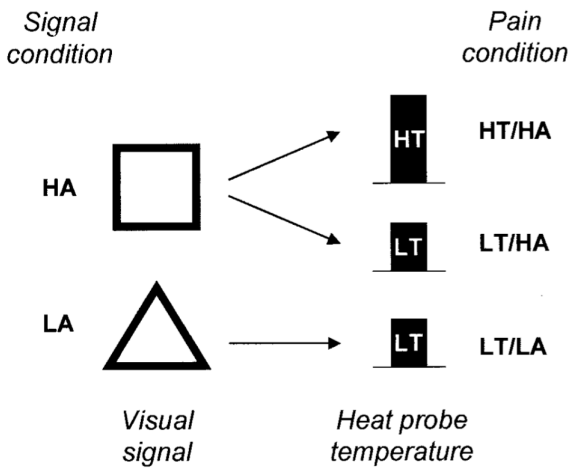

Figure 15. Manipulation expérimentale des niveaux d'anxiété. Contrairement au triangle qui assure de recevoir un stimulus inoffensif, le carré signale la possibilité de subir un stimulus très douloureux et cause donc de l'anxiété. HA (high anxiety), LA (low anxiety), HT (high temperature), LT (low temperature). Reproduit à partir de Ploghaus et al., 2001.

II. CORPS DE L'OUVRAGE

Article 1. Hypersensitivity to pain in congenital blindness

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Hypersensitivity to pain in congenital blindness

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Abstract

Vision is important for avoiding encounters with objects in the environment that may imperil physical integrity. We tested whether, in the absence of vision, a lower pain threshold would arise from an adaptive shift to other sensory channels. We therefore measured heat and cold pain thresholds and responses to suprathreshold heat stimuli in 2 groups of congenitally blind and matched normal-sighted participants. We also assessed detection thresholds for innocuous warmth and cold, and participants' attitude toward painful encounters in daily life. Our results show that, compared to sighted subjects, congenitally blind subjects have lower heat pain thresholds, rate suprathreshold heat pain stimuli as more painful, and have increased sensitivity for cold pain stimuli. Thresholds for nonpainful thermal stimulation did not differ between groups. The results of the pain questionnaires further indicated that blind subjects are more attentive to signals of external threats. These findings indicate that the absence of vision from birth induces a hypersensitivity to painful stimuli, lending new support to a model of sensory integration of vision and pain processing.

Keywords

Plasticity; Vision; Pain perception; Multisensory integration

1. Introduction

One of the key biological functions of acute pain is to prevent bodily injury [18]. Vision thereby plays a critical role, as it allows rapid detection and avoidance of stimuli that are potentially hazardous to the body. Absence of visual cues may therefore lead to an adaptive state of heightened vigilance for nociceptive stimuli. Thus, a landmark study by Zubek and colleagues (1964) showed that prolonged visual deprivation in normal-sighted subjects causes hypersensitivity to heat pain [21]. The role of vision in pain perception was further highlighted in recent studies showing that viewing the stimulated limb rather than another part of the body resulted in lower pain ratings [7] and [8]. Other studies have shown that the visual context in which pain occurs, such as the perceived size of the stimulated limb [9] or the viewing of partner photographs [10], also modulates pain perception. We here tested the hypothesis that the absence of vision from birth leads to a leftward shift in the stimulus–response function to painful stimuli.

In the first experiment, we compared pain thresholds and responses to suprathreshold pain stimuli in congenitally blind (CB) and normal-sighted (NS) participants. In a second experiment, we measured detection thresholds for innocuous warmth and cold perception to test whether the increased pain sensitivity measured in blind participants is specific for noxious stimuli or also applies to innocuous thermal stimuli. As pain can be strongly affected by attention and anxiety [16], participants also completed questionnaires that measure these attitudes toward painful encounters in daily life. Finally, in a third experiment, we tested the reproducibility of our results in an independent study population with a culturally distinct mode of responding to pain. There is evidence that, compared to people from northern countries (eg, Denmark), people in southern countries (eg, Italy) are more emotionally expressive [14] and responsive to pain [1] and [15].

2. Methods

2.1. Study subjects

Table 1. Characteristics of blind subjects.

Population	ID	Age	Gender	Onset	Ethiology	Visual perception
Italian	SL	42	M	0	Fibroplasia (incubator)	-
	DCL	72	M	0	Congenital optic atrophy	-
	RA	37	M	0	Congenital glaucoma	-
	GM	64	M	0	Congenital glaucoma	-
	SM	43	M	0	Congenital glaucoma	-
	GS	35	M	0	Fibroblasia (incubator)	-
	NV	51	F	0	Congenital atrophy optic nerve	-
	SG	40	M	0	Retina not developed	-
	CG	21	F	0	Microphthalmia	-
	BA	44	M	0	Congenital photophobic retinitis	-
	BM	63	M	6 months	Congenital cataract	-
Danish	ABV	43	M	0	Retinoblastoma	-
	OC	36	F	0	Retinopathy of prematurity	-
	GDK	37	M	0	Retinopathy of prematurity	-
	AHC	43	M	0	Retinopathy of prematurity	-
	AJ	39	M	0	Retinopathy of prematurity	Bright light
	HJ	58	M	0	Retinopathy of prematurity	-
	PK	42	M	6 months	Meningitis	Bright light
	HL	42	F	0	Retinopathy of prematurity	-
	DM	57	M	0	Retinopathy of prematurity	-
	EN	25	M	0	Retinopathy of prematurity	Bright light
	JO	49	M	0	Retinopathy of prematurity	-
	SO	20	M	0	Retinopathy of prematurity	-
	HP	36	M	3 months	Unknown	-
	VR	61	F	0	Retinopathy of prematurity	-
	CR	26	M	0	Retinopathy of prematurity	-
	PS	28	F	0	Retinopathy of prematurity	-
	JT	34	M	0	Retinopathy of prematurity	-
	PAM	50	M	0	Retinopathy of prematurity	-
	LAS	24	F	0	Retinopathy of prematurity	-
	HM	21	M	0	Leber's amaurosis	-
	CB	59	F	0	Retinopathy of prematurity	-

Participants were recruited from our database of congenitally blind subjects or by advertisement. In a first cohort, we recruited 11 congenitally blind (2 female and 9 male; mean age 46.5 ± 14.8 years, range 21–72 years) and 15 normal-sighted (2 female and 13 male; mean

age 37.2 ± 11.4 years; range 25–64 years) control subjects from an Italian population. In a second cohort, we included 18 congenitally blind (4 female and 14 male; mean age 40.3 ± 11.6 years, range 20–61 years) and 18 sighted control subjects (7 female and 11 male; mean age 41.2 ± 13.2 years, range 25–65 years) from a Danish population. Inclusion criteria were being in good health without known neurological or psychiatric problems, and having blindness of peripheral origin within the first year of life (blind subjects). Subject characteristics are listed in Table 1. The study protocol was approved by the ethics committees of the University of Copenhagen and the University of Pisa, and all participants gave informed consent.

2.2. Threshold assessments for innocuous and noxious heat and cold perception

We used a Peltier-based thermotest (TSA-II, Medoc, Haifa, Israel), with a thermal probe measuring 3 × 3 cm, to determine thresholds for innocuous and noxious thermal stimulation on the medial forearm. To reduce anxiety, blind subjects were allowed to explore the equipment by touch and received a detailed verbal description of it by the experimenter. In addition, most of the blind subjects already knew the experimenters from previous studies, making it further unlikely that they would be more anxious than the controls. The sighted subjects saw the equipment and the experimenter before testing but they were blindfolded during both threshold and suprathreshold testing. We first familiarized participants with the thermal stimuli and the pain rating procedures. Baseline temperature of the thermode was set to 32°C and ramp rate to 3°C per second for heat pain and cold pain thresholds (experiment 1) and to 1°C per second for nonpainful warmth and cold thresholds (experiment 2). Five measurements were taken for each threshold with an interstimulus interval of 10 to 15 seconds for nonpainful stimuli and 15 to 20 seconds for painful stimuli (Fig. 1A). A sound cue was presented 2 to 5 seconds before the temperature change. The participant was asked to press as quickly as possible a response button when he/she felt heat pain or cold pain (experiment 1) or detected warmth or cold (experiment 2).

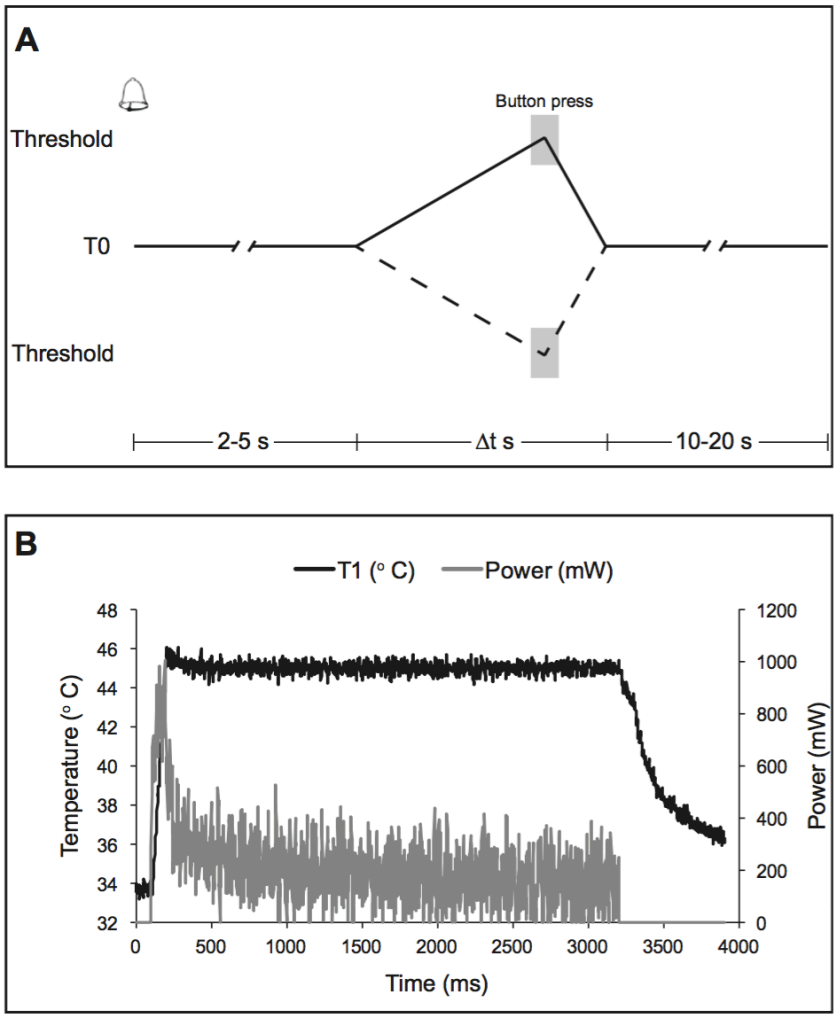

Fig. 1. Thermal thresholds and suprathreshold pain stimulation paradigms. (A) The contact-based thermode preheated the skin at 32°C (T0). A sound cue was presented 2 to 5 seconds before the ensuing increase (or decrease) in temperature. The participant pressed a button when he/she felt warm or cold (detection threshold) or pain (pain threshold). Thereafter, an interstimulus interval of 10 to 20 seconds was used. (B) The laser stimulator device stimulated the skin at a predetermined temperature (T1) for 3 seconds. Instant temperature control feedback allowed the delivery of enough power to stabilize the skin temperature throughout trials. The right axis shows the power output of the laser (expressed in mW) to maintain the skin at the predetermined temperature.

2.3. Suprathreshold pain ratings

For assessing responses to suprathreshold heat stimuli, we used a CO_2 laser stimulator device with a spot diameter of 6 mm (LSD, SIFEC, Ferrières, Belgium). As in the thermotest, blind subjects were allowed to explore the equipment by touch, and the experimenter gave a detailed verbal description of it. The stimuli were generated using a closed-loop control of laser power with online monitoring of target skin temperature. This allows highly accurate and contactless cutaneous stimulation of the thinly myelinated Aδ- and the unmyelinated C-fibers, without co-activation of the large myelinated Aβ-fibers [3]. A contactless skin temperature measurement unit, unique to this device, gives instant feedback, guaranteeing that the skin is brought and maintained with a high accuracy at the exact target temperature. We applied stimuli of 3-second duration at 43°, 45°, 47°, and 49°C targeted at the dorsal surface of the dominant hand (Fig. 1B). Stimuli were administered in a pseudo-randomized order to avoid the possibility that the same temperature would be delivered more than twice consecutively. An auditory cue preceded each laser stimulus. Participants rated their sensation verbally on a 10-point rating scale with "0" no pain, and "10" the most intense pain imaginable. Each stimulus intensity was presented 3 times and the average interstimulus interval was approximately 10 seconds (varying between 7 and 14 seconds). To avoid skin habituation, we moved the laser spot after each stimulation following a 3 × 3 dots matrix separated by 1 cm.

2.4. Pain questionnaires

Participants filled in the Pain Vigilance and Awareness Questionnaire (PVAQ) adapted for a nonclinical population [12] and the Pain Anxiety Symptoms Scale (PASS) [11]. Both pain questionnaires assess responses and attitudes toward painful encounters in daily life. The PVAQ comprises 16 items divided into the subscales "Intrusion," "Monitoring," and "Attention to changes in pain." The PASS consists of 20 items and is divided into the subscales "Physiological anxiety," "Cognitive anxiety," "Fear," and "Escape/Avoidance. Blind participants were presented with an audiotaped version of these questionnaires.

2.5. Statistical analyses

We used one-tailed unpaired t tests or Welch tests (depending on normality and equality of variance check) to assess group differences in thermal thresholds and suprathreshold pain ratings. In the suprathreshold experiment, the winsorized means/variances (20% of the ties were replaced) were calculated before performing the Welch tests [4]; the overall statistical group significance was calculated after averaging the suprathreshold heat ratings in the blind and sighted groups. Results were corrected for multiple comparisons (Bonferroni corrections, $\alpha = 0.05$). To estimate the relationships among demographic variables (ie, gender, age) and experimental data, we conducted a multiple linear regression analysis. We generated the regression models separately for the Italian and Danish sample and for threshold assessments and suprathreshold pain ratings. In each condition, we modeled age and gender as independent variables with thresholds and pain ratings as the dependent variables. We used the Fisher method for the summation of the single probability values to obtain an overall value of significance for each condition and sample. We applied a rough false-discovery rate correction to account for the 4 post-hoc tests of interest (adjusted $P = .030$).

The analysis of the PASS and PVAQ questionnaires data was performed using a Fisher linear discriminant analysis (FLDA). First, we tested for a discrimination function that could distinguish between sighted and blind subjects, separately in the Italian and Danish samples. The goodness of classification analysis was tested using leave-one-out cross-validation, and was balanced for unequal sample sizes. Second, we ran a principal component analysis (PCA; direct oblimin, $\delta = 0$) on the raw scores of the combined Italian and Danish samples to make a dimensionality reduction while preserving as much data variability as possible. Third, we performed an FLDA on the resulting PCA factor scores to test whether blind and sighted participants responded differently, irrespective of differences in cultural background.

3. Results

In the first experiment, we measured pain thresholds and responses to suprathreshold heat stimuli in the study cohort recruited from an Italian population. Compared to their sighted counterparts, blind participants had significantly lower heat pain (NS: 46.5 ± 2.2°C, CB: 43.9 ± 3.0°C; P = .009) and significantly higher cold pain (NS: 7.3 ± 4.8°C, CB: 14.2 ± 6.5°C; P = .002) thresholds (Fig. 2A). In line with the pain threshold data, blind participants rated the suprathreshold heat stimuli as being more painful than control participants (P = .002, Fig. 2B). More specifically, blind participants scored significantly higher than normal-sighted participants for the 43°C (NS: 2.2 ± 1.5, CB: 3.6 ± 1.4; P = .011), 45°C (NS: 2.9 ± 2.1, CB: 4.8 ± 1.5; P = .006) and 47°C (NS: 5.2 ± 1.8, CB: 7.0 ± .7; P < .001) stimuli, but not for the 49°C (NS: 6.9 ± 1.6, CB: 7.9 ± .8; P = .019). There was no significant effect of the variables age and gender in the threshold assessments (P = .250). For the suprathreshold pain ratings, age and gender had a significant effect on the 43°C ratings (P = .044), whereas the ratings of the 45°, 47°, and 49°C were not affected (respectively: P = .066, P = .164, P = .426).

In the second experiment, we tested whether the blind subjects' thermal hypersensitivity is specific for pain, or applies also to innocuous thermal stimuli. In contrast to the pain thresholds, we found no group differences in detection thresholds for innocuous warmth (NS: 33.9 ± .8°C, CB: 33.7 ± 1.0°C; P = .321) and cold (NS: 31.2 ± .2°C, CB: 30.8 ± 1.4°C; P = .156) (Fig. 2A). To rule out the possibility that the absence of a difference in innocuous warm and cold thresholds is due to a slower motor response in blind subjects, we measured reaction times to a very fast-rising A-δ fiber stimulus in a subset of blind and normal-sighted subjects (each n = 14). The results showed that the average reaction times of congenitally blind (477 ± 106 milliseconds) and sighted (437 ± 39 milliseconds) were not statistically different (P = .205), arguing against the possibility that the absence of a group difference in innocuous warm and cold thresholds is due to floor effects.

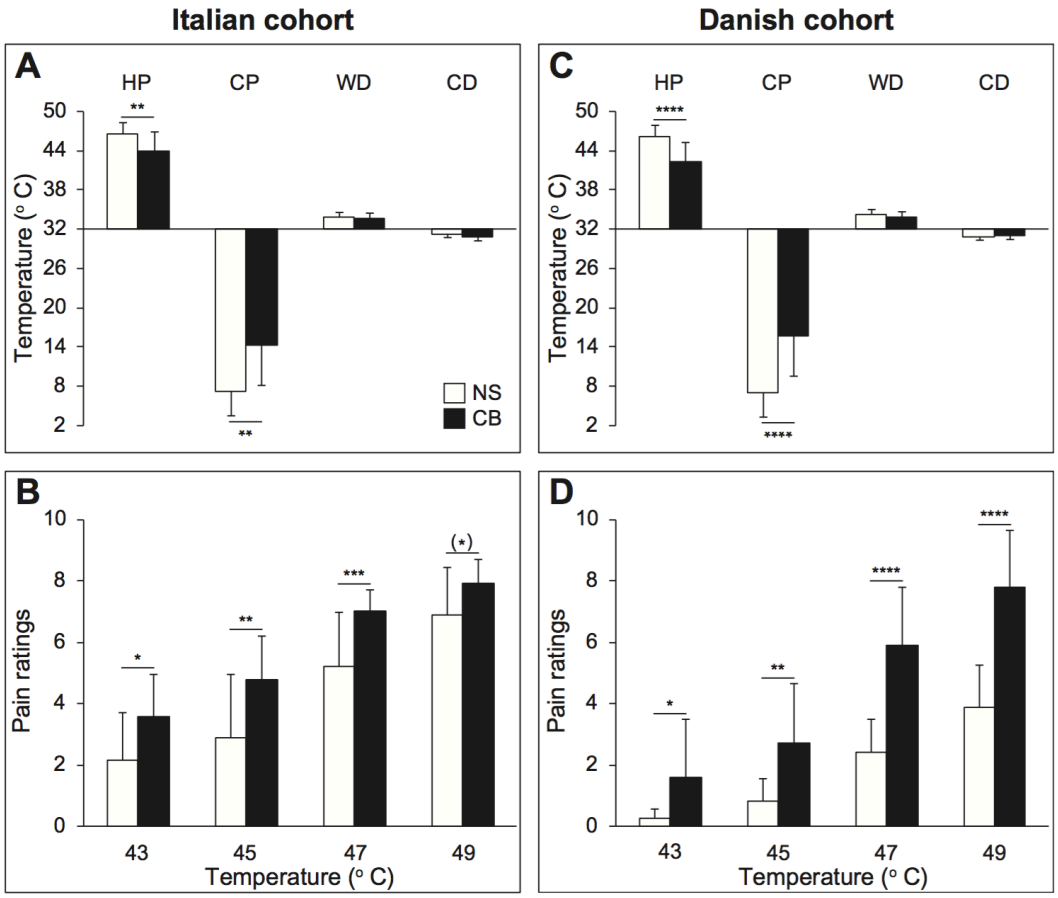

Fig. 2. Thermal sensitivity in congenitally blind (CB) and normal-sighted (NS) controls. (A–C) Blind participants had lower heat pain (HP) and cold pain (CP) thresholds compared to sighted controls. There were no group differences for innocuous warmth detection (WD) and cold detection (CD) thresholds. (B–D) Blind subjects rated suprathreshold pain stimuli as more painful than sighted controls. Error bars represent the standard deviation. (∗)P > .05 (not surviving Bonferroni correction); ∗P < .05; ∗∗P < .01; ∗∗∗P < .001; ∗∗∗∗P < .0001.

We assessed the impact of pain on everyday life with the PVAQ and the PASS. An FLDA analysis using the raw scores allowed us to predict with an accuracy of 80% (chance level: 50%) whether a participant was blind or sighted (canonical $r^2 = 0.72$, $\chi^2 = 18.16$, df = 4, P = .003). More specifically, the $PASS_{\_escape/avoidance}$ and $PASS_{\_cognitive\_anxiety}$ scores differentiated blind versus sighted participants.

In the third experiment, we tested the reproducibility of our results in an independent Danish study population. In line with the results from the Italian cohort, the Danish blind subjects had significantly lower heat pain (NS: 46.2 ± 1.7°C, CB: 42.3 ± 3.0°C; P < .0001) and cold pain (NS: 7.1 ± 3.7°C, CB: 15.6 ± 6.2°C; P < .0001) thresholds, and similar thresholds

for nonpainful thermal stimulation (Fig. 2C). Also in concordance with the results from the Italian sample, Danish blind subjects rated suprathreshold thermal stimuli as more painful than did their sighted peers ($P < .0001$). Indeed, blind subjects scored significantly higher than the sighted controls for the 43°C (NS: .3 ± .3, CB: 1.6 ± 1.9; $P = .011$), 45°C (NS: .8 ± .7, CB: 2.7 ± 1.9; $P = .002$), 47°C (NS: 2.4 ± 1.1, CB: 5.9 ± 1.9; $P < .0001$) and 49°C (NS: 3.9 ± 1.4, CB: 7.8 ± 1.9; $P < .0001$, Fig. 2D). Age and gender had no effect on pain threshold assessments ($P = .880$), nor on suprathreshold pain ratings ($P = .470$). An FLDA analysis of the PVAQ and PASS data differentiated blind from sighted subjects with an accuracy of 77% (canonical $r^2 = 0.46$, $\chi^2 = 8.7$, df = 1, $P = .003$). More specifically, the $PVAQ_{\_attention\_to\_changes\_in\_pain}$ scores differentiated blind versus sighted participants.

Finally, we conducted a PCA analysis on the 7 subfactors of the PVAQ and PASS on the combined Italian and Danish data-sets. After factor extractions, the variables $PVAQ_{\_monitoring}$, $PASS_{\_cognitive\_anxiety}$, $PASS_{\_escape/avoidance}$ that showed a complex structure (ie, loading more than 0.4 on the resulted components) and were hence discarded from the analysis. Correlations between the $PASS_{\_fear}$, $PASS_{\_physiological\_anxiety}$, $PVAQ_{\_attention\_to\_changes\_in\_pain}$, and $PVAQ_{\_intrusion}$ subfactors were sufficiently high to be retained (Bartlett's test of sphericity ($\chi^2 = 84.02$, df = 6, $P < .0001$). The ensuing FLDA on the PCA regression factor scores revealed 1 discriminant function by the all-variables-together method (canonical $R^2 = 0.41$, Eigenvalue = 0.20) that significantly differentiated between blind and sighted participants ($\chi^2 = 11.986$, df = 2, $P = .002$) with a cross-validated balanced accuracy of 72.1% (chance level = 50%). Because the blind scored higher than the sighted on factor II (Fig. 3), we can infer that they are more attentive to signals of external threats.

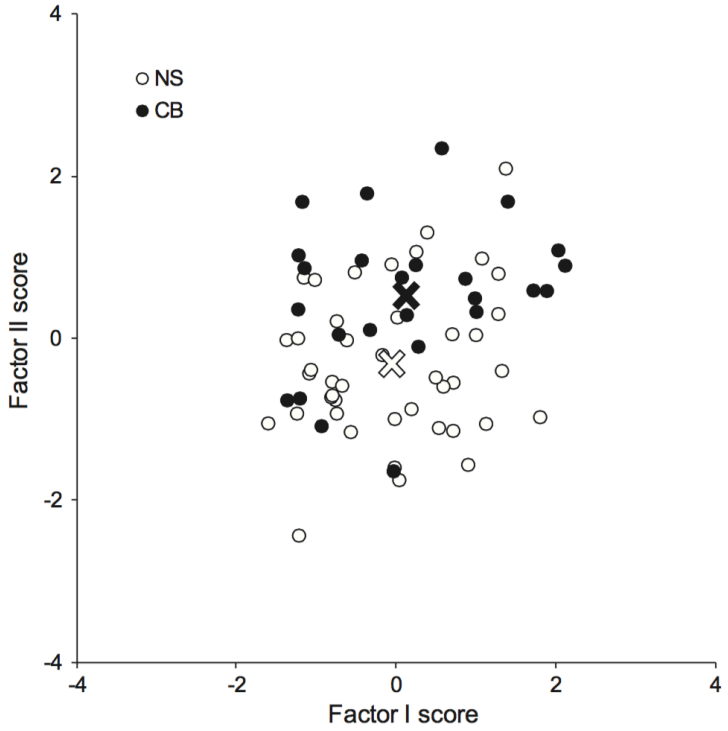

Fig. 3. Principal component analysis: projection of the data from the Pain Anxiety Symptoms Scale (PASS) and Pain Vigilance and Awareness Questionnaire (PVAQ) in Danish and Italian samples onto the first 2 principal components (80% of the cumulative variance explained). Congenitally blind (CB) and normal-sighted (NS) participants are represented as filled and open dots, respectively. Factors I and II result from an oblique rotation; higher values indicate higher correlation scores, with the average centered at 0. Filled and open crosses represent centroids after principal component analysis (PCA) of blind and sighted participants, respectively. Congenitally blind and sighted participants show a distinct pattern of factor loadings on the 2 resulting PCA components, where factor II (attention to pain) discriminates better than factor I (anxiety).

4. Discussion

Our data provide compelling evidence that congenitally blind individuals are hypersensitive to painful thermal stimuli. First, we found a consistent group difference, irrespective of the used outcome measure (pain thresholds or suprathreshold pain ratings), thermal modality (heat pain or cold pain) or stimulation type (contact-based heat or cold, or contactless infrared heat stimuli). Second, we obtained very similar findings in 2 different populations with a distinct mode of responding to pain [1] and [15]. Third, our psychometric results corroborated the quantitative sensory testing data. As thresholds for nonpainful thermal

stimuli were not altered, it is unlikely that our data are due to a generalized lower response criterion in blind subjects.

Previous studies conducted in normal-sighted subjects already showed that there exists an intricate interaction between vision and pain perception. The first demonstration of the effect of vision on pain perception was provided by Zubek and co-workers (1964) who reported that blindfolding over a 1-week period resulted in reduced heat pain thresholds, an effect that persisted for several days after removal of the blindfold [21]. More recent studies provided evidence that complete visual deprivation per se is not necessary, and that informative vision of the stimulated limb suffices to alter pain perception. These studies demonstrated that subjects report lower pain ratings when seeing the stimulated limb compared to a condition where the hand is occluded, or where participants see another body part or the hand of the experimenter [7], [8] and [9]. Interestingly, vision not only affects pain perception but the effect also goes the other way. Thus, Bingel and co-workers showed that pain modulates visual object processing, as evidenced by both reduced recognition accuracy and lowered activity in the lateral occipital cortex when performing a visual task during painful stimulation [2]. The present data reveal that the absence of vision from birth leads to a permanent state of pain hypersensitivity. Blind subjects had both lower pain thresholds and rated suprathreshold stimuli as more painful compared to their sighted counterparts. Whereas the heat pain threshold is a measure of first pain, mediated mainly by the more rapidly conducting Aδ-fibers, suprathreshold pain stimuli involve an important component of second pain that is mediated by C-fiber input. Blind participants showed hypersensitivity when tested for both heat pain and cold pain. It should be noted that these results were obtained with the sighted subjects in a condition in which they could not see the stimulated limb (because of the blindfolding), that is, a condition that would normally be associated with higher pain ratings [7] and [8]. It is therefore unlikely that the observed group difference can be explained by the fact that our control subjects were blindfolded and could not see the stimulated limb. However, we cannot exclude the possibility that blindfolding induced fear in the sighted subjects, which consequently elevated their pain thresholds [16]. Future studies need to examine whether the hypersensitivity also generalizes to nonthermal types of painful stimulation. Importantly, responses to nonpainful thermal stimulation were not different in

blind and sighted participants, suggesting that the results cannot be explained by an overall increase in the sensitivity to thermal stimuli.

Our psychophysical data are corroborated by the results of the pain questionnaires, which allowed us to classify participants with high accuracy as blind or sighted. The psychometric data further indicate that blind individuals are generally more attentive to signals of external threats, a factor that is known to enhance pain perception in sighted individuals [16] and [19]. The hypersensitivity to pain in congenitally blind participants might hence arise from an increased anxiety level caused by the absence of visual context in which pain occurs. Informative visual information increases the perceived level of control over a painful stimulus, which has been shown to reduce the subjective experience and neural responses to pain [17]. In view of the evolutionary importance of pain, blind individuals may hence up-regulate their pain alarm system to ensure body integrity. Together with recent findings of augmented responses to auditory signaling of threats in blind subjects [5], this suggests that the absence of vision leads to a general hypersensitivity to threatening stimuli, possibly mediated via increased amygdalar fight-or-flight responses [5].

Alternatively, our results may arise from the absence of normal inhibitory effects of vision on pain perception. This suggestion is supported by recent brain imaging studies showing that visual and noxious stimuli activate a partly overlapping cortical network [13], indicating an intricate integration of vision and pain processing. Anatomical evidence for this conjecture comes from a study showing the existence of a pathway linking the anterior cingulate cortex, a structure that plays a key role in pain processing, with visual cortex area 19 [20]. The observed hypersensitivity to pain in congenitally blind individuals is probably dependent on plastic processes that occur early in development [6], but the exact signaling pathways mediating it await future studies.

4.1. Conclusion

In conclusion, we have shown that the absence of vision from birth induces a hypersensitivity to painful stimuli, lending new support to a model of sensory integration of vision and pain processing.

Acknowledgments

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Pain perception is increased in congenital but not late onset blindness

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Abstract

There is now ample evidence that blind individuals outperform sighted individuals in various tasks involving the non-visual senses. In line with these results, we recently showed that visual deprivation from birth leads to an increased sensitivity to pain. As many studies have shown that congenitally and late blind individuals show differences in their degree of compensatory plasticity, we here address the question whether late blind individuals also show hypersensitivity to nociceptive stimulation. We therefore compared pain thresholds and responses to supra-threshold nociceptive stimuli in congenitally blind, late blind and normally sighted volunteers. Participants also filled in questionnaires measuring attention and anxiety towards pain in everyday life. Results show that late blind participants have pain thresholds and ratings of supra-threshold heat nociceptive stimuli similar to the normally sighted, whereas congenitally blind participants are hypersensitive to nociceptive thermal stimuli. Furthermore, results of the pain questionnaires did not allow to discriminate late blind from normal sighted participants, whereas congenitally blind individuals had a different pattern of responses. Taken together, these results suggest that enhanced sensitivity to pain following visual deprivation is likely due to neuroplastic changes related to the early loss of vision.

Introduction

In a recent study we showed that congenitally blind individuals have reduced thresholds to heat and cold pain, and rate supra-threshold nociceptive stimuli as more painful compared to normally sighted individuals [1]. In sharp contrast, thresholds for innocuous cold and warmth perception were not altered, suggesting a specific effect for noxious thermal processing. These results add to a growing body of evidence that vision may affect pain processing [2–8]. The purpose of this study is to examine whether the loss of vision later in life also causes a hypersensitivity to pain.

There is abundant evidence from animal experiments that visual deprivation from birth causes dramatic plastic changes in the structural and functional organization of the visual cortex. The extent of these neuroplastic changes depends more strongly on the onset than on the duration of visual deprivation [9–12]. These findings have been corroborated by recent behavioral and brain imaging studies in humans showing that early blindness leads to compensatory plasticity and to a reorganization of the visual cortex [13, 15]. In sharp contrast, studies on late blindness have led to conflicting results. Whereas some studies showed that late blind individuals do not differ from normally sighted controls in various sensory and cognitive tasks [15–22], other studies indicated that late blindness also leads to sensory compensation and cross-modal plasticity [23–27].

To investigate whether late blind individuals also show hypersensitivity to nociceptive stimulation, we compared thermal pain thresholds and supra-threshold pain ratings of late blind (LB), congenitally blind (CB) and normally sighted (NS) volunteers. Participants also had to answer questionnaires regarding attention and anxiety towards painful encounters in daily life, since these factors are known to influence pain perception [28]. Based on our previous results in congenitally blind individuals [1] and the results by Zubek and colleagues [29] showing that prolonged visual deprivation leads to increased sensitivity to pain, we hypothesized that LB would also show increased pain sensitivity.

Methods

Participants

Participants were recruited from our database of congenitally and late blind subjects or by advertisement. Our total study population consisted of 23 CB (7F; mean age: 38.7±12.5 years; range: 20–61), 12 LB (7F; mean age: 50.1±11.4 years; range: 25–63) and 48 NS (20F; mean age: 38.9±13.6 years; range: 20–66) volunteers of whom 18 NS and 18 CB were included in a previous study and their data reused [1]. The study samples used for each of our measurements are listed in Table 1.

Table 1. Study sample used for each of the measurements.

Measurement	Group	Gender	Age (years ± SD)
Detection thresholds	LB	4m/7f	49.6 ± 11.9
	CB	15m/6f	38.7 ± 11.7
	NS	18m/16f	38.1 ± 12.9
Supra-threshold ratings	LB	4m/5f	47.7 ± 12.1
	CB	14m/6f	37.7 ± 12.6
	NS	16m/7f	38.7 ± 14.9
Pain questionnaires	LB	4m/5f	47.7 ± 12.1
	CB	14m/6f	37.7 ± 12.6
	NS	21m/14f	38.0 ± 13.3

We calculated a blindness duration index (BDI) according to the formula "(age-age onset blindness)/age". The BDI score can vary from 0 to 1, expressing the relative amount of time a person has been blind, with low scores indicating recent onset of blindness and high scores long duration of blindness. All blind participants suffered from blindness due to peripheral origin (retina, optic nerve). In the LB group, the average onset of blindness was 19.7±14.5 years and the average BDI was 0.6±0.3. Blindness due to diabetic neuropathy was an exclusion criterion. None of the participants suffered from known neurological or psychiatric disorders that might interfere with the experiment's results. Demographic details on the blind participants are provided in Table 2. All participants, including the blind, provided their written informed consent to participate in this study. The ethics committee for the city of Copenhagen and Frederiksberg, Denmark approved the study and the consent procedure.

Table 2. Demographics of the blind participants.

			Blindness		
ID	**Age**	**Sex**	**Onset**	**Etiology**	**Residual vision**
CB1	43	M	0	Retinoblastoma	-
CB2	39	M	0	Retinopathy of prematurity	Bright light
CB3	58	F	0	Retinopathy of prematurity	-
CB4	26	M	0	Retinopathy of prematurity	-
CB5	57	M	0	Retinopathy of prematurity	-
CB6	25	M	0	Retinopathy of prematurity	Bright light
CB7	37	M	0	Optic nerve atrophy	Bright light
CB8	21	M	0	Leber's amaurosis	-
CB9	25	M	0	Retinopathy of prematurity	-
CB10	58	M	0	Retinopathy of prematurity	-
CB11	42	F	0	Retinopathy of prematurity	-
CB12	34	M	0	Retinopathy of prematurity	-
CB13	49	M	0	Retinopathy of prematurity	-
CB14	36	F	0	Retinitis pigmentosa and bilateral macular perforation	Bright light
CB15	24	F	0	Retinopathy of prematurity	-
CB16	50	M	0	Retinopathy of prematurity	-
CB17	36	F	0	Retinopathy of prematurity	-
CB18	29	F	0	Retinopathy of prematurity	-
CB19	20	M	0	Unknown	-
CB20	61	F	0	Retinopathy of prematurity	-
CB21	36	M	3 mo	Unknown	-
CB22	43	M	1	Retinoblastoma	-
CB23	42	M	1	Meningitis	Bright light
LB1	55	M	6	Surgical accident	-
LB2	43	F	6	Retinopathy of prematurity	-
LB3	36	F	8	Glaucoma	-
LB4	44	M	9	Retinitis pigmentosa	Bright light
LB5	56	M	10	Optic nerves sectioned by a bullet	-
LB6	56	F	10	Glass shards during accident	-
LB7	25	F	19	Taxoplasmosis	-
LB8	59	F	22	Iris infection	-
LB9	63	F	23	Retinitis pigmentosa	-
LB10	48	F	32	Retinopathy of prematurity	Bright light
LB11	53	M	45	Meningitis	-
LB12	64	M	46	Retinitis pigmentosa	-

Innocuous and noxious thermal thresholds assessment

We used a 3×3 cm Peltier-based thermotest (TSA-II, Medoc, Haifa, Israel) to determine thresholds for innocuous and noxious thermal stimuli on the dominant medial forearm. In order to reduce anxiety and fear, participants were familiarized with the thermal stimulation equipment and underwent practice trials prior to data acquisition. All participants were blindfolded after the familiarization period. The baseline temperature of the thermode was set to 32°C and we used a ramp rate of 1°C/s for the warmth and cool thresholds and 3°C/s for heat pain and cold pain thresholds. Stimuli were cued 2 to 5 s prior to onset. Participants had to click on a response key as soon as they detected warmth or cool or felt heat pain or cold pain. Thresholds were measured five times for each type of sensation with an inter-stimulus interval of 10–15 s for innocuous stimuli and 15–20 s for noxious stimuli.

Supra-threshold pain ratings

We used a CO2 laser stimulator device with a spot diameter of 6 mm (LSD, SIFEC, Ferrières, Belgium) to generate highly accurate and contactless heat stimuli. This device is equipped with a contactless measurement unit with online monitoring of target skin temperature that controls the laser power in a closed-loop. This instant feedback guarantees that the skin is brought and maintained with a high accuracy at the exact target temperature, allowing the stimulation of the thinly myelinated Aδ- and the unmyelinated C-fibers without co-activation of the large myelinated Aβ-fibers [30]. Following an auditory cue, we applied stimuli of 3 s at 43, 45, 47 and 49°C on the dominant dorsal hand. Participants had to rate their sensation verbally on a 10-point rating scale with “0” as no pain, and “10” as the most intense pain imaginable. Each stimulus intensity was presented 3 times in a pseudo-randomized order with an interstimulus interval of 10 s. In order to avoid skin habituation or sensitization, the laser beam was moved after each stimulation following a 3×3 dots matrix. The dots were 1 cm apart from each other.

Pain questionnaires

At the end of the session, participants filled in the Pain Vigilance and Awareness Questionnaire (PVAQ) adapted for a non-clinical population [31] and the Pain Anxiety Symptoms Scale (PASS) [32]. Both questionnaires comprise statements about pain encounters in everyday life. Participants had to rate at what frequency these situations apply to them. The PVAQ contains 16 items divided in 3 subscales: “Intrusion”, “Monitoring” and “Attention to changes in pain”. The PASS comprises 20 items divided into the 4 subscales “Physiological anxiety”, “Cognitive anxiety”, “Fear” and “Escape/Avoidance”. An audiotaped version of these questionnaires was presented to the blind participants.

Statistical analysis

In order to estimate and account for the influence of demographic variables (i.e. gender, age), we conducted a multiple linear regression analysis that generated the regression models separately for threshold assessments and supra-threshold pain ratings. In each condition we modelled age and gender as independent and thresholds/supra-thresholds as the dependent variables. We obtained new supra-threshold/threshold values for each subject from the residuals of the multiple linear regression modeling. Data are presented as means ± SD.

We used Levene's test for assessing equality of variances of the data distributions for noxious and innocuous thermal threshold assessments (factor = “group” and dependent variable = “threshold”). Then, we conducted two-tailed Student t-tests in order to compare groups for noxious and innocuous thermal thresholds. For supra-threshold ratings, we conducted a 1-way ANOVA with the factor “group” as independent variable and “temperature” as dependent variable, checking for the equality of variances of the data distribution with a Levene test. Post-hoc comparisons were done using two-tailed Student t-tests, correcting for multiple comparisons (Bonferroni-Holm corrections, $\alpha=0.05$).

To investigate the effects of onset of blindness and blindness duration index on pain perception, we performed Pearson's correlations between these variables and pain thresholds and supra-threshold pain ratings in the LB group.

We performed the analysis of the PVAQ and PASS data using a principal component analysis (PCA; direct oblimin, $\delta=0$) on the questionnaires' raw scores to make a dimensionality reduction while preserving as much data variability as possible. Thereafter, we performed a Fisher Linear Discriminant Analysis (FLDA) on the resulting PCA factor scores to test whether LB, CB and NS responded differently. The variables were entered using the "all-variables together" method, while the goodness of classification analysis was tested using "leave-one-out" cross-validation and balanced for unequal sample sizes.

Results

Innocuous and noxious thermal detection thresholds

The Levene's tests indicated equality of variances of our data distributions (heat pain: $F=2.902$, $df_1=2$; $df_2=63$, $p=0.062$; cold pain: $F=2.587$, $df_1=2$; $df_2=63$, $p=0.083$; innocuous warmth: $F=2.165$, $df_1=2$; $df_2=63$, $p=0.123$; innocuous cool: $F=0.198$, $df_1=2$; $df_2=63$, $p=0.821$). Comparisons of pain thresholds (Figure 1A) failed to show differences between LB and NS for either heat pain (LB=46.6±3.3°C, NS=46.2±2.0°C; $t=-0.49$, $df=43$, $p=0.628$) or cold pain (LB=10.8±6.8°C, NS=9.4±4.7°C; $t=-0.75$, $df=43$, $p=0.456$). Importantly, compared to CB, LB had a significantly higher heat pain threshold (CB: 43.0±2.7°C; $t=-3.3$, $df=30$, $p=0.003$) and a lower sensitivity to cold pain (CB: 16.7±5.8°C; $t=-2.5$, $df=30$, $p=0.015$). As shown before, CB had a lower heat pain threshold ($t=5.0$, $df=53$, $p<0.001$) and were more sensitive to cold pain than NS ($t=-5.1$, $df=53$, $p<0.001$). In contrast with the results of the pain thresholds, we found no group difference for innocuous warmth (NS=34.5±0.8°C, CB=34.4±0.7°C, LB=34.4±0.5°C; LB vs NS: $t=0.5$, $df=43$, $p=0.642$, LB vs CB: $t=0.03$, $df=30$, $p=0.981$, CB vs NS: $t=0.6$, $df=53$, $p=0.559$) and cold (NS=31.6±0.6°C, CB=31.7±0.6°C, LB=31.7±0.6°C; LB vs NS: $t=-0.7$, $df=43$, $p=0.515$, LB vs CB: $t=0.09$, $df=30$, $p=0.933$, CB vs NS: $t=-0.9$, $df=53$, $p=0.361$) detection thresholds. A Pearson correlation analysis indicated that the age of onset of blindness had no effect on heat pain (−0.238, $p=0.482$) or cold pain (0.008, $p=0.981$) thresholds. Likewise, BDI scores did not correlate with either heat pain (0.322, $p=0.334$) or cold pain (−0.120, $p=0.726$) thresholds.

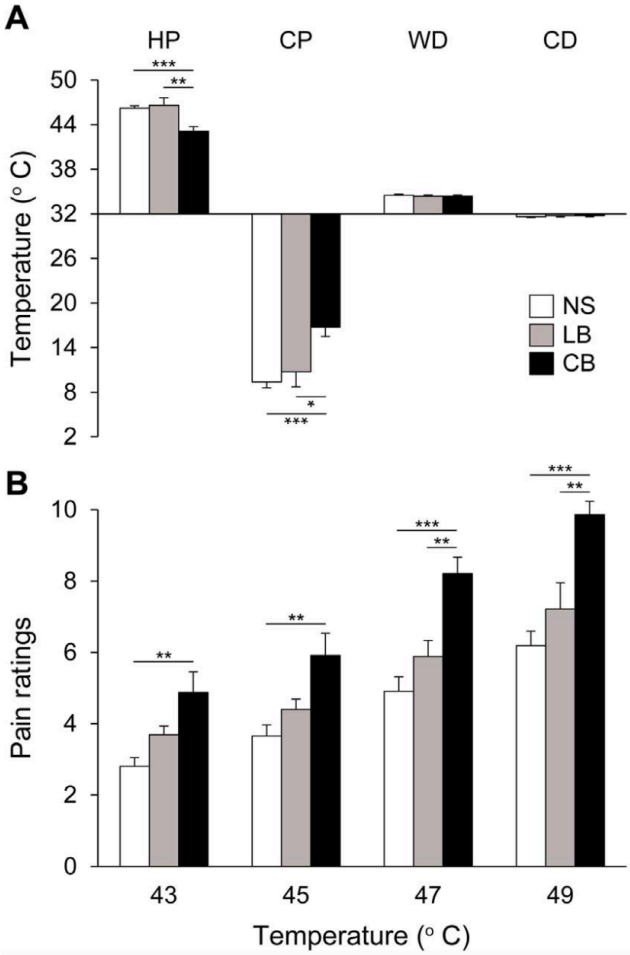

Figure 1. Thermal thresholds in normally sighted (NS), late blind (LB) and congenitally blind (CB) subjects. A: LB have heat pain (HP) and cold pain (CP) thresholds similar to NS. In contrast, HP and CP thresholds were significantly lower in CB compared to LB and NS. There were no group differences for innocuous warmth detection (WD) and cool detection (CD) thresholds. B: LB rate supra-threshold nociceptive stimuli similarly to NS. In contrast, CB rated supra-threshold stimuli as more painful compared to both LB and NS. Error bars represent the standard error of the mean. *p<0.05, **p<0.01, ***p<.001.

Supra-threshold pain ratings

The Levene's test indicated equality of variances of our data distributions ($F=2.193$, $df_1=2$; $df_2=49$, $p=0.122$). In line with the results of the pain thresholds, LB rated supra-threshold heat nociceptive stimuli (Figure 1B) similarly to NS (ANOVA: LB=5.3±1.2, NS=4.4±1.5; $p=0.110$) and lower than CB (7.2±1.9; $p=0.011$). As shown before, CB gave higher pain ratings than NS ($p<0.001$). More specifically, LB gave lower ratings than CB for

the 47°C (LB=5.9±1.4, CB=8.2±2.1; t=3.1, df=27, p=0.005) and 49°C (LB=7.2±2.2, CB=9.9±1.7; t=3.6, df=27, p<0.001) stimuli. Likewise, NSs pain ratings were lower than those of CB for the 43°C (NS=2.8±1.2, CB=4.9±2.6; t=−3.4, df=41, p<0.001), 45°C (NS=3.7±1.5, CB=5.9±2.8; t=−3.3, df=41, p=0.002), 47°C (NS=4.9±1.9; t=−5.4, df=41, p<0.001) and 49°C (NS=6.2±1.9; t=−6.6, df=41, p<0.001) stimuli. Average pain ratings in LB did not correlate with either onset of blindness (0.149, p=0.703) or BDI scores (−0.033, p=0.933).

Pain questionnaires

The Kaiser–Meyer–Olkin (KMO) measure verified the sampling adequacy of the PCA analysis we conducted (overall KMO=0.75; KMO for each sub-factor >0.5). Bartlett's test of sphericity (χ^2=237.6, df=21, p<0.001) indicated that correlations between PVAQ and PASS sub-factors were sufficiently high for PCA. Two components had eigenvalues over Kaiser's criterion of 1 and in combination explained 72.5% of the variance. Thereafter, we performed a FLDA to classify the participants on the basis of their regression factor scores derived from the PCA analysis. As illustrated in Figure 2, this analysis indicated that LB and NS had an undistinguishable response pattern, as we obtained a classification accuracy of only 54.1 % (chance level =50 %; canonical r^2=0.969, χ^2=1.3, df=2, p=0.521). On the other hand, the FLDA allowed us to correctly discriminate CB from NS with an accuracy of 75.3 % (canonical r^2=0.788, χ^2=12.4, df=2, p=0.002). Since the above classification scores were mainly driven by factor II (attention to pain), we infer that CB are more attentive to signals of threat than NS. Inversely, the poor contribution of factor I (anxiety) suggests that CB are not more anxious than NS about pain encounters in daily life. Pearson correlation analysis within LB indicated that the onset of blindness had no effect on either factor I (−0.294, p=0.443) or factor II (−0.504, p=0.167). Likewise, BDI scores also did not correlate with either factor I (−0.026, p=0.948) or factor II (0.423, p=0.257).

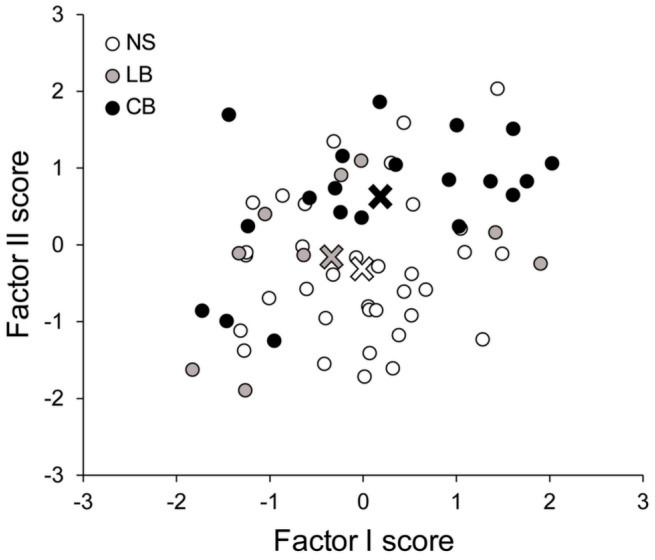

Figure 2. Principal component analysis of the Pain Anxiety Symptoms Scale (PASS) and Pain Vigilance and Awareness Questionnaire (PVAQ). Factors I (anxiety) and II (attention to pain) result from an oblique rotation. Higher values indicate higher correlation scores, with the average centered at 0. Color-coded crosses represent centroids after principal component analysis (PCA). LB have a similar responses pattern, whereas CB and NS show a distinct pattern of factor loadings, where factor II (attention to pain) discriminates better than factor I (anxiety). Normally sighted (NS), late blind (LB) and congenitally blind (CB) participants are represented with white, grey and black dots, respectively.

Discussion

The purpose of the present study was to investigate if individuals with acquired blindness show thermal hypersensitivity to noxious thermal stimulation as previously reported in congenital blindness [1]. In contrast with our hypothesis, late blind and sighted participants showed similar heat and cold pain thresholds and supra-threshold pain ratings. This indicates that onset of blindness, and not blindness per se, is the driving factor of thermal pain hypersensitivity in individuals lacking vision.

Our findings are in line with previous studies indicating that late blind individuals show no compensatory plasticity for auditory [15, 16] or tactile [15, 21, 22] information processing. Indeed, the extent of cortical reorganization strongly depends on the onset of visual deprivation, as many animal and human studies have shown that structural and functional brain changes following blindness are less likely to occur later in life [14, 33].

However, these data need to be interpreted with some caution due to our medium-sized study sample of late blind individuals. Our results further show that there was no correlation between pain perception and the blindness duration index or onset of blindness, indicating that individuals who have lost their vision relatively early do not differ in pain responsiveness from those who have lost their vision later in life. It should be noted that the earliest onset of blindness in our LB group was six years of age, which is possibly after the critical period during which absence of vision affects nociceptive processing. In support of this, studies have shown that the switch of body coordinates from anatomical to external frame of reference takes place before the age of six [34]. It has also been demonstrated that touch perception is hampered by conflicting inputs from anatomical and external body frames of reference in sighted [35–40] and late blind [37], but not congenitally blind individuals [37, 41]. Furthermore, there is evidence that pain perception is also affected by body frame of reference and body representation [9, 42, 43, 44].

Our psychophysical data are further corroborated by the psychometric results that also failed to find differences in attitude and responses to signals of threat in daily life between LB and NS. Indeed, results of the pain questionnaires indicated that LB and NS pay similar attention to environmental threats and react with the same level of anxiety to such threats. In sharp contrast, CB scored higher than NS on attention to pain. This increased awareness of potentially dangerous stimuli could partly explain the increased pain responsiveness in CB since attention is known to exacerbate the experience of pain [45]. This suggests that CB allocate more attentional resources to potentially threatening stimuli in order to avoid or reduce pain. This finding is in accordance with a recent study showing that CB are hyper-responsive to threatening auditory stimuli, and that this was associated with stronger amygdalar activations [46]. This increased awareness of danger could compensate for the lack of vision that is necessary to quickly adopt optimal defensive and protective behaviors [47].

Previous studies have shown that increased attention to threatening stimuli can be driven by augmented levels of anxiety [28]. One could therefore argue that the lack of vision may increase anxiety and consequently also attention towards nociceptive stimulation [1, 48]. However, our psychometric data rule out this possibility, as all three groups were equally anxious about environmental threats. Furthermore, since LB and NS did not differ in attention

to pain, it seems that early blindness is necessary to develop increased attention to environmental threats.

In conclusion, we show that blindness acquired at the age of six or later does not lead to pain hypersensitivity. Our data therefore suggest that hypersensitivity to noxious stimulation is the result of neuroplastic changes that occur early in development. Whether attention is the chief determinant of the exacerbated sensitivity to pain in congenitally blind individuals, or simply a potentiating factor, needs further investigation.

Author Contributions

Conceived and designed the experiments: RK MP HS. Performed the experiments: HS. Analyzed the data: HS SD. Contributed reagents/materials/analysis tools: RK SD. Wrote the paper: HS MP RK.

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Article 3. Enhanced heat discrimination in congenital blindness

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Enhanced heat discrimination in congenital blindness

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Abstract

There is substantial evidence that congenitally blind individuals perform better than normally sighted controls in a variety of auditory, tactile and olfactory discrimination tasks. However, little is known about the capacity of blind individuals to make fine discriminatory judgments in the thermal domain. We therefore compared the capacity to detect small temperature increases in innocuous heat in a group of 12 congenitally blind and 12 age and sex-matched normally sighted participants. In addition, we also tested for group differences in the effects of spatial summation on temperature discrimination. Thermal stimuli were delivered with either a 2.56 or 9 cm^2 Peltier-based thermode. We applied for 5–8 s lasting non-painful thermal stimuli to the forearm and asked participants to detect small increments in temperature (ΔT = 0.4, 0.8, 1.2 or 1.6 °C) that occurred at random time intervals. Blank trials (ΔT = 0 °C) were also included to test for false positive responses. We used signal detection theory model to analyze the data. Our data revealed that blind participants have a higher accuracy than the sighted (d': Blind = 2.4 ± 1.0, Sighted = 1.8 ± 0.7, p = 0.025), regardless of the size of the stimulated skin surface or magnitude of the temperature shift. Increasing the size of the stimulated skin area increased the response criterion in the blind (p = 0.022) but not in the sighted. Together, these findings show that congenitally blind individuals have enhanced temperature discrimination accuracy and are more susceptible to spatial summation of heat.

Keywords

Congenital blindness; Contact heat; Heat discrimination; Nociception; Spatial summation; Sensory compensation

1. Introduction

There is growing evidence that congenitally blind individuals outperform age-and sex-matched normally sighted individuals in various sensory tasks [1]. Indeed, congenitally blind individuals have supra-normal discrimination skills in tactile [2, 3, 4], auditory [5, 6, 7] and olfactory [8, 9, 10] modalities. In a previous study, we measured warmth and cold detection thresholds as well as heat and cold pain thresholds and responses to supra-thresholds heat stimulation in congenital blind subjects [11]. Although blind individuals showed increased responses to pain stimulation, thresholds for innocuous warmth and cold were not different from normal sighted controls. These results do not imply, however, that blind individuals would not perform any better than sighted controls in more complex temperature discrimination tasks. To date, nothing is known about the blind's ability to discriminate thermal stimuli. Based on anecdotal accounts from blind individuals about their use of thermal cues in daily-life activities, e.g. the difference in temperature gradient caused by sunlight hitting the forehead for purposes of spatial navigation, we hypothesized that they would have better heat discrimination skills.

It has been shown that people can discriminate between a broad range of materials by relying solely on thermal diffusivity properties [12, 13, 14]. Because of their lack of vision, blind individuals might rely more strongly on these thermal cues for object recognition, possibly leading to an enhanced sensitivity to detect subtle differences in thermal properties. Furthermore, thermoception also plays a role in avoiding thermal injury [15]. Indeed, nociceptive heat is encoded by the combined activity of thermoceptors and nociceptors, suggesting that warm fibers contribute to the experience of pain [15, 16, 17, 18]. Therefore, a rapid increase in temperature, even within the innocuous range, can be encoded as dangerous. Since congenitally blind individuals have lower heat pain thresholds compared to the sighted [11, 19], they may be more attentive to temperature shifts that may be indicative for an impeding painful stimulus.

Thermal perception is not only dependent on stimulus intensity but also on spatial summation [13, 20, 21]. Indeed, changing the size of a thermal stimulus drastically affects the perceived intensity. This property is especially important in warmth perception in which intensity and spatial extent of the stimulus have equal influence on the perceived intensity [13,

22]. Unpublished preliminary data from our lab suggested that the spatial extent of thermal stimulation more strongly affects perceptual decision making in blind compared to sighted participants. Therefore, we investigated here in a more systematic manner whether congenitally blind differ from normal controls with respect to spatial summation of heat.

2. Methods

Table 1. Demographic data of blind participants.

			Blindness		
ID	**Age**	**Sex**	**Onset**	**Etiology**	**Residual vision**
CB1	39	M	0	Retinopathy of prematurity	Bright light
CB2	26	M	0	Retinopathy of prematurity	-
CB3	57	M	0	Retinopathy of prematurity	-
CB4	37	M	0	Optic nerve atrophy	Bright light
CB5	25	M	0	Retinopathy of prematurity	-
CB6	42	F	0	Retinopathy of prematurity	-
CB7	24	F	0	Retinopathy of prematurity	-
CB8	50	M	0	Retinopathy of prematurity	-
CB9*	36	F	0	Retinopathy of prematurity	-
CB10	29	F	0	Retinopathy of prematurity	-
CB11	61	F	0	Retinopathy of prematurity	-
CB12	42	M	1	Meningitis	Bright light

* This participant was excluded due to the non-completion of the experiment

Participants were recruited from our database of congenitally blind subjects or by advertisement. Our study population consisted of 12 congenitally blind (5F; mean age: 39.0 ± 12.2 years; range: 24–61) and 12 normally sighted (5F; mean age: 38.8 ± 14.7 years; range: 21–66) participants. One blind participant and her matched control were excluded from the data analysis due to non-completion of the experiment. All blind participants suffered from blindness due to peripheral origin. Blindness due to diabetic neuropathy was an exclusion criterion [23]. None of the participants suffered from known neurological or psychiatric disorders that might interfere with the experiment's results. Demographic details on the blind participants are provided in Table 1. All participants, including the blind, provided their

written informed consent to participate in this study. The ethics committee for the city of Copenhagen and Frederiksberg, Denmark approved the study and the consent procedure.

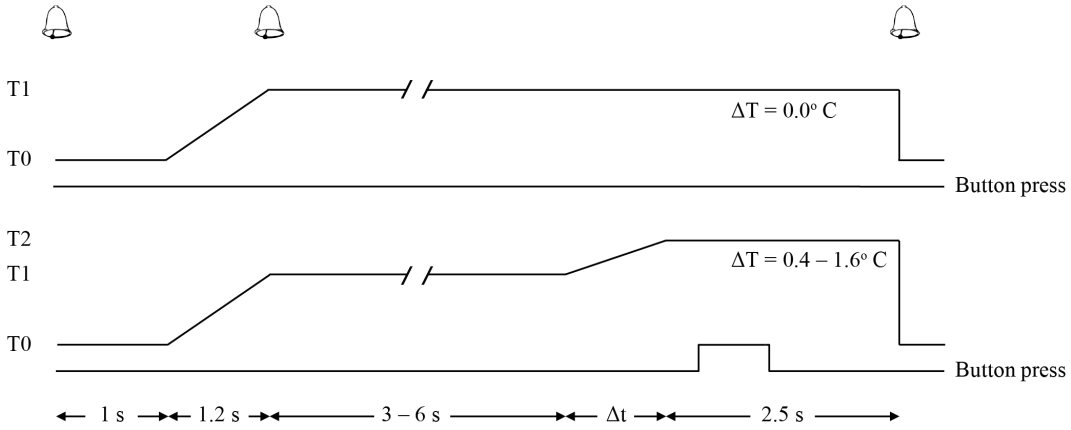

Fig. 1. Experimental procedure. We used a baseline temperature of 32 °C prior to each trial. Following a first sound cue, the skin was heated up at a rate of 5 °C/s. The second sound cue announced the stabilization of skin temperature at 38 °C. This first temperature was maintained for a time varying randomly between 3 and 6 s. Thereafter, the temperature increased by $\Delta T = 0.4$, 0.8, 1.2 or 1.6 °C at a rate of 3 °C/s and was maintained for 2.5 s. Participants had to click on a response key as soon as they detected the temperature increase. A third sound cue indicated the end of the trial. The inter-stimulus interval was set at 10 s. Each temperature shift was presented 20 times. We also included 20 blank trials in which the temperature was maintained at 38 °C ($\Delta T = 0.0°$ C). Stimuli were presented in a pseudo-randomized order to avoid the same temperature shift to be delivered more than twice in a row.

We used a Peltier-based thermotest (TSA-II, Medoc, Haifa, Israel) to deliver innocuous heat stimuli. The device was gently strapped to the dominant volar forearm, thereby avoiding too much pressure as this may affect skin temperature [24]. Participants were first familiarized with the procedure and underwent a number of practice trials. All participants, including the blind, were blindfolded during data acquisition. The baseline temperature of the probe was kept at 32 °C. At the beginning of each trial, the skin temperature was brought to a conditioning temperature of 38 °C, a temperature that was clearly above the baseline skin temperature for all participants, using a ramp rate of 5 °C/s. Skin temperature was maintained at this level for 3 to 6 s; following a second sound cue, temperature increased by a ΔT of 0.4, 0.8, 1.2 or 1.6 °C at a rate of 3 °C/s and was maintained at this temperature for 2.5 s, after which a third sound cue announced the end of the trial (Fig. 1). Participants were instructed to press a response key as soon as they detected the second temperature increase. Each

temperature shift was presented 20 times. We also included 20 blank trials in which the temperature was maintained at 38 °C ($\Delta T = 0.0$ °C). Stimuli were presented in a pseudo-randomized order to avoid the same temperature shift to be delivered more than twice in a row. The inter-stimulus interval was set at 10 s.

To investigate the effect of spatial summation, we used a small (2.56 cm^2) and a large (9 cm^2) thermode. Half of the blind participants and their matched sighted controls were assigned to the small thermode first, the other half to the large one first. There was a minimum time interval of 1 week between the two sessions.

We evaluated task performance using a signal detection theory model of analysis. The probability of a "hit" (P(H)) was calculated for each level of stimulation ($\Delta T = 0.4$, 0.8, 1.2 or 1.6 °C) by dividing the number of correct detections of a temperature increase (hit) by the number of stimulus presentations. Next, the probability of a "false alarm" (P(FA)) was calculated as the proportion of trials in which the subject responded detecting a temperature shift during a blank trial ($\Delta T = 0.0$ °C). Thereafter, we calculated the discrimination accuracy (d') for each stimulus intensity by subtracting a z-score calculated from P(FA) from a z-score calculated for P(H). Finally, the decision criterion (c), a value that indicates the participant's response bias, was calculated by subtracting z(H) from d'. We used Levene's test for assessing equality of variances of the data distributions for d' and c assessments (factor = "group" and dependent variable = "d'"/"c"). We then compared groups for d' by conducting a repeated measures ANOVA with the factors "group", "size" and "temperature shift" as independent variables and "d'" as dependent variable. In order to compare groups for "c", we also performed a repeated measures ANOVA with the factors "group" and "size" as independent variables and "c"' as dependent variable. Two-tailed Student t-tests were used for single comparisons of the different variables listed above. Correction for multiple comparisons was done using Bonferroni ($\alpha = 0.05$).

3. Results

Levene's tests indicated equality of variance for all data distributions, as illustrated in Table 2. The first ANOVA showed that congenitally blind (CB) participants had a higher

accuracy in detecting temperature changes than the normally sighted (NS) (d': CB = 2.4 ± 1.0, NS = 1.8 ± 0.7; F = 5.903, df = 1, p = 0.025).

Table 2. Levene tests of normality.

Device	Variable	df1	df2	F	*p*
2.56 cm²	d' (0.4° C)	1	20	0.117	0.735
	d' (0.8° C)	1	20	4.318	0.051
	d' (1.2° C)	1	20	0.702	0.412
	d' (1.6° C)	1	20	0.038	0.848
	c	1	20	0.383	0.543
9.00 cm²	d' (0.4° C)	1	20	0.274	0.606
	d' (0.8° C)	1	20	2.579	0.124
	d' (1.2° C)	1	20	0.499	0.488
	d' (1.6° C)	1	20	0.061	0.807
	c	1	20	0.427	0.521

Further comparisons indicated that all participants –regardless of the group– performed better when using the large 9 cm^2 thermode (d': 2.56 cm^2 = 1.8 ± 0.7, 9 cm^2 = 2.5 ± 0.7; F = 7.636, df = 3, p < 0.001). Interestingly, we found a significant "size" × "temperature shift" interaction (p < 0.001), indicating that spatial summation only influenced performance for the temperature shifts that were larger than 0.4 °C (Table 3). Fig. 2A illustrates the detailed performance of each group.

The ANOVA performed on the decision making component of our data showed that, on average, blind and sighted participants have similar response criteria (c: CB = 1.2 ± 0.7, NS = 1.3 ± 0.5, df = 1, F = 0.217, p = 0.647). Comparisons of c specific to each stimulus size also failed to show significant group differences (2.56 cm^2: CB = 0.95 ± 0.5, NS = 1.2 ± 0.4; df = 1, F = 1.889, p = 0.185; 9 cm^2: CB = 1.5 ± 0.7, NS = 1.4 ± 0.7; df = 1, F = 0.073, p = 0.790). Importantly, spatial summation affected decision making in the blind but not in the sighted group (Fig. 2B). Indeed, there was a significant increase in c when increasing the area of stimulation from 2.56 cm^2 to 9 cm^2 in blind (CB: df1 = 1, df2 = 20, F = 6.158, p = 0.022), but not in sighted participants (NS: df1 = 1, df2 = 20, F = 0.778, p = 0.388).

Table 3. Influence of stimulation size on performance.

Temperature increase (°C)	Size of stimulation (cm²)	*d′*	t	df	*p*
0.4	2.56	1.0 ± 0.6	1.7	21	$p = 0.113$
	9.00	1.2 ± 0.6			
0.8	2.56	1.6 ± 0.8	4.8	21	$p < 0.001$
	9.00	2.4 ± 0.9			
1.2	2.56	2.0 ± 0.9	4.2	21	$p < 0.001$
	9.00	2.9 ± 1.0			
1.6	2.56	2.5 ± 0.7	4.6	21	$p < 0.001$
	9.00	3.5 ± 0.7			

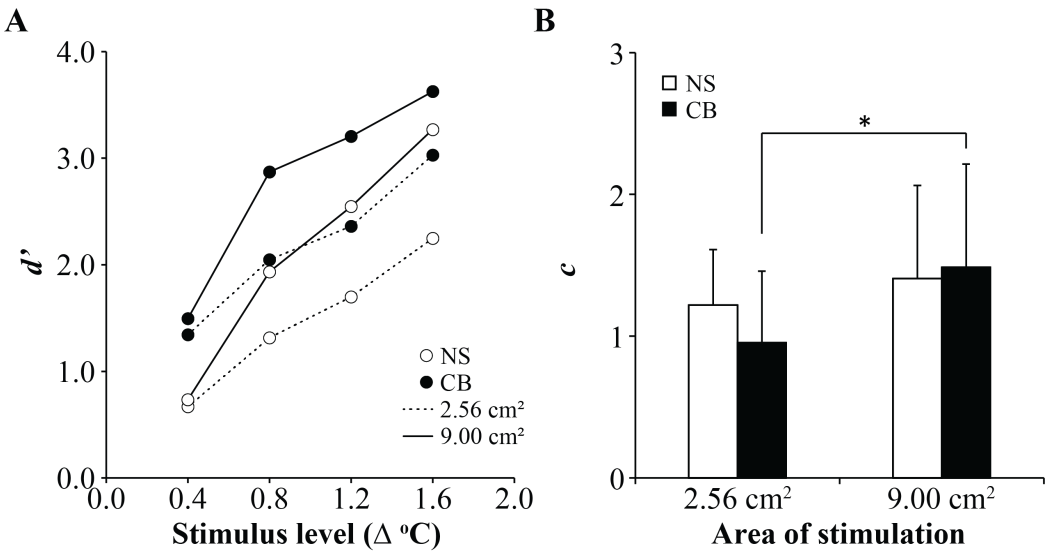

Fig. 2. Performance of congenitally blind (CB) and normally sighted (NS) participants in the temperature discrimination task. A – Overall, CB had a better performance (d') than NS in detecting small changes in temperature ($p = 0.025$). Increasing the area of stimulation from 2.56 cm^2 (dashed lines) to 9 cm^2 (solid lines) enhanced both groups' accuracy in all temperature shifts ($p < 0.001$), but $\Delta T = 0.4°$ C ($p = 0.113$). B – CB and NS had a similar response criterion (c), regardless to stimulus size ($p = 0.647$). A significant increase in criterion was observed when increasing the area of stimulation ($p = 0.027$). Error bars represent the standard deviation.

4. Discussion

The aims of this study were to test whether congenitally blind individuals (1) are better in discriminating small increases in innocuous warmth and (2) are more prone to spatial summation effects of heat. In accordance with our hypothesis, results showed that congenitally

blind participants are better than the normally sighted at discriminating temperature changes, regardless of the amplitude of the temperature increase or the spatial extent of the stimulated area. Our findings further indicated that the effect of spatial summation on performance accuracy did not differ for blind and sighted subjects, whereas it exerted a differential effect on the response criterion. Indeed, increasing the spatial extent of stimulation lead to an enhanced performance in both groups, but to a reduction in false positives in the blind only.

There is strong evidence that congenitally blind individuals outperform their sighted peers in discrimination tasks involving auditory, tactile and olfactory sensory modalities [1], but few data are available for thermal perception. Here we present the first demonstration that visual deprivation from birth is associated with enhanced temperature discrimination accuracy. This adds new evidence on cross-modal compensatory plasticity in congenital blindness.

Two hypotheses have been put forward to explain increased sensory sensitivity in congenital blindness. According to the sensory deprivation hypothesis, blind individuals perform better in non-visual sensory tasks because the mere absence of vision leads to compensatory changes in the other sensory modalities. According to the training-induced hypothesis, it is not the absence of vision per se that drives hypersensitivity but training-induced plasticity. For instance, for the tactile domain, superior grating orientation discrimination was shown for the fingertips but not for the facial area, and improved performance correlated with the amount of Braille reading, which was interpreted as supporting the training-induced plasticity hypothesis [4]. Since we tested the volar forearm, a body region that is unlikely being used extensively by the blind in temperature discrimination tasks, it seems rather unlikely that our results are due to training-induced plasticity. Alternatively, the increased thermal sensitivity in congenital blindness might be explained by their hypersensitivity to nociceptive stimulation [11, 19]. Indeed, a more efficient computing of rapid temperature raises will help in avoiding possible encounters with noxious thermal stimuli. In general, most thermally harmless objects of the environment are colder than the skin, whereas the dangerous ones are warmer [13]. Therefore, the activation of heat-sensitive C-fibers of the skin when touching an object can indicate impeding danger.

We propose that blind individuals have learned to better use these thermal cues in order to prevent thermal injuries. This is supported by our recent findings that congenitally blind

individuals are hypersensitive to thermal pain [11, 19]. The same studies, however, indicated that thresholds for innocuous thermal perception in congenitally blind and sighted participants were not different. This, of course, does not preclude the possibility that the blind are better at tasks that require higher order perceptual skills such as fine temperature discrimination. Indeed, it is now well documented that congenitally blind individuals show sensory compensation in discrimination and identification tasks rather than simple detection thresholds [1, 25, 26].

A recent study from Wong et al. [27] showed that temporarily light depriving sighted participants worsens their performance on a tactile spatial task. One could therefore argue that blindfolding the sighted participants in the present study would worsen their performance. Nonetheless, we decided to blindfold our sighted participants because it has been shown that there is an important effect of vision on thermal perception [28]. A subsequent experiment could measure discrimination thresholds in normal sighted subjects with and without blindfold to address this issue.

We also studied the effects of spatial summation of heat on temperature discriminability. Increasing the stimulation surface from 2.56 to 9 cm^2 enhanced stimulus discriminability in both groups, whereas it affected the response criterion only in the blind group. Indeed, blind participants showed a larger increase in response criterion when increasing the size of the thermode, and hence became less prone to false positive responses. Previous studies have attributed the increased performance in various non-visual sensory tasks in congenitally blind subjects to the recruitment of the occipital cortex [1]. In addition, congenitally blind subjects also show increased occipital activity at rest [29]. If we assume that the increased performance in thermal discriminability is due to a similar mechanism of occipital recruitment, we propose that stimulating a small skin area is insufficient to bring neuronal activity within the occipital cortex above the physiological noise level. In contrast, stimulating a larger skin area will, through spatial summation, clearly raise the signal above the physiological noise levels.

5. Conclusions

Altogether, our findings indicate that congenitally blind individuals' hypersensitivity to nociceptive thermal stimuli extends to innocuous warmth and add to a growing literature on cross-modal compensatory plasticity in congenitally blind individuals [1]. An improved capacity for thermal information processing may help blind individuals in object recognition based upon thermal diffusivity characteristics of materials [12, 13]. Our data therefore suggest that when sight is absent since birth in man, dormant mechanisms of sensory information processing regain a more relevant functional role.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HS, MP and RK conceived and designed the experiments. RK and MP contributed with experimental equipment and analysis tools. HS performed the experiments and the data analysis. HS, MP and RK wrote and edited the manuscript. All authors read and approved the final manuscript.

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Article 4. Pain hypersensitivity in congenital blindness is associated with faster central processing of C-fibre input

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Pain hypersensitivity in congenital blindness is associated with faster central processing of C-fibre input

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Abstract

Background: We have recently shown that visual deprivation from birth exacerbates responses to painful thermal stimuli. However, the mechanisms underlying pain hypersensitivity in congenitally blindness are unclear.

Methods: To study the contribution of Aδ- and C-fibres in pain perception, we measured thresholds and response times to selective C-fibre and Aδ-fibre activation in congenitally blind, late blind and normally sighted participants. Ultrafast constant-temperature heat pulses were delivered to the hand with a CO_2 laser using an interleaved adaptive double staircase procedure. Participants were instructed to respond as quickly as possible when detecting a laser-induced sensation. We used a 650 ms cut-off criterion to distinguish fast Aδ- from slow C-fibre mediated sensations.

Results: Congenitally blind participants showed significantly faster reaction times to C-fibre but not to Aδ-fibre-mediated sensations. In contrast, thresholds for Aδ- and C-fibre stimulation did not differ between groups. Late blind individuals did not differ from sighted controls in any aspect. A follow-up experiment using only supra-threshold stimuli for Aδ- and C-fibre activation, confirmed these findings and further showed that congenitally blind individuals detected significantly more C-fibre mediated stimuli than sighted controls. A decomposition of the reaction times analysis indicated that the faster response times in the congenitally blind are due to more efficient central processing of C-fibre mediated sensations.

Conclusion: The increased sensitivity to painful thermal stimulation in congenital blindness may be due to more efficient central processing of C-fibre mediated input, which may help to avoid impending dangerous encounters with stimuli that threaten the bodily integrity.

Introduction

Vision is important for the detection, identification and localisation of threats that may imperil the bodily integrity (Combe and Fujii 2011). Similarly, the key biological function of acute pain is to trigger escape and protective behaviours to avoid physical harm. Several studies have shown that the lack of informative vision exacerbates the experience of pain (Haggard et al., 2013; Longo et al., 2009; Mancini et al., 2011; Master et al., 2009; Valentini et al., 2015; Zubek et al., 1964), suggesting an interaction between vision and pain processing (but see Torta et al., 2015). We recently showed that congenitally blind, but not late blind, individuals have lower heat pain and cold pain thresholds and respond more strongly to supra-threshold noxious heat stimuli (Slimani et al., 2014; Slimani et al., 2013). However, the mechanisms underlying this hypersensitivity to pain remain unclear. One hypothesis that has been put forward is that this hypersensitivity is caused by a general increased selective attention to threatening stimuli (Mancini 2013; Slimani et al., 2014; Slimani et al., 2013). Indeed, congenitally blind individuals are more attentive to painful encounters in daily life (Slimani et al., 2014; Slimani et al., 2013), have augmented responses to auditory signalling of threats (Klinge et al., 2010), and are better at identifying odours of negative emotional valence, such as fear and disgust (Iversen et al., 2015).

In order to probe into the physiological mechanisms underlying the increased pain hypersensitivity in congenital blindness, we studied central processing of Aδ- and C-fibre mediated inputs by measuring reaction times (RTs) and detection frequency to brief nociceptive radiant heat stimuli. We reasoned that if pain hypersensitivity is due to increased vigilance towards stimuli that threaten the bodily integrity, congenitally blind subjects should be faster in responding to and detect more stimuli within the nociceptive range. In sharp contrast, we did not expect that late blind subjects would differ in their response times since we have shown that their response pattern to painful stimuli is not different from that of sighted individuals (Slimani et al., 2014). To test this hypothesis, we used a CO_2 laser to present brief heat stimuli to the skin, thereby taking advantage of the anatomo-physiological organization of the nociceptive system to disentangle the respective contributions of the thinly myelinated Aδ-fibres and the unmyelinated C-fibres. Due to the difference in conduction velocity of these two sets of fibres, pain is often referred to as a double alarm system, in which

the first and second alarm are mediated by the fast conducting Aδ-fibres and the slow conducting C-fibres, respectively (Lewis and Pochin 1937; Plaghki et al., 2010). Consequently, RTs to ultrafast, highly synchronized nociceptive radiant heat are distributed in a bimodal manner, whereby the first part of the distribution with relatively short RTs represent responses to the activation of the Aδ-fibres, whereas the second part of the distribution is caused by responses to the slower conducting C-fibres (Churyukanov et al., 2012).

Methods

Participants

We recruited 14 congenitally blind (5F; mean age: 38.6 ± 13.2 years, range: 20-61), 8 late blind (5F; mean age: 46.9 ± 12.8 years, range: 25-64) and 14 normally sighted (4F; mean age: 40.1 ± 15.4 years, range: 20-65) participants. All participants were in good health and without known neurological or psychiatric disorders. All blind participants suffered from blindness of peripheral origin, starting in the first year of life for congenitally blind subjects, or after 6 years for late blind individuals (Table 1). The ethics committee for the city of Copenhagen and Frederiksberg had approved the experimental procedures and all participants gave informed consent.

Stimuli

Thermal stimuli were delivered to the dorsum of the non-dominant hand using a CO_2 laser stimulator device with a spot diameter of 6 mm (LSD, SIFEC, Ferrières, Belgium). Prior to testing, blind subjects were allowed to explore the equipment by touch and were given a detailed verbal description of it. A closed-loop control of laser power with online monitoring of target skin temperature was used to generate heat stimuli. This allowed highly accurate and contactless cutaneous stimulation of Aδ- and C-fibres without co-activation of Aβ-fibres (Churyukanov et al., 2012). An integrated contactless skin temperature measurement unit, built-in in the stimulator head, allowed skin temperature measurement at a sampling rate of 0.5 kHz and stimulus adjustment in real time, resulting in highly controlled stimuli.

Table 1. Demographics of the blind participants.

			Blindness		
ID	**Age**	**Gender**	**Onset**	**Etiology**	**Residual vision**
CB1	50	M	0	Retinopathy of prematurity	-
CB2	24	F	0	Retinopathy of prematurity	-
CB3	26	M	0	Retinopathy of prematurity	-
CB4	61	F	0	Retinopathy of prematurity	-
CB5	49	M	0	Retinopathy of prematurity	-
CB6	28	F	0	Retinopathy of prematurity	-
CB7	39	M	0	Retinopathy of prematurity	Bright light
CB8	59	F	0	Retinopathy of prematurity	-
CB9	21	M	0	Leber's amaurosis	-
CB10	37	M	0	Retinopathy of prematurity	-
CB11	42	F	0	Retinopathy of prematurity	Bright light, shapes
CB12	43	M	0	Retinopathy of prematurity	-
CB13	20	M	0	Retinopathy of prematurity	-
CB14	42	M	1	Meningitis	Bright light, shapes
LB1	43	F	6	Retinopathy of prematurity	-
LB2	36	F	8	Glaucoma	-
LB3	44	M	9	Retinitis pigmentosa	Bright light
LB4	56	M	10	Optic nerves sectioned by a bullet	-
LB5	25	F	19	Toxoplasmosis	-
LB6	59	F	22	Iris infection	-
LB7	48	F	32	Retinopathy of prematurity	Bright light
LB8	64	M	46	Retinitis pigmentosa	-

Procedures

Aδ- and C-fibre detection thresholds

Each trial started by the measurement of the baseline skin temperature (T_0) during 1 s prior to stimulation. The skin was then pre-heated at a conditioning temperature (T_1) to examine whether the skin temperature immediately preceding the stimulus has an influence on Aδ- and C-fibre thresholds (Churyukanov et al., 2012; Darian-Smith et al., 1979a; Darian-Smith et al., 1979b; Hallin et al., 1982; Johnson et al., 1979; LaMotte and Campbell 1978; Peng et al., 2003; Plaghki et al., 2010). The skin temperature was raised to either 32 or 35 °C using a 1 s heating ramp and maintained steady for 2 s. Thereafter, an additional heat pulse was delivered to bring the skin to target temperature (T_2), using a steep heat ramp of 10 ms; target temperature was maintained (Lacouture and Cousineau 2008) for 90 ms. Participants

were instructed to press as quickly as possible upon detecting T_2 (Figure 1A). The T_2 temperatures ranged between 36 and 60 °C following an adaptive up/down staircase algorithm based on RTs. This is justified by the fact that the nerve conduction velocity of unmyelinated C-fibres is much slower than that of myelinated Aδ-fibres (±1 m/s vs. ±10 m/s) (Bjerring and Arendt-Nielsen 1988; Bromm and Treede 1983; Mouraux et al., 2003; Mouraux and Plaghki 2007). Opsommer et al. (1999) showed that the time interval between the two peaks of the bimodal distribution of reaction-times increases with peripheral distance. We chose a criterion of 650 ms to discriminate between C-fibre and Aδ- fibre responses which was based on 1) the peripheral conduction distance of afferent input originating from the hand and 2) the distribution of reaction times to laser stimuli after blockade of the myelinated fibres (Bromm et al., 1983; Nahra and Plaghki 2003). The C-fibre staircase algorithm was therefore based on a detection/no detection criterion, whereas the Aδ-fibre staircase was based on RTs (Churyukanov et al., 2012).

We always assessed the C-fibre detection threshold first to prevent that the lower intensity stimuli might be masked by the higher intensity stimuli. To reduce skin habituation, a 10 s interstimulus interval was used and successive stimuli were delivered 2 cm apart from each other, following a 5 x 5 matrix. To avoid response bias by anticipation, staircases corresponding to the two conditioning temperatures were interleaved. Threshold values were then obtained by averaging the target stimulus temperatures T_2 at which the 6 staircase reversals had occurred within a range of 2 °C (Figure 1B). We also calculated RT frequency distributions.

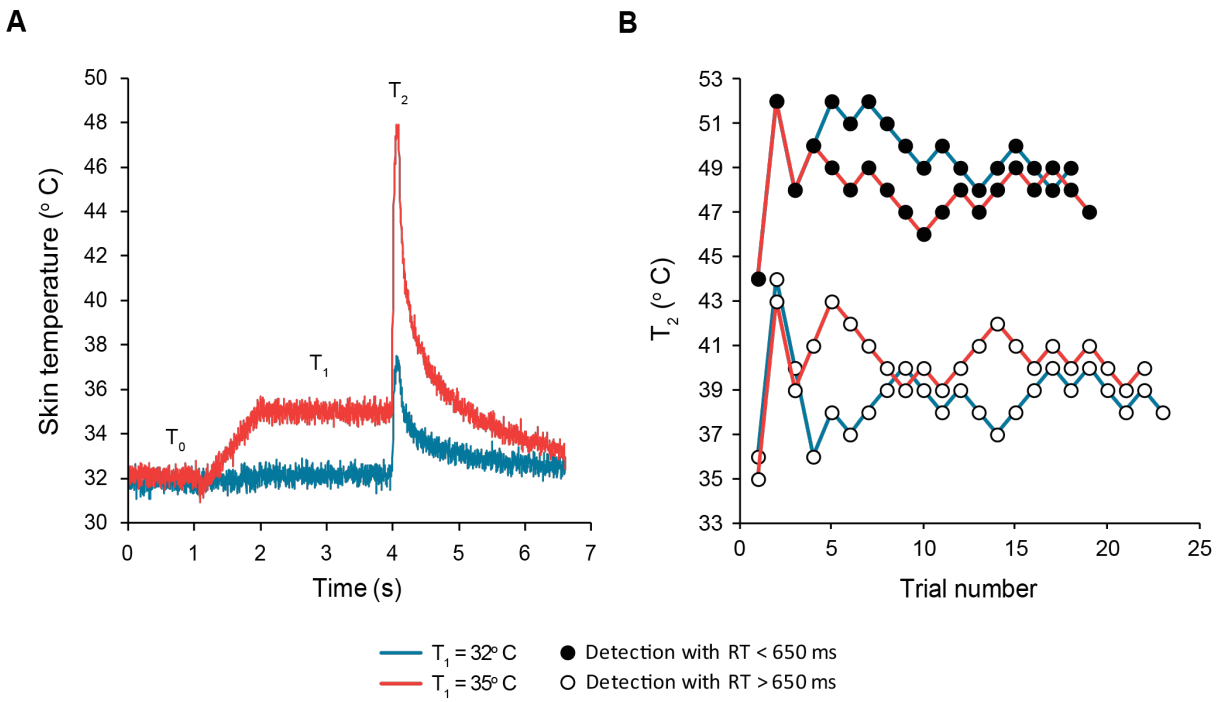

Figure 1. Experimental paradigm. A – Thermal stimulation profiles. Thermal stimuli were applied to the dorsum of the non-dominant hand using a CO_2 laser (beam diameter: 6mm). The red and blue lines illustrate the real-time recordings of the skin temperature in two trials. After measuring the baseline skin temperature (T_0) for 1 second, the skin was raised to either the 32 or 35 °C skin conditioning temperatures (T_1) using a 1 s heating ramp and was maintained for 2 s. Thereafter, a 100 ms pulse (10 ms heating ramp and 90 ms plateau) was delivered (T_2). **B** – Staircase algorithm. T_2 consisted of varying temperatures that followed an adaptive up/down staircase algorithm. Subjects had to press a response button as quickly as possible when T_2 was perceived. Reaction times (RTs) were used to discriminate between C-fibre related detections (detections with RTs > 650 ms) and Aδ-fibre related detections (detections with RTs ≤ 650 ms). C-fibre thresholds were assessed first to avoid effects of habituation and/or sensitization effects that could be induced by high intensity stimulations. Conditioning temperature staircases were presented in an interleaved fashion to prevent expectation bias. Staircases were stopped after the first 6 consecutive inversions within a 2 °C range. Thresholds were determined by averaging the temperature values of these 6 reversals.

Reaction times

Since the procedure for threshold assessments described above only requires a relatively low number of trials (on average 44 ± 13 trials per subject), we performed a second series of experiments with a much higher number of trials in order to obtain more robust estimates of RT frequency distributions. Thereto, we recruited 5 congenitally blind (2 F; mean age: 41.6 ±10.2 years, range: 30-54) and 5 normally sighted (2 F; mean age: 42.2 ±11.1 years,

range: 26-54) participants. We only used one T_1 temperature (35 °C) since the results of the first experiment showed that baseline temperature has no effect on thresholds. We delivered 300 T_2 stimuli, half of them at 44 °C and the other half at 52 °C. Preliminary tests indicated that the 44 °C stimulus is a clear supraliminal stimulus for C-fibre nociceptor activation with a minimal contamination by Aδ-related responses. In a similar fashion, we chose the 52 °C stimuli to obtain clear supraliminal Aδ-fibre related responses. To reduce the effect of habituation and receptor fatigue or sensitisation, we started with the low intensity stimuli first and moved the laser beam after each trial by 2 cm, following a 5 x 5 matrix, using a 4 s interstimulus interval. Every 25 trials, we introduced a short break to assure maximal attention from the participants.

Statistical analysis

To assess group differences in Aδ- and C-fibre thresholds and to examine the effect of differences in baseline temperature, we performed a three-way ANOVA using SPSS with "nociceptor type" (Aδ- or C-fibres) and "T_1" (32 or 35 °C) as the within-subject factors and ''group'' (NS, CB, LB) as the between-subject factor. The analysis of RTs was performed for each subject separately without any *a priori* on the distribution of responses. A kernel smoothing density algorithm was applied to the empirical distribution, followed by a nonlinear regression procedure that fitted a two-term finite mixture of ex-Gaussian probability density functions. This model was chosen over a double Gaussian distribution because it takes into account the asymmetry of the response frequency distributions that is inherent to RT based experiments (Churyukanov et al., 2012; Lacouture and Cousineau 2008; Luce and Green 1972). Furthermore, the model allowed us to decompose RT data into the parameters τ, μ and σ for the two fibre classes, as well as pAδ (Figure 2). The latter determines the proportion of Aδ-fibre related responses, whereas the parameter "(1-pAδ)" refers to the proportion of C-fibre related responses in the distribution. The other parameters fall into the categories central decisional processing and residual latencies (Luce 1984). The central processing latency, expressed by the parameter "τ", is defined as the time necessary to compute the sensation and to initiate a motor response (Matzke and Wagenmakers 2009). It is generally assumed that the

central processes constitute the exponential component of the frequency distribution and account for the asymmetry of the RT data (Ratcliff and Van Dongen 2011). Finally, the residual latencies are expressed by the parameters "μ" and "σ" that constitute the average and standard deviation of the Gaussian components of the RT distribution, respectively (Matzke and Wagenmakers 2009). These residual latencies include 1) the transmission of heat from the cutaneous surface to the transducers, 2) the transduction and action potential generation, 3) the transit time, 4) the conduction and synaptic transmission in the CNS and 5) the initiation of the motor response (Luce 1984). Assuming that processes 1 to 4 are similar in blind and sighted individuals, between group differences in μ would translate to a difference in processing the motor response. Importantly, the bimodal ex-Gaussian model avoids the use of an arbitrary separator for the two distributions.

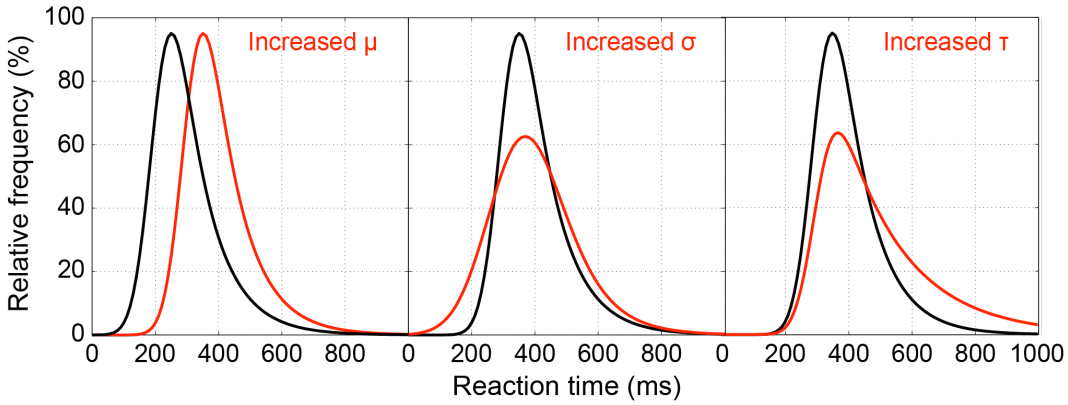

Figure 2. Parameters of the ex-Gaussian probability density function. The parameters "μ" and "σ" account for the mean and standard deviation of the function's Gaussian component. The exponential parameter "τ" is responsible for the skewedness of the function and pertains to the central processing time.

Standard error and confidence intervals of the mean difference between groups in Aδ- and C-fiber mediated RT peak values of the RT distributions were computed by a non-parametric bootstrap procedure (1000 resamplings with replacement). Groups were considered to have a significant difference in peak values if the 95% bootstrap confidence interval for the difference did not include the value 0. All computations were performed with Matlab Statistical toolbox (Mathworks: http://www.mathworks.com).

Results

Aδ- and C-fibre detection thresholds

Table 2 shows the thresholds of Aδ-fibre (RT ≤ 650 ms) and C-fibre mediated responses (RT > 650 ms) of the three groups (NS, CB and LB) and for the two skin conditioning temperatures (T_1 = 32 or 35 °C). The repeated measures ANOVA indicated that there were no significant group differences in Aδ- or C-fibre thresholds (F = 0.168, p = 0.846). The skin conditioning temperature T_1 had also no influence on the thresholds (F = 0.518, p = 0.477). As expected, the ANOVA analysis showed a highly significant main effect of the factor "nociceptor type" (F = 434.155, $p \leq 0.001$), indicating that the Aδ-fibre mediated threshold (48.8 ± 3.3 °C) was markedly higher than the C-fibre mediated one (40.0 ± 2.4 °C). No further significant interactions were found. Since T_1 had no influence on the thresholds, we pooled the Aδ- and C-fibre related responses of the two skin-conditioning temperatures. The average thresholds of the pooled C-fibre mediated responses were T_2: NS = 40.3 ± 2.1 °C, CB = 39.7 ± 2.4 °C and LB = 40.0 ± 3.2 °C and the thresholds of the pooled Aδ-fibre mediated responses were T_2: NS = 48.9 ± 3.4 °C, CB = 49.2 ± 3.1 °C and LB = 47.8 ± 3.9 °C.

Table 2. Thresholds of C- and Aδ-fibre mediated detections using 32 and 35 °C skin conditioning temperatures (T_1).

Subjects	T_1 = 32 °C		T_1 = 35 °C	
	C-fibre (°C)	Aδ-fibre (°C)	C-fibre (°C)	Aδ-fibre (°C)
NS	40.3 ± 2.2	49.2 ± 3.4	40.3 ± 2.0	48.7 ± 3.5
CB	39.7 ± 2.4	49.3 ± 3.4	39.7 ± 2.5	49.1 ± 2.8
LB	39.9 ± 3.6	47.9 ± 4.0	40.2 ± 3.0	47.7 ± 3.9

Reaction times

Figure 3A shows the contour plots of the RT distributions of the first experiment as a function of stimulus strength (T_2). As illustrated, the RTs have a clear bimodal distribution. The first peak corresponds to higher target skin temperatures that triggered short-latency detections compatible with the peripheral conduction velocity of myelinated Aδ-fibres,

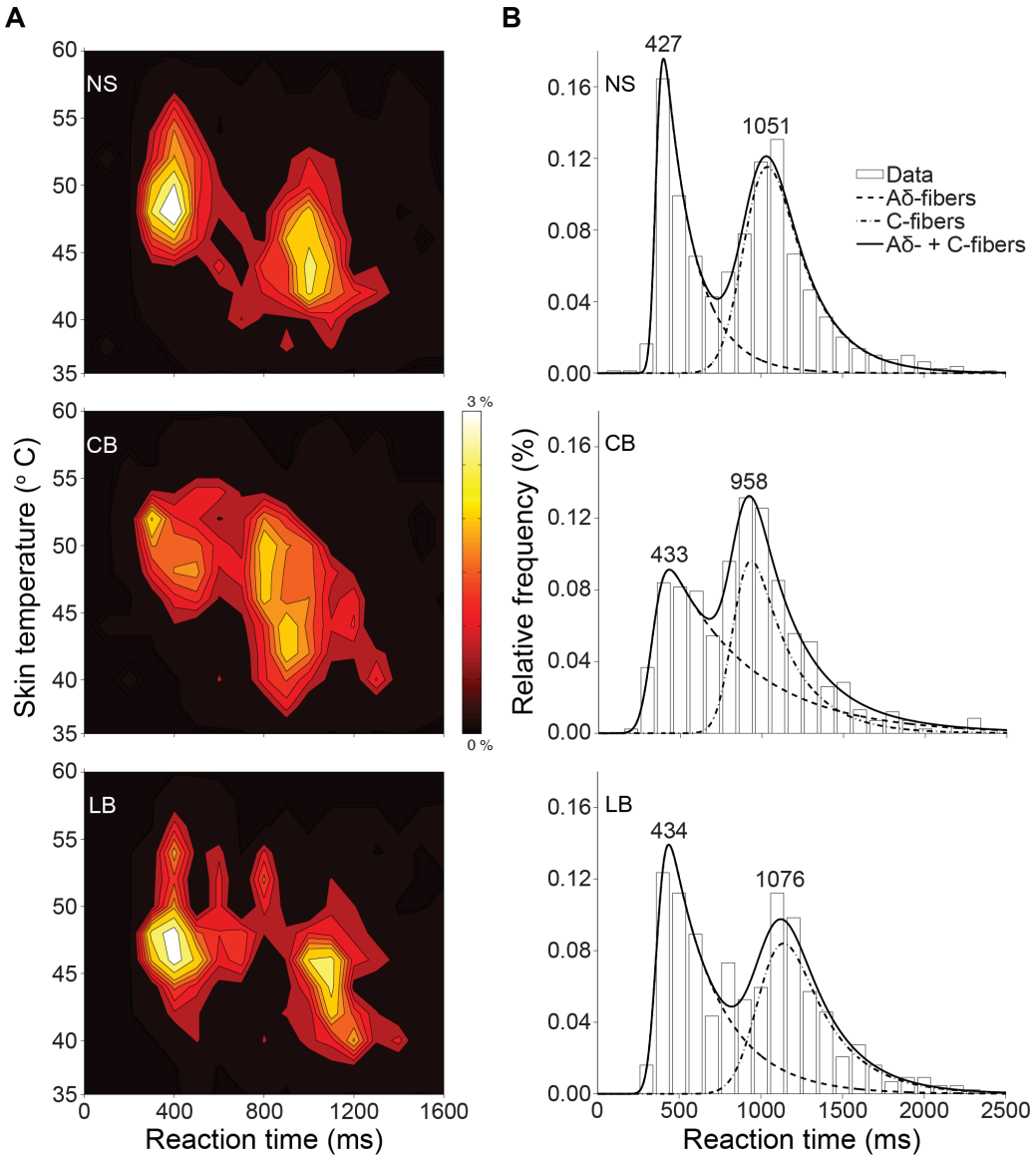

Figure 3. Reaction times frequency distributions to brief heat pulses. A – Contour plots illustrating the frequency distribution of reaction times (RTs) paired to the temperature of the stimulus. The first (fast responses, high temperatures) and second (slow responses, low temperatures) peaks correspond to Aδ- and C-fibre distributions, respectively. CB's C-fibre peak reaction time is shifted leftwards compared to NS and LB. B – Ex-Gaussian fitting on the RT data. The bimodal frequency distribution histograms were obtained with the pooled RTs of each group regardless to the target skin temperature (T_2) and reflect the Aδ- and C-fibres difference in conduction velocity. In each group, the black continuous line corresponds to the two-term finite mixture model with ex-Gaussian probability density functions. The dashed and dotted/dashed lines represent the contribution of the Aδ- and C-fibre related RTs, respectively. Compared to NS and LB, CB had a faster C-fibre peak reaction time ($p < 0.001$). Abbreviations: NS = normally sighted, CB = congenitally blind, LB = late blind.

whereas the second peak corresponds to lower target skin temperatures that triggered long-latency detections compatible with the peripheral conduction velocity of unmyelinated C-fibres (Campbell and LaMotte 1983; Churyukanov et al., 2012; Plaghki et al., 2010). In comparison with the sighted and the late blind groups, the long latency RTs of the congenitally blind appear to be globally shifted to the left on the time axis. This is confirmed by the RT distributions to C-fibre mediated sensations in figure 3B. As illustrated, congenitally blind participants responded faster to C-fibre (peak frequency of RTs in CB = 958, LB = 1076, NS = 1051 ms) but not to Aδ-fibre stimulation compared to the two other groups (peak frequency of RTs in CB= 433, LB = 434 and NS = 427 ms). This was confirmed by computing the distributions of mean differences in RT peaks between groups by means of a non-parametric bootstrapping procedure (Table 3).

Table 3. Mean difference of peak frequencies in RT distributions.

	Aδ-fibre mediated			**C-fibre mediated**		
	NS - CB	**NS - LB**	**LB - CB**	**NS - CB**	**NS - LB**	**LB - CB**
Mean	7	-22	29	93	-25	118
+ 95% CI	51	24	86	168	64	203
- 95% CI	-37	-68	-27	17	-114	43
T-statistic	0.298	0.936	1.035	2.411	0.558	2.729
P	0.383	0.175	0.150	*0.008	0.286	*0.003

This result was also corroborated by the second series of experiments that allowed a more robust estimate of the RT frequency distributions because of the much higher number of trials (Figure 4). Congenitally blind participants responded significantly faster to the 44 °C stimuli than their sighted peers (peak values CB = 792 ± 72 ms, NS = 961 ± 84 ms; $p < 0.01$). Further investigation of the C-fibre RT distribution revealed that congenitally blind individuals had a faster τC and μC than their sighted peers (Table 4). It is noteworthy that the RT distribution of the C-fibre mediated sensations was four times more skewed than that of the Aδ-fibres. Overall, these results indicate that visual deprivation from birth leads to a facilitated detection and faster RTs to C-fibre mediated sensations, probably due to a more efficient central processing of these nociceptive signals. Importantly, blind participants also had a significantly

higher detection rate (CB = 93 ± 5 %, NS = 77 ± 11 %; $p < 0.05$) of C-fibre stimuli. In contrast, for the more intense stimuli of 52 °C (Figure 4B), there were no group differences in Aδ-fibre peak RTs (NS = 210 ± 21 ms and CB = 234 ± 54 ms; $p > 0.05$), nor in the detection rates (95 ± 2 % and 96 ± 7 %, respectively; $p > 0.05$). Overall, these results indicate that visual deprivation from birth leads to a facilitated detection and faster RTs to C-fibre mediated sensations.

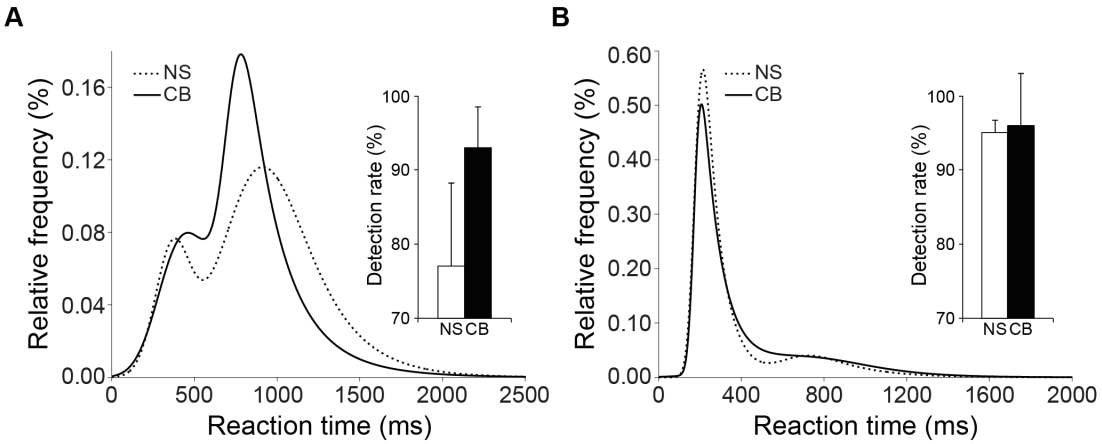

Figure 4. Reaction times frequency distributions to suprathreshold C- and Aδ-fibre heat pulses. A – Stimuli given at 44 °C. CB had a higher detection rate ($p < 0.05$) and a faster C-fibre peak RT ($p < 0.01$) than NS. **B** – Stimuli given at 52 °C. NS and CB had a similar detection rate ($p > 0.05$) and Aδ-fibre peak RT ($p > 0.05$).

Table 4. Decomposition of the ex-Gaussian probability density function parameters (mean ± sd) from 44 °C nociceptive heat stimuli.

	μC	**σC**	**τC**
NS	752 ± 12	206 ± 20	250 ± 21
CB	702 ± 9	73 ± 7	193 ± 33
P	< 0.001	< 0.001	< 0.001

Discussion

The aim of this study was to test the role of Aδ and C-fibres in hypersensitivity to heat pain in congenitally blind individuals (Slimani et al., 2014; Slimani et al., 2013). We addressed this question through the investigation of Aδ- and C-fibre response times and detection frequencies to brief nociceptive radiant heat stimuli. Results indicated that compared to late blind and sighted participants, congenitally blind subjects reacted faster to C-fibre

mediated sensations. In addition, these subjects also detected significantly more C-fibre mediated heat stimuli. These data provide a possible physiological basis for the earlier reported hypersensitivity to heat in congenital blindness.

Faster response times to C-fibre mediated sensations

We previously showed that congenitally blind individuals are hypersensitive to noxious thermal stimulation (Slimani et al., 2014; Slimani et al., 2013). In these studies, we measured pain thresholds using the method of limits. It has been argued that this method is prone to anticipatory responses, particularly when using a slow stimulus ramp rate, because anxiety may build up and participants may respond before the stimulus becomes painful, leading to an underestimation of the true pain threshold (Kunz and Lautenbacher 2014). In the current study, we circumvented this problem by making two important changes to our testing paradigm. First, we minimized response bias by anticipation by interleaving two adaptive up/down staircase algorithms. As a result, participants in the first experiment were unable to predict the relationship between their response and the relative temperature of the upcoming stimulus (higher or lower than the last presented one). Second, by using very fast ramped and short laser pulses, 10 and 90 ms, respectively, we avoided the "reaction time artefact" generated by threshold assessment procedures that involve RTs (Yarnitsky and Ochoa 1991). This artefact is particularly consequential when estimating sensory modalities with longer RTs like those mediated by unmyelinated C-nociceptors. Also, anxiety build-up, caused by slowly increasing stimuli, may contribute to this reaction time artefact. Using this new method, we found that compared to sighted and late blind participants, congenitally blind subjects responded significantly faster to C-fibre mediated sensations. This result was confirmed in the second experiment that employed a much higher number of stimuli, allowing a more precise estimation of RTs. Since we recently showed that congenitally blind individuals outperform the sighted in a non-painful heat discrimination task (Slimani et al., 2015), one could argue that the shorter RTs to C-fibre mediated sensations are due to a faster processing of innocuous warmth stimuli through low threshold C-warm receptors. However, this seems rather unlikely since low threshold C-warm responses represent less than 10% of the responses in the first

experiment (Figure 3A). We therefore explain our results by the activation of C-fibre polymodal nociceptors. This is in line with results reported in primates, showing that rapidly adapting C-fibre polymodal nociceptors already respond to heat of ~40.8 °C (Wooten et al., 2014). The results obtained in the second experiment further support our conjecture since the temperature that was used (44 °C) is well in the range for C-nociceptor activation and far above that for activating C-warm receptors. Together, these data indicate a faster accumulation rate of sensory evidence in congenitally blind subjects for C-fibre mediated input. This conjecture was supported by a decomposition analysis of the RTs of the second experiment showing that congenitally blind individuals had a faster τC – which provides an estimate of the decisional component of response times – than their sighted peers, indicating a more efficient central processing of C-fibre mediated nociceptive signals.

Both congenitally blind and sighted controls responded faster in the second experiment in which we only used supra-threshold stimuli for C-fibre nociceptor activation. However, the gain in response time in the second experiment was double in the congenitally blind compared to the sighted controls. This means that when the stimulus is more salient, the gain in central processing time becomes even larger for the congenitally blind subjects. In addition, the results of the second experiment indicate that congenitally blind subjects also had a higher detection rate of C-fibre mediated heat responses. This finding further supports our hypothesis that increased responses to painful stimulation in congenital blindness are due to a hyper-vigilance to threatening stimulation.

We did not find a significant difference for Aδ mediated responses between the three groups. This result may be explained by a ceiling effect. Response times are already so fast in the control subjects, around 200 ms when using supra-threshold stimuli, that a further gain in reaction time in the congenitally blind group is not possible. This interpretation could be tested in future studies whereby responses are recorded to Aδ mediated responses that are only slightly above threshold and that are applied to more distal areas such as the lower leg or the dorsum of the foot. Indeed, augmenting the peripheral distance allows a better separation of the bimodal distribution of RTs of the C and Aδ-fibre mediated responses. An alternative interpretation for the lack of a group difference for the Aδ-mediated responses is that the Aδ-fibres, because of their higher threshold, play a lesser important role than C-fibers in approach

behaviour towards stimuli that may cause skin injury. For example, shorter RTs to C-fibre mediated responses around threshold will assure that a blind person will get too close to a hot stove, hence protecting him from skin injury. However, for higher stimulus intensities that activate Aδ-fibres, tissue injury has already taken place and default RTs are already so fast that increasing vigilance adds little in terms of protection from injury. This suggests a more automatic processing of the Aδ-fibre input that is less dependent on top-down modulatory influences than C-fibre mediated responses. This conjecture is supported by the observation that the RT distribution to C-fibre mediated sensations was four times more skewed than that to Aδ-fibre mediated sensations, indicating that it is a less reliable channel (Figure 4). Here, reliability refers to the precision, or the inverse variance of the probability density function of sensory responses, with larger variances indicating less reliable response rates. The inverse variance can be interpreted as a measure of the noisiness in a sensory channel (Green and Swets 1988). This may result from the fact that Aδ-fibre inputs are more salient than C-fibre inputs (Churyukanov et al., 2012; Nahra and Plaghki 2003; Vierck et al., 2004), leading to a faster central accumulation of sensory information and ultimately to a faster decision-making (Ratcliff and Van Dongen 2011). This, together with the already very short response latencies to Aδ-fiber stimulation, makes it unlikely that congenitally blind individuals would show faster reaction times to this type of input. The C-fibre channel, however, is more open for improvement through other central processes such as multimodal integration and top-down attentional modulation. In line with our previous finding that congenitally blind individuals are more attentive to signs of threat (Slimani et al., 2014; Slimani et al., 2013), this provides a possible mechanism for faster responses to C-fiber mediated input.

Aδ- and C-fibre mediated detection thresholds

We chose a cut-off of 650 ms to discriminate between Aδ- and C-fibre mediated responses. This criterion was based on the peripheral conduction distance of afferent input originating from the hand, and on the distribution of reaction times to laser stimuli after blockade of the myelinated fibres (Bromm et al., 1983; Nahra and Plaghki 2003). The RT analysis that was performed without any *a priori* on the distribution of the responses,

confirmed the validity of our criterion in the adaptive staircase algorithm. In contrast with the RT data, there were no group differences in Aδ- and C-fibre mediated detection thresholds. Although this finding may seem surprising at first sight, it does not contradict our earlier finding of lower heat pain thresholds in congenitally blind individuals (Slimani et al., 2014; Slimani et al., 2013). Indeed, in the current study, we asked participants to respond whenever they felt a stimulus, irrespective of whether it was painful or not. Although the stimulation intensities we used mainly activated C-fibre nociceptors, the induced sensation was not always painful. This finding can be explained by the fact that we stimulated a very small surface area and that stimulus duration was very short (100 ms). Indeed, the induction of pain perception is critically dependent on the magnitude of spatial summation by applying a single stimulus with an increasing area (Defrin et al., 2003; Defrin and Urca 1996; Kojo and Pertovaara 1987; Machet-Pietropaoli and Chery-Croze 1979), or on temporal summation by C-fibre wind-up (Torebjörk and Hallin 1974).

Hypervigilance to threat

The hypersensitivity to threat hypothesis takes into account that attention provides top-down modulation that, with development, shapes bottom-up signals by strengthening synaptic connections. Therefore, the increased use of non-visual senses can lead to an enhanced selective attention for non-visual types of stimuli that would ultimately lead to neuroplastic changes in the visually deprived brain (Kupers and Ptito 2014). Indeed, blind individuals employ different strategies, including other detection criteria for tactile exploration and object localisation than the sighted (Beaulieu-Lefebvre et al., 2011; Pietrini et al., 2009; Sterr et al., 2003). This may explain why congenitally blind individuals score higher for odour awareness (Beaulieu-Lefebvre et al., 2011), pay more attention to painful encounters in daily life (Slimani et al., 2014; Slimani et al., 2013), have augmented responses to auditory threats (Klinge et al., 2010) and are better at identifying odours with negative emotional valence (Iversen et al., 2015). We therefore suggest that congenitally blind individuals use such mechanisms for attention orienting towards potentially harmful stimuli in order to quickly identify and react to dangerous events. Indeed, not only do congenitally blind subjects react

faster to C-fibre mediated sensations, but they also have a higher accuracy of detection of C-fibre mediated heat at supra-threshold levels.

Late blind individuals

Unlike congenitally blind subjects, late blind subjects did not differ from sighted controls. This observation indicates that the lack of visual experience, rather than blindness *per se,* is responsible for the hyper-responsiveness to nociceptive stimuli. This is in line with our previous results showing that late blind participants do not have an enhanced sensitivity to pain, nor a heightened vigilance towards painful stimuli (Slimani et al., 2014). More broadly, this finding also fits with studies indicating that these individuals are less susceptible to compensatory plasticity (Alary et al., 2008; Collignon et al., 2009; Grant et al., 2000; Wan et al., 2010). In fact, many animal and human studies have shown that structural and functional brain changes following blindness are less likely to occur later in life (Desgent and Ptito 2012; Kupers and Ptito 2014). In contrast, it is well established that early visual deprivation causes cross-modal plastic changes that lead to the recruitment of the visual cortex in non-visual tasks (Kupers and Ptito 2014).

Conclusion

In conclusion, using a new method allowing for a psychophysically unbiased measurement of Aδ- and C-fibre mediated thresholds, we showed that hypersensitivity to heat pain in congenital blindness is associated with a more efficient central processing of C-fibre mediated input. This may help these subjects to avoid impending dangerous encounters with stimuli that may threaten their bodily integrity. As a corollary, the present results also reveal how the use of reaction times to selective Aδ- and C-fibre input may be a helpful tool to probe into mechanisms of pain perception.

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Author contributions

HS, LP, MP and RK conceived and designed the experiments. RK and MP contributed with experimental equipment. LP contributed with the data analysis tools. HS performed the experiments. HS and LP performed the data analysis. HS, LP, MP and RK wrote and edited the manuscript. All authors read and approved the final manuscript.

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Article 5. Anticipation of strong pain increases ratings to mild painful stimuli in congenitally blind individuals

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Anticipation of strong pain increases ratings to mild painful stimuli in congenitally blind individuals

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Abstract

Background: We have previously shown that congenitally blind are more sensitive to painful heat compared to their sighted counterparts. One possibility is that this hypersensitivity is mediated by psychological and cognitive factors such as pain expectation and anxiety. Here we investigate how uncertainty about the intensity of a pending painful stimulus affects pain in congenitally blind and sighted control subjects.

Method: We measured pain and anxiety in a group of 11 congenitally blind and 11 age- and sex-matched normal sighted control participants. Painful stimuli were delivered under two psychological conditions, whereby participants were either certain or uncertain about the intensity of a pending noxious stimuli.

Results: Although both groups had increased anxiety ratings in the uncertain condition, pain ratings increased only in the blind participants. Blind and sighted participants had similar state and trait anxiety levels. Analysis of the "Pain Vigilance and Awareness Questionnaire" and the "Pain Anxiety Symptoms Scale" allowed to discriminate the blind from the sighted participants with an accuracy of 86.4%, and suggests that blind individuals are more attentive and anxious towards external signals of threat.

Conclusions: Our data indicate that anxiety affects pain perception more strongly in blind individuals and that blind individuals are more attentive towards external signals of threat. We suggest that a heightened state of vigilance and attention towards external signals of threat is at the basis of the hyperalgesia in congenital blindness.

1. Introduction

Acute pain has an important alarm function that protects us from bodily harm by inducing escape and avoidance behavior from tissue damaging stimuli (Tracey, 2011). Similarly, vision is important for detecting and averting possible external threats. In line with this, there is an increasing amount of data supporting the role of vision in pain perception. Indeed, long-term visual deprivation in normally sighted individuals can increase pain perception (Zubek et al., 1964), while seeing the stimulated limb may reduce pain ratings (Longo et al., 2009; Mancini et al., 2011; Longo et al., 2012).

We have previously shown that congenitally blind (CB) subjects are hypersensitive to painful stimuli compared to their sighted peers, and are more attentive to signals of external threat (Slimani et al., 2013; 2014). This raises the possibility that anxiety plays a role in the hypersensitivity to pain in congenital blindness. Indeed, studies in normal sighted (NS) individuals have shown that pain perception is strongly influenced by the psychological state of an individual, and that anxiety increases ratings of experimentally induced pain (Ploghaus et al., 2001; Tang & Gibson, 2005; Gondo et al., 2012; Yang et al., 2012). According to the hypersensitivity to threat hypothesis, the lack of informative vision increases anxiety levels in congenitally blind individuals, thereby causing an overall hypersensitivity to threatening stimuli such as pain (Mancini, 2013; Slimani et al., 2013; 2014).

The aim of the current study was therefore to test the hypothesis that congenitally blind individuals experience more anxiety in response to a strong impeding painful stimulus compared to matched sighted controls, and that this will cause higher pain ratings. Thereto, we used a previously validated experimental pain paradigm that induces anxiety by creating uncertain expectations regarding the intensity of a pending noxious stimuli (Sawamoto et al., 2000; Ploghaus et al., 2001; Tang & Gibson, 2005; Oka et al., 2010; Meulders et al., 2012; Yang et al., 2012). If a heightened state of anxiety is indeed the main driver behind the hypersensitivity to pain in congenitally blind subjects, we expect that they will report increased pain and anxiety ratings compared to a matched control group of sighted individuals.

2. Method

2.1. Participants

Participants were recruited from our database of congenitally blind participants or by advertisement. In total, we included 11 congenitally blind (CB: 4 F; mean age 34.4 ± 6.4 years, range 23 – 65) and 11 age and sex-matched normal-sighted (NS: 4 F; mean age 34.3 ± 6,9: range 23 – 61) control subjects. Inclusion criteria for the congenitally blind subjects were blindness of peripheral origin within the first year of life. For all participants, inclusion criteria were being in good health with no known self-reported neurological or psychiatric disorders. All participants gave informed consent and the ethics committee of the city of Copenhagen and Frederiksberg (Denmark) approved the study protocol.

2.2. Equipment

We used a CO_2 laser stimulator device with a circular spot diameter of 6 mm (LSD, SIFEC, Ferrières, Belgium) to apply highly accurate and contactless heat stimuli to the skin. Blind participants received a detailed verbal description of the equipment and they were allowed to inspect it by touch. A contactless temperature measuring unit provided online monitoring of the target skin temperature to control laser power output in a closed-loop control system. This ensured that the skin was brought to and maintained at the correct target temperature. As the device is contactless, only the thinly myelinated A∂ and unmyelinated C-fibers were activated without co-activation of the large myelinated Aß-fibers (Churyukanov et al., 2012).

2.3. Procedure

We applied 3-s lasting laser stimuli to the dorsal part of the dominant hand 5 s after a verbal cue. After each stimulus, the laser beam was moved to another spot within a 3 x 5 matrix to avoid habituation. Each spot was placed 1 cm apart from the other. Participants rated pain intensity and pain unpleasantness on an 11-point numerical rating scale, with “0”

indicating no pain or not unpleasant and “10” the highest pain intensity or unpleasantness that they were willing to tolerate in the experimental setting. The standard instructions by Price et al. (1989) were used to explain the difference between pain intensity and unpleasantness (Price et al., 1989).

Sighted participants were blindfolded during all testing. Since there is a large inter-individual variability in pain thresholds, temperatures for both the low pain and high pain stimulus were individually adjusted for each participant as following. First, participants were familiarized with the sensation evoked by the laser and trained in using the numerical rating scales. Then, each participant received four stimulations of each of the following temperatures in a randomized order: 41, 43, 45, 47, 49, 51 and 53 °C. Following each stimulus, the participants rated perceived pain intensity. The low pain temperature chosen for each subject corresponded to his/her pain intensity rating of 3, while the high pain temperature corresponded to a pain intensity rating of around 7 on the 11-point rating scale. To avoid burn injury, no participant received a stimulus temperature above 53 °C even if they had not rated the 53 °C temperature as “7“ or more.

We applied a total of 30 stimuli per trial and participants rated pain intensity and unpleasantness directly after each stimulation. In the certain condition, participants received 30 consecutive stimulations of the same low intensity temperature. Participants were told that they would only receive mildly painful low temperature stimuli. In the uncertain condition, participants were told that they would receive a range of pain stimuli, going from mildly to highly painful, and that the order and intensity of the stimuli were chosen randomly. The participant then received 30 consecutive stimulations consisting of 24 low and 6 high pain intensity stimuli. The order of the six high temperature stimulations was pseudo-randomized such that participants received one within each block of five stimuli. Participants received a total of 60 stimuli, 30 in each condition. The order of the certain and uncertain conditions was randomized across participants.

Experienced anxiety in each condition was rated on an 11-point numerical rating scale. Here, “0” was defined as no anxiety and “10” as highest level of anxiety endurable in this setting. The ratings were done only once in each condition after stimulus number 25, as

conscious self-assessment of both pain sensation and anxiety can lead to a hypothesis-driven bias (Gross, 1981).

2.4. Pain questionnaires

At the beginning of the session participants filled out the STAI-Y questionnaire in order to measure state (STAI-1) and trait anxiety (STAI-2) (Spielberger et al., 1983). Questions regarding eating and sleeping habits and physical activity levels were added to mask the focus on anxiety and thus reduce hypothesis-driven artefacts (Gross, 1981). After the session, all participants filled out the Pain Anxiety Symptom Scale (PASS) (McCracken & Dhingra, 2002) and the Pain Vigilance and Awareness Questionnaire (PVAQ), adapted for a non-clinical population. These questionnaires measure individual reactions to painful stimuli encountered in everyday life (McWilliams & Asmundson, 2001). Specifically, the PASS consists of the subscales "Physiological Anxiety" (PASS_PA), "Cognitive Anxiety" (PASS_CA), "Fear" (PASS_F) and "Escape/Avoidance" (PASS_EA). The PVAQ consists of the subscales "Intrusion" (PVAQ_I), "Monitoring" (PVAQ_M) and "Attention to changes in pain" (PVAQ_APC). The items of the two questionnaires were all read to the blind participants by the same experimenter.

2.5. Statistical analysis

We used Levene's and Shapiro-Wilk tests to check for equal of variances and normality of the distributions of our collected data. We applied an unpaired T-test for between-group comparisons of normally distributed data, and a paired T-test for within-group comparisons (high vs. low anxiety). We ran Mann-Whitney or Wilcoxon tests for non-normally distributed data. We used Kendall's tau to test for correlations on the whole sample.

The analysis of the pain rating data was performed using General Linear Models (GLM) that only included dependent variables and covariates that had passed Levene's Test. Specifically, we ran a GLM multivariate analysis with between group factors experimental group (CB versus NS) and gender (female versus male), and within group factor psychological

condition (uncertain, UC, vs. certain, CC). Dependent variables were pain intensity and unpleasantness ratings, while STAI-1 and age were used as covariates. Here, the between condition comparison took only the values of the pain temperature ratings into account. Thereafter, we ran a GLM univariate analysis on the high temperature ratings [between factors: group (CB vs. NS) and gender (female vs. male); dependent variable: intensity rating; covariates: STAI-1 and age]. We calculated effect size and Cohen's d for the pain intensity measurements.

Results of the PASS and PVAQ were explored using a Fisher linear discriminant analysis (FLDA) to search for a discrimination function that could distinguish between CB and NS. Here, variables were entered using the ''all-variables together'' method, and the goodness of classification analysis was tested using the leave-one-out technique.

In all the analyses, we choose $\alpha = 0.05$ and Bonferroni correction for multiple comparisons.

3. Results

All data except the anxiety VAS ratings and the state anxiety scores were normally distributed and Levene's test indicated homogeneity of variance. Consequently, we used non-parametric tests for the anxiety VAS ratings and state anxiety scores. The effect size of pain intensity changes was 0.47 (Cohen's d = 1.07).

3.1. Low and high pain temperatures

Overall, the temperatures needed to elicit the same subjective pain ratings were lower in CB compared to NS. More specifically, the temperatures for the low (CB: 41.8±2.5°C; NS: 45.9±1.6°C) and high (CB: 47.4 ± 2.4 °C; NS: 51.9 ± 1.2 °C) pain ratings were more than four degrees lower in the congenitally blind compared to the normally sighted group ($p < 0.001$). Statistical analysis confirmed that there were no significant group differences for either low (CB: pain intensity: 2.3 ± 0.6; pain unpleasantness: 2.6 ± 1.1; NS: pain intensity: 2.3 ± 0.6;

pain unpleasantness: 1.7 ± 0.9) or high temperature ratings (CB: pain intensity: 6.5 ± 2.2; pain unpleasantness: 6.4 ± 2.5; NS: pain intensity: 7.6 ± 0.7; pain unpleasantness: 7.3 ± 2.3).

3.2. Anxiety ratings

Anxiety ratings were significantly higher in the uncertain compared to the certain condition for both the congenitally blind ($p = 0.007$) and the sighted controls ($p = 0.026$). A between-group comparison did not reveal differences in anxiety ratings in either the certain (CB: 0.5 ± 1.0, NS: 1.0 ± 1.0, $p = 0.217$) or uncertain (CB: 2.5 ± 2.1, NS: 2.2 ± 1.3, $p = 0.898$) condition (Figure 1). Hence, being uncertain about pending stimuli made both groups equally more anxious. Gender did not play a role as no significant gender differences in either the certain ($p = 0.059$) or uncertain condition ($p = 0.145$) were found.

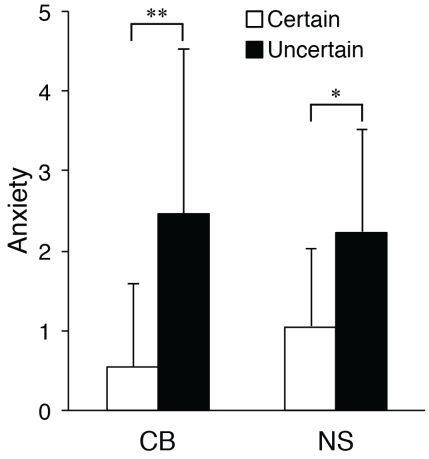

Figure 1. Anxiety ratings in congenitally blind and normally sighted participants. Congenitally blind **(**CB) and normal sighted (NS) controls both report an increase in anxiety in the uncertain compared to the certain condition. *$p < 0.05$, **$p < 0.01$.

3.3. Pain intensity and unpleasantness ratings

The GLM Multivariate analysis revealed a significant group x condition interaction for both pain intensity ($p = 0.021$) and pain unpleasantness ($p = 0.032$) ratings. The congenitally blind increased their ratings for both pain intensity (Δ: 0.8) and pain unpleasantness (Δ: 0.4) in the uncertain condition, whereas the scores did not change in the sighted controls (Δ: 0.1 and 0.0 for intensity and unpleasantness, respectively) (Figure 2A and B).

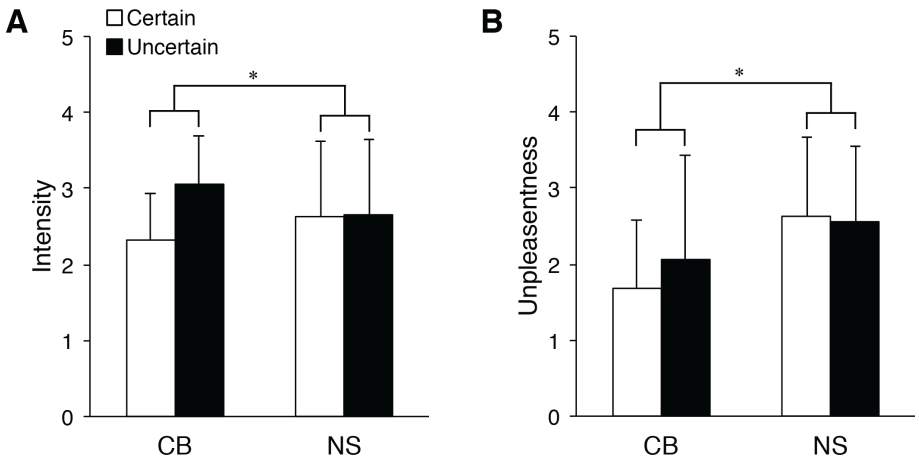

Figure 2. Pain intensity and unpleasantness ratings in the congenitally blind and normally sighted subjects. There was a significant group x condition interaction for both pain intensity (A) and pain unpleasantness (B) ratings, with congenitally blind (CB) participants giving higher ratings in the uncertain compared to the certain condition. Error bars represent standard error of the mean. *$p < 0.05$.

3.4. Questionnaires

Congenitally blind participants scored higher than the sighted controls on the PVAQ (CB: 61 ± 8; NS: 39 ± 10, $p < 0.001$) and the PASS (CB: 45 ± 20; NS: 29 ± 11, $p = 0.036$). The FLDA showed that PVAQ and PASS scores discriminated the blind from the sighted with an accuracy of 86.4%, indicating that the congenitally blind are more attentive and more anxious than the sighted controls to pain encounters in daily life.

4. Discussion

In this study we investigated the effect of anxiety on pain perception in congenital blindness. Thereto, we compared pain ratings for the same stimuli when participants were either certain or uncertain about the intensity of an imminent noxious stimulus. Uncertainty about the intensity of a pending noxious stimuli increased anxiety ratings in both congenitally blind and sighted individuals, however pain ratings only increased in the blind participants. Our psychometric data further showed that congenitally blind individuals are generally more anxious, attentive and vigilant towards painful encounters compared to matched normal sighted controls.

4.1. Hypersensitivity to pain in the congenitally blind

In line with our previous studies, blind participants had significantly lower pain thresholds compared to the sighted controls. The temperatures used to evoke low and high pain were on average four degrees lower for the blind participants. This is very similar to what we observed earlier and hence confirms our previous findings that congenitally blind individuals are hypersensitive to pain (Slimani et al., 2013; 2014).

4.2. Anxiety ratings

In line with our expectations, priming the participants to be uncertain about the intensity of an upcoming noxious stimuli resulted in higher anxiety ratings for both groups. However, we did not find a between-group difference in the induced anxiety levels, meaning that the stronger effect of anxiety on pain ratings in the blind is not due to stronger experimentally induced anxiety ratings. In line with the self-reported anxiety scores, state and trait anxiety scores also did not differ between the blind and the sighted, indicating that congenitally blind individuals are not more anxious at the overall level.

The literature as to whether general anxiety levels are altered in congenital blindness is very sparse. Previous studies from our group failed to show differences in state anxiety ratings between congenitally blind and age -and sex-matched sighted controls (Meaidi et al., 2014). The present data extend these data by showing that when explicitly manipulating anxiety levels by a standardized procedure, anxiety ratings increase to the same extent in blind and sighted participants. Together, these data suggest that increased pain ratings in congenitally blind subjects are not due to higher anxiety levels per se.

It could be argued that blindfolding the control participants during the experiment may have made them more anxious than they would normally have been under conditions of full vision. Although we cannot rule this out completely, anxiety ratings in the baseline condition in the sighted controls were low and anxiety increased to the same extent as in the blind following the anxiety-inducing procedure.

There is a still ongoing debate with respect to the question when anxiety or fear is induced by an experimental manipulation (Rhudy & Meagher, 2000). A cue-conditioning paradigm is often chosen to induce anxiety by creating uncertainty over the upcoming stimulus. In this type of trials, participants are either told about the contingency there is between a cue and the ensuing stimulus intensity, or they learn it by experience. In either situation, participants will usually have felt the highly painful stimulus before or during the trial, and thus they have an idea of what to expect. Rhudy and co-workers have argued that this situation will induce fear rather than anxiety, anxiety being defined as stemming from an unknown source. Further according to Rhudy et al., fear will lead to a decrease in pain perception, whereas anxiety will induce an increase in pain perception (Rhudy & Meagher, 2000). It is therefore possible that these cue-conditioning paradigms produce a mixture of fear and anxiety in the participants.

On the other hand, Walters proposed that it is the probability of injury that differentiates fear from anxiety, with fear stemming from a high probability and anxiety from a low probability of injury (Walters, 1994). In our experiment, the participants were equipped with an emergency stop button and they were explicitly instructed that the CO_2 laser device would not cause any permanent damage within the temperature range used. The likelihood of bodily injury would therefore most likely be perceived as low. Hence, according to Walters' reasoning, our experimental procedure should have induced anxiety and not fear. A third theory that has been advanced is the psychological theory of attentional account (Malow, 1981). This theory goes against both Walters and Rhudy et al.'s points of view, and suggests that moderate levels of either fear or anxiety cause hyperalgesia, whereas high levels attenuate pain (Malow, 1981; Malow et al., 1987; Cornwall & Donderi, 1988; Arntz et al., 1991; 1994). Following this theory, it stands to reason that our moderate level of induced anxiety is indeed prone to create hyperalgesia.

4.3. Increases in pain ratings in an uncertain context

We observed a significant group x condition interaction for both pain intensity and pain unpleasantness ratings. The increase in anxiety made pain ratings go up in the uncertain condition for the congenitally blind but not for the sighted, indicating that anxiety affects pain

perception to a larger extent in the former group. Hence, congenitally blind participants appear to be more prone to the effects of anxiety on pain perception. An explanation to this effect can be found in our PVAQ and PASS questionnaire data that highly accurately discriminated the blind from the sighted participants. These data suggest that the congenitally blind are generally more attentive, anxious and vigilant towards external signals of threat. As vision plays an important role in detecting and avoiding possible external threats, it stands to reason that the loss of sight might elevate one's attention and vigilance towards external threatening signals. It is therefore possible that an increased baseline level of attention and vigilance towards external signals of threat would lower the amount of anxiety needed to produce hyperalgesia in the congenitally blind.

Support for the link between anxiety, attention and pain perception can be found in the literature showing that attentional focus can modulate pain perception. Here, intentional directing attention away from a painful stimulus has resulted in decreased pain ratings, whereas the opposite manipulation has led to hyperalgesia (Bingel et al., 2007; Seminowicz & Davis, 2007a; 2007b). Previous cognitive studies indicated that anxiety is characterized by increased attentional capture by threat-related stimuli (MacLeod et al., 1986; Williams et al., 1996). This is most likely resulting from a hyper-responsive pre-attentive threat-detection system (Mathews et al., 1997; Bishop et al., 2004; Öhman, 2005; Bishop, 2009). With this increased attention towards external signals of threat it stands to reason that anxiety would lead to an increase in pain perception. In line with this, from a clinical setting it is known that anxiety can have an hyperalgesic effect, with anxiety levels predicting pain severity and pain behavior in both acute and chronic pain patients (Kain et al., 2000; van den Hout et al., 2001; Jack B Nitschke et al., 2009). In addition, Tang et al. found that a higher state anxiety score correlated with higher pain ratings of experimentally induced pain (Tang & Gibson, 2005). Thus, it is possible that increased anxiety and/or uncertainty modulates pain perception by recruiting attentional resources towards noxious stimuli (Dunckley et al., 2007; Legrain et al., 2009). Taken together, our results could be explained by the fact that a smaller increase in attentional focus on aversive stimuli caused by increased anxiety in the congenitally blind leads to an increased pain perception. More research is needed to investigate the fine details behind this.

The normally sighted participants did not report an increase in pain ratings concurrent with an increase in anxiety ratings. There are several possible explanations for this. First, although previous studies have shown that anxiety caused by uncertainty in an experimental setting can cause higher pain ratings in healthy volunteers (Ploghaus et al., 2001; Tang & Gibson, 2005; Yang et al., 2012), these studies have used different stimulus modalities and stimulation sites, which can lead to different results (Arendt-Nielsen & Yarnitsky, 2009). In addition, participants were only blindfolded in our study, hence a direct comparison between the studies cannot be made. Finally, the self-reported anxiety levels were higher in the aforementioned studies compared to ours (Ploghaus et al., 2001). It is therefore possible that we did not induce a high enough level of anxiety to induce an increase in pain ratings in normal sighted participants.

We have recruited 11 participants in each group, which is a limiting factor of this study. We cannot rule out that our CB sample is not quite representative of the CB population and that further studies need to be conducted to confirm our findings. To aid this, we have calculated the effect size for pain intensity changes between the two conditions in the sighted compared to the normally sighted. We found an effect size of 0.47. Since it accounts for almost 25% of the variance, it can be considered a large effect (Cohen, 1988; 1992).

5. Conclusion

We suggest that increased anxiety, attention and vigilance towards external signals of threat are involved in hypersensitivity to painful stimuli in congenitally blind subjects. This provides new insights into the mechanisms of hyperalgesia in the congenitally blind, and also into the cognitive state of individuals deprived of sight from birth. Lastly, these results have important implications for pain management within the congenitally blind population.

Author contributions:

SH-R, HS, MP and RK conceived and designed the experiments. RK and MP contributed with experimental equipment. SH-R performed the experiments. SH-R and SD

performed the data analysis. SH-R and RK wrote and edited the manuscript. All authors read and approved the final manuscript.

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III. DISCUSSION

Les résultats des expériences présentées ci-haut confirment la majorité de nos hypothèses de départ concernant la cécité congénitale. Le premier article a effectivement montré que les aveugles congénitaux sont plus sensibles à la douleur et qu'ils sont plus attentifs aux dangers de la vie courante que les voyants. Cette étude a aussi démontré que les différences culturelles affectent bel et bien la perception de la douleur, autant chez les aveugles congénitaux que chez les voyants. Notre prédiction d'une meilleure habileté à détecter de petits changements de température chez les aveugles de naissance a été confirmée par le troisième article. Dans cette étude, nous avons aussi observé que ces individus sont plus sensibles à la sommation spatiale de la chaleur. Le quatrième article, quant à lui, a montré que l'hypersensibilité à la douleur chez les aveugles congénitaux est associée à une détection plus fine et un traitement central plus rapide des stimuli nociceptifs acheminés au CNS par les fibres C. Quant au dernier article, il a permis de montrer que l'anticipation d'un stimulus douloureux exacerbe l'expérience douloureuse des non-voyants, suggérant ainsi que la cécité congénitale entraine une plus grande susceptibilité aux facteurs psychologiques qui modulent la douleur.

Nos hypothèses concernant les aveugles tardifs ont par contre été infirmées. En effet, il est impossible de les distinguer des voyants, que ce soit pour leur sensibilité à la douleur, pour leurs temps de réponses aux stimulations nociceptives ou encore pour leur comportement quotidien face à la douleur.

1. Impact de la cécité sur la composante sensorielle-discriminative de la douleur

1.1. Validité des résultats obtenus

Nos travaux démontrent indéniablement que la cécité à la naissance facilite le traitement des intrants nociceptifs et module à la hausse la sensation de douleur. Nous en arrivons à cette conclusion, peu importe le type de mesure (seuils, rapports subjectifs ou temps

de réaction), la modalité thermique (chaud ou froid) ou encore le type d'administration (avec contact ou énergie radiante). De plus, la plupart de nos résultats ont été répliqués dans plus d'un échantillon. L'hypersensibilité observée chez les aveugles congénitaux s'étend même aux sensations non douloureuses du système thermique, comme démontré par leur habileté à détecter plus facilement de petits changements de température non douloureux. Ce constat s'ajoute aux nombreuses études qui montrent que les non-voyants ont de meilleures performances dans des tâches de discrimination tactile, auditive et olfactive (Kupers & Ptito, 2014). Cependant, l'hypersensibilité thermique conséquente à la cécité de naissance ne semble pas être généralisée, mais plutôt spécifique à certaines tâches. En effet, les aveugles congénitaux ont des seuils de détection de chaud et de froid, et des seuils d'activation des fibres A∂ et C similaires à ceux des voyants et des aveugles tardifs. Ceci renforce l'idée que les mécanismes de compensation sensorielle suivant la perte de vision s'opèrent pour des processus cognitifs de haut niveau qu'exigent des tâches de discrimination et d'identification, plutôt que pour de simples tâches de détection (Niemeyer & Starlinger, 1981; Starlinger & Niemeyer, 1981; Bavelier & Neville, 2002; Collignon & De Volder, 2009; Kupers & Ptito, 2014).

1.2. Compensation sensorielle induite par l'expérience

Une des pistes d'interprétation qui a été mise de l'avant afin d'expliquer les mécanismes de compensation observés chez les non-voyants veut que l'affinement des fonctions sensorielles résiduelles résulte d'une plasticité cérébrale induite par l'expérience (Kupers & Ptito, 2014). Nous n'avons qu'à penser à la supériorité des aveugles dans des tâches tactiles, un avantage qui est intimement lié à la lecture du Braille (Burton & McLaren, 2006; Ptito *et al.*, 2008; Wong *et al.*, 2011). Nos résultats s'insèrent bien dans ce contexte, car nous sommes constamment soumis aux stimulations thermiques de l'environnement. Il n'est donc pas difficile de concevoir que ces sensations prennent plus d'importance dans le quotidien des personnes atteintes de cécité, notamment pour la reconnaissance d'objets. En effet, plusieurs études indiquent qu'il est tout à fait possible de discriminer des matériaux uniquement sur la base de leurs propriétés thermiques (Ho & Jones, 2006; Yang *et al.*, 2008;

Kahrimanovic *et al.*, 2009). De la même manière, l'hypersensibilité à la douleur des aveugles congénitaux pourrait être le résultat d'un remaniement cortical engendré par l'expérience. En effet, la douleur est une sensation subie au quotidien, surtout chez les non-voyants qui rapportent souvent se heurter à des obstacles lors de la navigation ou encore se brûler en cuisinant. Ainsi, le système nociceptif, prompt à une grande plasticité, serait simplement hypersensibilisé par une exposition plus fréquente à des stimulations douloureuses.

1.3. Absence des effets inhibiteurs de la vision

Au-delà des rapports anecdotiques présentés ci-haut, il est aussi possible que nos résultats soient dus à l'absence des interactions vision-nociception. Nous savons, par exemple, que la douleur module le traitement visuel d'objets. Bingel et collaborateurs (2007) ont effectivement montré que subir une stimulation douloureuse altère considérablement la capacité de reconnaissance d'objets et réduit significativement l'activité cérébrale du cortex occipital. Inversement, plusieurs études ont montré que de voir le membre stimulé réduit l'expérience douloureuse (Longo *et al.*, 2009; Hansel *et al.*, 2011; Mancini *et al.*, 2011; Romano & Maravita, 2014), un effet qui est associé à un couplage entre des zones corticales visuelles et nociceptives (Longo *et al.*, 2012). En effet, les stimuli visuels et nociceptifs activent des réseaux corticaux qui se chevauchent (Figure 16) et il existe une intégration centrale complexe des ces deux intrants sensoriels (Mouraux *et al.*, 2011). De plus, des études anatomiques montrent l'existence d'une voie reliant le cortex cingulaire antérieur – une structure qui joue un rôle clef dans le traitement de la douleur – à l'aire 19 du cortex visuel

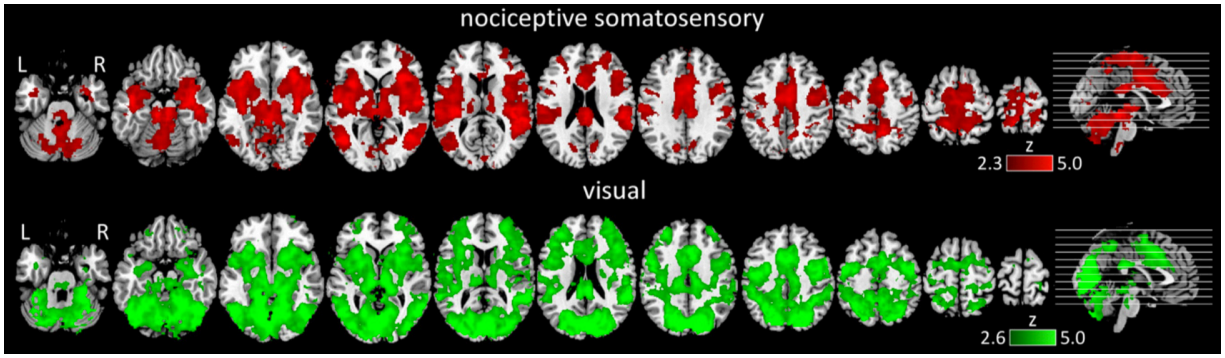

Figure 16. Activations cérébrales en réponse à des stimuli laser nociceptifs (en haut) et à des flashs lumineux (en bas). Reproduit à partir de Mouraux et al., 2011.

(Vogt & Pandya, 1987). Sachant que la cécité cause une altération de l'activité GABAergique dans plusieurs régions corticales reliées au cortex visuel (Desgent & Ptito, 2012), il est tout à fait possible que nos résultats découlent de l'absence d'effets inhibiteurs de la vision sur la perception de la douleur. En effet, nous montrons non seulement que les aveugles congénitaux sont plus sensibles à la douleur, mais aussi qu'ils ont des temps de réaction plus rapides aux stimuli nociceptifs. De plus, l'analyse approfondie des paramètres de la fonction psychométrique des temps de réaction aux intrants nociceptifs C indique que les aveugles congénitaux ont un traitement central plus efficace de ces sensations, ce qui se traduit par une prise de décision plus rapide.

1.4. Limites de la compensation sensorielle

Certains de nos résultats semblent toutefois indiquer que la compensation sensorielle observée chez les non-voyants est limitée. Par exemple, les aveugles congénitaux réagissent peut-être plus rapidement à l'activation des fibres C, par contre, ils ont des temps de réaction similaires aux voyants lorsqu'il s'agit de la stimulation des fibres A∂. Ceci peut être interprété de plusieurs manières. D'un point de vue comportemental, si nous assumons qu'un aveugle est plus prudent qu'un voyant lorsqu'il sonde son environnement, il est tout à fait possible que dans un processus d'approche d'une source de chaleur, le signal des fibres C arrive au CNS avant même que leur peau atteigne le seuil, 8 ˚C plus élevé, des fibres A∂. Ainsi, ce serait à force d'expérience que les aveugles congénitaux développent leur plus grande sensibilité et leur traitement plus efficace de signaux nociceptifs C. Cela dit, une analyse comportementale des patrons exploratoires des aveugles serait certainement nécessaire pour valider cette argumentation.

Autrement, nos résultats démontrent que, comparé aux détections A∂, il y a une asymétrie quatre fois plus élevée dans la courbe psychométrique des détections C, indiquant que cet intrant sensoriel est prompt à beaucoup plus de bruit physiologique et qu'il est donc moins fiable (Green & Swets, 1988). Ce constat prend racine dans le fait que les sensations A∂, souvent perçues comme un picotement (Beissner *et al.*, 2010), sont plus saillantes que celles produites par les fibres C (Nahra & Plaghki, 2003; Vierck *et al.*, 2004; Churyukanov *et*

al., 2012), perçues comme une chaleur diffuse (Beissner *et al.*, 2010). Les sensations A∂ produisent donc une accumulation plus rapide d'indices sensoriels (Ratcliff & Van Dongen, 2011) et engendrent ainsi des temps de réaction très courts. La vitesse de traitement de ces sensations est donc peu prompte à l'amélioration, car elle est grandement propice à un effet plancher.

1.5. Impact de l'expérience visuelle

Les résultats obtenus par l'étude des aveugles tardifs indiquent que la compensation sensorielle que nous observons est limitée à la cécité congénitale. Ce résultat va à l'encontre de notre hypothèse, mais il n'est pas pour autant surprenant. Comme décrit plus tôt, il n'y pas de consensus clair dans la littérature quant au potentiel de plasticité cérébrale en cas de cécité tardive et nos résultats corroborent plusieurs études qui montrent que la perte de vision tard dans le développement engendre peu, voire même pas du tout, de compensation sensorielle (Grant *et al.*, 2000; Burton & McLaren, 2006; Alary *et al.*, 2008; Wan *et al.*, 2010). Par contre, cela n'invalide pas nécessairement les raisons qui nous ont poussé à formuler notre hypothèse. Notre argumentation reposait sur l'idée que si la vision a un effet analgésique (Longo *et al.*, 2009; Hansel *et al.*, 2011; Mancini *et al.*, 2011; Romano & Maravita, 2014), la cécité devrait avoir l'effet contraire. Cette inférence a trouvé appui dans l'étude de Zubek et collaborateurs (1964) qui ont montré que de bander les yeux à des voyants pendant une semaine cause une hypersensibilité thermique et nociceptive qui persiste au-delà de la période de privation visuelle (Figure 10). Comment donc concilier ces travaux et nos résultats?

Le fait que la perception de la douleur soit intimement liée à l'image corporelle et à la représentation de l'espace péri-personnel (Craig, 2002; Gallace *et al.*, 2011; Haggard *et al.*, 2013; Sambo *et al.*, 2013; De Paepe *et al.*, 2014) pourrait constituer une piste d'explication. En effet, l'analgésie visuelle semble, elle aussi, dépendre de facteurs spatiaux, car des études plus récentes et mieux contrôlées indiquent que ce phénomène ne prend effet que lorsque les mains des participants sont croisées (Gallace *et al.*, 2011; Valentini *et al.*, 2015). Les auteurs suggèrent que c'est l'incongruence entre les coordonnées spatiales visuelles et proprioceptives, plutôt que la vision du membre stimulé, qui cause l'analgésie visuelle. De

même, d'autres études ont montré que des représentations spatiales conflictuelles (mains/jambes croisées) réduisent la capacité à localiser des stimuli tactiles et nociceptifs lorsqu'ils sont présentés quasi simultanément aux deux membres opposés (Yamamoto & Kitazawa, 2001; Shore *et al.*, 2002; Shore *et al.*, 2005; Schicke & Roder, 2006; Azañón & Soto-Faraco, 2008; Sambo *et al.*, 2013; De Paepe *et al.*, 2014). Ce qui est d'autant plus intéressant, c'est que dans la plupart de ces expériences, la performance des participants est réduite même si ceux-ci ne voient pas leurs mains (Yamamoto & Kitazawa, 2001; Shore *et al.*, 2002; Shore *et al.*, 2005; Azañón & Soto-Faraco, 2008; Sambo *et al.*, 2013). Ceci suggère qu'il n'est pas nécessaire de voir pendant la tâche pour que le cadre de référence visuel interfère avec les coordonnées proprioceptives. Ceci a été confirmé par des études dans lesquelles on a soumis des non-voyants à ces mêmes manipulations expérimentales. On y montre que la performance des aveugles tardifs est réduite par le croisement des mains (Röder *et al.*, 2004), mais que celle des aveugles congénitaux est immuable (Röder *et al.*, 2004; Röder *et al.*, 2008). On en arrive donc à la conclusion que le transfert du cadre de référence proprioceptif vers des coordonnées spatiales visuelles nécessite d'avoir déjà vu et qu'il persiste tout au long de la vie d'adulte. Ceci a été corroboré par Pagel et collaborateurs (2009) qui ont montré que 5 ½ ans d'expérience visuelle sont suffisants pour que cette adaptation cognitive se fasse. Étant donné que les aveugles tardifs testés dans nos expériences ont tous perdu la vue après l'âge de 6 ans, il est possible que le transfert de coordonnées spatiales – ou un autre type de maturation du système visuel qui nécessite 6 ans de vision ou moins – explique la similarité de leur sensibilité à la douleur avec celle des voyants. Cette interprétation est renforcée par le fait que nous n'ayons trouvé aucune corrélation entre l'index de durée de cécité (« blind duration index ») et la sensibilité à la douleur des aveugles tardifs. Ainsi, quel que soit le processus de maturation responsable de leur perception normale de la douleur, comme pour le transfert de cadre de référence spatiale, il s'établit certainement très tôt dans le développement et il semble persister tout au long de la vie d'adulte. À l'inverse, le fait de n'avoir jamais vu empêche sûrement l'établissement des circuits neuronaux qui sont normalement impliqués dans la modulation visuelle de la douleur. Il se pourrait même que l'hypersensibilité à la douleur des aveugles congénitaux soit en partie ou en totalité due au traitement de stimuli nociceptifs par leur cortex visuel, comme on l'a démontré pour d'autres modalités sensorielles (Kupers & Ptito, 2014).

2. Impact de la cécité sur la composante affective-motivationnelle de la douleur

2.1. Influence de la culture

Dans le processus de validation de nos résultats, nous avons notamment répliqué une partie de nos travaux dans une population culturellement différente. Cet aspect est important, car, comparé aux gens des pays nordiques (ex. Danemark), les gens des pays du sud de l'Europe (ex. Italie) sont émotionnellement plus expressifs (Pennebaker, 1982) et répondent plus fortement à la douleur (Breivik *et al.*, 2006; Rahim-Williams *et al.*, 2012). Il était donc possible que ces facteurs, non contrôlables en laboratoire, aient nourri les différences observées entre aveugles et voyants dans notre échantillon italien. Nous notons effectivement que, malgré qu'ils aient des seuils de douleur similaires à leurs homologues danois, les aveugles congénitaux italiens répondent plus fortement à la douleur. Cela dit, la différence de sensibilité entre aveugles et voyants est comparable dans les deux échantillons.

2.2. Facilitation centrale de la douleur chez les non-voyants

Si la culture influence l'expérience douloureuse, c'est qu'elle façonne la composante affective-motivationnelle de la douleur (Pennebaker, 1982; Breivik *et al.*, 2006; Rahim-Williams *et al.*, 2012). De la même façon, étant donné que le cerveau des aveugles de naissance subit une réorganisation corticale majeure (Kupers & Ptito, 2014), il est possible que le système de modulation centrale de la douleur de ces individus se développe de manière à faciliter le traitement nociceptif. Ce postulat expliquerait non seulement l'hypersensibilité à la douleur des aveugles congénitaux, mais aussi le fait que ces derniers soient plus susceptibles à des manipulations expérimentales qui promeuvent l'exacerbation de la douleur. En effet, les résultats de notre dernière étude montent que la menace d'un stimulus douloureux augmente les rapports subjectifs de douleur des aveugles congénitaux, mais pas ceux des voyants.

2.2.1. Contribution de l'anxiété

Vu que le paradigme expérimental utilisé est anxiogène (Ploghaus *et al.*, 2003), il serait logique de croire que c'est l'anxiété qui est responsable des résultats obtenus. Cette interprétation est toutefois difficile à défendre, car le niveau d'anxiété produit dans notre étude est nettement inférieur à celui rapporté par les études sur lesquelles nous nous sommes basés (Sawamoto *et al.*, 2000; Ploghaus *et al.*, 2001; Tang & Gibson, 2005; Oka *et al.*, 2010; Meulders *et al.*, 2012; Yang *et al.*, 2012). Ceci est probablement dû à des différences méthodologiques telles que la modalité ou le site de stimulation, ou encore le fait que nous ayons bandé les yeux à tous nos participants (Arendt-Nielsen & Yarnitsky, 2009). De plus, nous n'avons décelé aucune corrélation qui pourrait établir un lien direct entre les rapports d'anxiété et les rapports de douleur des participants. Finalement, nos résultats montrent que les aveugles et les voyants ont un trait d'anxiété et une anxiété situationnelle similaires. Bref, l'hypersensibilité des aveugles congénitaux en réponse à l'incertitude est sûrement due à un autre processus cognitif que l'anxiété. Ceci suggère que l'anxiété n'a pas non plus affecté les résultats de nos autres études, malgré que l'utilisation de la méthode des limites (seuils de douleur) et que le recours à des stimuli phasiques à progression rapide (rapports subjectifs de douleur) aient pu en causer (Kunz & Lautenbacher, 2014).

2.2.2. Contribution de l'attention

En guise de piste alternative d'interprétation, nous proposons que des mécanismes attentionnels sont à la base des différences que nous observons entre aveugles et voyants. Ce postulat s'appuie sur le fait que l'anticipation d'un stimulus douloureux cause un recrutement de ressources attentionnelles supplémentaires (Rhudy & Meagher, 2000; Ploghaus *et al.*, 2003; Tracey & Mantyh, 2007). L'évaluation psychométrique des aveugles congénitaux indique, en effet, que c'est l'attention que ceux-ci portent à des situations douloureuses de la vie quotidienne, plutôt que l'anxiété qu'elles peuvent leur causer, qui les distingue le mieux des voyants. Ce résultat, répliqué dans trois de nos études, s'insère bien dans une littérature récente qui montre que les aveugles congénitaux répondent plus fortement aux menaces auditives (Klinge *et al.*, 2010), qu'ils sont plus attentifs aux odeurs ambiantes (Beaulieu-

Lefebvre *et al.*, 2011) et qu'ils détectent plus facilement les odeurs à valence négative, telles que la peur et le dégoût (Iversen *et al.*, 2015). Ceci renvoie à une de nos hypothèses de départ qui stipule que la cécité engendrerait un état permanent d'hyper-vigilance qui modulerait les signaux nociceptifs à la hausse. Ce serait donc parce qu'ils sont plus attentifs aux menaces externes que les aveugles congénitaux sont plus sensibles à la douleur. Ceci expliquerait même le fait qu'ils soient plus performants à la tâche de discrimination de températures non douloureuses. En effet, la thermoception participe activement à l'évitement de brûlures (Green, 2004), car les thermorécepteurs contribuent aussi au traitement de stimuli nociceptifs et à l'expérience douloureuse (Bushnell *et al.*, 1983; Craig *et al.*, 2001; Defrin *et al.*, 2002; Green, 2004). Ainsi, une augmentation rapide de la température de la peau indique souvent que l'objet touché est dangereux (Yang *et al.*, 2008). Donc, grâce à une plus grande vigilance, les aveugles congénitaux auraient appris à mieux utiliser ces indices thermiques pour identifier plus efficacement des menaces externes et ainsi mieux s'en protéger.

Un état d'alerte constant chez les aveugles congénitaux expliquerait aussi le fait que ces derniers ont des temps de réaction plus courts aux détections C, mais pas aux détections A∂. En effet, être plus vigilant a certainement un plus grand impact sur la détection de stimuli nociceptifs à basse qu'à haute intensité, d'autant plus que les sensations produites par les deux types de fibres diffèrent grandement. Les fibres C génèrent une sensation diffuse et difficile à percevoir alors que les fibres A∂ génèrent une sensation de picotement très saillante (Beissner *et al.*, 2010; Mouraux *et al.*, 2011). Vu que les détections A∂ monopolisent plus facilement les ressources attentionnelles, on assiste à une saturation de la facilitation centrale de ces sensations par l'attention.

Suivant le même raisonnement, c'est sûrement parce que leur paradigme expérimental a causé une saturation attentionnelle que Kunz et Lautenbacher (2012) ont mesuré une sensibilité à la douleur similaire entre aveugles congénitaux et voyants. En effet, les auteurs ont utilisé la méthode d'ajustement pour la détermination des seuils ; une méthode qui exige que le participant augmente lui-même l'intensité du stimulus jusqu'à ce qu'il le perçoive comme douloureux. Contrairement à la méthode des limites où le sujet est en attente passive de la sensation de douleur, la participation active que nécessite la méthode d'ajustement

demande beaucoup plus d'attention, réduisant ainsi la possibilité d'un recrutement additionnel de ressources attentionnelles (voir annexe 2 pour plus de détails).

2.2.3. Impact de l'expérience visuelle

Si les aveugles congénitaux montrent des signes d'hyper-vigilance, on ne peut pas en dire autant des aveugles tardifs. En effet, leurs données psychométriques sont très similaires à celles des voyants, indiquant qu'ils ne sont ni plus anxieux, ni plus attentifs à la douleur. Ceci est à l'image de leurs données comportementales qui montrent qu'ils sont comparables aux voyants en termes de sensibilité à la douleur et de temps de réponse aux stimuli nociceptifs. Il semblerait donc que cette hyper-vigilance soit une conséquence de processus plastiques qui se produisent tôt dans le développement. Cette conjecture est supportée par le fait que, durant le développement du CNS, l'attention façonne les circuits neuronaux du système nociceptif en renforçant les connexions synaptiques (Polley *et al.*, 2006; White *et al.*, 2013). Ceci, combiné au fait que l'activité GABAergique d'un cerveau privé de vision à la naissance est débalancée (Desgent & Ptito, 2012), suggère que l'absence d'expérience visuelle cause un remaniement du système de modulation centrale de la douleur qui permet d'en réduire les effets inhibiteurs au travers d'un état d'hyper-vigilance. Ceci dit, le poids qu'a ce processus cognitif dans la perception de la douleur des aveugles congénitaux ainsi que les voies de signalisation qui y sous-tendent nécessitent des études additionnelles.

3. Conclusion

En résumé, nos travaux montrent que la cécité congénitale facilite le traitement des intrants nociceptifs et module à la hausse la sensation de douleur. Cette compensation sensorielle confirme que le système nociceptif peut pallier l'absence des fonctions protectrices de la vision. D'une part, l'hypersensibilité à la douleur des aveugles de naissance pourrait refléter une plasticité intermodale conséquente à la cécité. Ainsi, l'absence des effets inhibiteurs de la vision sur la perception de la douleur causerait, à force d'expérience, un remaniement des circuits neuronaux qui faciliterait le traitement des stimuli thermiques et

nociceptifs. D'autre part, cette compensation sensorielle pourrait être le résultat d'un état permanent d'hyper-vigilance, où l'appréhension du danger modulerait à la hausse la sensation de douleur grâce à un recrutement plus efficace des ressources attentionnelles. Afin de conjuguer ces deux interprétations, nous proposons un modèle intégratif qui rallie les conséquences de l'absence de vision sur les composantes sensorielle-discriminative et affective-motivationnelle de la douleur (Figure 17). Ce modèle s'appuie d'abord sur la relation particulière qui existe entre la douleur et l'attention (1). En effet, la douleur a comme propriété intrinsèque d'attirer l'attention qui, paradoxalement, exacerbe l'expérience douloureuse (Tracey & Mantyh, 2007). Ensuite, le modèle tient compte des effets de l'absence de vision. D'une part, celle-ci rend impossible l'analgésie visuelle (2). D'autre part, elle cause de l'appréhension face au danger (3), ce qui promeut le recrutement supplémentaire de ressources attentionnelles et ainsi, exacerbe l'expérience de la douleur. Ceci explique, entre autres, le fait que les aveugles tardifs ressemblent en tous points à notre groupe contrôle. En effet, le fait d'avoir bandé les yeux à nos participants voyants les a probablement mis dans un état d'hypersensibilité à la douleur (Zubek *et al.*, 1964). Il n'est donc pas exclu, que les aveugles tardifs soient plus sensibles à la douleur que des voyants aux yeux ouverts. Finalement, le modèle rend compte des conséquences de l'absence d'expérience visuelle (4). Comme les aveugles congénitaux se distinguent nettement des voyants aux yeux bandés et des aveugles tardifs, nous suggérons que la perte de vision à la naissance engendre un remaniement du système nociceptif qui serait responsable de l'établissement d'un état d'hyper-vigilance permanent (5) et de la facilitation centrale de stimuli douloureux (6). Ce modèle est supporté par plusieurs études électroencéphalographiques qui ont mis en évidence un lien entre l'état d'hyper-vigilance des aveugles congénitaux et la réorganisation corticale qui s'opère chez ces individus. Elles montrent que leurs aires corticales postérieures participent au traitement de stimuli qui se produisent à l'extérieur du focus attentionnel (Alho *et al.*, 1993; Kujala *et al.*, 1995). De même, une étude récente a démontré que les aires occipitales médiales des non-voyants sont significativement activées par des signaux qui annoncent le début d'un essai, mais pas par des signaux qui annoncent un non-essai (Stevens *et al.*, 2007). Il est intéressant de noter que cette activité préparatoire du cortex occipital médian ressemble grandement à l'activité anticipatoire qui a été observée chez des voyants dans des tâches de discrimination visuelle (Kastner *et al.*, 1999; Ress *et al.*, 2000). L'activité cérébrale des cortex strié et extra-

strié des voyants peut même être anticipatoire à la présentation de stimuli non visuels (Jack *et al.*, 2006). Il est donc possible que les mécanismes d'attention sélective du cortex visuel persistent chez les aveugles congénitaux et qu'ils aient ainsi une influence sur les circuits neuronaux réorganisés (Stevens *et al.*, 2007). Un exemple de cette préservation des fonctions attentionnelles du cortex visuel chez les non-voyants a d'ailleurs été illustré par Després et collaborateurs (2005). Les auteurs ont observé que les mouvements oculaires de saccade vers un nouveau stimulus influencent la localisation de sons autant chez les voyants que chez les aveugles congénitaux. À la lumière de ces études, nous proposons que les aveugles de naissance utilisent des mécanismes similaires d'orientation attentionnelle envers de stimuli nociceptifs afin de mieux identifier un danger et de réagir plus rapidement.

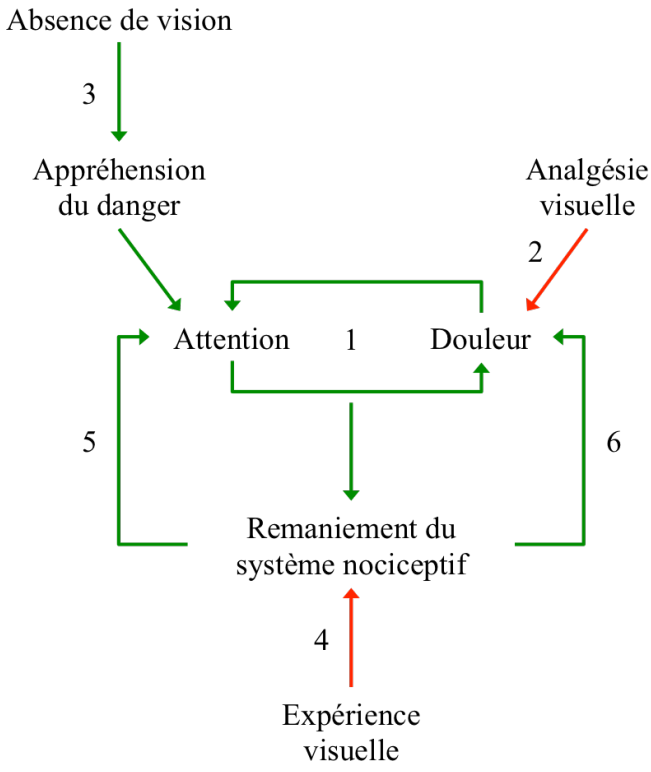

Figure 17. Modèle théorique de l'hypersensibilité à la douleur en l'absence de vision. → *= stimulation,* → *= inhibition. Schéma original.*

Plusieurs composantes de ce modèle découlent de preuves expérimentales indirectes et sont donc à faire valider par des expériences futures. D'abord, comme l'attention constitue le point névralgique du modèle, la mesure directe des effets de ce processus cognitif sur la

douleur des non-voyants est nécessaire. Il serait aussi intéressant de savoir quels types de mécanismes attentionnels seraient impliqués. En effet, des études ont montré que les aveugles congénitaux réagissent plus vite à des stimuli tactiles et auditifs dans des paradigmes d'attention sélective et d'attention divisée (Kujala *et al.*, 1997b; Collignon *et al.*, 2006; Collignon & De Volder, 2009), suggérant que ces individus ont des capacités attentionnelles supérieures peu importe la modalité sensorielle (Collignon *et al.*, 2006). Ensuite, les données obtenues chez les aveugles tardifs suggèrent que l'hypersensibilité à la douleur se développe grâce à des changements plastiques qui se produisent tôt dans le développement. Par contre, seules des études d'imagerie cérébrale pourront confirmer que c'est bel et bien un remaniement cortical qui facilite le traitement nociceptif chez les aveugles congénitaux. Il serait notamment intéressant de savoir si le cortex visuel de ces derniers est impliqué dans leur perception de la douleur. Finalement, il serait pertinent d'explorer d'autres avenues qui pourraient compléter ce modèle. Pensons par exemple à l'influence de l'image corporelle sur la perception de la douleur ou encore aux aspects spatiaux de la douleur. En effet, nos résultats ont montré que les aveugles congénitaux sont plus susceptibles à la sommation spatiale de la chaleur, mais des données additionnelles sont nécessaires pour donner un sens concret à ce résultat. Il faudrait aussi tester la sensibilité des non-voyants à d'autres types de douleur, notamment à la douleur par pression et ainsi étudier l'implication des fibres Aß dans leur traitement nociceptif.

Dans un cadre clinique, nos résultats ouvrent la porte à des études en adaptation-réadaptation qui exploreraient des avenues possibles pour que les non-voyants optimisent leur utilisation des indices thermiques de l'environnement dans leur quotidien. À titre d'exemple, Ralph Read, lui-même aveugle, a écrit un livre d'astuces culinaires pour les gens atteints de cécité intitulé « When the Cook Can't Look: A Cooking Handbook for the Blind ». Ses conseils permettent non seulement de mieux réussir les recettes, mais aussi d'éviter les dangers de la cuisine (Read, 1981). Des plans d'adaptation-réadaptation qui iraient dans ce sens procureraient aux non-voyants plus de sécurité dans leurs activités quotidiennes et une meilleure qualité de vie.

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ANNEXE I

Focus on pain in the blind

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Commentary

Focus on pain in the blind

Until recently, the cross-modal consequences of unisensory deprivation have been extensively studied in almost every sensory domain other than nociception. In this issue of PAIN®, Slimani et al. [8] explore, for the first time, the sensory consequences of congenital blindness on thermal sensitivity and pain perception.

Their study has provided evidence that congenitally blind participants are hypersensitive to pain. Slimani et al. [8] observed lower pain thresholds to cold and heat in blind participants, relative to matched sighted volunteers, as well as higher ratings of pain intensity in response to suprathreshold laser stimuli. Interestingly, detection thresholds of innocuous warmth and cold were not different between blind and sighted participants. This suggests that thermal hypersensitivity in blindness could be specific to pain. These results were replicated in 2 European populations, Italian and Danish, which were previously reported to be differently sensitive to pain [7].

Slimani et al. [8] also assessed attitudes and responses towards signals of threat in daily life in both blind and sighted participants. The results from 2 questionnaires (Pain Anxiety Symptoms Scale, and Pain Vigilance Awareness Questionnaire) show that blind participants were more attentive to potential threat in daily life than their sighted counterparts.

The novel finding of pain hypersensitivity in blindness has several important implications for both basic and clinical science. This study is noteworthy for research on multisensory interactions and plasticity because it shows a strong link between vision and pain. This link is supported by a previous report of increased pain sensitivity in sighted volunteers who were temporarily visually deprived [11]. Studies conducted on sighted participants also showed that the visual context can modulate the perception both of acute [3] and chronic pain [4]. The next step is to understand the nature of the interaction between visual loss and pain sensitivity. Which aspect of pain processing is involved in the interplay with vision, and what is its neural basis?

Fig. 1 shows 2 putative mechanisms that could underlie the hypersensitivity to pain reported by Slimani et al. [8]. First, pain hypersensitivity could reflect cross-modal plasticity of brain circuitry after blindness. Indeed, visual loss from birth induces structural and functional changes in brain connectivity [2,6], which may underlie the increased tactile sensitivity previously reported in blindness [2]. Future studies could investigate whether similar mechanisms of brain reorganization underlie changes in tactile and nociceptive sensitivity in blind people. Enhanced attention to threat and anxiety experienced by blind participants in daily life would then be the consequence of the hypersensitivity to sensory stimuli (Fig. 1a). Alternatively, the hypersensitivity to pain in blind individuals might be caused, in first instance, by uncertainty about threat, due to lack of vision (Fig. 1b). Uncertain expectation of pain is often associated to anxiety and increased pain sensitivity [5]. The hypersensitivity to pain would thus actually reflect a hypersensitivity to threat rather than processes specific to Aδ pathways. This hypothesis would predict that top-down, descending modulation from anterior cortical regions [5,9] would amplify incoming sensory signals (Fig. 1b). Finally, a combination of bottom-up and top-down processes might underlie the results described by Slimani et al. [8].

The 'hypersensitivity to threat' hypothesis (Fig. 1b) predicts that the increased sensitivity to potentially harmful stimuli would not be specific to the Aδ pathway, and so could theoretically affect every sensory stimulus presented in a context of danger. However, the authors found no significant differences between the detection thresholds of innocuous thermal stimulation in sighted and blind participants. Importantly, innocuous and noxious thresholds were tested in separate blocks, cued for the level of stimulation. Hence, it cannot be excluded that the lack of modulation of innocuous thresholds is a consequence of knowing in advance that one stimulus would not be harmful. Future studies using event-related designs, in which all the stimuli would be randomized and unpredictable, could shed light on the role of pain expectation on thermal perception in blindness. Specifically, the 'hypersensitivity to threat' hypothesis would predict increased sensitivity to innocuous stimulation in blind participants, when the stimuli are unpredictable.

The study by Slimani et al. [8] also deserves attention for its clinical implications. The World Health Organization estimates that in 2012, 39 million of people were blind [10]. If the results by Slimani et al. [8] are confirmed in larger samples of blind individuals, it becomes of primary importance to examine the potential short- and long-term risks of being hypersensitive to pain due to blindness. Could it increase the risk of developing both acute and chronic pain conditions?

Unfortunately, the assessment of thermal sensitivity requires expensive equipment, which could thwart routine testing of large samples of people. However, there are several low-cost alternative methods (e.g., punctate probes to stimulate Aδ mechanical fibers [1]) that could be used to routinely assess pain perception outside pain laboratories and clinical settings. These methods are often easy and quick to use, but they do not provide selective-stimulation Aδ fibers. Therefore, similar applied studies can complement

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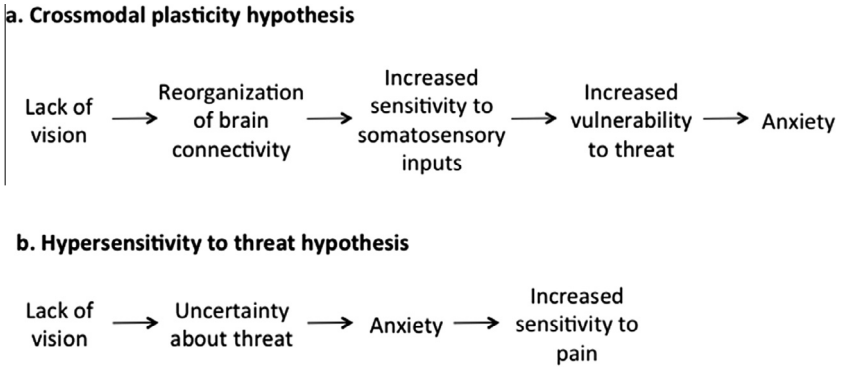

Fig. 1. Putative mechanisms underlying pain hypersensitivity in blindness.

but not substitute rigorous laboratory testing using nociceptive selective stimulation.

The hope is that the work by Slimani et al. [8] will open the door to pain investigations into the world of sensory loss, left unexplored for too long.

Conflict of interest statement

The author is aware of no conflicts of interest regarding this commentary.

Acknowledgement

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ANNEXE II

Response to Letter to the editor

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Letter to the Editor

We read with great interest the recently published paper by Slimani et al. [2] in *PAIN*®. The authors investigated pain sensitivity in congenitally blind individuals, and found reduced pain thresholds as well as increased pain report to suprathreshold pain stimuli in blind participants compared with sighted controls. Based on these findings, the authors come to the conclusion that the absence of vision from birth leads to a permanent state of pain hypersensitivity. Although their findings undoubtedly corroborate such a conclusion, we were somewhat surprised that the authors completely disregarded a recently published study of our group [1], where we used very similar methods to study pain responses in congenitally blind individuals and found—in contrast to Slimani et al.—no changes in pain threshold or in suprathreshold pain ratings in blind individuals compared with sighted individuals. This neglect of our findings is quite surprising, since our study is the only other study (to our knowledge) that has investigated pain responses to experimentally induced pain in congenitally blind individuals.

We used similar pain induction methods (Peltier-based thermotester, TSA-II, Medoc, Haifa, Israel) and studied similar samples of individuals (as regards onset and cause of blindness, as well as sample size) but found no clear indication of pain hypersensitivity. Reasons for the discrepancy might lie in the methods used to assess pain thresholds. Slimani et al. applied the method of limits whereas we used the method of adjustment to assess pain thresholds. Having to respond (by pressing a button) to a rather quickly ascending temperature increase (3°C per second; method of limits as used by Slimani et al.) might have elicited more anxiety in blind individuals than if they had been able to adjust the stimulus temperature at their own pace (method of adjustment that we used). Thus, heightened anxiety might have contributed to the pain hypersensitivity in congenitally blind individuals reported by Slimani et al. The same might hold true for the increased pain report to suprathreshold pain stimuli in blind participants. Slimani et al. used phasic laser stimuli (3 seconds duration) with a very rapid onset/increase, whereas we used tonic heat stimuli (6 minutes duration) that are very predictable in their time course. Thus, the suprathreshold protocol used by Slimani et al. might have elicited more anxiety in the participants than our protocol and, given that blind individuals had higher scores on pain anxiety and pain vigilance questionnaires, it is likely that the factor of anxiety contributed to the group differences found by Slimani et al.

In summary, the absence of vision from birth does not seem to lead automatically to a generalized state of pain hypersensitivity. Instead, the occurrence of increased pain sensitivity in congenitally blind individuals might depend on factors like the protocol used to induce pain, the methods used to assess pain sensitivity and the level of anxiety that accompanies the pain experience.

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Response to Letter to the Editor

We thank Drs. Kunz and Lautenbacher [3] for their interest in our paper on pain sensitivity in congenitally blind individuals [4]. The reasons for their letter were 2-fold: (1) the fact that we did not cite their findings and (2) their disagreement with the interpretation of our data. As for the former, the fact that we did not cite their *Biological Psychology* paper [2] was not deliberate. Although a PubMed search did indeed draw our attention to this paper, the abstract dealt uniquely on facial expression of physical distress in congenitally blind subjects, without mentioning anything about pain sensitivity. Our reviewers were probably also not aware of the Kunz et al. study [2] since they did not ask us to include it.

We agree with Kunz and Lautenbacher that the occurrence of increased pain sensitivity in congenitally blind subjects may depend on factors like the protocol used to induce pain, the methods used to assess pain sensitivity, and the level of anxiety that accompanies the pain experience. Indeed, increased sensitivity to pain in congenitally blind individuals may be due to changes in brain connectivity, uncertainty about impending threat and associated anxiety, response bias, or systematic error underlying perception and judgment (eg, demand characteristics). Kunz et al. [3] did not find evidence for increased pain sensitivity in their study group and they therefore claim that our results were due to higher levels of anxiety in our blind subjects. Kunz and Lautenbacher base their conclusion on differences in methodology between the 2 studies, such as the use of a faster stimulus ramp rate in our study and our use of the method of limits to assess pain responsiveness.

We disagree with their interpretation for the following reasons. First, in a subsequent study, we used a stimulus ramp rate that was much faster even than in our 2013 study [4] to measure reaction times to selective Aδ and C-fiber stimulation (Slimani et al., in preparation). Our results failed to find a group difference in reaction times to the faster and more salient Aδ fiber-evoked responses. Second, we used the method of constant stimuli for assessing suprathreshold pain responses [4]; we found again that congenitally blind individuals were more sensitive to painful stimuli than sighted individuals. In conclusion, neither stimulus ramp rate nor the use of the method of limits can account for our results.

As mentioned in our paper [4], we took several measures to reduce potential sources of stress and anxiety. However, we cannot fully exclude that such influences did occur, as we did not measure anxiety state just prior to the onset of the psychophysical testing. Anxiety caused by uncertainties about expectation of pain may largely contribute to increased pain sensitivity [5]. Our psychophysical data clearly showed that congenitally blind subjects are generally more anxious towards painful or threatening stimulation. If Kunz and Lautenbacher were able to minimize these factors in their experiments, this may be one of the reasons that they did not find evidence for pain hypersensitivity in their blind subjects. Another possible explanation may relate to the body area that was targeted. Whereas we stimulated the forearm [4], Kunz et al. [2] stimulated the inner upper leg. This area is unlikely to have undergone cross-modal plastic rearrangements in congenitally blind individuals, is rarely exposed to thermal stimuli, and is of lesser importance for behaviors essential to fitness and survival such as ingestive, defensive, and exploratory behaviors.

A final comment concerns what Kunz and Lautenbacher precisely mean by ‘‘pain sensitivity’’ and ‘‘response bias’’. Pain is a multidimensional experience, whereof the emotional and motivational dimension constitutes an integral part. This means that one cannot consider anxiety, attention, and other psychological factors as merely causing response bias. As we [4] and others [1] have shown, congenitally blind subjects are more attentive to signals of external threat, which may well be the chief determinant for their stronger pain responsiveness.

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ANNEXE III

Out of sight but not out of mind: The role of vision in pain perception

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CHAPTER 13

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Out of Sight but Not Out of Mind: The Role of Vision in Pain Perception

Vanessa Harrar, Sophie Vandenbroucke, Hocine Slimani, Maurice Ptito, and Ron Kupers

When we are first taught about the senses, we learn that they function independently and that eyes are for vision, ears are for hearing, and skin is for touch. However, the senses do not work independently. A growing body of research has demonstrated that our perception of the world is multisensory and that information from individual senses is most often combined before reaching awareness. A classic audiovisual illusion occurs when a ventriloquist speaks without lip movements while moving a puppet's mouth vigorously, which causes the illusion that the sound comes from the puppet's mouth [1]. In this chapter, we will investigate how vision can affect our sense of touch and pain, and more specifically, how viewing the body affects the perception of painful tactile or thermal stimuli.

Even though audiovisual and audio–tactile integration have been well investigated, the interactions between vision and pain have received comparatively little attention. The first experimental evidence that vision may affect pain processing came from the pioneering studies by Zubek and colleagues [51] in the early 1960s, and we had to wait until recently for a real breakthrough in the interest in the role of vision in pain perception. In recent years, a number of well-controlled laboratory studies were published on the effects of visual information on thermal pain perception and on the role of visual input in pain empathy and vicarious responses to pain. At the same time, studies assessed the effect of manipulating visual input to treat some forms of clinical pain.

PAIN FRAMEWORK AND PATHWAYS

According to a crude but still vivid biomedical model, pain is a direct representation of noxious sensorial input—that is, physiological damage. In this model, a direct and unchangeable relationship exists between the experience of pain and a particular sensory input. However, since the late 20th century, the biomedical model has been replaced by a biopsychosocial one that provides a more thorough explanation for the human pain experience [29]. While pain has specific sensory and perceptual characteristics, the biopsychosocial model claims that there is no absolute congruency between pain and tissue damage [9]; a person may have tissue damage without feeling pain, and pain can occur in the absence of tissue damage [7]. The psychological state of mind also appears to affect pain perception since certain mental health conditions are more prevalent in chronic pain patients compared to the general population [5]. Thus, psychological and social factors, in addition to biological factors, are crucial to fully understand pain [9]. The effects of vision on pain perception are likely mediated by these psychological and social factors. The shift from the biomedical to the biopsychosocial perspective has fostered new research on how vision affects pain perception, and has supported nonmedical alternative treatments to pain relief rooted in these lines of research.

The International Association for the Study of Pain (IASP) defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" ([28], p. 210). Nociceptive stimuli trigger activity in an extensive cortical network, including somatosensory, insular, and cingulate areas, as well as prefrontal and parietal areas, the so-called pain matrix. The pain matrix is traditionally considered as the conglomerate of brain areas whose neural activity is associated with the sensory and affective processing of a nociceptive stimulus that elicits a painful percept [22]. However, recent experiments revealed that non-nociceptive stimuli, provided that they are salient, can elicit cortical responses with a spatial configuration very similar, although not identical, to that of the pain matrix [30], and that the intensity of a painful stimulus is not linearly represented in the pain matrix [4, 15]. The "new" view of the pain matrix suggests that its functional significance is adaptive—the purpose of pain is to elicit action from the organism: fight or flight. Legrain and colleagues [22] suggest that the "pain matrix" is a cortical network with a more basic function of detecting events that threaten the body's integrity, regardless of the sensory channel through which they are conveyed (Fig. 13-1). The pain matrix is viewed as a neural network that includes a combination of detection, orienting attention toward, and reacting to, the occurrence of salient sensory events. The emphasis is no longer on the quality of the sensation elicited by the noxious stimulus but on the action prompted by the occurrence of potential threats. This view remains controversial though, as there is recent evidence that γ-band activity in primary somatosensory cortex correlates with subjective pain reports independent of saliency [52].

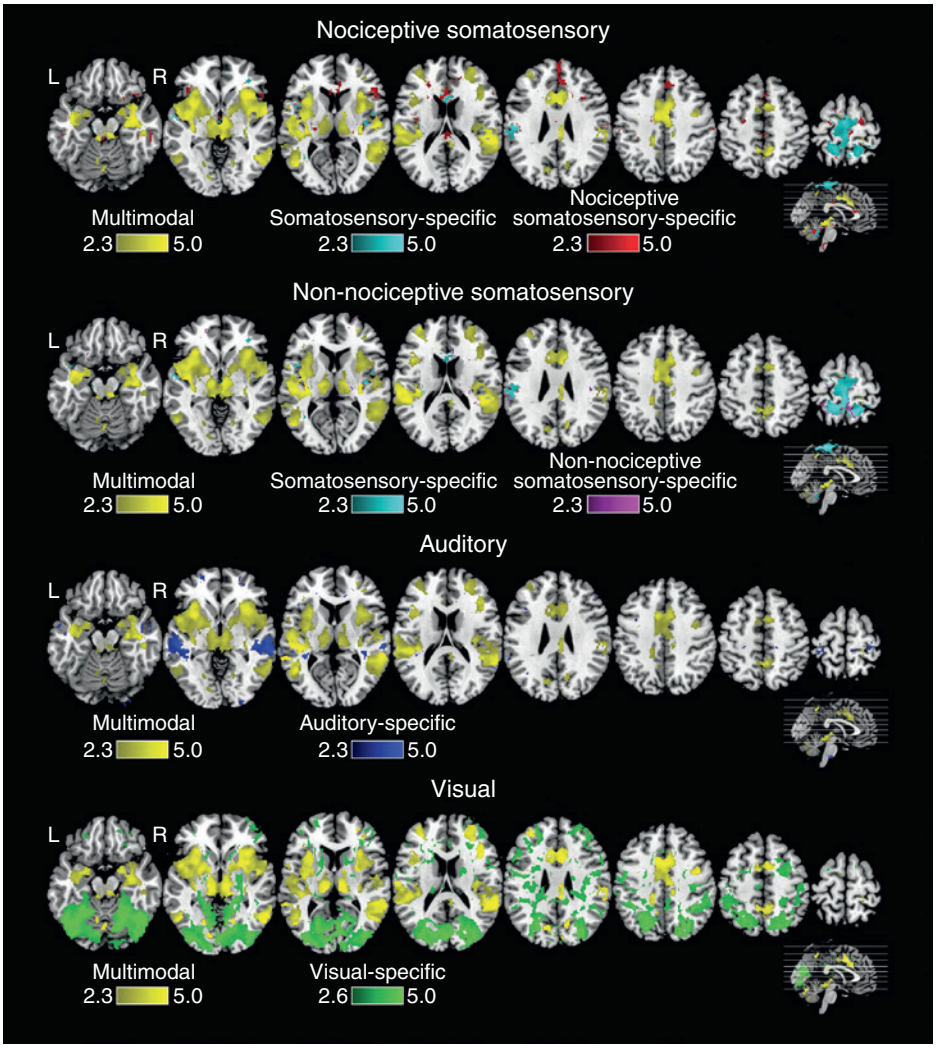

FIGURE 13-1 Modality-specific and multimodal brain responses in response to nociceptive, non-nociceptive somatosensory, auditory, and visual stimulation. Brain areas displaying a significant activation to all four types of sensory stimuli are shown in yellow. Voxels displaying selective activation to nociceptive and non-nociceptive somatosensory stimulation are shown in cyan. Voxels displaying significant activation only to nociceptive somatosensory stimuli are shown in red. Non-nociceptive somatosensory-specific, auditory-specific, and visual-specific voxels are shown in purple, blue, and green, respectively. (Adapted from Mouraux et al. [30].)

THE ROLE OF VISION IN SOMATOSENSORY PERCEPTION IN SIGHTED INDIVIDUALS

When information is transmitted to the brain through multiple senses, there are significant performance benefits in terms of speed and accuracy [42]. The effects are enhanced when different sensory stimuli are presented in a spatially and temporally congruent manner.

Visual–Tactile Integration

The multisensory benefits of visual–tactile integration have been repeatedly demonstrated. People are more likely to detect a near-threshold tactile stimulus when it is presented concurrently with a visual stimulus, compared to when it is presented alone [19]. Even if the visual stimulus is entirely task-irrelevant, it can enhance the detection of a tactile stimulus. Serino et al. [38] showed enhanced detection of subthreshold tactile stimuli on observers' faces when they saw a face being touched by hands rather than a face being merely approached by hands. Even when the visual stimulus, seeing the forearm, was both uninformative and irrelevant to the task, performance benefited, suggesting that vision is able to focus tactile attention and to modulate somatosensory cortical activity [43].

Visual Information of One's Own Body Modulates Pain

Similar to the effects of vision on touch, pain perception is also modulated by specific visual information. As many of us have probably already experienced, after banging our knee the perception of pain can be minimized or exacerbated, depending on whether the knee looks normal or injured. This anecdotal observation has been confirmed in controlled studies reporting that viewing an undamaged body part can have an analgesic effect [23]. This "visually induced analgesia" suggests an interplay between the brain's pain network and a posterior network for body perception, which modulates the experience of pain. Mancini and colleagues [25] further explored the relationship between pain and body perception by artificially distorting the image of the hand so that it appears excessively larger or smaller than usual. When participants gazed toward the distorted reflection of their hands while receiving a noxious thermal stimulus, their experience of pain was inversely correlated with the relative size of their hands: enlarging the hand had an analgesic effect, whereas reducing its size resulted in increased pain ratings [25]. Interestingly, the analgesic effect of vision is strongly linked to embodiment; the magnitude of the effect is positively correlated with the belief that the hand is one's own [25].

Neural networks involved in body image overlap considerably with the pain matrix, making these regions (especially the posterior parietal and somatosensory cortices) possible candidates for involvement in visual analgesia [24]. Neuroimaging studies have shown that extensive areas of the posterior parietal and inferotemporal cortices are involved in body representation, including the extrastriate body area, the fusiform body area, and have revealed a topographic map of viewed body parts throughout the visual cortex [6, 31, 33]. Interestingly, Longo et al. [24] reported that activity within parts of the pain matrix, like the primary somatosensory and the operculoinsular cortices, shows reduced activity to a noxious heat stimulus when viewing the body compared to viewing an object. These authors further reported an increased functional coupling between the posterior parietal nodes of the visual body network and areas of the cortical pain network during viewing of the stimulated hand, compared to viewing an object. This finding suggests that multisensory interactions involving the perception of one's own body underlie visual analgesia [12]. However, the direct relationship to the perception of one's own body does not necessarily underlie visual analgesic effects because opposite effects are reported when we view other people's bodies in pain. Reports of vicarious pain demonstrate a relationship between observed and experienced pain [2, 48].

Visual analgesia may seem somewhat a bit paradoxical as one would rather expect that directed attention would lead to enhanced pain responses [34]. Indeed, not all studies have replicated the visual analgesic effect. In fact, Valentini and colleagues [47] found no analgesic effect when seeing the hand in a normal position. Instead, these authors reported that viewing the hand in a crossed position had an analgesic effect compared to viewing the hand in its hemispace, or viewing an object placed in the contralateral space, suggesting that proprioceptive information can modulate pain perception. Another recent study also failed to replicate the visual analgesic effect [44]. The authors compared the effects of direct versus mirror vision of the stimulated hand or an object on nociceptive and non-nociceptive stimuli, while measuring event-related potentials (ERPs). Results showed that looking at the hand compared to an object did not modulate the subjective pain perception; however, it reduced the magnitude of the nociceptive N240 wave, and enhanced the magnitude of the non-nociceptive P200. The results of these two recent studies question both the robustness and the ubiquity of visual analgesia. Skin color can also affect pain responses. Inflamed or injured skin tends to be red, whereas a more bluish skin color is typically associated with cold skin. When painful thermal stimuli are applied to a red patch of skin on an embodied virtual arm, participants have lower thresholds for pain compared to when the embodied arm is blue [26]. An increased pain perception is also observed when a painful stimulus is felt at the same time as viewing a hand being pricked with a needle, compared to viewing a hand poked with a Q-tip [13]. Unlike the visual analgesic effect, this increased pain response is associated with reduced α-band activity in the posterior cingulate cortex and fusiform gyrus [14].

Visual Information of Someone Else' Body Modulates Visual-Nociceptive Integration

Seeing another person in pain makes people more sensitive to pain [17], whereas observing a stoic person's lack of response to pain can inhibit the experience of pain in the observer [46]. Several factors, in particular empathy, facilitate or interfere with somatosensation as a result of observing someone in pain. Empathy is generally defined as the capacity to understand and respond to the unique affective experiences of another person [11]. Although empathy for a co-fellow's pain and pain in one's own body are perceived differently, they are represented very similarly in the brain [17, 39].

Associative learning plays an important role in explaining whether a stimulus is perceived as painful or not. During our lives, we learn to associate the visual images of our wounds with pain. Thus, through classical conditioning, seeing injuries (such as others bleeding) may induce a conditioned autonomic response of pain. The conditioned response to painful images, such as those of other persons in pain, can then modulate one's own pain perception [36]. The association has been demonstrated through a conditioning paradigm in the laboratory study conducted by Wunsch and colleagues [50]. They found that painful and nonpainful thermal stimuli were perceived as more intense and more unpleasant when they were immediately preceded by one of the conditioned aversive stimuli (e.g., an image of a mutilated body), compared to the same tactile stimulation preceded by one of the images that were used in the neutral or positive conditioning sequences.

Vicarious Pain or "I Feel Your Pain"

Vicarious somatosensory experiences occur when one has a sensation of pain, or more often a "tingling," without being touched at all, after observing another in pain. In contrast to empathic pain, where a tactile stimulus is perceived as more unpleasant when empathy is activated, vicarious pain is a tactile or nociceptive sensation without any direct input to the skin. Vicarious pain sensations have been reported both in patients and in healthy control populations.

Vicarious pain intense enough to be problematic has only been reported in patients with a history of intense, traumatic pain [2]. Since phantom pain is often triggered by thinking about, observing, or inferring that another person is in pain, it is often categorized as a vicarious pain [10]. Thus, the population with the highest number of vicarious pain reports are amputees with phantom pain [10]. Indeed, memories from painful experiences appear to play a role in determining where on the body the vicarious pain is felt [18].

Normal individuals without a history of trauma also sometimes report sensations simply from observing others in pain, without any stimulation to the skin [48].

Vicarious "pain" is fairly weak and low in intensity, and does not resemble the pain that is actually felt. Roughly 30% of a normal population will report low-intensity vicarious sensations, labeled as "tingling," from looking at images and video clips depicting painful events [32]. When looking at painful scenes, vicarious pain responders have stronger activation of emotional (insular cortex) and sensory (i.e., secondary somatosensory cortex) brain regions associated with pain, compared to people who do not report such sensations [32].

Fitzgibbon and colleagues [8] proposed that vicarious sensations are caused by a dysfunctional mirror neuron system that causes the perceptual state to exceed threshold, leading to consciously experienced sensations. They further speculate that the painful and/or traumatic history of amputees may be the catalyst for the disinhibition of the mirror system for pain and touch.

PAIN PERCEPTION IS THE ABSENCE OF VISION

After reviewing the now extensive evidence demonstrating that visual information influences pain perception, the question then becomes how does blindness, either from birth or acquired later in life, affect pain processing? It has been well documented that the loss of one sense is sometimes compensated by improved development in the remaining senses. Numerous studies have shown that congenitally blind individuals demonstrate compensatory plasticity for their lack of vision with more efficient auditory, tactile, and even olfactory senses (see reference [21] for a recent review). Even after only 1 week of complete visual deprivation, otherwise normal people increase their tactile and thermal acuity [51]. This blindfolding also caused a drop in heat pain thresholds, indicating that lack of vision may induce hypersensitivity to pain. Vision, when present, can signal potential threats to the body, for example, a red-hot stove. In the absence of this warning function, blind individuals might instead adopt a chronic state of hypervigilance as a way to avoid tissue injury.

In our pioneering study of pain and temperature perception in congenital blindness, we demonstrated that blind subjects had significantly lower heat pain and cold pain thresholds than matched controls [41]. Further, while congenitally blind subjects did not differ from matched controls in terms of their ability to detect innocuous warmth and cold, they rated suprathreshold heat stimuli as significantly more painful than their sighted counterparts. Results of pain questionnaires further revealed that blind subjects were more anxious about pain (Fig. 13-2). These findings were replicated in a cohort of blind and sighted control subjects from another ethnic background [41]. We demonstrated that hypersensitivity to pain is not culturally based, and is specific to noxious thermal stimulation, rather than to thermal stimulation in general. Taken together with findings of augmented responses to threatening

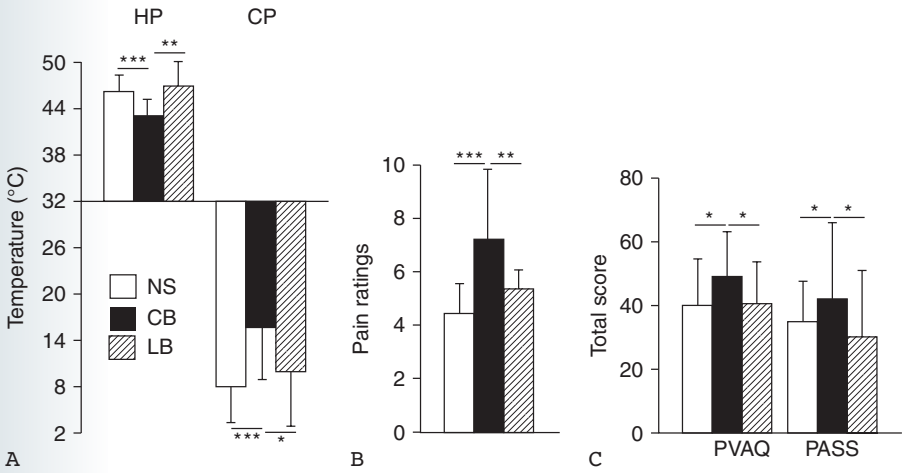

FIGURE 13-2 Pain sensitivity in normally sighted (NS), late blind (LB), and congenitally blind (CB) subjects. **A:** CB have lower heat pain (HP) and cold pain (CP) thresholds compared to NS and LB. **B:** CB rate suprathreshold nociceptive stimuli as more painful than NS and LB. **C:** Unlike NS and LB, CB score higher on the Pain Vigilance and Awareness Questionnaire (PVAQ) and the Pain Anxiety Symptoms Scale (PASS). Error bars represent standard errors. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. (Adapted from Slimani et al. [40].)

auditory stimuli in blind subjects [20], these data provided compelling evidence that congenitally blind individuals are more attentive to signals of external threats.

In order to determine if the hypersensitivity to threatening stimuli arises from a compensatory neural plasticity that is rooted in the critical period of development, we compared the pain sensitivity in early and late blind subjects. In fact, data from late blind subjects was very similarly to that of sighted individuals, including both responses to painful heat stimuli, and questionnaires assessing awareness and anxiety toward pain [40]. This suggests that visual deprivation per se does not determine the development of pain hypersensitivity—the time at which the visual system is deprived is equally important.

In a third study we tried to disentangle the individual roles of Aδ- and C-fiber activation in the pain hypersensitivity of congenitally blind subjects. Due to the difference in conduction velocity of the Aδ- and C-fiber sets, pain is often referred to as a double-alarm system, in which the first and second alarms are mediated by the fast-conducting Aδ-fibers and the slow-conducting C-fibers, respectively [35]. Consequently, reaction times to ultrafast, highly synchronized nociceptive radiant heat are distributed in a bimodal manner, whereby the first part of the distribution represents responses to Aδ-fiber activation, and the second part is caused by responses to the slower-conducting C-fibers [3]. We therefore measured reaction times to brief nociceptive radiant heat stimuli, applied by a CO_2 laser, thereby taking advantage of the

anatomophysiological organization of the nociceptive system. Results showed that congenitally blind participants detected more C-fiber–mediated stimuli and with faster reaction times compared to sighted controls [Slimani, Plaghki, Ptito, & Kupers, 2015, manuscript submitted for publication]. Analysis of the reaction times indicated that the faster response times in the congenitally blind participants were due to a more efficient central processing of C-fiber–mediated sensations. AQ:2

Two competing hypotheses have been proposed to explain pain hypersensitivity, following congenital blindness [40, 41]. According to the first hypothesis, the pain hypersensitivity reflects cross-modal plasticity of brain circuits as a result of a lack of visual input. Thus, due the lack of inhibitory effects of vision on pain perception (c.f. visual analgesia), early visual deprivation rewires the brain circuitry, causing increased sensitivity to nociceptive inputs [23, 24, 51]. According to the second hypothesis, the pain hypersensitivity is the result of a hypervigilance to threatening stimuli in congenitally blind individuals. This more integrative interpretation of the pain hypersensitivity can also account for the observations that congenitally blind individuals show increased responses to auditory threats [20] and are better at identifying body odors with a negative emotional valence [16]. This interpretation is also in line with the view that stimulus salience detection is one of the basic functions of the pain matrix, regardless of the sensory channel through which the stimuli are conveyed. Indeed, as shown in recent brain imaging studies, salient visual and noxious stimuli activate a partly overlapping cortical network [30], supporting the hypothesis that there is an intricate integration of vision and pain processing.

VISION-BASED TREATMENT OF CHRONIC PAIN CONDITIONS

While the causes and underlying mechanisms of pain remain elusive, research reviewed here clarifies that vision plays an important role in signaling, monitoring, exciting, or inhibiting pain signals. Our increased understanding of the integration of vision and pain has been used to reduce pain and improve people's quality of life.

Pioneering but largely anecdotal work has shown that simply seeing unharmed limbs can reduce the feeling of pain in amputated patients with phantom limb pain [37]. In much the same way that viewing the body can reduce acute pain [23], viewing the body can also reduce chronic pain. In the mirror-box setup, amputees view a reflection of their unaffected limb in the anatomical position of their amputated limb. Phantom limb patients perceive their body to be intact and that they have regrown their amputated limb (which is really only a reflection of their healthy limb), and that it is unharmed. Simply seeing an intact unharmed limb in the place of their phantom significantly reduced phantom limb pain, and sometimes even removed it completely after a few hours of visual exposure with the mirror box [37].

Unfortunately, no rigorously controlled studies have been carried out on the effect of mirror therapy in large cohorts of phantom limb patients.

Mirror-box therapy is inexpensive, simple, and versatile, and in contrast with medication therapy devoid of adverse effects. Consequently, clinicians have tried to extend its use to other chronic pain conditions that are hard to treat, including complex regional pain syndrome [27] and lower back pain [49]. As for phantom limb pain, few well-controlled studies have been carried out; a recent critical review concluded that there is no conclusive evidence that mirror box therapy works for complex regional pain syndrome [45]. Even though it is still controversial, using mirrors and visual cues as a way to reduce pain is a minimal risk treatment program. It can be done at home, it is inexpensive, and there are no negative side effects. Keeping in mind that chronic pain keeps people out of the workforce, there is an economic as well as a social benefit to continued research into the effects of vision on pain, and alternative treatments to pain relief that capitalize on the multisensory nature of pain.

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