February 2008

THE ROLE OF THE AMYGDALA IN EMOTIONAL PERCEPTION AND MEMORY IN HEALTHY AND SCHIZOPHRENIA POPULATIONS

A thesis submitted to McGill University in partial fulfillment
of the requirements for the degree of
Ph.D. in Neuroscience

by

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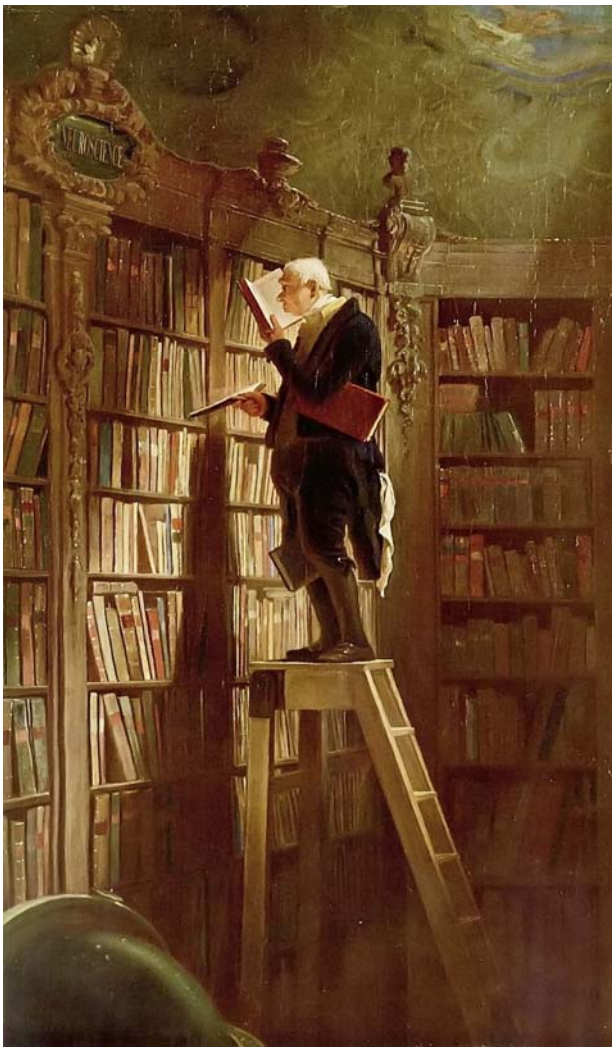

Adapted from: *The Bookworm* by Carl Spitzweg (1850)

À ma mère, à mon père
Avec tout mon amour

"No hay ejercicio intelectual que no sea finalmente inútil"[1]

Jorge Luis Borges

[1] *"* There is no intellectual exercise which is not ultimately useless*"*

Acknowledgements

Pursuing a Doctoral degree is certainly a unique experience. Besides being an obviously intellectually enriching experience, it gave me the opportunity to develop my research skills in an environment that encouraged flexibility, creativity, and independence. This is due, in large part, to two individuals who are very dear to me: my co-supervisors. You both provide your students with the help and resources they need to succeed – I feel privileged to have received your excellent guidance. Thanks to you, I had the chance to reach the higher levels of research, and become the scientist I am today.

On an individual level, I especially want to thank Dr. Jorge L. Armony for the wonderful times we've had over these past few years. I wish to express my sincere gratitude for giving me the opportunity to work with you. Especially, I want to thank you for your endless support, invaluable insight, expertise (both scientific and technical that helped me disentangle the mystery that is SPM), and most importantly, your friendship. Your ability to resolve all manners of problems is fascinating. Our years of collaboration have transmitted to me your critical sense, scientific integrity/rigor, and above all, unconditional passion for research. I, too, am now an ardent supporter of the amygdala! It is also thanks to you that this dissertation can be written up in a language other than my own. I am infinitely grateful to you! I will deeply miss our 3pm coffee breaks, and it is my sincerest hope that we will have more opportunities to collaborate in the future.

Mes sincères remerciements vont également à Dr. Martin Lepage pour son soutien, ses conseils, sa disponibilité sans faille, son souci de la valorisation des travaux accomplis

de même que pour son calme inébranlable devant mes angoisses ou face aux imprévus/difficultés lors de la réalisation des projets. Je tiens aussi à le remercier de la confiance qu'il a mise en moi en me donnant toute la latitude dont j'avais besoin pour mener à bien ces études. Merci aussi pour ces échanges enrichissants lors de nos réunions. Qu'il trouve ici l'expression de ma profonde gratitude.

I would like to thank my colleagues (in both laboratories) for their friendship, enthusiasm, and the support they have shown me and my projects. Erin, Karin, and Caroline: you are incredibly brilliant young women! I wish you all the best of luck in your future endeavors. You will undoubtedly succeed in all you undertake. Caroline, I wish to thank you especially for all the countless hours you spent on the interminable data entry for the meta-analysis. Your help was invaluable. It was a pleasure to share an office with you.

I would equally like to thank Drs. Alain Dagher and Sonia Lupien, and also my mentor, Dr. Louis Collin, who were present at my committee meetings, and who took the time to examine my thesis proposal. Thank you for your thoughtfulness and the interest you have taken in my work. Your advice, comments and suggestions allowed me to improve substantially the quality of this dissertation. I would also like to thank the external and internal examiners of my thesis for their helpful feedback.

Et toi ma grande amie Geneviève, ma complice de tant de merveilleux moments. Je vais m'ennuyer de nos fous rires, de nos discussions autour d'un petit café et de nos soirées cinéma/pharmacie. Permets-moi d'exprimer ici toute ma gratitude pour ta patience et ton amitié extraordinaire. Je me sens privilégiée et honorée de te connaître et tu as toute mon admiration pour tout ce que tu as accompli au cours des dernières années. Ta volonté et ta détermination sont une source d'inspiration pour moi. Tu n'as pas idée à quel point

tu vas me manquer! Tu m'es très précieuse et ne t'inquiètes pas, je suis certaine que la distance ne réussira pas à nous éloigner.

Je tiens à remercier tout spécialement mon p'tit frère Yan qui est, depuis peu, docteur lui aussi. Je me souviens de toi haut comme trois pommes et me voici aujourd'hui à remercier l'homme merveilleux que tu es devenu. Merci frérot de cette magie dont tu as saupoudrée ma vie! Tu as en toi ce bon dosage d'intelligence, de modestie et de bonté qui fait de toi une personne unique. Merci pour ton support, ton amour et tous ces moments inoubliables qui m'ont tant fait rigoler (e.g. chaise berçante et ping pong). Je suis certaine qu'il y en aura pleins d'autres.

Cette thèse n'aurait pu voir le jour sans le soutien et l'amour sans faille de mes parents. Il n'existe pas de mots assez puissants pour vous exprimer toute ma reconnaissance. Vous êtes des parents extraordinaires qui ont su m'inculquer l'importance du travail, de la détermination mais aussi, le sens du devoir et de la famille. Votre infinie générosité et votre dévouement sans borne ont fait rosir mes joues à plus d'une reprise. Tout ce qu'il y a de bon en moi, vous me l'avez enseigné. Je vous aime très fort, vous êtes merveilleux.

Contributions of Authors

Sergerie K., Chochol C., Armony JL. (2008) The role of the amygdala in emotional processing: A quantitative meta-analysis of functional neuroimaging studies, Neuroscience & Biobehavioral Reviews, Epub ahead of print.

For this meta-analysis (included in Chapter 2 and Appendix A), I did the literature review, extracted some of the relevant information from the original papers, develop the methodology, performed the meta-analysis, and finally I wrote the paper.

Caroline Chochol extracted most of the relevant information from the original papers and reviewed the paper.

Dr. Jorge L. Armony helped me to develop the methodology, write the paper and he supervised the project.

Sergerie K., Lepage M., Armony JL. (2007) Influence of emotional expression on memory recognition bias: A functional magnetic resonance imaging study, Biological Psychiatry, 62, 1126-1133.

For this paper (included in Chapter 3 and Appendix B), I was responsible for the design, recruitment of subjects, scanning, and analyses of the functional magnetic resonance data. I also wrote the paper.

Dr. Martin Lepage helped to improve the paper.

Dr. Jorge L. Armony supervised my work and made this study possible by providing the necessary funds. He also helped me with the analyses and to write the paper.

Sergerie K., Armony JL., Menear M., Sutton H., Lepage M. (2007) Influence of Emotional Expression on Memory Recognition Bias in Schizophrenia as revealed by fMRI, Archives of General Psychiatry, in revision.

For this paper (included in Chapter 4), I was responsible for the design, recruitment of subjects, scanning, and analyses of the functional magnetic resonance data. I also wrote the paper.

Matthew Menear and Hazel Sutton were responsible for the recruitment, the clinical evaluation and the scanning.

Dr. Martin Lepage made this study possible by providing the necessary funds. He also supervised the project (recruitment, evaluation and scanning of the patients and matched-control subjects) and helped to improve the paper.

Dr. Jorge L. Armony helped me with the analyses and the improvement of the paper.

Armony JL. & Sergerie K. (2007) Own-sex effects in emotional memory for faces, Neuroscience Letters, 426, 1-5.

For this paper (included in Chapter 5 and Appendix C), I was responsible for the design, recruitment of subjects, scanning, and analyses of the functional magnetic resonance data. I also help to write paper.

Dr. Jorge L. Armony made this study possible by providing the necessary funds. He also helped me with the analyses. Finally, he wrote the paper.

Abstract

A large body of work, both in experimental animals and more recently in humans, has showed that the amygdala is a critical component of the brain network underpinning emotional processing. However, controversies still exist about specific aspects of its role in emotion, particularly in terms of hemispheric specialization, sex differences and its sensitivity to stimulus valence and/or arousal. The large functional neuroimaging literature developed over the past two decades can help us clarify whether these and other factors influence the magnitude of the amygdala response. To this end, I performed a quantitative meta-analysis of published functional brain imaging studies of emotional perception that have reported an amygdala activation. Critically, this meta-analysis included the magnitude (effect size) and reliability (variance) associated with each of the activations. Our main findings were that the amygdala responds to a larger extent to positive than negative stimuli, and for emotional faces than scenes, pictures, words or films. No evidence for amygdala lateralization as a function of sex or valence was observed. Instead, our findings provide strong support for a functional hemispheric dissociation in terms of temporal dynamics, namely that the right amygdala is more involved in the initial rapid and transient response to the presence of an emotional stimulus, which is followed by a slower and more sustained activation by the left amygdala. We also explored the question of amygdala lateralization in emotional memory, in particular in terms of sex differences. To do so, we re-analyzed data from our previous fMRI study of emotional memory for fearful faces (Sergerie et al. 2006). We observed a sex-specific hemispheric laterality of the amygdala involvement in successful memory for fearful faces only when the sex of the face stimuli was also taken into account.

Specifically, the left amygdala was more active in the successfully remembered female fearful faces in women, whereas, for men, the right amygdala was more involved in memory for male fearful faces. These findings provide support and further refine existing models of sex-specific lateralization of the amygdala in emotional memory. I also investigated the emotion-specificity of memory for faces by conducting an fMRI study of recognition memory for sad, happy and neutral faces. The main goal of this study was to assess whether memory for sad faces, a negatively valenced but low arousal emotion, was similar or not to that for fearful faces. Our behavioral results revealed that sad faces were associated with a decrease in recognition accuracy, compared to both happy and neutral expressions, in stark contrast to the previously observed enhanced memory for fearful faces. This effect, however, was due to a significant familiarity bias; that is, subjects were more likely to believe that they had previously seen a sad face, regardless of whether this was true or not. In contrast, happy faces were associated with a novelty response bias. This bias correlated with amygdala and prefrontal cortex activity, whereas the familiarity bias was associated with a superior temporal gyrus activation.

In a follow-up experiment, the same paradigm was applied to individuals with schizophrenia to further investigate their often reported behavioral and neural abnormalities in memory and emotional processing. Despite an overall lower memory performance, patients showed the same influence of emotion on memory as controls, both in terms of accuracy and response bias. For sad faces, this similar behavioral pattern was mirrored by a largely overlapping neural network, mostly involved in familiarity-based judgments (e.g., parahippocampal gyrus). In contrast, controls activated a larger network for happy faces, including regions involved in recollection-based memory retrieval (e.g.,

hippocampus) suggesting that the two groups may utilize different strategies or processes when retrieving emotional information from memory.

Résumé

De nombreuses études menées chez l'animal et plus récemment chez l'homme ont montré que l'amygdale est une structure cruciale du réseau cérébral sous-tendant le traitement des émotions. Toutefois, il existe encore de nombreuses controverses quant aux spécificités de son implication, telles que la spécialisation hémisphérique, les différences liés au sexe, ainsi que de la sensibilité à la valence et/ou intensité des stimuli. Depuis les deux dernières décennies, l'intérêt pour ces questions n'a cessé de croître comme en témoigne la vaste littérature en neuroimagerie fonctionnelle. J'ai ainsi pu recourir à cette littérature afin de clarifier l'influence des facteurs décrits précédemment sur l'activité neuronale de l'amygdale. À cet effet, j'ai réalisé une méta-analyse quantitative incluant les études en imagerie cérébrale fonctionnelle ayant rapporté une activation de l'amygdale lors de la perception des émotions. Plus précisément, cette méta-analyse inclut la magnitude (i.e. la taille de l'effet) et la fidélité (i.e. la variance) associées à chacune des activations. L'analyse a permis d'établir que le niveau d'activation de l'amygdale est plus important pour des stimuli positifs que pour des stimuli négatifs, et plus important pour les expressions émotionnelles comparativement aux scènes, images, mots ou films. Aucun effet significatif du sexe des sujets ou de la valence des stimuli sur la latéralisation de la réponse de l'amygdale n'a été constaté. Toutefois, les résultats montrent qu'il existe une différence inter-hémisphérique de la réponse en termes de dynamique temporelle. En effet, il apparaît que l'amygdale droite est préférentiellement impliquée dans la réponse initiale rapide et transitoire à la présence d'un stimulus émotionnel. Elle serait suivit par une activation plus lente mais aussi plus soutenue de l'amygdale gauche. Nous avons également essayé de déterminer si les différences liées au sexe des participants pouvaient

avoir une incidence sur l'activité de l'amygdale en mémoire émotionnelle. À cette fin, nous avons ré-analysé les données provenant d'une précédente étude en imagerie par résonance magnétique fonctionnelle (IRMf), et portant sur la mémorisation de visages présentant une expression neutre, de peur et de joie (Sergerie et al., 2006). Nous avons observé une différence inter-hémisphérique de la réponse de l'amygdale en fonction du sexe des participants pour les visages correctement mémorisés. Cette différence était significative uniquement lorsque le sexe des visages utilisés comme stimuli était pris en compte. Ainsi, l'activation de l'amygdale gauche chez les femmes était plus importante lorsque des visages de femmes présentant une expression de peur étaient correctement mémorisés, comparativement à des visages d'hommes. Chez les hommes, l'amygdale droite présentait une activation plus importante pour des visages d'hommes présentant une expression de peur correctement mémorisés, relativement aux visages de femmes. Ces résultats, tout en les affinant, sont en accord avec les modèles existants de latéralisation de l'amygdale en fonction du sexe en mémoire émotionnelle. J'ai également étudié l'influence d'émotions spécifiques sur la mémoire des visages en réalisant une étude IRMf sur la reconnaissance des visages présentant différentes expressions faciales (tristesse, joie et neutre). Le but principal de cette étude était de déterminer si la mémorisation pour les visages présentant une expression de tristesse (i.e. une émotion de valence négative mais d'intensité réduite) serait similaire à celle des visages présentant une expression de peur. Les résultats comportementaux mettent en évidence une diminution du taux de reconnaissance des visages exprimant la tristesse par rapport aux visages exprimant la joie ou d'expression neutre. Ce résultat diverge de celui observé précédemment pour les visages présentant une expression de peur, et pour lesquels une augmentation du taux de reconnaissance avait été constatée. Ce résultat est toutefois

imputable à un biais significatif de familiarité; i.e. que les sujets étaient plus disposés à croire qu'ils avaient déjà vu un visage exprimant la tristesse, que ce soit le cas ou non. Au contraire, les visages exprimant la joie étaient associés à un biais de nouveauté. Ce biais présentait une corrélation significative avec l'activation de l'amygdale et du cortex préfrontal, alors que le biais de familiarité présentait une corrélation significative avec l'activation du gyrus temporal supérieur.

Dans une étude subséquente, le même paradigme a été utilisé chez des patients schizophrènes afin d'explorer les anomalies/déficits observées en mémoire et traitement des émotions. En dépit d'un taux de reconnaissance globalement inférieur, l'effet des émotions sur la mémoire (en terme de taux de reconnaissance et de biais de réponse) était similaire chez les patients que chez les sujets sains. En ce qui concerne les visages exprimant la tristesse, la similarité du patron comportemental se traduisait par le chevauchement entre les deux groupes d'un vaste réseau neuronal essentiellement associé aux jugements de reconnaissance basés sur la familiarité (e.g., gyrus parahippocampique). Pour les visages exprimant la joie, le réseau neuronal impliqué chez les sujets sains était plus vaste que celui des patients. Celui-ci inclut principalement des régions impliquées dans les jugements de reconnaissance basés sur la ''recollection'' (e.g. hippocampe). Ces résultats suggèrent donc que les deux groupes pourraient utiliser des stratégies ou processus différents lors la récupération d'informations émotionnelles.

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Chapter 1

Introduction

1. General Introduction

Throughout human history, there has been a long tradition of an opposition between cognition and emotion. However, the emergence of the long-lasting primacy of cognition or forces of rationality (logos) over the atavistic forces of emotion or passion (pathos) was resolutely imposed with the early Greek philosophers. This view is reflected in the assumption that emotions undermine the capacity to reason, a view reflected in the Simile of the Cave of Plato, where he places mankind deep within the bowels of the earth, entrapped by their desires, self-indulgently prevented from moving up and out into the light of reason. In the same vein, Aristotle wrote in *Politics* (Aristotle, 350 BCE/1985), "It is clear that the rule of the soul over the body, and of the mind and the rational element over the passionate, is natural and expedient; whereas the equality of the two or the rule of the inferior is always hurtful". In fact, Aristotle *defined* emotion as "that which leads one's condition to become so transformed that his judgment is affected" (Aristotle, 350 BCE/1984). That is, the very essence of emotion lied on its negative influence on reasoning. Therefore, the wisdom of reason was situated as superior to the dangerous impulses of emotion that were detrimental to rationality and clarity of judgment, and thus needed to be suppressed or forced into submission through the steady application of an iron will.

As a consequence, the imperative of reason over emotion was largely accepted for centuries to come (attaining its extreme with the Stoics, who considered emotions as conceptual errors and therefore stated that people must learn sole reliance on reason and exclude emotion from any part of their lives), until the philosopher David Hume turned things around, by declaring in his classic book *Treatise of Human Nature* (Hume,

1739/1928) that "reason is, and ought only to be, the slave of the passions, and can never pretend to any other office than to serve and obey them". Hume suggested that reason yields analysis but, absent of emotional motivation or drives, reason cannot itself impels us to act. This pivotal position was later enriched by Nietzsche, who stated that, the emotions contain their own logic, their own reason and that, in contrast to the traditional Aristotelian view on the dominance of reason over emotions, "the will to overcome an emotion is ultimately only the will of another emotion" (Nietzsche, 1886/1990).

In the scientific domain, however, the emancipation of emotion from its cognitive master was laborious and lengthy to accomplish. For instance, the Cognitive Science movement that dominated the psychology research in the 1950s, explicitly left out emotions from any model that tried to explain the workings of the mind (J.E. LeDoux, 1996). There were, nonetheless, passionate debates about the nature of the cognitive-emotional interactions (for example, (Lazarus, 1984, 1991; Leventhal & Scherer, 1987; R. Zajonc, 1980; R. B. Zajonc, 1984)), but they were predominantly revolving around semantic issues related to the exact significance of the concepts associated with the terms "cognition" and "emotion". It is nonetheless worth mentioning that some early cognitive pioneers had already acknowledged that information processing is intricately linked to emotional and motivational forces. For example, Herbert Simon stated in the late 60's that "since in actual human behavior motive and emotion are major influences on the course of cognitive behavior, a general theory of thinking and problem solving must incorporate such influences" (Simon, 1967). Two decades later, Marvin Minsky wrote "the question is not whether intelligent machines can have any emotions, but whether machines can be intelligent *without* any emotions" (Minsky, 1985). This conceptualization of emotion as another form of information processing was promising as

it allowed researchers to investigate emotions in a systematic, "scientific" way, like it was already the case with other psychological processes and their neural correlates, such as memory or sensory processing. As a result, the integration and application of this new perspective by researchers within the field of neuroscience led to considerable progress in the understanding of the neural systems underlying emotional processing; especially fear but also other basic emotions (e.g. happiness and sadness) and, more recently, more complex social ones (e.g. guilt and envy) (J.E. LeDoux, 1996) . In addition, the use of the same approaches and techniques to study emotion and cognition allowed researchers to directly explore how these two processes interact, not as master and slave, but as dynamic partners influencing each other and, together, determining our thoughts and behaviour.

1.1. Neural circuitry of Emotion

Brown and Schaffer (S. Brown & Schafer, 1888) were the first to report that large temporal lesions changed fierce monkeys into tame animals. Later, Heinrich Kluver and Paul Bucy (Kluver & Bucy, 1939) observed that removing both temporal lobes in rhesus monkeys resulted in a dramatic alteration on the animals' behaviour, in particular, in term of their emotional responses. Specifically, the monkeys presented, among other things, hypersexuality and a drastic diminution of their emotional reactivity (e.g., absence of arousal, little emotion in their facial expressions and vocalizations). They also showed a reduced capacity to experience fear, as these monkeys were generally more quiet and approached objects, animals or humans, which they would normally consider as threatening. This pattern of behaviour was called *psychic blindness* by Kluver and Bucy; as the animals seemed to be severely impaired in the processing of emotional stimuli although they did not exhibit any significant sensory or motor deficits. Later, Weiskrantz

(Weiskrantz, 1956) reported that a similar pattern of behaviours as the one encountered in the Kluver-Bucy syndrome lesions was observed even though the lesion was restricted to only include the amygdala complex. Consistent with a general role in fear, it is now well accepted that the amygdala is also involved in aversive learning such as conditioned emotional responses in monkeys (Weiskrantz, 1956), rats (Blanchard & Blanchard, 1972) and humans (Buchel & Dolan, 2000; Knight *et al.*, 2005; LaBar *et al.*, 1998). Indeed, these results suggested an involvement of the amygdala in emotionally motivated behaviours, and more specifically in the formation of associations between stimuli and negative reinforcement (for a review, see (Baxter & Murray, 2002)).

1.2. What is the Amygdala?

The anatomist Karl Friedrich Burdach was the first to use the term "amygdalar nucleus" to identify an almond-shaped cell mass of grey matter within the human medial temporal lobe (Swanson, 2003). Later, J.B. Johnston described in a landmark paper (Johnston, 1923) the amygdalar region in a variety of mammalian species, nonmammalian vertebrates and human embryos. He identified six main nuclei: central (CE), medial (ME), cortical (CO), basal (B), accessory basal (AB) and lateral (LA) nuclei, based on their relative locations within the amygdaloid complex (see Figure 1). In fact, the area identified as the amygdala by Burdach actually referred to the three latter nuclei, what is now named the basolateral amygdala complex. It is also worth mentioning that, depending of the classification scheme used, AB is also named the basomedial nucleus and B the basolateral nucleus (McDonald, 2003)

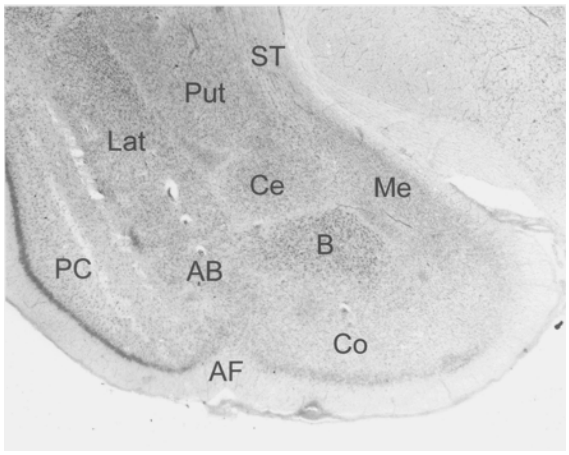

FIGURE 1. Coronal section of the amygdala. This neutral red-stained section was obtained from a brain used in Johnston's classic study of the amygdala. Note that an infolding of cortex at the amygdaloid fissure (AF) is continuous with portions of the basolateral amygdala, including the accessory basal (AB) and basal (B) nuclei, and the deep part of the cortical nucleus (Co). Other abbreviations: Ce, central nucleus; Lat, lateral nucleus; Me, medial nucleus; PC, piriform cortex; Put, putamen; ST, stria terminalis. *Taken from: (McDonald, 2003)*

While there is still no agreement on the exact borders of the amygdaloid complex, it is now generally accepted that it is composed of approximately 13 different nuclei and cortical areas, which can be further subdivided into subregions, with different physiological, cytoarchitectonic, and connectivity properties (Pitkanen *et al.*, 1997). Moreover, it appears that the fundamental structure and organization of the amygdala is similar across mammalian species, including rats, monkeys and humans (Amaral *et al.*, 1992). In fact, it has been argued that even birds and reptiles have amygdala-like structures which are believed to fulfil similar functions as in mammals, especially in terms of fear-related behaviour (J.E. LeDoux, 1996), thus suggesting that the amygdala has been highly conserved throughout evolution.

Although there have been numerous studies investigating the anatomical and functional aspects of amygdaloid connectivity, especially in rodents, much remains unknown. Nonetheless, organizational principles of the amygdalar intrinsic connections

have been recently revealed by tract-tracing studies (Pitkanen & Amaral, 1998). Essentially, it has been revealed that the flow of information is mostly unidirectional in a lateral-to medial direction. Specifically, the lateral nucleus receives sensory information from neocortex and sensory thalamus and projects to the basal, accessory basal, and periamygdaloid complex, which in turn project to the medial and central nucleus (Pitkanen et al., 1997). The amygdala also has a large amount of afferent and efferent connections with a multitude of other brain structures. It receives sensory information numerous areas including the thalamus, neocortex or hippocampus, as mentioned above, depending of the stage of processing. This information is subsequently transmitted to the central nucleus, which in turn, projects to several hypothalamic and brainstem target regions that mediate specific signs of fear and anxiety (Pitkanen & Amaral, 1991). For instance, freezing responses rely on the projections to the central grey nuclei, whereas sympathetic autonomic and startle ones depend on those to the lateral hypothalamus and to the reticular region, respectively (J. E. LeDoux, 1995). In addition, the amygdala also has widespread feedback projections to cortical structures such as primary sensory areas and frontal regions, especially the orbitofrontal cortex (Carmichael & Price, 1995; Krettek & Price, 1977).

1.3. Amygdala and other emotions

Most of what is known about the role of the amygdala in processing of emotion, especially in experimental animals has come from studies using fear-related stimuli (e.g. fear conditioning). This critical role of the amygdala in the processing of fear-related information has been confirmed by lesions and functional imaging studies in humans. By contrast, far fewer studies have systematically examined the amygdala's role in

processing other emotions. However, there is growing evidence, particularly from the functional neuroimaging field, suggesting that the amygdala may also be important for other emotions, both positive and negative. For instance, a meta-analysis conducted by Phan and colleagues (Phan *et al.*, 2002) on 55 studies reported that studies including happy and sad stimuli found an amygdala activation in a proportion of approximately 25 and 15%, respectively, and that the proportion increased to 60% in studies investigating fear. On the other hand, none of the studies using anger or disgust stimuli were been found to activate the amygdala. Since the publication of this meta-analysis, no clear consensus has been obtained and results are still inconsistent. For example, in a recent fMRI study, Fitzgerald and colleagues (Fitzgerald *et al.*, 2006) presented photographs of individual depicting 6 different facial expressions (fearful, disgusted, angry, sad, neutral, happy), and found that the left amygdala was activated by each facial expression separately, and that its response was not selective for any particular emotion category. In contrast, other studies failed to find an influence of non-fear basic emotions (happy, sad, disgust, anger) on amygdala activity (Aalto *et al.*, 2005; Britton *et al.*, 2006; Goldin *et al.*, 2005; Han *et al.*, 2007; Lee *et al.*, 2005; Mitterschiffthaler *et al.*, 2007; Phillips *et al.*, 2004; Strauss *et al.*, 2005; Surguladze *et al.*, 2003). An examination of the experimental paradigms and variables of interests employed could provide valuable insights into the potential reasons for these apparent inconsistencies. For example, differences in the results across studies may come from the large variability in the type of stimuli (e.g. word, scene, faces), control conditions (e.g. fixation cross, scramble pictures, neutral faces), design (block/event-related), methodology, population, sex of the subjects, tasks, level of consciousness, or technique employed. However, conflicting views on the role of the amygdala in the processing of different emotions also exists at the conceptual level. This

is reflected in the existence of different models of amygdala function. For instance, one model, proposed by Adolphs and colleagues, considers that the amygdala is part of a neural system allowing the rapid, automatic evaluation of information indicating potential threat or danger in the environment, of which fearful expressions may be signals (Adolphs *et al.*, 1999). According to this view, the amygdala would be involved in the processing of only fear-related stimuli and possibly anger. Another model posits that the role of the amygdala is to process of signals of distress (Blair *et al.*, 1999), thus including fear and sadness, or processing ambiguous emotional information that indicate potentially important environmental information that should be clarified (Whalen *et al.*, 2001; Yang *et al.*, 2002), therfore adding surprise and potentially other emotions. Finally, some researchers have suggested that the amygdala acts as a "relevance detector" to biologically salient stimuli, regardless of valence (Sander *et al.*, 2003; Williams *et al.*, 2006) and would be more sensitive to emotional arousal, rather than valence (Hamann *et al.*, 1999; Kensinger, 2004; Kensinger & Corkin, 2004). Thus, although all these models agree that the amygdala is important for fear-related processing, the exact nature of its role in the other emotions remains unclear. The story gets even more complicated when the hemispheric lateralization of the amygdala is taken into account, as more inconsistencies, and models, appear.

1.4. Lateralization models

One of the oldest models of emotion lateralization, based on animal and lesions studies, posits that the right hemisphere is more involved than the left in the processing of emotional information in general (Sackeim & Gur, 1978; Schwartz *et al.*, 1975), whereas another one, the valence asymmetry model, suggests that the positive and negative

information are preferential processed by the right and left hemispheres, respectively (R. J. Davidson, 1984; R. J. Davidson *et al.*, 1990; Sackeim *et al.*, 1982; Silberman & Weingartner, 1986). Since then, technical advances, in particular the increased use of functional imaging techniques such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) have allowed researchers to study the human amygdala in vivo and reliably measure its activity. Interestingly, a considerable number of functional imaging studies reported unilateral activation of the amygdala (Baas *et al.*, 2004; Murphy *et al.*, 2003; Phan et al., 2002; Wager *et al.*, 2003). Findings were, however, inconsistent in term of the specific role of each side in the different types of emotion and processes (Baas et al., 2004; Zald, 2003). Numerous models have thus been proposed in an attempt to clarify and explain the putative functional difference between the right and the amygdala in emotional processing. Markowitsch and colleagues (Markowitsch, 1998), for instance, proposed a material specificity lateralization model consistent with the dominance of the left hemisphere for the semantic material. Specifically, it was suggested that the left amygdala is more involved in the encoding of affective information related to language (e.g. words, sentences, scripts), while the right amygdala is more closely related to retrieval of pictorial or image-related emotional information (e.g., faces, pictures). Similarly, Phelps and colleagues (Phelps *et al.*, 2001) suggested that the involvement of the right amygdala is more important when the emotional stimulus is visual in nature, whereas the left amygdala has higher affinity for emotional material learned through verbal communication. Other existing (nonemotional) models of hemispheric lateralization, such as the global (right) vs. local (left) feature processing one, have been brought forward to help explain some of the observed hemispheric differences in amygdala involvement in emotional processing (Cahill,

2003b). In addition, a more specific model has been proposed in terms of stimulus awareness, such that consciously perceived emotional stimuli are processed mainly by the left amygdala whereas stimuli presented below conscious awareness (e.g., using backward masking) engage the right amygdala (Morris *et al.*, 1998).

Finally, a more recent model suggested by Gläscher and Adolphs proposed a differential involvement of the right and left amygdala in terms of their temporal dynamics (Glascher & Adolphs, 2003). Specifically, they proposed that the response of the right amygdala is rapid, undifferentiated and most likely automatic, providing an overall level of autonomic activation in response to any type of emotionally arousing stimulus. This initial response would then be followed by a more distinct and specific emotional reaction, mediated by the left amygdala, that discriminates or decodes the difference in arousal magnitude signalled by the specific stimulus (see also (Markowitsch, 1998)). This model is supported by studies investigating the habitation of amygdalas response to emotional material. For instance, in an fMRI study, Wright and colleagues observed a more rapid reduction in fMRI signal in the right than in the left amygdala following the repeated presentation of emotional faces (Wright *et al.*, 2001). Moreover, higher amygdala activation in the left than in the right amygdala was found for the contrast fear versus happy suggesting a more sustained response of the left amygdala. Similar findings have been reported by other researchers (Phillips *et al.*, 2001; Whalen *et al.*, 1998).

In addition to these amygdala lateralization models, which are more related to the perception of emotional stimuli, other models more specific to emotional memory have also been proposed. An example is the well-known sex-related amygdala lateralization put forward by Cahill and colleagues (Cahill, 2003a, 2003b; Cahill *et al.*, 2004). In this

model, the right amygdala activity is more related to emotional memory in men whereas the left is more involved in women. Finally, there is also the recent process-specific lateralization hypothesis suggested by our group, according to which the encoding of emotional material is mediated by the right amygdala and the recognition by the left (Sergerie *et al.*, 2006).

1.5. Emotional memory

What is the exact relation between emotion and memory? It is remarkable how this seemingly simple question has generated such a great deal of research, especially during the past few decades. The idea that emotional memories are somehow special is certainly not new. For example, back in 1890, William James wrote, "An experience may be so exciting as to almost leave a scar on the cerebral tissue" (James, 1950). A few years later, in 1919, George M. Stratton referred to hypermnesia for events experienced in a state of emotional excitement, so that an individual would recall "in almost photographic detail the total situation at the moment of shock" (Stratton, 1919). It is the same notion of this almost "photographic" aspect of emotional memories that inspired Brown and Kulik to put forward the concept of "flashbulb memories" (R. Brown & Kulik, 1977). They proposed an explanation of this phenomenon based on an evolutionary perspective: remembering biologically relevant but unexpected events has a survival value. Therefore, it is reasonable to assume that there may be a mechanism in the brain that will enable these memories to be recalled with almost perfect accuracy. Today, the indelibility hypothesis of emotional memory has been abandoned or, perhaps more specifically, refined, as researchers have demonstrated that the vividness and detail characterizing

memories associated with emotionally charged event are far from being error-free (McCloskey *et al.*, 1988; Neisser, 1982).

Although it is now generally accepted that memory for emotional events is not perfect, there is strong evidence showing that there is a true enhancement of memory for those events. Indeed, a large number of studies performed in controlled laboratory settings have consistently shown that emotionally arousing, particularly negative, stimuli, such as stories (Cahill *et al.*, 1996; Heuer & Reisberg, 1990) pictures (Hamann *et al.*, 1999) and words (Buchanan *et al.*, 2001), are better remembered than similar material without emotional value. Based on the fear conditioning animal literature, it has been hypothesized that the amygdala plays a key role in the enhancement of memory by emotion. Lesion studies with patients with unilateral temporal lobectomy (surgical treatment for intractable epilepsy) or selective unilateral or bilateral lesions of the amygdala (e.g. Urbach-Wiethe disease, Herpes simplex encephalitis, or sclerosis due to epilepsy) have largely confirmed this hypothesis, as these individuals, though not amnesic, do not show the expected enhancement for memories with emotional content (Adolphs *et al.*, 1997; Adolphs *et al.*, 2000; Adolphs et al., 1999; Cahill *et al.*, 1995; Cahill et al., 1996; LaBar & Phelps, 1998; Markowitsch *et al.*, 1994; Phelps *et al.*, 1997; Richardson *et al.*, 2004).

There is also a large body of neuroimaging literature that has investigated the neural bases of emotional memory, with specific focus on the amygdala**.** Cahill and colleagues were among the first to assess the role of the human amygdala in emotional memory using functional neuroimaging techniques (Cahill et al., 1996). Male subjects were scanned with Positron Emission Tomography (PET) while viewing emotionally-arousing negative and neutral films. In a surprise free recall test administered three weeks later,

subjects recalled significantly more information from the negative films clips than from the neutral videos. Critically, a positive correlation was observed between the activity in the right amygdala during encoding and the number of emotional videos recalled, whereas no correlation was observed for neutral film clips. Interestingly, a follow-up study with only women found a similar correlation but within the left amygdala, thus suggesting a potential influence of gender in the lateralization of emotional memory (Cahill *et al.*, 2001). However, no clear consensus regarding the lateralization and/or gender difference in amygdala responses to emotional stimuli (either in perception or memory) has been obtained on the basis of imaging studies, as different studies, some even employing the same experimental conditions, have reported left-side, right-side or bilateral activation (see (Wager et al., 2003; Zald, 2003)).

This amygdala-mediated memory enhancement for negative material has since been replicated and extended to other types of stimuli such as pictures (e.g. International Affective Pictures System, IAPS) and words (Canli *et al.*, 1999; Hamann et al., 1999), employing a variety memory measures (e.g., free recall and recognition). Although these studies significantly contributed to a better understanding of the role of the amygdala in emotional memory, some important open questions remain. For example, is the memory enhancement equal for all negative emotions? In fact, as it can be seen in Table 1 which includes, most, if not all, the neuroimaging studies of emotional memory in healthy individuals, that the large majority of studies have used stimulus sets that combine different negative emotions (e.g. the IAPS database that consists of images representing sadness, disgust, fear and anger).

Author	Year	Journal	Subjects	M	F	Tech	Stimuli	Emotional stimulus	Stimulus tested	Emotion
Armony et al.	2007	Neurosci Letters	18	9	9	fMRI	faces	face	face	Fear, Happy, Neu
Cahill et al.	1996	PNAS	8	8	0	PET	films	film	film	Neg, Neu
Cahill et al.	2001	Neurobio Learn Mem	11	11	0	PET	films	film	film	Neg, Neu
Cahill et al.	2004	Learning & Memory	15	8	7	fMRI	pictures	picture	picture	Neg, Neu
Canli et al.	1999	Psychobiology	10	0	10	fMRI	pictures	picture	picture	Neg, Neu
Canli et al.	2000	J Neurosci	10	0	10	fMRI	pictures	picture	picture	Neg, Neu
Depue et al.	2007	Science	16	11	5	fMRI	pictures/faces	picture	picture/face	Neg, Neu
De Ruiter et al.	2007	Neuroimage	43	18	25	fMRI	words	word	word	Neg, Neu
Dolan et al.	2000	Neuroimage	10	10	0	PET	pictures	picture	picture	(Pos+Neg), Neu
Dolcos et al.	2005	PNAS	9	0	9	fMRI	pictures	picture	picture	Pos, Neg, Neu
Dolcos et al.	2004	Neuron	18	0	18	fMRI	pictures	picture	picture	Pos, Neg, Neu
Dougal et al.	2007	Cogn Affect Behav Neurosci	14	5	9	fMRI	words	word	word	Pos, Neg, Neu
Erk et al.	2003	Neuroimage	10	7	3	fMRI	pictures, words	picture	word	Pos, Neg, Neu
Erk et al.	2005	NeuroImage	10	7	3	fMRI	pictures/words	picture	word	Pos, Neg, Neu
Fenker et al.	2005	European J of Neuroscience	20	6	14	fMRI	words/faces	face	word	Fear, Neu
Fossati et al.	2004	NeuroImage	11	4	7	fMRI	words	word	word	Pos, Neg
Hamann et al.	1999	Nature Neurosci	10	10	0	PET	pictures	picture	picture	Pos, Neg, Neu
Harvey et al.	2007	J Cogn Neurosci	17	9	8	fMRI	pictures	picture	picture	Pos, Neg, Neu
Kensinger et al.	2004	PNAS	28	14	14	fMRI	words	word	word	Neg, Neu
Kensinger et al.	2005	NeuroImage	16	8	8	fMRI	pictures/words	picture/word	word	(Pos+Neg), Neu
Kensinger et al.	2005	Neuropsychologia	16	7	9	fMRI	pictures/words	picture/word	word	(Pos+Neg), Neu
Kensinger et al.	2006	J Neurosci	21	11	10	fMRI	pictures/words	picture/word	picture/word	Pos, Neg, Neu
Kensinger et al.	2007	J Cogn Neurosci	21	11	10	fMRI	objects	object	object	Pos, Neg, Neu
Kensinger et al.	2007	Neuropsychologia	19	9	10	fMRI	objects	object	object	Pos, Neg, Neu
Kuchinke et al.	2006	NeuroReport	20	8	12	fMRI	words	word	word	Pos, Neg, Neu
Liberzon et al.	2000	Neuropsychopharm	10	0	10	PET	pictures	picture	picture	Neg, Neu
Mackiewicz et al.	2006	PNAS	40	22	18	fMRI	pictures	picture	picture	Neg, Neu
Maratos et al.	2001	Neuropsychologia	12	5	7	fMRI	words in sentences	sentence	word	Pos, Neg, Neu
Medford et al.	2005	Psychiatry Research: NeuroImaging	12	12	0	fMRI	words in sentences	word	word	Neg, Neu

Mitchell et al.	2006	NeuroReport	19	9	10	fMRI	pictures	picture	picture	Neg, Neu
Sergerie et al.	2005	Neuroimage	18	9	9	fMRI	faces	face	face	Fear, Happy, Neu
Sergerie et al.	2006	J Cogn Neurosci								
Sergerie et al.	2007	Biol Psychiatry	19	10	9	fMRI	faces	face	face	Sad, Happy, Neu
Phillips et al.	1998	Psych Res: Neuroimaging	8	7	1	fMRI	faces	face	face	Neu
Sharot et al.	2004	Nat Neurosci	13	5	8	fMRI	pictures	picture	picture	Neg, Neu
Smith et al.	2004	NeuroImage	15	7	8	fMRI	objects on pictures	picture	object	Pos, Neg, Neu
Smith et al.	2005	Learn Mem	18	10	8	fMRI	objects on pictures	picture	object	Pos, Neg, Neu
Smith et al.	2006	Neuron	18	10	8	fMRI	objects on pictures	picture	object/picture	Neg, Neu
Somerville et al.	2006	J Cogn Neurosci	16	7	9	fMRI	faces/sentences	sentence	face/sentence	Pos, Neg, Neu
Sterpenich et al.	2006	J Neurosci	30	14	16	fMRI	faces/pictures	picture	faces	Neg, Neu
Strange et al.	2004	PNAS	24	12	12	fMRI	words	word	word	Neg, Neu
Tabert et al.	2001	Neuropsychologia	9	0	9	fMRI	words	word	word	Neg, Neu
Taylor et al.	1998	NeuroImage	8	0	8	PET	pictures	picture	picture	fear+disgust, Neu
Todorov et al.	2006	Neuropsychologia	11	8	3	fMRI	faces/sentences	sentence	face/sentence	Aggr, Disgust, Nice, Neu
Wittmann et al.	2008	Neuropsychologia	25	13	12	fMRI	pictures	picture	picture	Pos, Neg, Neu

Table 1. List of the neuroimaging studied of emotional memory

Furthermore, emotional stimuli are typically more unusual and complex (especially when using pictures or films) than neutral ones. This makes it difficult to isolate the specific effect of emotion on memory, independently of these other factors that are also likely to influence memory. It is important to note that some studies have attempted to take into account some of these issues in their design. For example, Hamann and colleagues (Hamann et al., 1999) contrasted the emotional pictures with two different nonemotional control conditions, namely a non arousing neutral one (e.g. chess players or plants) and another including pictures designed to attract interest and attention and to be highly memorable (e.g. a scene from a surrealistic film or an exotic parade). Interestingly, they did observed an enhancement of memory for the "nonemotional interesting" stimuli which, however, was amygdala independent. Finally, another potential confounding factor in interpreting the results from previous studies is their use of different contrasts which, in some cases (e.g., comparing hits only (Dolan *et al.*, 2000) or valence regardless of accuracy (Taylor *et al.*, 1998)), may not be the ideal ones for isolating the neural structures specifically associated with successful emotional memory.

In a previous study (Sergerie et al., 2006), which was part of my M.Sc. thesis, we sought to minimize some of these confounds by exploring the influence of emotional expression on memory for faces. Faces are powerful stimuli which convey crucial information used for social interactions, and which have been extensively employed to examine the neural correlates of emotional processing in healthy individuals (Pessoa *et al.*, 2005; Pessoa *et al.*, 2002; Posamentier & Abdi, 2003) as well as in psychiatric populations (Leppanen, 2006; Mandal *et al.*, 1998; Karin Mogg & Bradley, 1998). Critically, faces are less susceptible than other stimuli (e.g., pictures) to the potential confounding overlap between stimulus emotionality and complexity and/or unusualness

(Adolphs *et al.*, 2001; Ochsner, 2000; Talmi & Moscovitch, 2004). Furthermore, because of the nature of face stimuli, it is possible to objectively determine the degree of physical similarity among stimuli within and between emotional categories (e.g. with eigenfaces, see Chapter 3). Specifically, we conducted an event-related functional magnetic resonance imaging study of memory for faces with different emotional expressions, in which both encoding and recognition were scanned. In order to have a reasonable balance between high statistical power (sufficient number of events per condition) and an acceptable behavioural performance, we restricted the number of emotional negative categories to one, namely fear. We chose this emotion as there is a large body of literature highlighting the critical role of the amygdala in the detection of fear-related stimuli. In addition, we included faces depicting happy and, as control, neutral expressions. Behaviourally, we observed that fearful faces were better remembered than neutral ones. In contrast, there was no difference in memory accuracy between happy and neutral faces. We also found significant amygdala activation associated with both successful encoding and retrieval of fearful faces. Interestingly, a direct comparison between encoding and recognition revealed that the anterior aspect (possibly the lateral nucleus) of the right amygdala was activated during emotional memory formation, whereas the retrieval of those memories appeared to rely on a more dorso-caudal region (possibly the central nucleus) of the left amygdala. No sex differences were observed for any of the conditions.

Thus, these findings confirmed the critical role of the amygdala in both the formation and retrieval of emotional memories and also highlighted a hemispheric specialization for these two processes. Importantly, we observed that the enhancement of memory appeared to be valence specific, as it was not observed for happy expressions. Our choice of fear as the negative emotion was partly motivated by the fact that this

emotion, as mentioned above, has arguably been the most studied one, both in experimental animals and in humans. However, other negative emotions, such as sadness and anger, are also very important in our everyday life and in social interactions. Yet, very little is known about their potential influence on cognitive processes, in particular episodic memory. That is, the question of whether our results, both behavioural and neural, obtained for fearful faces also apply to other negative emotion remained unknown. In addition, the influence of these other negative emotions on psychiatric populations such as schizophrenia has been little explored.

1.6. Emotional memory in schizophrenia

Schizophrenia is a severe psychiatric disorder which is equally prevalent in men and women, affecting approximately 1% of the population. It is one of the top ten causes of disability across the world in people between 15 to 44 years old (4^{th} in developed countries) (Lopez & Murray, 1998). It usually begins in late adolescence or early adulthood, although the onset occurs generally earlier in men. Notably, the diagnostic is based only on clinical grounds, yet none of its clinical characteristics are pathognomonic, that is, none of the identified sign or symptoms can be used to unequivocally determine the presence or absence of the disorder (Bentall *et al.*, 1988). Schizophrenia symptoms are usually categorized into positive, negative and cognitive symptoms. Positive symptoms, which can be treated more successfully with antipsychotics include different types of delusions such as delusions of reference, paranoid delusions, hallucinations (for the most part hearing voices) and catatonic behaviour. Negative symptoms refer to the inability to experience pleasure (anhedonia), low energy, lack of interest in life, affective flattening, alogia (poverty of speech), inappropriate social skills, lack of ability to develop

friendship and social withdrawal. Cognitive symptoms that are sometimes classified as negative symptoms consist of abnormalities or impairments in attention, memory, and executive functions. According to The *Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)* (*Diagnostic and statistical manual of mental disorder, 4th ed.*, 1994) a diagnosis of schizophrenia can be established if there is a concomitant appearance of at least two of the following symptoms, each present for a significant portion of time during a 6-month period: delusions, hallucinations, disorganized speech, disorganized or catatonic behaviour and negative symptoms, such as affective flattening, alogia, or avolition (general lack of desire, motivation, and persistence).

The aetiology of schizophrenia is not entirely understood, but it has been found that abnormal dopamine and glutamate transmission, as well as structural and functional abnormalities in cerebral cortical and subcortical areas are likely to be involved in this disorder (Chua *et al.*, 2007; Kasai *et al.*, 2002; Pantelis *et al.*, 2003; Schultz & Andreasen, 1999; Staal *et al.*, 2000; Winterer & Weinberger, 2004).

1.6.1. Onset and course

The time course of schizophrenia can be divided into three major phases: the acute, the stabilization and stable phases, and is preceded by a premorbid stage (*Practice guideline for the treatment of patients with schizophrenia. 2nd ed.*, 2004). The premorbid state, which is characterized by non-specific cognitive, motor, and social impairments, is followed by an extended prodromal stage where cognitive, emotional, psychosocial, and sometimes mild psychotic symptoms that vary in severity and duration can be observed. Few individuals, however, do not go throughout the first phase and instead, acutely develop psychotic symptoms. The length of the prodromal state is extremely variable

from weeks to years, and precedes the first onset of typical symptoms of schizophrenia, especially in young people. During this phase, the individual does not fulfill all the criteria of the disorder. For example, a number of non-specific symptoms may be present, such as a general loss of interest, avoidance of social interactions or work, increase irritability and sensitivity, or odd beliefs or behaviours. The prognosis is typically worse when the prodromal phase is longer (Andreasen, 1995; Andreasen *et al.*, 2005). During the acute phase of the illness, psychotic symptoms such as delusions, odd behaviour and hallucinations are prominent and generally come with marked affect such as fear, distress, anxiety, or depression. It is during this phase that the vast majority of individuals ask for treatment, whether it is their first presentation or an exacerbation of their symptoms. With appropriate treatment (primarily medication) the active phase is usually brought under control and psychotic symptoms typically recede or at least are less intense and frequent. This is the stabilization phase. Nonetheless, symptoms can persist or even intensify during this phase and the frequency and timing of these relapses are unpredictable. Indeed, it appears that some conditions such as drug abuse and stressful situations can have an incidence on the likelihood of relapse (Linszen *et al.*, 1994). Later, patients move to the subsequent stable phase with reduced symptom severity and relative symptom stability. Psychotic symptoms usually respond well to treatment with antipsychotic medication, whereas the negative symptoms are less responsive to this type of medication and become gradually more prominent during the course of Schizophrenia. In general, most patients alternate between acute psychotic episodes and stable phases with full or partial remission (*Practice guideline for the treatment of patients with schizophrenia. 2nd ed.*, 2004).

1.6.2. Treatment and outcome

Pharmacotherapy constitutes the mainstay of treatment and is largely effective in treating acute psychosis and in preventing the frequency of relapse. Nonetheless, 5 to 25% of individuals are resistant to these first-line antipsychotic drugs (Christison *et al.*, 1991; Meltzer, 1992, 1997) or may experience unwanted and unpleasant side effects, reducing adherence to the treatment. Pharmacological treatment typically involves the use of antipsychotic drugs, all of which act as antagonists at central dopamine D2 receptors, although some have additional effects at other receptors such as the serotonergic ones. The oldest antipsychotic medications are known as conventional or typical antipsychotics (e.g. chlorpromazine and haldoperidol). While these first-generation schizophrenia medications effectively reduce the positive symptoms, they are now prescribed less frequently since they have been shown to often cause neurological side effects. For instance, long-term adherence to typical antipsychotics medication increases the risk of developing tardive dyskinesia. Today, atypical antipsychotic drugs are available (e.g. clozapine and risperidone). In addition to acting on dopamine, they are believed to also affect other neurotransmitters such as serotonin. One of their advantages is that they produce fewer extrapyramidal side effects than the typical antipsychotics . In addition, it has been proposed that the atypical antipsychotics are more efficient in reducing the negative symptoms, which are notoriously difficult to treat and show little response to the older antipsychotic medications (Meltzer, 1993; Moller, 2005a, 2005b). Finally, some of the newer atypical antipsychotics have been suggested to also improve memory and cognitive functioning (Leucht *et al.*, 2003). Furthermore, the combination of antipsychotic medication with anti-depressant or anti-anxiety medications helps to prevent suicide and minimizes re-hospitalization.

While medication is almost always a necessary component of schizophrenia treatment, it does not offer a complete solution. People with schizophrenia also need concomitant psycho-cognitive and -social therapies treatments, in combination with medication to help them cope with their illness and improve their quality of life. Indeed, people suffering from schizophrenia who adhere to this type of treatment are more likely to take their medication regularly and avoid relapse and hospitalization. An example of these treatments is cognitive-behavioral therapy (CBT), which is based on modifying cognitions, assumptions, beliefs and behaviors, and aims to improve self-esteem, social/emotional functioning and insight, as well as to reduce symptoms. Another example is remediation therapy, which focuses on the remediation of the neurocognitive deficits. Other examples include family and rehabilitation therapies.

In term of prognosis, a clinical study (Robinson *et al.*, 2004) using strict recovery criteria from the University of California at Los Angeles –namely 1) concurrent remission of positive and negative symptoms and 2) adequate social/vocational functioning continuously for two years– found a recovery rate of 14% within the first five years (Liberman RP *et al.*, 2002). Moreover, several factors have been proposed to be associated with a better prognosis: acute (vs. more subtle) onset of symptoms, older age of first episode, being female, predominance of positive symptoms, mood symptoms and good premorbid adjustment ((L. Davidson & McGlashan, 1997; Lieberman *et al.*, 1996). Most studies, however, are correlational and it cannot be assumed that there is a clear cause-to-effect relationship.

Finally, it is worth mentioning that there is now a consensus in the field about the operational criteria for symptomatic and social/functional remission (Andreasen *et al.*,

2005). Specific items reflecting the five dimensions of the DSM-IV (delusion, hallucinations, disorganized speech, disorganized or catatonic behaviour and negative symptoms) have to be scored as mild or less simultaneously on all items. For example, within the Scale for Assessment of Positive Symptoms (SAPS) and the Scale for Assessment of Negative Symptoms (SANS) those items are delusion, hallucinations, positive formal thought disorder, bizarre behaviour, affective flattening, avolition/apathy, anhedonia/asociality and alogia (Andreasen NC, 1983, 1984). In addition, to achieve remission, this reduced symptom severity has to persist for at least 6 months. It is important to note that individuals may remain in remission while experiencing minor changes in symptoms, in the absence of appreciable effects on daily function or subjective well-being (Andreasen et al., 2005).

1.6.3. Emotional processing in schizophrenia: from perception to memory

As mentioned above, emotional abnormalities are among the most striking features in schizophrenia. Indeed, individuals with schizophrenia appear to have impaired ability to properly express emotions and perceive the emotional expressions in others, often resulting in difficulties in social communication and adjustment. Individuals with schizophrenia have been found to frequently fail to contextualize and assign appropriate emotional significance to events or sensory stimuli encountered in different situations (Bentall & Slade, 1985). In particular, these incorrect associations can affect their motivation and regulation of emotional states, as well as the appropriate selection of their future behavioral responses based on their previous experience. Thus, the deficits observed in schizophrenia in terms of emotional perception and episodic memory could partly explain the abnormal patterns of emotional memory sometimes reported in this

group. Alternatively (or in addition), a specific impairment in the integration of emotional information into memory could exist. Below, I briefly review the main findings related to these processes in order to provide a better picture of the state of knowledge and, critically, on the inconsistencies that exist in the literature.

1.6.3.1. Emotional perception

There is a significant body of literature showing evidence of impairments in perception of facial emotional expressions, especially negative ones, in schizophrenia (Edwards *et al.*, 2002; C. G. Kohler & Martin, 2006; Mandal et al., 1998). Specifically, schizophrenia patients show deficits in facial affect discrimination (Heimberg *et al.*, 1992; C. G. Kohler & Martin, 2006; Salem *et al.*, 1996), facial affect identification or matching (Borod *et al.*, 1993; Kerr & Neale, 1993; Martin *et al.*, 2005; Salem *et al.*, 1996) and facial affect labeling (Edwards *et al.*, 2001; Feinberg *et al.*, 1986; Walker *et al.*, 1984). However, the fact that several studies have reported deficits in face perception in general (not specific to the emotional component) complicates the interpretation of the previous findings (Edwards et al., 2002; Hooker & Park, 2002; C. G. Kohler *et al.*, 2000; Martin et al., 2005; Salem et al., 1996). Still, other studies have observed discrimination impairments specific to emotional expressions, as compared to other features such as color, age and neutral face discrimination (Habel *et al.*, 2000; Mandal et al., 1998). These deficits in emotional perception have been associated with reduced activity in the amygdala in schizophrenia patients compared to healthy controls. In fact, this decreased amygdala response has been observed even when the emotional evaluation of the stimuli was similar for both groups (Aleman & Kahn, 2005).

1.6.3.2. Episodic memory

Deficits in episodic memory are another critical feature of schizophrenia (Achim & Lepage, 2005; Aleman *et al.*, 1999; Danion *et al.*, 1999; Gold *et al.*, 1992; Heinrichs & Zakzanis, 1998; Huron *et al.*, 1995). Importantly, memory deficits appear to be a primary impairment which cannot be fully explained as a consequence of the core dysfunction of executive functions (e.g., attention, planning, sequencing, decision making, initiation and inhibition), usually associated with the prefrontal cortex (Aleman et al., 1999). The majority of studies report larger memory deficits in free recall of an event or learned material than in recognition (Aleman et al., 1999; Fossati *et al.*, 1999; Gold et al., 1992; Huron et al., 1995; Mathews & Barch, 2004; Sullivan *et al.*, 1997). For example, in a meta-analysis of memory deficits in schizophrenia, Aleman and colleagues (Aleman et al., 1999) reported that impairments are more frequently observed in free recall (large composite effect size) than in cued recall or recognition (significant effect size, although less marked), even when taking into account the level of difficulty across conditions. This could be partly explained by the fact that whereas recall requires a complete conscious recollection (including the spatio-temporal context associated to the learning episode), both conscious recollection and familiarity can contribute to recognition (Yonelinas, 2001). Consistent with this hypothesis, recognition memory appears to be more impaired when patients have to rely on conscious recollection rather than on a sense of familiarity (Danion et al., 1999; Huron et al., 1995; Rushe *et al.*, 1999; Thoma *et al.*, 2006; Weiss *et al.*, 2003). In their meta-analysis of neuroimaging studies of episodic memory in schizophrenia, Achim and Lepage (Achim & Lepage, 2005) performed a clustering analysis on peak of activations and observed, for schizophrenia patients, a deactivation of the hippocampus, a region that has been shown to be involved in conscious recollection,

when comparing high vs. low retrieval conditions. In addition, they also reported a higher activation of the parahippocampal gyrus, a region previously implicated in familiarity assessment. The authors concluded that individuals with schizophrenia may have impairments in conscious recollection and thus rely more on a sense of familiarity to perform memory tasks. The use of a remember/know paradigm (Endel. Tulving, 1985) supports this conclusion, as patients exhibit normal memory associated with familiarity (know responses), but show a selective deficit for memory retrieval that relies on conscious recollection (remember responses) (Danion *et al.*, 2003; Danion et al., 1999; Huron & Danion, 2002; Huron et al., 1995; Tendolkar *et al.*, 2002).

In addition to the differences in activation in the medial temporal lobe between schizophrenia and control groups, abnormal activation patterns have been reported within the prefrontal cortex (Achim & Lepage, 2005; Boyer *et al.*, 2007). In fact, it has been suggested that a dysfunction in the functional and/or structural connectivity between hippocampal regions and the dorsolateral prefrontal cortex may underlie some of the observed memory deficits in this patient population (Ragland *et al.*, 2004).

Although the above mentioned studies primarily focused on memory accuracy, there is also a growing field of research investigating memory errors and response bias in individuals with schizophrenia. For instance, it has been shown that hallucinations significantly correlated with response bias, i.e. a tendency to falsely recognize as old an item never seen before (new) or to report a stimulus as present when it is not the case (Bentall & Slade, 1985). Consistent with this, Brebion and colleagues (Brebion *et al.*, 2000; Brebion *et al.*, 2005; Brebion *et al.*, 1998) used tasks consisting of learning lists of words and observed a significant correlation between hallucinations and false alarms rates for new words (lures). Although this group reported no significant relationship between

delusion scores and response bias, Ragland and colleagues (Ragland *et al.*, 2003) did find a significant correlation between this symptom and the tendency to have a more liberal bias in a task requiring patients to perform deep encoding.

Negative symptoms appear to have the opposite effect on the pattern of memory errors: a significant correlation was observed between certain negative symptoms such as alogia, affective flattening and anhedonia, as well as lack of spontaneity and emotional withdrawal, and a propensity towards a more conservative response bias in source memory tasks (Brebion et al., 2000; Brebion *et al.*, 1999). In another experiment using an incidental learning task of words and pictures, Brébion and colleagues (Brebion et al., 2005) reported a relationship between anhedonia and a more conservative response bias, but only in the delayed recognition of words (a trend was also observed for blunted affect). As in the case for positive symptoms, however, inconsistent results have been obtained: Ragland et al. (Ragland et al., 2003) failed to find a correlation between response bias and any of the negative symptoms.

In summary, although there is ample evidence for memory deficits in schizophrenia, this impairment appears to critically depend on how and when memory is measured. In particular, differences emerge when comparing memory retrieval based on recollection and familiarity, or when the response criterion (conservative or liberal) is taken into account.

1.6.3.3. Emotional memory

Despite the important separate literatures on emotion and memory in schizophrenia, there has been relatively little done regarding the influence of emotion on memory, and so far the results obtained have been largely inconsistent. For example, in a study

investigating both recall and recognition of emotional memories for verbal material, Matthews and Barch (Mathews & Barch, 2004) observed that for recall, despite an overall lower performance for the schizophrenia group, the effect of arousal and valence was similar between patients and controls, both remembering better negative than positive words. For the recognition test a different pattern emerged, as although no significant group differences in general performance was observed, there was an interaction between valence and group, mainly driven by the better discrimination index of individuals with schizophrenia for negative than positive words (not present in the control group). In contrast, two studies using the remember/know paradigm with words (Danion et al., 2003; Neumann *et al.*, 2007b) found that the influence of emotional valence on memory was the same for patients and controls.

Conflicting results have also been obtained in recognition memory for emotional pictures. For example, Neumann and colleagues (Neumann *et al.*, 2007a) observed that patients exhibited better recognition for positive stimuli than negative ones, whereas the opposite pattern was found in healthy subjects. In contrast, in a 24h delay recognition task, Herbener et al. (Herbener *et al.*, 2007) reported that patients failed to show an enhancement of memory for positive material, with no difference between groups for negative pictures. Interestingly, similar response biases for emotional stimuli were reported in both groups, as indicated by the higher false positive rates for both positive and negative pictures compared to neutral ones (Herbener et al., 2007). Finally, in a 3-week delay recognition test, Hall and coworkers (Hall *et al.*, 2007) observed that control subjects showed an enhancement of memory for emotional images, which was absent in the schizophrenia group. Immediate and delayed recall tests, however, revealed that schizophrenia patients were only impaired in the recall of the most negative stimuli.

Interestingly, in all these studies, no differences between the control and schizophrenia groups were reported in the emotional rating of the stimuli.

1.7. Methodological considerations

1.7.1. Memory

Memory is a cognitive function composed of separate interacting systems that allows us to acquire and store information for subsequent use. The dissociations in memory deficits following bilateral medial temporal resection in the famous patient HM and other amnesic individuals led to a classification of memory types based on their dependence on medial temporal integrity. These studies, together with those conducted on experimental animals, have permitted researchers to identify the specific contributions of different medial temporal lobe regions to memory, such as the hippocampus and adjacent cortical areas that are anatomically related to the it, namely the entorhinal, perirhinal and parahippocampal cortices (Eichenbaum *et al.*, 1994; Otto *et al.*, 1991; Squire *et al.*, 2004). For example, long-term memory can be distinguished from short-term memory, such as digit-span, which is intact following medial temporal damage (Shallice & Warrington, 1970). The classical view on the organization of long-term memory systems and the associated brain structures is presented in Figure 2. The major distinction in terms of long-term memory is usually done between declarative (or explicit) memory and several nondeclarative (or implicit), nonconscious forms of memory (Cohen & Squire, 1980; Squire et al., 2004; Squire & Zola, 1996).

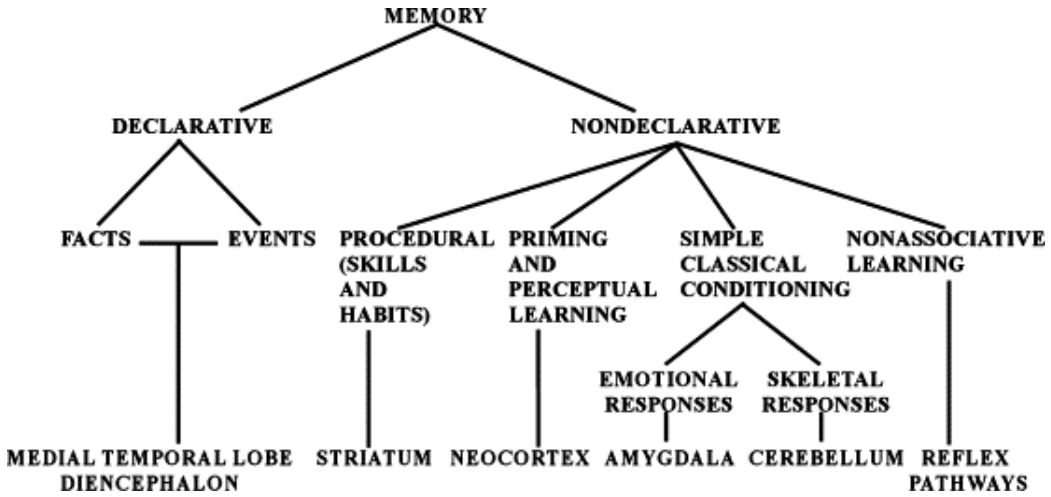

Figure 2. A taxonomy of long-term memory systems together with specific brain structures involved in each system. *Adapted from: (Squire & Knowlton, 1994)*

Briefly, nondeclarative memory is neither true nor false. In the case of nondeclarative memory, performance changes as a result of experience, which justifies the term memory, but performance changes without providing conscious access to any prior episodes (Schacter & Tulving, 1994). This type of memory is fully intact in the presence of hippocampal damage (Squire *et al.*, 1993). An example of nondeclarative memory is classical conditioning. Declarative memory, on the other hand, is dependent on the medial temporal lobes and allows to consciously recollect episodes and facts (Squire, 1992). Declarative memory is propositional, being either true or false. It is fast, not always reliable (i.e. forgetting and retrieval failure can occur), and flexible, in the sense that declarative memories are accessible to multiple response systems. Declarative memory can be further subdivided into episodic memory, which is the memory for events that compose a unique personal experience, and semantic memory, corresponding to factual information that is independent of the specific episodes in which that information was acquired (E. Tulving, 1972, 1983). These two components of declarative memory can be shown to dissociate if one tries to remember the episode that led to the learning of a

particular fact. We know that Paris is the capital of France but are unlikely to remember the episode that led to the learning of this fact.

Three successive stages of processing can be defined in episodic memory. The first one is encoding, which consists in the acquisition of information and the formation of a neural representation of this information (the mnesic trace). The second stage refers to storage and permits the maintenance and consolidation of memory traces over time. Finally, retrieval is the process by which we recuperate these stored memory traces. As we will see later, functional neuroimaging constitutes a powerful technique to investigate the neuroanatomical correlates of encoding and retrieval separately, because of the temporal separation between them. Storage is however, not as easily assessed by neuroimaging techniques because it appears to be temporally distributed and not stimulus-locked (Buckner & Koutstaal, 1998).

1.7.2. Measuring memory

In humans, tests of episodic memory can be broadly divided, based on the presence and nature of the cues or information provided, into free recall and recognition. Both consist of a learning or encoding phase during which some items (e.g. words, images, pictures) are presented. The encoding can be intentional (subjects may be explicitly instructed to memorize the stimuli) or incidental (subjects are given a task unrelated to memory, such as judging the gender of the faces to encode). After a variable delay, performance for memory is assessed. In recall tests, the subject is required to produce, with (cued-recall) or without (free-recall) the help of cues, the target stimuli encountered during the encoding phase. A typical target event is the presentation of a list of words, pictures, or sentences, although it could be an event in the subject's personal history

(autobiographical memory). When cues are presented at test, they might form part of the stimuli presented during encoding (e.g. ro__ for the item rose), or they might be related in some way to the target item (e.g. semantically (flower) or phonemically (nose). Some limitations are inherent to recall tests, as performance in this task also depends on a variety of metacognitive abilities and executive processes that may prove to be confounding factors (e.g. more extensive use of encoding or retrieval strategies). In a recognition test, the subject is provided with targets intermixed with nontargets (lures) and required to discriminate them. Recognition does not require the self-generation of targets, but relies on the capacity to distinguish targets (studied or old items) and nontargets (non studied or new items). This leads to four possible outcomes as previously presented items may be correctly identified as old (hit) or incorrectly categorized as new (miss), whereas lures can be properly classified as new (correct rejection) or incorrectly as old (false alarms) .

Although memory performance can be intuitively measured as the percentage of correctly remembered items (old ones), there is an important limitation to this approach. For instance, according to this measure, if a subject responds ‘‘old’’ to all trials, his memory performance would be considered perfect (100 % “olds”), despite the fact that all the lures had been incorrectly classified as old. The discrimination index Pr, derived from the Two-High Threshold Model (Snodgrass & Corwin, 1988) overcomes this confound by providing an unbiased measure of memory performance. The Pr is obtained by subtracting the false alarms rate from the hit one. Therefore, if a subject always responds old, he maximizes the number of hits but at the expense of increasing the number of false alarms, so that the corresponding Pr value is zero. Another aspect of memory performance that is evaluated in the Two-High Threshold model is the response bias (Br),

which represents an index of the overall tendency of an individual to respond "old" or "new" regardless of accuracy (see Chapter 3). Positive values of Br indicate a tendency to say "old" (i.e., a familiarity bias), whereas the negative side of the scale represents a novelty bias (that is, a propensity to say "new"). Importantly, the Pr and Br measures are independent (Snodgrass & Corwin, 1988).

There are two main variants of the standard recognition test: the old/new recognition test and the forced-choice recognition test. In the old/new test, subjects are presented with one item at a time and are asked to judge whether the item is old or new. In the forced-choice test, several items (at least one old and one new) are shown simultaneously and subjects are instructed to point to the old item(s) and ignore the new item(s).

Another type of recognition memory test, the "remember–know" procedure, was introduced by Tulving in 1985 to investigate the awareness states accompanying memory retrieval (Endel. Tulving, 1985). Participants in this procedure indicate with a remember (R) judgment those stimuli that evoke recollection of a specific episode or contextual details, in which the stimuli were previously experienced. That is, R judgments typically entail memory for the spatiotemporal context in which stimuli occurred or the mental associations triggered by their occurrence ("source"memory) (Johnson *et al.*, 1993). On the other hand, K judgments typically rely on a sense of familiarity, in the absence confirmatory contextual information. In terms of processes, R responses are though to be related to recollection-based judgment whereas the K ones are believed to reflect the familiarity-based judgments (Endel. Tulving, 1985; Yonelinas, 2001). Another approach employed to explore familiarity- vs. recollection-based memory is the use of an old/new

memory test together with a confidence rating (low to high) assigned to each judgment (Fleck *et al.*, 2006; Rotello *et al.*, 2006).

1.7.3. Emotion

Much like memory, the term emotion does not refer to a unitary process. Instead, it represents a wide range of mental operations, which may or may not engage similar neural mechanisms. In fact, there is still no consensus on how many emotions there are or how they can be measured. A dominant view posits the existence of a few so-called basic emotions, including anger, fear, sadness, happiness and disgust (and sometimes a few more or less) (Ekman, 1992; Panksepp, 1998). According to this model, other more complex emotions, such as guilt, jealousy and pride, arise from a combination of the primary emotions. Other researchers, however, have proposed these basic emotions are simply specific points in a two-dimensional emotion space, with valence and arousal (or intensity) as the main orthogonal axes (Posner *et al.*, 2005; J. Russell, 1980). Variations on this circumplex model of emotion have been proposed, in terms of the relevant dimensions necessary to fully characterize the emotional space. For instance, a model has recently been proposed with four dimensions, namely evaluation-pleasantness, potency-control, activation-arousal, and unpredictability (Fontaine *et al.*, 2007; Scherer & Ellgring, 2007).

Regardless of which model one subscribes to, the issue of valence vs. arousal is an important one. Indeed, a growing number of studies suggest that the effects of emotion on cognition, including memory, may be more related to arousal than valence (Hamann et al., 1999; Kensinger, 2004; Kensinger & Corkin, 2004). Unfortunately, although these two

dimensions can be separated when testing several emotions, they are highly correlated for each specific emotion, as I will show later.

1.7.4. Measuring emotion

Most studies of the neurobiology of human emotion can be broadly divided into two categories: those studying the feeling associated with a particular emotional state and those focusing on the effects of stimuli with emotional value on the brain and/or on other cognitive processes, such as perception, attention, awareness, decision making and memory.

Although the former appears to be more closely related to what is commonly thought of as emotion, it is also more difficult to study, as it relates to subjective internal processes of the participant, which may be difficult to define and/or categorize. Indeed, several studies have shown that while people are very good at assigning emotional adjectives to given situations, they have difficulty in defining the emotions themselves (Fehr & Russell, 1984). Nonetheless, objective measures can also be used, such as physiological responses (e.g., heart rate, skin conductance). A typical paradigm used to study emotional states is mood induction. In this procedure, participants are put in a particular emotional state (e.g., sadness) through some procedure, usually involving the presentation of stimuli congruent with the target emotion (e.g., sad faces, music, films or autobiographical memory). Then, by comparing different emotional states (e.g., sad vs. happy), it is possible to isolate the neural structure involved in a particular emotional or mood state.

The second approach, largely inspired by the animal literature, places less emphasis on the actual subjective feelings elicited by the stimulus or procedure and, instead, seeks

to explore the responses --behavioral, neural or physiological-- that they elicit. Thus, in these experiments stimuli with known emotional value (e.g., pictures, faces, etc) are presented, often in rapid succession and alternating different emotions, specifically to prevent the induction of a particular emotional state in the participants. This category can be further subdivided into those studies which seek to delineate the neural structures involved in the perception of emotional stimuli and those trying to understand the effects of this material on cognitive processes. As mentioned below, the former usually involves comparing two conditions or stimulus types, such emotional vs. neutral or, in some cases contrasts between different emotions or between emotional stimuli and a low-level control condition (e.g., scrambled image, fixation cross, etc). In the case of the influence of emotion on cognition, these comparisons are conducted taking into account the cognitive process of interest, typically by dividing the stimuli as a function of behavioral performance (e.g., accuracy, memory success, etc) or correlating brain activity with overall performance in these behavioral measures. Additionally, participants are often asked to confirm the a priori assignment of stimuli to an emotional category by performing emotional ratings (categorical or through a Likert-type or continuous scale). These measures are also useful when studying individual differences or clinical populations.

1.7.5. Functional Magnetic Resonance Imaging

1.7.5.1. Measuring brain activity

Positron Emission Tomography (PET) and Functional Magnetic Resonance Imaging (fMRI) constitute the two most used imaging techniques based on the hemodynamic

properties of the brain. Both techniques indirectly explore quantitative changes in neural activity by measuring fluctuations in regional cerebral blood flow (Raichle, 1998; Roland, 1993), which are believed to reflect neural activity (Logothetis & Wandell, 2004; Raichle, 1998). However, whereas PET employs an exogenous radiolabelled substance injected into the bloodstream (often O15 in water) to produce a functional image of the brain, the most common form of fMRI relies on endogenous contrast mechanisms to produce a measure of local changes of levels of blood oxygenation, namely blood oxygenation level dependent signal (BOLD). Briefly, this technique relies on the different properties of oxy- and deoxy-hemoglobin in the presence of an external magnetic field: whereas the former is diamagnetic, and thus does not interact with the field, deoxyhemoglobin is paramagnetic, and therefore its presence results in small local changes in the magnetic field, leading to changes in the overall signal being measured. Increases in neural activity in a specific area of brain tissue are thought to yield a parallel raise in oxyhemoglobin level beyond the actual oxygen demands. This, in turn, leads to a relative decrease in local deoxyhemoglobin concentration, producing an increase in the BOLD signal detected with fMRI.

There are some limitations to these two techniques related to spatial and temporal resolution, particularly in PET. The spatial resolution of PET and fMRI is on the order of a few millimetres and therefore can only provide information related to relatively large clusters of neurons, whose responses are averaged together. In fMRI, temporal resolution is limited by the slow dynamics of the hemodynamic response. Following a stimulus presentation, and after a delay of about one second, a hemodynamic response begins to appear, reaching its peak about 4-6 seconds later, and taking up to 15 seconds to return to baseline.

1.7.5.2. Neurocognitive activation paradigms

The aim of a typical neurocognitive imaging study is to identify brain regions involved in a specific cognitive task. The most common way to accomplish this is through the use of a subtractive design, which relies on the principle of pure insertion (Donders, 1868/1969; Friston *et al.*, 1999). In this case, a minimum of two conditions have to be scanned, an experimental task, which is the task of interest, and a control task that usually involves similar perceptual processing and motor responses than the experimental task, but not the same cognitive process of interest. The differences in neural activity induced by the two tasks are reflected by the observed variation in blood flow or oxygenation in the different regions of the brain. Hence, the neural activity associated to a specific cognitive process is always expressed in relative terms (particularly in the case of fMRI). That is, the activity measured during a given experimental task is always expressed relative to neural activity measured during the reference task (Cabeza & Nyberg, 2000; Friston et al., 1999). A related approach is the parametric design, where changes in signal are measured as a function of a continuous external variable, either trial-based (e.g., reaction time) or subject-based (e.g., behavioural performance).

In fMRI, there are essentially two different experimental designs that can be used, namely block- and event-related designs. In a block design, each experimental condition lasts for about 30-60 seconds. This measurement of the integrated hemodynamic (and thus neural) activity over an extended period of time results in high statistical power for the analyses. On the other hand, this approach contains little or no information regarding the time course of the responses and thus has a poor temporal resolution. In addition, it can introduce several confounding factors related to stimulus habituation (critical in the case of the amygdala, as discussed below) and expectation, among others. In contrast, the

event-related design (not possible with PET), allows for the presentation of different conditions or stimuli in a (pseudo-)random order and the analysis of the response to each presentation separately. Two significant advantages of event-related designs are 1) the randomisation of the order of presentation of stimuli minimizes potential confounds such as the subject's cognitive set and the systematic influence of previous trials that could affect the subject's response and 2) individual trials can be categorised or parametrized *a posteriori* according to the subject's own behavioral performance. This approach is therefore particularly well-suited for memory tasks, where remembered (correct) and forgotten (incorrect) stimuli —which naturally cannot occur in blocks— can be directly compared during the encoding or recognition phases. This then allows for the identification of areas specifically involved in successful memory or memory response bias without the potential confounds related to differences in stimulus perceptual characteristics, task demands, or attentional load between different conditions (Buckner *et al.*, 1999). Hence, event-related was the approach adopted in the experiments reported in this thesis.

1.7.5.3. Functional image analysis

There are different ways of analyzing fMRI data (AFNI (Cox, 1996), fmristat (Worsley *et al.*, 2002), SPM (Friston *et al.*, 1995), FSL (Smith *et al.*, 2004)). Here, we focus on the standard "SPM approach", which is the one employed in the analysis of the data presented in this thesis. The first step in the analysis of fMRI data is the slice timing correction, which corrects for differences in acquisition time between slices during sequential imaging (particularly important for event-related designs). Essentially, the correction shifts the phase of the time-courses of the voxels (unit of volume composing

the three-dimensional brain images) within each slice to provide data as if each slice would have been acquired at exactly the same time. The next step is the spatial realignment, involving a series of spatial transformations of the images that reduce artifactual variance components in each voxel time series due to subject's movement during scanning. After realignment, a normalization procedure is applied. This can be divided into two steps: 1) the determination of the best affine transformation (from an image to a template) including twelve parameters (translations, rotations, zooms & shears); 2) a nonlinear estimation of local deformations (Friston et al., 1995). These parameters are then used to transform the functional images into a standard anatomical space. This permits the averaging of data across subjects and to report data within a standardised reference coordinate system (the Tailarach space). Subsequently, a spatial smoothing with a Gaussian kernel is applied. Throughout this procedure, a new value for each data point is generated from the Gaussian curve that is a function of the original value at that point and the surrounding data points. This will ultimately increase the signal to noise ratio, at the cost of a reduction in spatial resolution. Finally, a high pass filter is applied to all time series in order to remove low-frequency temporal drifts. Following this preprocessing, the data are ready for statistical analysis. In the absence of prior information or a priory hypothesis related to the physical location of a particular function, the experimentally-induced effects on each voxel need to be tested independently. To do so, a statistical model is needed to draw inferences about changes in regional brain activity between different experimental conditions (Friston et al., 1995). Therefore, trial-related activity for each participant is assessed by convolving a vector of trial onsets with a canonical hemodynamic response function (Friston *et al.*, 1998). A general linear model (GLM) is then specified for each participant to model the effects of

interest (event types such as facial expression or recognition memory) and, optionally, the six covariates capturing residual motion-related artefacts. After constructing contrast maps for each participant by creating linear contrasts of the parameter estimates of interest, a random effects analysis is performed to assess group effects. In the case of single group studies, one sample t-tests for main effects and interactions, as well as regression for correlations with experimental variables (e.g. performance, rating) can be performed for all the voxels. Finally, a statistical criterion (threshold) is applied to identify significant differences in activation between two conditions across all subjects. Between-groups comparisons can also be performed to investigate differences in brain activation between, for example, a clinical population and a control group of healthy individuals. These between-groups contrasts are achieved through two-sample t-tests on the within-subject contrasts. Usually, these statistical brain parametric maps reflect the group by task interactions.

1.8. Description of the studies

Before directly investigating the effects of emotion on memory, and given the controversy in terms of the specific role of the amygdala in emotional processing, I decided to perform a review of the existing neuroimaging literature to clarify this issue. In particular, I sought to determine the involvement of the amygdala in the perception of different visual emotional stimuli and how it could be affected by experimental factors such as sensory modality, stimulus type, subjects' sex, etc. In doing so, I hoped to be able to test the different models of amygdala lateralization proposed in the literature, described above. One particularly well-suited approach to do this in a quantitative fashion is through the use of meta-analytic techniques. Results from meta-analyses can be then used to extract the commonalities between studies, once the study-specific differences have been taken into account, as well as highlight the variables that may account for a significant part of the inter-study variability observed. In addition, results from meta-analyses can be used to refine working models of emotion and generate new hypotheses. In particular, I decided to perform a more quantitative meta-analysis that would take into account not only the presence or absence of an activation, but also its magnitude (i.e., effect size). This should allow me to directly, and statistically, test the potential influence of various experimental factors on these activations. I have thus conducted this type of meta-analysis of neuroimaging studies of emotional processing (**Study 1, Chapter 2**), with particular emphasis on the amygdala and the different models proposed in terms of its lateralization. With this information in hand, I was then in a better position to investigate the influence of other emotions, besides fear, on memory.

I then set out to examine the influence of other negative emotions on memory. Because of the constraints in terms of the number of events necessary to obtain sufficient

statistical power in an event-related fMRI experiment, on the one hand, and the time constraints associated with a standard scanning session, on the other, I conducted a neuroimaging study similar to the original one (see the above emotional memory section) (Sergerie et al., 2006), but replacing fear by another negative facial expression. Such an approach also had the added advantage of allowing me to compare the findings from both studies. For this study (**Study 2, Chapter 3**), I chose sadness as the negative emotion, because although it has a high negative valence similar to that of fear, it is, in contrast to the latter, a low arousal emotion (see below Chapter 3) (J. A. Russell, 2003). This is of particular interest, as it has been argued that the enhancement of memory for emotional material is related to arousal rather than valence (Kensinger, 2004; Kensinger & Corkin, 2004). In addition, sad and happy expressions are basic emotions that are encountered in everyday life, have powerful social value and are easily decoded, even in clinical groups (Heimberg *et al.*, 1992; Christian G. Kohler *et al.*, 2003; Leppanen, 2006; K. Mogg *et al.*, 2000).

The study of emotional memory has important implications not only for our understanding of the workings of the healthy emotional brain, but it can also have clinical relevance. Indeed, several psychiatric disorders are associated with deficits in emotional perception and memory. In particular, schizophrenia is characterized, as much by the more thoroughly studied cognitive deficits (e.g., memory, executive functions, attention, etc) as it is by a variety of emotional and social disturbances. Critically, these impairments have a substantial negative impact in the patients' quality of life. Thus, it becomes crucial to gain a better understanding of the emotional deficits associated with this disorder. In particular, studying the influence of emotional expressions, particularly those with a social relevance, on perception and memory can contribute to a better

understanding of the aetiology of some of the symptoms associated with this disorder. I thus conducted an fMRI study of the influence of facial expressions memory in this population (**Study 3, Chapter 4**). Specifically, I used the same paradigm as in healthy controls in order to directly compare the two groups both at the behavioral and neural levels.

Finally, the last study **(Study 4, Chapter 5)** is a reanalysis of my M.Sc. fearful memory study where the sex of the participants as well as that of the face stimuli was taken into account in order to directly explore possible sex differences in emotional memory, particularly in terms of previously proposed models of amygdala lateralization.

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Chapter 2

The role of the amygdala in emotional processing: A quantitative meta-analysis of functional neuroimaging studies

Abstract

Functional neuroimaging studies have provided strong support for a critical role of the amygdala in emotional processing. However, several controversies remain in terms of whether different factors —such as sex, valence and stimulus type— have an effect on the magnitude and lateralization of amygdala responses. To address these issues, we conducted a meta-analysis of functional neuroimaging studies of visual emotional perception that reported amygdala activation. Critically, unlike previous neuroimaging meta-analyses, we took into account the magnitude (effect size) and reliability (variance) associated with each of the activations. Our results confirm that the amygdala responds to both positive and negative stimuli, with a preference for faces depicting emotional expressions. We did not find evidence for amygdala lateralization as a function of sex or valence. Instead, our findings provide strong support for a functional dissociation between left and right amygdala in terms of temporal dynamics. Taken together, results from this meta-analysis shed new light on several of the models proposed in the literature regarding the neural basis of emotional processing.

Keywords: amygdala; functional magnetic resonance imaging; positron emission tomography; emotion; fear; happy; sad; anger; disgust; facial expressions; meta-analysis; effect size

"Au commencement était l'émotion"
Louis-Ferdinand Destouches, dit Céline

2.1. INTRODUCTION

The field of Human Affective Neuroscience has greatly benefited from the use of functional neuroimaging techniques. In particular, results from several hundred studies in healthy participants have helped delineate the neural circuitry involved in emotional processing, as well as the interactions between emotion and other cognitive processes, such as attention, memory and decision-making. Overall, these studies have confirmed the critical role of the amygdala in emotion, in agreement with findings from research on experimental animals (LeDoux, 2000) and neurological patients (Adolphs & Spezio, 2006). Furthermore, these studies have allowed researchers to test and refine existing models of amygdala function, and to develop new ones.

For instance, a widely held view is that the amygdala is a key component of a neural system specialized for the rapid and automatic evaluation of stimuli that signal potential threat or danger in the immediate environment (Adolphs et al., 1999). However, other researchers have proposed a more general role of this structure in the processing of signals of distress (Blair et al., 1999), including other negative emotions such as sadness, or in the processing of signals that indicate potentially important environmental information that must be disambiguated (Whalen et al., 2001) (e.g., facial expressions of surprise (Kim et al., 2003)). Finally, a recent model postulates that the human amygdala acts as a "relevance detector," involved in the processing of biologically relevant stimuli, regardless of their valence (Sander et al., 2003).

In addition, several theories have been proposed regarding possible hemispheric differences in emotion, thus raising the possibility of a differential involvement of the left

and right amygdala in emotional processing. One of the oldest models of emotion lateralization, first proposed by Luys in 1881, posits that the right hemisphere is more involved than the left in emotional processing in general, including both positive and negative emotions (Sackeim & Gur, 1978; Schwartz et al., 1975). Another one suggests a hemispheric dissociation based on emotional valence, namely preferential processing of positive and negative information by the left and right hemispheres, respectively (e.g., Sackeim et al., 1982). This lateralization theory, especially in relation to the role of prefrontal cortex, has been refined by Davidson and colleagues, who proposed a hemispheric differentiation in terms of approach and withdrawal behaviour, rather than valence (Davidson, 1984; Davidson et al., 1990; Sackeim et al., 1982)

More specific to the amygdala, a lateralization model has been proposed based on the established hemispheric differences associated with language. Namely, left amygdala would be involved in the processing of semantic material (e.g., scripts, sentences or words), whereas non-semantic information (e.g., faces, pictures) would engage the right amygdala (Markowitsch, 1998; Phelps et al., 2001).

Finally, more recent models have been proposed in terms of the temporal dynamics of the amygdala in response to emotional stimuli, based on its differential patterns of habituation (Phillips et al., 2001; Whalen et al., 1998; Wright et al., 2001). For instance, Wright and colleagues (Wright et al., 2003) have proposed that whereas the right amygdala is involved in the rapid detection of emotional stimuli, the left amygdala plays a role in the more elaborate stimulus evaluation (see also (Markowitsch, 1998)). In a similar vein, Glascher and Adolphs (Glascher & Adolphs, 2003) suggested that the right amygdala is engaged in the initial, possibly automatic detection of an emotional stimulus,

followed by a more detailed and specific analysis of variations in the magnitude of arousal associated with the stimulus mediated by the left amygdala.

In addition, sex differences in amygdala responses to emotional stimuli have also been proposed, specifically, a stronger and more bilateral amygdala activity in women than in men (Hamann, 2005; Killgore & Yurgelun-Todd, 2001). These putative neural differences are thought to underlie the often reported enhanced emotional reactivity in women (Hall & Matsumoto, 2004).

Although all these theories have received considerable support from the neuroimaging literature, many other studies have yielded contradictory results. The reasons for these discrepancies remain to be determined, especially given the large differences in methodology, paradigms, population, stimuli, and other experimental parameters across studies. One way to avoid these potential confounds and draw conclusions from disparate studies is through the use of meta-analytical approaches. This "analysis of analyses" (Glass, 1976) combines the findings of many studies investigating a common topic within a unifying framework. This technique is particularly well-suited for functional neuroimaging studies, where different paradigms are used and the number of statistical results typically reported (i.e., voxels activated in a particular contrast) can be quite large, making it difficult to interpret without the aid of a quantitative instrument.

A few meta-analyses of neuroimaging studies on emotion have been published in recent years. In the first one, which included 55 studies, Phan and colleagues (Phan et al., 2002) investigated brain responses to emotional stimuli as a function of emotion type (happiness, fear, anger, sadness, disgust), valence (positive and negative), induction method (visual, auditory, recall/imagery) and cognitive load or demand. They focused their analysis on 20 *a priori* defined regions, including the amygdala. They concluded

that fear specifically recruits the amygdala since out of the 8 studies investigating fear, 6 reported activations in this region. Interestingly, 50 % of studies using visual induction activated the amygdala, compared to only 7% and 0% for recall and auditory induction methods, respectively. Finally, cognitive demand did not appear to significantly influence the proportion of studies reporting amygdala activation.

In a follow-up meta-analysis, Wager et al. (Wager et al., 2003) increased the number of studies to 65 and specifically focused on the effects of sex, valence (as well as withdrawal/approach), and lateralization of the different patterns of activations. As with the previous study, they used a region-of-interest analysis (11 regions) and, in addition, calculated peak density maps based on the coordinates reported for each activation. Their main findings regarding the amygdala were: (1) more peaks were reported on the left than the right hemisphere, (2) the amygdala was more often activated for withdrawal than approach conditions (though no differences were observed for the positive vs. negative contrast), and (3) no significant sex main effects or interactions were observed in the proportion of activation peaks. However, density-map analyses revealed a more left-lateralized activation density for women and a right-lateralized one for men in the sublenticular area, partly extending into the amygdala/hippocampus region. Similar results, namely a larger proportion of activation peaks in the left hemisphere, albeit with no differences in terms of valence, was reported by Murphy et al. (Murphy et al., 2003) in their meta-analysis including 106 studies. Finally, a meta-analysis of 54 neuroimaging studies focusing on the amygdala confirmed the left lateralization of amygdala activation (Baas et al., 2004). Importantly, no interaction between laterality and stimulus type, task instructions or stimulus novelty was found.

Although these meta-analyses have provided critical insights into the neuroanatomy of emotion, they all used the so-called vote-counting technique, which may have given rise to potential confounds in the conclusions drawn. Indeed, in this approach each study has an equal weight in the overall counting; therefore the degree of statistical significance of individual activation peaks, either in terms of the magnitude of the observed effect (e.g., effect size) or its reliability (e.g., variance, sample size), is not taken into account (Deeks, 2001). However, modified vote-counting methods, including the sample size as an estimation of the study variance have been recently applied to neuroimaging (Etkin & Wager, 2007). Perhaps more importantly, vote-counting methods test whether a difference in the number of significant effects is itself significant, but do not provide an estimate of the magnitude of that difference. In the case of neuroimaging, this means that the vote-counting technique can tell us whether a particular condition results in more activations than another one, but gives no information regarding whether the activations themselves are different or not. This can be particularly problematic as the threshold for statistical significance can vary widely across studies, depending on factors such as the use of a priori regions of interest or the different methods employed, if any, for correcting for multiple comparisons (Genovese et al., 2002; Worsley et al., 1996).

One way to circumvent the problems associated with simple vote counting is to take into account not only whether each result is significant or not, but also how strong it is. This can be done by including the effect size corresponding to each activation in the statistical comparison across experimental conditions. Here, we conducted such a meta-analysis. Specifically, we investigated whether different experimental parameters and manipulations, such as participants' sex, stimulus type, experimental design and

technique, had a significant influence on the strength of amygdala activation and its lateralization during the perception of emotional visual stimuli.

2.2. General Methods

2.2.1. Literature search

We performed a search on Medline for articles of fMRI and PET studies referring to emotion in their title and/or abstract, written in English and published within the years 1993 and 2006. We used the following combination of key words: (1) Emotion and (fMRI or functional magnetic resonance imaging) and (2) Emotion and (PET or positron emission tomography). We also used similar search criteria for each of the basic emotions, namely fear, sadness, happiness, anger and disgust (and their related terms). This initial search covered all the articles included in the four previous neuroimaging meta-analyses of emotion (Baas et al., 2004; Murphy et al., 2003; Phan et al., 2002; Wager et al., 2003) and yielded 1505 studies. Data sets that were used in several different publications were included only once in the meta-analysis.

2.2.2. Inclusion Criteria

The initial sample was then restricted to studies that met the following inclusion criteria: (1) included contrasts involving healthy adults (placebo groups in pharmacological manipulations or controls for clinical populations were also included); (2) investigated perceptual processes using visual stimuli (in studies investigating other processes, such as memory or attention, we only included the contrasts involving perception); (3) measured regional cerebral blood flow (PET) or BOLD signal (fMRI); (4) coordinates were

reported in the standardized Montreal Neurological Institute (MNI) or Talairach space (Talairach & Tournoux, 1988) (i.e., ROIs without indication of the location of the peak activation were excluded); and (5) sufficient information was provided so that an effect size could be derived for each activation (see below). This initial selection resulted in 444 studies.

We then kept only those studies which reported an activation in the amygdala. We included all the peaks that were referred to in the original studies as being in the amygdala or related areas (i.e., amygdala, extended amygdala, amygdaloid complex/region, amygdala-hippocampal junction, periamygdala and periamygdaloid complex/region). Peaks whose effect size or distance to the center of gravity were larger than 3 times the interquartile range (IQR), a measure of statistical dispersion of the data, were considered outliers and thus removed from the final analysis.

2.2.3. Effect size

The standardized effect size is a dimensionless number that permits summarizing results across studies that use different types of measurements. Concretely, it is the magnitude of an effect divided by the variance (Glass, 1976). Although neuroimaging articles do not usually report the magnitude of the effect or the standard deviation, they often provide the z-score associated with a given significant activation, from which an effect size can be derived. Effect sizes can also be obtained from t-scores (and degrees of freedom) as well as from (exact) p values. In those studies in which only an upper limit of the p value was given (e.g., $p < 0.001$), this number was used to calculate a minimum effect size.

Because the usual effect size *g* is slightly biased, especially for small sample sizes, an unbiased estimator *d* of the effect size was used instead (Hedges & Olkins, 1985):

$$d_{ij} \cong \left(1 - \frac{3}{4N_{ij} - 9}\right) g_{ij}$$

where N_{ij} is the sample size (typically subjects or scans) of study j included in the factor of interest i (e.g., left/right, male/female).

The reliability of each effect size was included by calculating the weighted mean unbiased estimator of the effect size for each factor i:

$$d_{i+} = \sum_j \frac{d_{ij}}{\hat{\sigma}^2(d_{ij})} \Big/ \sum_j \frac{1}{\hat{\sigma}^2(d_{ij})}$$

where

$$\hat{\sigma}^2(d_{ij}) = \frac{1 + {d_{ij}}^2/2}{N_{ij}}$$

is an estimate of the variance associated with each effect size d_{ij}.

These values can then be used to construct the goodness-of-fit statistics

$$Q_T = \sum_i \sum_j \frac{\left(d_{ij} - d_{++}\right)^2}{\hat{\sigma}^2(d_{ij})}$$

where

$$d_{++} = \sum_i \sum_j \frac{d_{ij}}{\hat{\sigma}^2(d_{ij})} \Big/ \sum_i \sum_j \frac{1}{\hat{\sigma}^2(d_{ij})}$$

is the grand mean.

The total weighted sum of squares Q_T can be partitioned into Q_W and Q_B:

$$Q_T = Q_W + Q_B$$

with

$$Q_W = \sum_i \sum_j \frac{\left(d_{ij} - d_{i+}\right)^2}{\hat{\sigma}^2(d_{ij})}$$

and

$$Q_B = \sum_i \sum_j \frac{(d_{i+} - d_{++})^2}{\hat{\sigma}^2(d_{ij})}$$

Q_W and Q_B follow a chi-square distribution of (k-p) and (p-1) degrees of freedom, respectively, with k being the total number of observations (activation peaks in our case) and p is the number of factors (typically two). They can be interpreted as representing the within- and between-factors fit, respectively (similar to the partitioning of the sum of squares in an ANOVA). Therefore, Q_B can be used to test whether a significant amount of the total variance can be explained by taking into account that the observations belong to different factors or groups. In other words, a significantly non-zero Q_B means that the effect sizes for the different factors are significantly different from each other. For a more detailed discussion of the methods, the reader is referred to (Hedges & Olkins, 1985).

In those cases where there was a large difference in the number of activation peaks between conditions, we also conducted a modified version of the standard jackknife analysis (Miller, 1974) to confirm the results obtained with the chi-square test described above. Briefly, this analysis consisted of randomly selecting a subset of data points from the larger group of the same size as the smaller one, and computing the difference in effects size between the groups. We repeated this procedure 10,000 times and calculated the proportion of instances in which the mean effect size for one condition was larger than the other one, thus obtaining an exact p-value (p_{jk}) associated with the effect of interest.

2.3. RESULTS

2.3.1. Number of activations

Our search yielded a total of 365 activation peaks in the amygdala (Figure 1). Five values were removed as their associated effect sizes were considered outliers (d>3.65). Another 6 peaks (3 in the left and 3 in the right hemisphere) were also removed, as their distance to the center of gravity of the all the data points (left: -21, -5, -16; right: 22, -4, -15) was larger than the cut-off for outliers (3*IQR; left: 26mm, right: 22mm). Thus, the final analysis was performed on data from 354 peaks, derived from 148 different studies. A list of these studies, depicting their main characteristics, is shown in Table 1 (the full references are provided in Appendix 1).

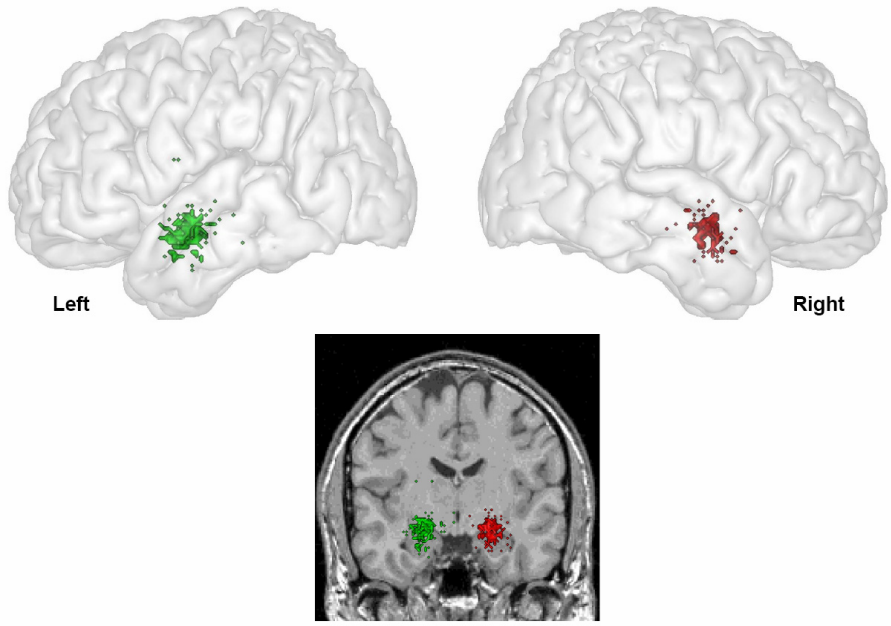

Figure 1. Three-dimensional rendering of all the amygdala peaks included in the meta-analysis.

Table 1. Main characteristics of the studies included in the meta-analysis

#	Authors	Year	Journal	Ss	M	W	age	Tech	Emotional stimulus type	F	H	S	Su	D	A	N	Valence +	Valence -	Valence N
1	Breiter	1996	Neuron	10	10	0	27.1	fMRI	face	x						x		x	x
2	Lane	1997	Neuropsychologia	12	0	12	18-45[a]	PET	picture							x	x	x	x
3	Phillips	1997	Nature	7	2	5	27.0	fMRI	face	x				x		x		x	x
4	Reiman	1997	Am J Psychiatry	12	0	12	23.3	PET	picture		x	x		x		x	x	x	x
5	Morris	1998	Brain	5	4	1	42.8	PET	picture	x	x					x	x	x	x
6	Phillips	1998	Proc Bio Sci	6	6	0	37.0	fMRI	face	x				x		x		x	x
7	Taylor	1998	NeuroImage	8	0	8	27.9	PET	picture	x				x		x		x	x
8	Whalen	1998	J Neurosci	10	10	0	23.8	fMRI	picture	x	x						x	x	
9	Blair	1999	Brain	13	13	0	25.3	PET	face			x			x	x		x	x
10	Isenberg	1999	Proc Natl Acad Sci	6	2	4	26.4	PET	semantic							x		x	x
11	Paradiso	1999	Am J Psychiatry	17	7	10	31.2	PET	picture							x	x	x	x
12	Canli	2000	J Neurosci	10	0	10		fMRI	picture							x		x	x
13	Critchley	2000	Hum Brain Mapp	9	9	0	27.0	fMRI	face		x				x	x	x	x	x
14	Hariri	2000	NeuroReport	16	8	8	25.3	fMRI	face	x					x			x	
15	Simpson	2000	J Cog Neurosci	18	9	9	24.9	fMRI	picture							x		x	x
16	Taylor	2000	NeuroPsychologia	14	9	5	32.1	PET	picture							x		x	x
17	Gorno-Tempini	2001	NeroImage	10	5	5	25-30[a]	fMRI	face		x			x		x	x	x	x
18	Iidaka	2001	J Cogn Neurosci	12	6	6	25.1	fMRI	face							x	x	x	x
19	Maratos	2001	Neuropsychologia	12	5	7	18-30[a]	fMRI	semantic							x	x	x	x
20	Vuilleumier	2001	Neuron	12	6	6	27.7	fMRI	face	x						x		x	x
21	Whalen	2001	Emotion	8	4	4	25.0	fMRI	face	x					x	x		x	x
22	Williams	2001	NeuroImage	11	11	0	30.0	fMRI	face	x						x		x	x
23	Wright	2001	NeuroReport	8	8	0	28.0	fMRI	face	x	x						x	x	
24	Canli	2002	Science	15	4	11		fMRI	face	x	x						x	x	
25	Gur	2002	Am J Psychiatry	14	10	4	27.4	fMRI	face	x	x	x		x	x	x	x	x	x
26	Hamann	2002	NeuroReport	14	14	0	20-31[a]	fMRI	semantic							x	x	x	x
27	Hamann	2002	Psychol Sci	10	10	0	22.8	PET	picture							x	x	x	x
28	Hariri	2002	NeuroImage	12	6	6	28.0	fMRI	face	x					x	x		x	x
29	Hariri	2002	Neuropsychopharmacology	12	5	7	33.0	fMRI	face	x					x	x		x	x
30	Kosaka	2002	Schizophr Res	12	6	6	24.4	fMRI	face		x	x		x	x	x	x	x	x
31	Liberzon	2002	PNAS	12	12	0	45.8	PET	picture							x		x	x
32	Schienle	2002	NeuroReport	12	0	12	26.3	fMRI	picture	x				x		x		x	x
33	Tessitore	2002	J Neurosci	10	7	3	61.0	fMRI	face	x					x	x		x	x
34	Wright	2002	NeuroReport	16	8	8	30.0	fMRI	face		x				x	x	x	x	x
35	Yang	2002	NeuroReport	17	6	11	23.0	fMRI	face	x	x	x			x	x	x	x	x

36	Abel	2003	NeuroReport	8	8	0	28.8	fMRI	face	x						x		x	x
37	Anderson	2003	J Neurosci	12	3	9	22.1	fMRI	face	x				x		x		x	x
38	Carr	2003	PNAS	11	7	4	29.0	fMRI	face	x	x	x	x	x	x		x	x	
39	Compton	2003	Cogn Affect Behav Neurosci	12	8	4	25.2	fMRI	semantic							x	x	x	x
40	Erk	2003	Neuroimage	10	7	3	27.1	fMRI	picture							x	x	x	x
41	Eugène	2003	NeuroImage	20	0	20	24.3[b]	fMRI	film			x				x		x	x
42	Gunning-Dixon	2003	Neurobiol Aging	8	4	4	25.8	fMRI	face	x	x	x		x	x	x	x	x	x
43	Hadjikhani	2003	Curr Biol	7	4	3		fMRI	film	x	x	x			x	x	x	x	x
44	Hariri	2003	Biol Psychiatry	11	5	6	32.0	fMRI	picture							x		x	x
45	Hendler	2003	NeuroImage	11	11	0	33.0	fMRI	picture							x		x	x
46	Kim	2003	NeuroReport	15	8	7	22.3	fMRI	face				x			x		x	x
47	Klein	2003	Pharmacopsychiatry	20	10	10	41.6[b]	fMRI	picture							x	x	x	x
48	Lange	2003	Biol Psychiatry	9	9	0	29.0	fMRI	face	x						x		x	x
49	Lévesque	2003	Biol Psychiatry	20	0	20	24.3	fMRI	film			x				x		x	x
50	Liberzon	2003	Neuropsychopharmacology	10	6	4	27.5	PET	picture							x	x	x	x
51	Maddock	2003	Hum Brain Mapp	8	2	6	24-45[a]	fMRI	semantic							x	x	x	x
52	Mataix-Cols	2003	Biol Psychiatry	10	5	5	27.6	fMRI	picture							x		x	x
53	Phan	2003	Neuropsychopharmacology	8	3	5	24.4	fMRI	picture							x		x	x
54	Shirao	2003	Neuropsychobiology	15	0	15	25.0	fMRI	semantic							x		x	x
55	Stark	2003	Int J Psychophysiol	19	9	10	27.2	fMRI	picture	x				x		x		x	x
56	Surguladze	2003	NeuroImage	9	5	4	39.6	fMRI	face	x	x	x		x		x	x	x	x
57	Taylor	2003	NeuroImage	10	6	4	21.2	PET	picture							x		x	x
58	Vuilleumier	2003	Nat Neurosci	13	6	7	27.0	fMRI	face	x						x		x	x
59	Winston	2003	Current Biol	14	6	8	30.0	fMRI	face	x						x		x	x
60	Winston	2003	NeuroImage	11	6	5	26.0	fMRI	face	x	x	x		x		x	x	x	x
61	Benuzzi	2004	Brain Res Bull	14	7	7	21-27[a]	fMRI	face	x						x		x	x
62	Bishop	2004	J Neurosci	27	7	20	18-38[a]	fMRI	face	x						x		x	x
63	Cannistraro	2004	Biol Psychiatry	10	4	6	24.9	fMRI	face	x	x					x	x	x	x
64	Cunningham	2004	J Cog Neurosci	20				fMRI	face							x	x	x	x
65	de Gelder	2004	PNAS	7	4	3		fMRI	film	x	x					x	x	x	x
66	Etkin	2004	Neuron	17	9	8	20-33[a]	fMRI	face	x						x		x	x
67	Fichtenholtz	2004	Brain Res Cogn Brain Res	22	13	9	20-47[a]	fMRI	picture							x	x	x	x
68	Gläscher	2004	BMC Neurosci	11	3	8	25.6	fMRI	face	x	x					x	x	x	x
69	Kensinger	2004	PNAS	28	14	14		fMRI	semantic							x		x	x
70	Killgore	2004	NeuroImage	12	0	12	23.7	fMRI	face		x	x				x	x	x	x
71	Lee	2004	Cogn Behav Neurol	10	5	5	29.5	fMRI	picture							x	x	x	x
72	Mathews	2004	J Cogn Neurosci	22	6	16		fMRI	picture	x						x		x	x
73	Nomura	2004	NeuroImage	10	5	5	23.5	fMRI	face		x				x	x	x	x	x
74	Ochsner	2004	NeuroImage	24	0	24	20.6	fMRI	picture							x		x	x

75	Phan	2004	NeuroImage	12	6	6	22.7	fMRI	picture							x	x	x	x
76	Phillips	2004	NeuroImage	8	8	0	31.9	fMRI	face	x				x		x		x	x
77	Sato	2004	Brain Res Cogn Brain Res	22	10	12	26.5	fMRI	face	x	x					x	x	x	x
78	Sato	2004	NeuroImage	10	5	5	24.4	fMRI	face						x	x		x	x
79	Stark	2004	Neuropsychobiology	24	24	0	25.5	fMRI	face	x				x		x		x	x
80	Takahashi	2004	NeuroImage	15	9	6	29.1	fMRI	picture							x	x	x	x
81	Vuilleumier	2004	Nat Neurosci	13	7	6	35.8[b]	fMRI	face	x						x		x	x
82	Wang	2004	J Am Acad Child Adolesc Psychiatry	12	12	0	11.8	fMRI	face	x					x	x		x	x
83	Whalen	2004	Science	20	20	0	21.9	fMRI	picture	x	x					x	x	x	x
84	Williams	2004	Am J Psychiatry	22	14	8	27.2	fMRI	face	x						x		x	x
85	Williams	2004	Brain Res Cogn Brain Res	22	15	7	27.5	fMRI	face	x						x		x	x
86	Anand	2005	Biol Psychiatry	15	4	11	28.0	fMRI	picture							x		x	x
87	Das	2005	NeuroImage	28	14	14	30.1	fMRI	face	x						x		x	x
88	Erk	2005	NeuroImage	10	7	3	24.3	fMRI	picture								x	x	
89	Ferstl	2005	J Cogn Neurosci	20	8	12	25.0	fMRI	semantic							x	x	x	x
90	Fischer	2005	Neurosci Lett	24	12	12	24.7	fMRI	face						x	x		x	x
91	Goldin	2005	NeuroImage	13	0	13	19.7	fMRI	film		x	x				x	x	x	x
92	Habel	2005	NeuroImage	26	26	0	33.4	fMRI	face		x	x					x	x	
93	Hennenlotter	2005	NeuroImage	12	6	6	24.5	fMRI	face		x					x	x		x
94	Hutcherson	2005	NeuroImage	28	0	28	18-21[a]	fMRI	film		x	x				x	x	x	x
95	Johnston	2005	Eur J Neurosci	10	8	2	31.2	fMRI	face	x	x	x	x	x	x	x	x	x	x
96	Kensinger	2005	NeuroImage	16	8	8	18-30[a]	fMRI	picture, semantic							x	x	x	x
97	Kensinger	2005	Neuropsychologia	16	7	9	18-30[a]	fMRI	picture, semantic							x	x	x	x
98	Liddell	2005	NeuroImage	22	11	11	32.0	fMRI	face	x						x		x	x
99	Moll	2005	Cogn Behav Neurol	13	7	6	25.5	fMRI	semantic					x		x		x	x
100	Noesselt	2005	Curr Biol	12	7	5	22.6	fMRI	face	x						x		x	x
101	Phan	2005	Biol Psychiatry	14	6	8	27.6	fMRI	face									x	
102	Protopopescu	2005	Biol Psychiatry	14	7	7	27.0	fMRI	semantic							x	x	x	x
103	Ray	2005	Cogn Affect Behav Neurosci	24	0	24	20.6	fMRI	picture							x		x	x
104	Reinders	2005	Eur J Neurosci	15	7	8	25.8	fMRI	face	x						x		x	x
105	Schienle	2005	Neuropsychobiology	63	0	63	27.3	fMRI	picture					x		x		x	x
106	Schienle	2005	Neurosci Letters	13	0	13	23.9	fMRI	picture	x				x		x		x	x
107	Shäfer (b)	2005	Int J Psychophysiol	40	20	20	23.9	fMRI	face, picture	x				x		x		x	x
108	Shin	2005	Arch Gen Psychiatry	13	13	0	49.7	fMRI	face	x	x						x	x	x
109	Skuse	2005	Brain	12	0	12	25.6	fMRI	face	x						x		x	x
110	Smith	2005	Learn Mem	18	10	8	21.0	fMRI	picture							x	x	x	x
111	Stark	2005	Biol Psychol	12	6	6	28.2	fMRI	picture					x		x		x	x
112	Straube	2005	Neuropsychobiology	9	4	5	22.7	fMRI	face		x				x	x	x	x	x

113	Strauss	2005	NeuroImage	8	8	0	26.5	fMRI	face						x	x		x	x
114	Takahashi	2005	NeuroImage	13	13	0	29.2	fMRI	picture							x		x	x
115	Tessitore	2005	Psychiatry Res: Neuroimaging	12	6	6	25.0	fMRI	face	x					x			x	
116	van Stegeren	2005	NeuroImage	30	15	15	20.9	fMRI	picture							x		x	x
117	Wang	2005	Emotion	12	5	7	25.9	fMRI	picture			x				x		x	x
118	Williams	2005	NeuroReport	13	5	8	24.0	fMRI	face	x				x	x	x		x	x
119	Ashwin	2006	Neuropsychologia	13	13	0	25.6	fMRI	face	x						x		x	x
120	Bermpohl	2006	Hum Brain Mapp	17	8	9	21-37[a]	fMRI	picture							x	x	x	x
121	Britton	2006	NeuroImage	12	6	6	21.4	fMRI	face, picture	x	x	x			x	x	x	x	x
122	Erk	2006	Eur J Neurosci	14	0	14	21-25[a]	fMRI	picture							x		x	x
123	Fitzgerald	2006	NeuroImage	20	10	10	26.0	fMRI	face	x	x	x		x	x	x	x	x	x
124	Garrett	2006	NeuroImage	9	4	5	38.7	fMRI	picture							x		x	x
125	Grosbras	2006	Cereb Cortex	20	10	10	28.6	fMRI	film						x	x		x	x
126	Harenski	2006	NeuroImage	10	0	10	18-29[a]	fMRI	picture							x		x	x
127	Herwig	2006	NeuroImage	16	6	10	23-26[a]	fMRI	picture							x	x	x	x
128	Holt	2006	Schizophrenia Res	16	16	0	48.2	fMRI	face	x	x					x	x	x	x
129	Kensinger	2006	Cogn Affect Behav Neurosci	21	11	10	18-35[a]	fMRI	picture, semantic							x	x	x	x
130	Lewis	2006	Cereb Cortex	19	10	9	30.0	fMRI	semantic								x	x	
131	Lobaugh	2006	NeuroReport	10	6	4	10.3	fMRI	face	x	x	x	x	x	x	x	x	x	x
132	Mackiewicz	2006	PNAS	40	22	18	20.7	fMRI	picture							x		x	x
133	Mobbs	2006	Soc Cogn Affect Neurosci	14	6	8	27.5	fMRI	face, picture	x	x					x	x	x	x
134	Moser	2006	J Neurosci Methods	12	7	5	27.7	fMRI	face, picture	x	x	x		x	x	x	x	x	x
135	Nakic	2006	NeuroImage	13	5	8	32.0	fMRI	semantic							x		x	x
136	Ogino	2006	Cereb Cortex	10	10	0	26.3	fMRI	picture							x		x	x
137	Pessoa	2006	Cereb Cortex	37	19	18	28.1	fMRI	face	x	x					x	x	x	x
138	Reinders	2006	NeuroImage	15	7	8	25.8	fMRI	face	x						x		x	x
139	Sambataro	2006	Eur J Neurosci	24	11	13	26.8	fMRI	face					x		x		x	x
140	Schienle	2006	Neurosci Lett	12	0	12	19-41[a]	fMRI	picture							x		x	x
141	Simon	2006	Pain	17	8	9	23.1	fMRI	face						x	x		x	x
142	Smith	2006	Neuron	16	8	8		fMRI	picture							x		x	x
143	Taylor	2006	Biol Psychiatry	30	12	18		fMRI	face	x					x	x		x	x
144	Williams	2006	Hum Brain Mapp	15	7	8	35.8	fMRI	face	x						x		x	x
145	Williams	2006	NeuroImage	13	7	6	34.8	fMRI	face	x						x		x	x
146	Williams	2006	J Neurosci	15	7	8	35.8	fMRI	face	x						x		x	x
147	Wright	2006	Neurobiol Aging	18	6	12	24.0	fMRI	face	x						x		x	x
148	Wright	2006	NeuroImage	12	6	6	29.0	fMRI	face	x	x				x	x	x	x	x

[a] Age range. No mean age was reported

[b] Represents the mean age of all the participants from the two groups tested (control and experimental), although only the control group was included in the meta-analysis

2.3.2. Control condition

The contrasts involving a comparison between emotional and control stimuli were assigned to two categories, depending on whether the control condition was the same type of stimulus but of neutral emotional value (e.g., neutral faces, pictures or words), called the "neutral" condition, or whether a lower-level condition was used, such as scrambled pictures, fixation cross or a blank screen (the "baseline" condition). As expected, effect sizes were larger ($Q_B = 14.1$, $p = 0.0002$; see Figure 2 and Table 2) for the comparison of emotional stimuli to low-level controls (E>B) than when using a similar but neutral stimulus (E>N). A jackknife analysis (see Methods) confirmed this result ($p_{jk} = 0.0002$), ruling out the possibility of a bias due to the different number of peaks included in each condition.

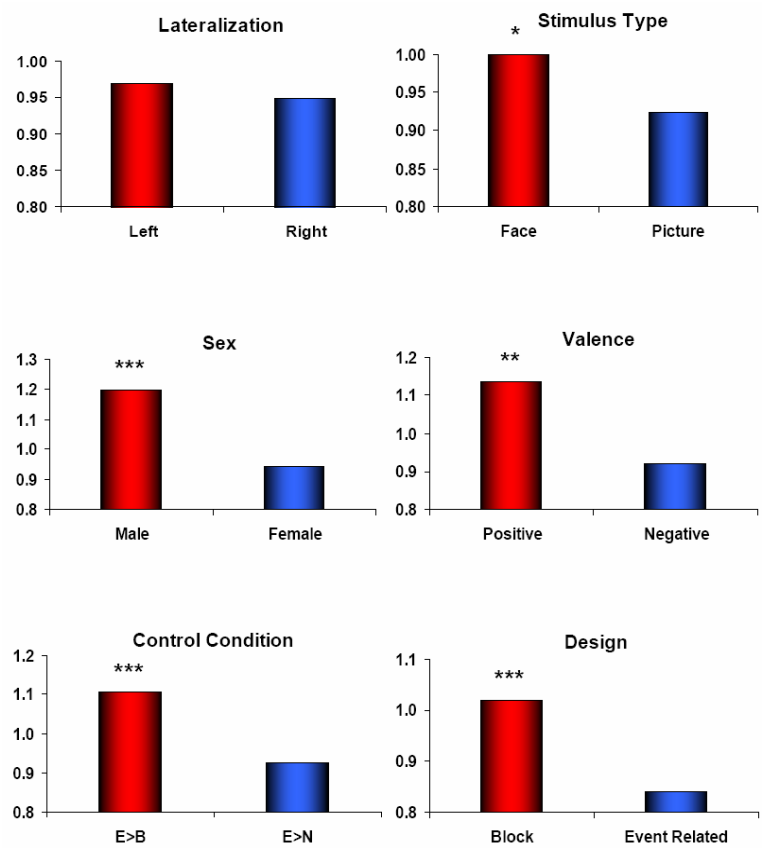

Figure 2. Mean effect sizes associated with the amygdala activation for the different conditions of interest. *p<0.05, **p<0.01, ***p<0.001.

Table 2: Mean effect size and number of peaks and studies for the different factors included in the analysis

Factors	Effect size	Number of peaks	Number of studies
Lateralization			
Left	0.97	199	122
Right	0.95	155	112
Sex[a]			
Male	1.20	53	24
Female	0.92	40	20
Control condition			
E>C	1.11	63	24
E>N	0.92	220	107
Stimulus type			
Face	1.01	191	76
Picture	0.92	123	55
Film	1.02	12	6
Semantic	1.02	23	14
Valence[b]			
Positive	1.14	28	16
Negative	0.92	227	109
Emotion			
Happy	1.11	19	9
Fear	0.89	84	46
Disgust	0.85	22	13
Angry	0.99	15	10
Sad	0.93	12	10
Technique			
PET	1.10	27	12
fMRI	0.95	327	136
Design[c]			
Block	1.01	266	111
Event-Related	0.85	88	38

[a]Studies including only male or female participants.
[b]Indicates studies in which a positive or negative condition was contrasted to a control one.
[c]One study (Shafer et al., 2005) conducted both block and event-related experiments.

2.3.3. Sex

A comparison between studies testing only male or female participants revealed a main effect of sex ($Q_B = 15.1$, $p = 0.0001$), due to a larger effect size for men than for women. This sex effect was confirmed by a positive correlation between effect size and the relative proportion of male participants for studies with participants of both sexes ($r = 0.12$, $z=3.62$, $p < 0.001$). In terms of proportion of reported peaks within the amygdala, relative to all brain activations, across studies involving only male or female participants, no significant differences were observed (male=64%, female=67%, p=0.8).

2.3.4. Stimulus type

A significantly stronger effect size was observed for faces compared to pictures ($Q_B = 6.3$, $p = 0.01$). In addition, there was a trend for a larger effect size for semantic stimuli than for pictures in the left amygdala (p=0.08). No differences between films and any of the other stimulus types were observed (p>0.3).

2.3.5. Valence and Individual Emotions

We observed an influence of stimulus valence on mean effect sizes ($Q_B = 9.7$, $p = 0.002$; $p_{jk} = 0.0075$), although it was in the opposite direction of what is commonly assumed: the effect size was larger for positive than negative material. In order to exclude the possibility that the effect was due to differences between studies unrelated to the valence of the stimuli, we conducted the same analysis on the subset of experiments (N = 13) that used both negative and positive material and reported amygdala activation for both conditions, relative to control. A similar valence effect was obtained, namely larger

magnitude for positive than negative stimuli (Q_B = 6.1, p = 0.01), as illustrated by the effect size histograms shown in Figure 3.

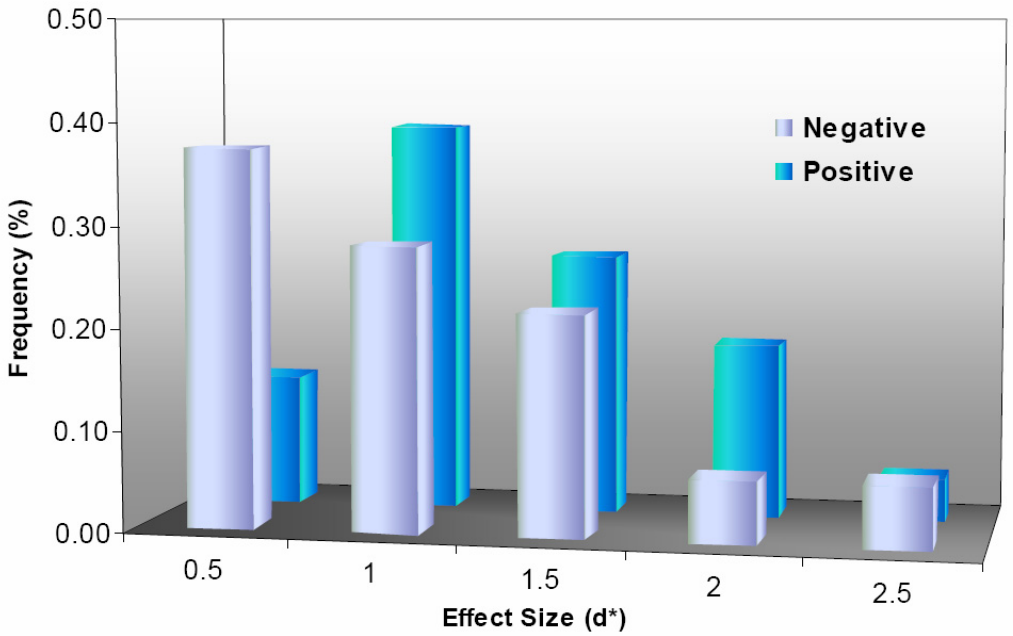

Figure 3. Histogram of the effect sizes for the amygdala activations associated with the presentation of positive and negative stimuli for the studies in which both types of material were used (N=13).

We directly tested the valence lateralization model, which postulates a right hemisphere advantage for positive material and a left one for negative, by performing an interaction analysis between valence and hemisphere. No significant effect was observed (p = 0.6).

A further emotion-specific analysis — including happiness, fear, sad, disgust and anger — revealed that happy stimuli consistently elicited stronger effect sizes compared to all negative emotions, although it only reached statistical significance for comparisons with fear (Q_B = 6.1, p = 0.01) and disgust (Q_B = 6.0, p = 0.01). No pairwise differences between negative emotions were observed (all p > 0.3). Other emotions (e.g., surprise, contempt) could not be separately analyzed due to insufficient number of studies.

2.3.6. Laterality

Consistent with previous meta-analyses, a significantly larger number of activation peaks across studies were reported in the left than in the right amygdala (χ^2=5.46, p = 0.02; see Figure 1). In contrast, no difference in terms of mean value or distribution of the effect sizes of these activation was observed (Q_B = 0.4, p = 0.5).

2.3.7. Experimental Design and Technique

When comparing studies using PET and fMRI, a trend for a larger magnitude in the PET activations was observed (Q_B = 3.1, p = 0.08; p_{jk} = 0.08). Further analyses revealed that this difference was driven by stronger effect sizes associated with block designs compared to those using an event-related analysis (only possible in fMRI). Indeed, the comparison between block and event-related designs for fMRI studies was significant (Q_B = 17.8, p < 0.00005; p_{jk} < 0.00001), while there was no significant difference between PET and fMRI studies when only considering block designs (Q_B = 1.4, p = 0.24; p_{jk} = 0.26), as shown in Figure 4.

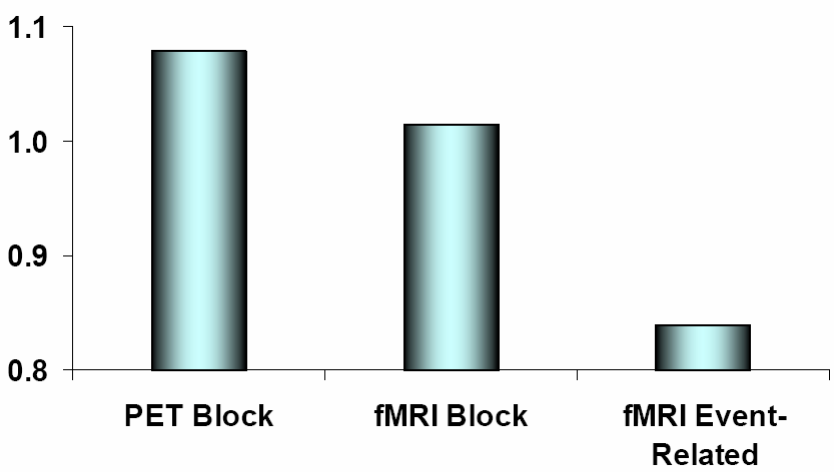

Figure 4. Mean effect sizes associated with the amygdala activation as a function of technique (fMRI/PET) and experimental design (block/event-related)

2.3.8. Interaction between experimental design and laterality

Because of the previously hypothesized differential habituation rates of left and right amygdala (Phillips et al., 2001; Whalen et al., 1998; Wright et al., 2001), we explored the interaction between hemispheric lateralization and experimental design. Specifically, we compared the number of activations in left and right amygdala for block and event-related designs separately. Whereas no difference between hemispheres in the number of activations was observed for event-related studies ($p > 0.5$), significantly more activations were reported in the left than in the right amygdala for experiments using a block design ($p = 0.007$). Notably, no significant differences in mean effect size between hemispheres were observed for either type of paradigm.

2.4. DISCUSSION

The main goal of this study was to examine the influence of specific experimental parameters on the magnitude and laterality of amygdala activations across functional neuroimaging studies of emotional perception within the visual modality. Unlike previous meta-analyses of emotion using vote-counting approaches, each activation peak was represented by its effect size and weighted by the corresponding estimated variance. Taking into account the strength and reliability of each activation reported in the literature allowed us to derive an index of the strength of amygdala activation associated with the different conditions of interest and, critically, to compare them in a quantitative fashion.

2.4.1. Experimental design

The results from this meta-analysis confirm the importance of the control condition when assessing neural responses to emotional stimuli using neuroimaging techniques (Gusnard

et al., 2001). Indeed, a stronger amygdala activation was associated with those contrasts in which the emotional stimuli were compared to a low-level baseline condition, such as fixation cross or scrambled images, than when a neutral stimulus (of the same type as the emotional one) was used. This difference is likely due to the fact that the amygdala also responds, albeit more weakly, to neutral stimuli, such as faces or pictures (Holt et al., 2006; Iidaka et al., 2002; Kesler/West et al., 2001; Liberzon et al., 2002; Taylor et al., 2002; Taylor et al., 2000; Taylor et al., 2005). This would result in a smaller difference between the two stimulus categories than when using low-level baseline conditions, which are less effective in driving the amygdala.

The stronger effect size associated with experiments using a block design compared to those using an event-related one supports the notion that the former are more efficient from a statistical point of view (Josephs & Henson, 1999). Notably, our findings show that such an increase in efficiency holds even for a structure such as the amygdala, which has been proposed to be particularly susceptible to habituation effects following the repeated presentation of stimuli belonging to the same category (see below). Interestingly, despite the possibility of signal loss in the amygdala in fMRI due to susceptibility artefacts, the mean effect sizes obtained in blocked fMRI and PET designs were not significantly different.

2.4.2. Valence models

Contrary to the traditional view of the amygdala as a structure specialized in the detection of negative information, presentation of positive stimuli appeared to consistently elicit activation in this structure. This finding is in accord with some of the previous meta-analyses of emotion (Murphy et al., 2003; Wager et al., 2003) and provides further

support for the notion of the amygdala as being involved in the processing of biologically relevant information, regardless of valence (Sander et al., 2003).

In fact, the mean effect size associated with amygdala response to positive stimuli was significantly larger than for negative ones. Because of the usual *a priori* expectation of an amygdala involvement in the processing of negative stimuli, it was critical to rule out the possibility that the observed difference in mean effect size as a function of valence could be due to a bias in the accepted statistical threshold between positive and negative stimuli. In others words, studies using negative material could have adopted a more liberal statistical threshold for the amygdala than those using positive stimuli, therefore resulting in a larger proportion of reported activations for negative valences with smaller effect sizes. This explanation was explicitly tested by selectively comparing the effect sizes associated with positive and negative stimuli in those studies in which both types of material were presented (and thus the same thresholds used for both conditions). Similar results —i.e., larger magnitude for positive than negative material— were obtained as when analyzing the entire data set. Although this valence effect was unexpected and somewhat counter-intuitive, it is consistent with electrophysiological recordings in monkeys showing not only that amygdala neurons respond to both positive and negative material (Nishijo et al., 1988), but that there in fact is a larger proportion of cells that respond to positive than negative stimuli (Paton et al., 2006).

When contrasting individual emotions separately, similar valence effects were observed; namely, happy stimuli elicited larger activations than each of the negative emotions included in the analysis (fear, angry, sad and disgust), indicating that the general valence effects described above were not driven by any single negative emotion. Unfortunately, there were not enough data points to test whether the results observed also

applied to other positive emotions (e.g., pleasure), as the majority of studies did not analyze separately the various positive emotions contained in their stimulus set (e.g., affective pictures from IAPS).

The stronger amygdala response to faces compared to pictures is in agreement with studies comparing both types of material (e.g., (Hariri et al., 2002)), and it may reflect the key role of this structure in our evolutionarily-shaped ability to rapidly and efficiently decode conspecifics' emotional expressions. The trend for a larger response in the left amygdala to semantic material is in line with the proposed hemispheric specialization for processing of this type of information.

2.4.3. Sex differences

Our findings do not support the sometimes hypothesized (Hamann, 2005) stronger amygdala response in women than in men, as no significant difference in the proportion of amygdala activations between male- and female-only studies was observed, in agreement with results from the previous meta-analysis that examined this issue (Wager et al., 2003). Notably, our results show a significantly larger mean amygdala effect size in studies involving only men than in those testing only women, as well as a correlation between effect size and relative proportion of male participants in studies with participants from both sexes. This sex effect may be partly explained by the established anatomical and physiological dimorphism in the amygdala. Specifically, MRI studies have reported a larger amygdala volume and/or grey matter density in men, even after controlling for overall brain size (Goldstein et al., 2001). Furthermore, animal studies have demonstrated that the male amygdala has a greater dendritic density, putatively associated with a larger number of excitatory synapses (Cooke & Woolley, 2005).

Alternatively, the smaller effect size observed in female participants could be due to a larger amygdala response to neutral stimuli. Such an enhanced baseline activity would then result in a reduced difference between emotional and control stimuli in women, as compared to men.

Finally, another, more speculative explanation could be based on the variability in anxiety-like behavior and amygdala responsivity throughout the menstrual cycle in women. Indeed, it has often been reported that female rats exhibit less fear than males, although this difference varies with the estrous cycle (Toufexis et al., 2006). Specifically, female rats exhibit reduced anxiety-like behaviors, compared to males, during their proestrous (follicular) phase, when progesterone is at its peak level, but they show similar levels during the other phases (Frye et al., 2000). Consistent with findings in experimental animals, amygdala response to positive and negative stimuli in women are largest during their follicular phase (Dreher et al., 2007; Goldstein et al., 2005). Thus, it is possible that the observed sex differences in amygdala activation were due to the fact that most neuroimaging studies do not take into account the phase of the menstrual cycle of the female participants at the time of testing, and therefore the response reported represents an average across all phases, leading to an overall reduced activation.

2.4.4. Laterality

The larger proportion of activation foci in the left amygdala than in the right is consistent with findings from previous meta-analyses (Baas et al., 2004; Murphy et al., 2003; Wager et al., 2003). However, there was no difference in terms of effect sizes between hemispheres, either in the mean values or their distributions. Taken together, these results suggest that when amygdala activations were reported, the magnitude of the effect was

similar, regardless of the hemisphere, but that activations were reported more often in the left than in the right amygdala. Critically, further analysis that took into account the design used in the studies showed that the difference in the proportion of activation peaks between hemispheres was only apparent in experiments using a block design, and not when an event-related paradigm was employed.

This finding supports the often observed hemispheric differences in temporal dynamics and/or habituation rates, namely a short-duration response in the right amygdala and a more sustained one in the left. Indeed, block designs typically involve the repeated presentation of stimuli of the same category (e.g., positive, negative or neutral) for relatively long periods of time (the mean block duration for studies included in this meta-analysis was 107 sec). Therefore, averaging the activity over a block would result in a lower, below significance magnitude in the right amygdala due to its rapid return to baseline levels. In contrast, the pseudo-random stimulus presentation order used in event-related designs would prevent such a habituation from taking place and therefore both left and right amygdala responses would be consistently stronger than baseline/control conditions. In other words, our analysis leads to the prediction that a difference in the likelihood of observing significant amygdala activation between hemispheres (more on the left than on the right) should only be expected in experiments using a block design.

2.4.5. Limitations

A number of limitations of this study need to be highlighted. First, we only examined contrasts involving the perception of emotional stimuli. Therefore, our conclusions may not apply to the expression or experience of emotions, which have been proposed to

engage different neural systems, particularly in term of hemispheric lateralization (Lanteaume et al., 2007).

As shown in Table 2, the number of activation peaks for some of the conditions was substantially smaller than for others, which may have introduced a bias in some of the comparisons. Unfortunately, this was unavoidable as this relative difference in number of studies across conditions reflects the predominance of some methodological approaches (e.g., block vs. event-related designs), as well as theoretical assumptions (e.g., amygdala preferential role in negative emotions) in the existing literature. However, as we confirmed our results using the jackknife method, which minimizes this potential problem, we can be fairly confident that the main conclusions are not confounded by relative differences in sample sizes across conditions.

As mentioned in the Methods section, we included all activations that were labelled as being in the amygdala by the authors themselves, even if they fell outside the traditional anatomical borders of this structure (Mai et al., 2004). We chose this approach rather than only including the peaks falling within an a priori anatomical mask because of the likely inter-study differences in spatial localization and resolution caused by spatial smoothing and subject normalization. Additionally, the Authors' assignment of an activation to the amygdala may have relied not only on the location of the voxel with the most significant p-value (the "peak voxel" typically reported in tables), but also on the entire activation cluster, of which the coordinates are very rarely provided. Nonetheless, a few points that were clearly outliers were removed based on their distance to the center of gravity of the data.

Finally, an inherent limitation of all meta-analytical techniques relates to the so-called file drawer problem (Rosenthal, 1979), that is, the potential bias introduced by the

non-significant results that are not published. It is important to emphasize that this issue was less of a problem in our study than in other meta-analyses which use the vote-counting method, as our goal was not to assess the presence or absence of amygdala activation under different conditions but, rather, to determine whether the magnitude of the activation depended on a set of specific *a priori* experimental factors. Nevertheless, it is possible that other variables not included in the present analysis may have also a significant influence on the magnitude and/or lateralization of amygdala responses to emotional stimuli. For instance, a growing literature suggests that individual differences beyond sex, such as personality (e.g., trait anxiety (Bishop, 2007)) or genotype (e.g., the serotonin transporter gene (Hariri & Holmes, 2006)), modulate amygdala activity. To date, there is not a sufficient number of studies to include these individual-differences in a meta-analysis, although, based on the rapid expansion of this field of research, this is likely to change in the near future.

2.4.6. Summary and Conclusions

The findings from our study show that the amygdala responds to all visual emotional stimuli, regardless of valence, with a stronger activation for faces, thus providing strong support for the relevance detector model, which posits a general role of this structure in the detection of innate, biologically and socially relevant information. In contrast, our results do not support a stronger right amygdala involvement in emotional processing, nor a hemispheric lateralization based on valence or sex. Instead, our results are in agreement with the hemispheric lateralization models based on temporal dynamics (Glascher & Adolphs, 2003; Wright et al., 2001), although our analysis cannot be used to provide a

mechanistic explanation of this difference, especially as to whether it represent a physiological or psychological process.

In practical terms of the concrete implementation of neuroimaging studies of emotional perception, our findings suggest that a block design will be statistically more efficient, and thus result in stronger effect sizes, but at the potential cost of losing significant activations due to habituation, especially in the right amygdala. In addition, stronger responses would be expected when using a low-level control condition, although such contrasts may lead to significant activations within the amygdala that are not directly related to the emotional properties of the target stimuli.

In conclusion, we have shown that through the use of a novel quantitative meta-analytical approach to functional neuroimaging, findings from previous studies can be integrated to generate new results which can, in turn, be used to directly test some of the existing hypotheses regarding the role of the amygdala on visual emotional processing, as well as refine theoretical models. Critically, our conclusions give rise to specific predictions which can be tested in future functional neuroimaging studies.

Acknowledgments

This study was funded by the Canadian Institutes of Health Research and the Natural Sciences and Engineering Research Council of Canada. J.L.A. was supported by the Canada Research Chairs Program. K.S. was supported by a CIHR Doctoral Fellowship.

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The previous study showed that the amygdala responds not only to fear-related stimuli, but also to other visual emotional stimuli, both positive and negative. With this information in hand I then set out to examine the influence of other negative emotions on memory. Because of the constraints in terms of the number of events necessary to obtain sufficient statistical power in an event-related fMRI experiment, on the one hand, and the time constraints associated with a standard scanning session, on the other, I conducted a neuroimaging study similar to the original one (see Introduction) (Sergerie et al., 2006), but replacing fear by another negative facial expression. Such an approach also had the added advantage of allowing me to compare the findings from both studies. For this study, I chose sadness as the negative emotion, because although it has a high negative valence similar to that of fear, it is, in contrast to the latter, a low arousal emotion (J. A. Russell, 2003). This is of particular interest, as it has been argued that the enhancement of memory for emotional material is related to arousal rather than valence (Kensinger, 2004; Kensinger & Corkin, 2004). In addition, sad and happy expressions are basic emotions that are encountered in everyday life, have powerful social value and are easily decoded, even in clinical groups (Heimberg *et al.*, 1992; Christian G. Kohler *et al.*, 2003; Leppanen, 2006; K. Mogg *et al.*, 2000). Thus, nineteen healthy individuals performed a recognition memory task on faces with happy, sad and neutral expressions while undergoing functional magnetic resonance imaging (fMRI). We focused on the behavioral and neural-related emotional modulation of response bias (overall tendency to classify items as new, or old, regardless of the accuracy of the response).

Chapter 3

Influence of Emotional Expression on Memory Recognition Bias: A Functional Magnetic Resonance Imaging Study

"I never forget a face, but in your case I'll be glad to make an exception"
Groucho Marx

3.1. INTRODUCTION

Research into the modulation of memory performance by emotion and its neural underpinnings in healthy individuals has significantly contributed to our understanding of the abnormal patterns of emotional memory observed in psychiatric populations, such as schizophrenia (Calev & Edelist, 1993; Exner *et al.*, 2004; Moritz *et al.*, 2004; Neumann *et al.*, In press), anxiety disorders (Gilboa-Schechtman *et al.*, 2002) and depression (Pine *et al.*, 2004; Watkins *et al.*, 1992; Watkins *et al.*, 1996; Weniger *et al.*, 2006). Numerous studies have shown an enhancement of memory for emotional (Canli *et al.*, 1999; F. Dolcos *et al.*, 2004b; S. Hamann, 2001; S. B. Hamann *et al.*, 1999), especially negative (Cahill *et al.*, 1996; Canli *et al.*, 2000; Heuer & Reisberg, 1990; Kensinger & Corkin, 2004; Sergerie *et al.*, 2005, 2006), stimuli in healthy individuals. They have also made significant progress in delineating the neural network involved in this modulation of memory accuracy by emotion. Yet, there is some evidence supporting the idea that emotion can also influence other aspects of memory. For example, some authors have found that negative stimuli are more likely to be classified as old (Maratos *et al.*, 2001; Windmann & Kutas, 2001), independently of whether they are actually old or new, although the opposite effect (i.e., tendency to classify them as new), has also been reported (Phaf & Rotteveel, 2005). Furthermore, an increased rate of false recognition errors or intrusions for emotional items has been shown to partly explain some of the enhanced mood-congruency effects of memory found in patients with anxiety disorders (K. Mogg & Mathews, 1990) and major depression (Moritz *et al.*, 2005; Ridout *et al.*, 2003), as well as in high trait-anxiety individuals (Dowens & Calvo, 2003). These

findings suggest that some of the observed effects of emotion on memory in healthy individuals and the corresponding abnormal patterns reported in psychiatric groups may not only be due to differences in the formation or retrieval of true memories. For instance, these patterns could also reflect an influence of emotional valence on the relative number of false memories or in the willingness to endorse ambiguous stimuli as previously seen.

In a memory recognition paradigm, this tendency to judge items as previously seen, regardless of whether it is the case or not, can be dissociated from true memory success and operationalized in terms of the response bias (Snodgrass & Corwin, 1988). Specifically, whereas accuracy is measured by the rate of hits minus false alarms, false memories are assessed by the response bias, which measures the tendency to incorrectly classify a new item as previously seen (corrected for overall accuracy). Importantly, these two aspects of memory are largely independent (Snodgrass & Corwin, 1988). For example, completely random responses would correspond to chance accuracy and no response bias, whereas a classification of all stimuli as previously seen (saying always "old") would also result in a chance level for accuracy but would correspond to an extreme value of familiarity bias.

In terms of neural substrates of the memory-related response bias, several studies have highlighted the role of prefrontal cortex. Patients with frontal damage show a higher false alarm rate (Curran *et al.*, 1997; Swick & Knight, 1999), while having comparable hit rates to control subjects (Swick & Knight, 1999). Consistent with this, Windmann and colleagues observed differences in the early ERP components (ca. 300ms) of the response in prefrontal cortex sites for the subjective old (hits and false alarms) versus new (misses and correct rejections) responses as a function of the participants' overall behavioral familiarity bias, without any differences for the objective old/new comparison

(Windmann *et al.*, 2002). Furthermore, this early prefrontal signal difference between subjective old and new was modulated by the emotional valence of the stimuli, possibly reflecting an automatic, preattentive influence of emotion on recognition bias (Windmann & Kutas, 2001).

Another structure that is likely to be involved in the emotional modulation of response bias is the amygdala. Indeed, this region has been implicated not only in the enhancement of memory for emotional stimuli (Dolan *et al.*, 2000; F. Dolcos et al., 2004b, 2005; S. Hamann, 2001; Kensinger & Schacter, 2005; Maratos et al., 2001; Phelps, 2004; Sergerie et al., 2006; Strange & Dolan, 2004; Tabert *et al.*, 2001), but also in the subjective feeling of remembering negative stimuli (Sharot *et al.*, 2004).

Here, we conducted a fMRI study to directly investigate the behavioral and neural correlates of response bias in recognition memory for emotional stimuli in healthy volunteers. We used faces depicting different emotional expressions, as these are powerful stimuli which convey crucial information used for social interactions and which have been extensively employed to examine the neural correlates of emotional processing in healthy individuals (Haxby *et al.*, 2002; Luiz Pessoa *et al.*, 2002; L. Pessoa & Ungerleider, 2004; Posamentier & Abdi, 2003) as well as in psychiatric populations (Leppanen, 2006; Mandal *et al.*, 1998; Karin Mogg & Bradley, 1998). We specifically chose sad and happy expressions, as these are basic emotions that are encountered in everyday life and are easily decoded, even in clinical groups, (Heimberg *et al.*, 1992; Kohler *et al.*, 2003; Leppanen, 2006; K. Mogg *et al.*, 2000).

Another important advantage of using facial expressions as emotional stimuli is that they do not suffer from the potential confounds due to the overlap between stimulus emotionality and complexity and/or unusualness which are often encountered with words

or pictures (Adolphs *et al.*, 2001; Ochsner, 2000; Talmi & Moscovitch, 2004). Furthermore, because of the nature of face stimuli, it is possible to objectively determine the degree of physical similarity among stimuli within and between emotional categories. This latter point is critical when investigating the potential expression-induced modulation of memory performance, although it has not been taken into account in the previous research. Here, we directly addressed this issue by performing an eigenface analysis (Turk & Pentland, 1991) of the stimuli and calculating similarity matrices for the three emotional categories.

3.2. MATERIAL AND METHODS

3.2.1. Subjects

Twenty healthy right-handed volunteers (ten male) participated in the study (age 26.9±3.4 years). None of the participants had a history of neurological conditions, psychiatric disorders or substance abuse, based on self report, nor were they taking any psychotropic medications at the time of study. All procedures were approved by the Research Ethics Committee of the Montreal Neurological Hospital and Institute. One subject (female) was removed from the final analysis due to excessive movement.

3.2.2. Stimuli

Photographs of individuals depicting sad, happy or neutral facial expressions were selected from four databases (Sergerie et al., 2006). A total of 168 stimuli were used, each corresponding to a different individual. Stimuli were converted to gray-scale and

adjusted for face size, contrast, and resolution. Stimuli were divided into two subsets, each with 28 sad, happy and neutral faces (half male).

3.2.3. Task Procedure

The experiment consisted of two runs, encoding and recognition. During the encoding phase, 84 faces taken from one subset (counterbalanced across subjects) were presented twice, in a pseudo-random order. Subjects were instructed to make a gender judgment by clicking on a mouse and to remember the stimuli.

During the recognition phase, the same stimuli were presented with a same number of new faces never seen before. Subjects were asked to judge whether each face had been previously presented or not (old/new judgment). Following the scanning session, subjects were asked to rate all the faces in terms of valence using a visual-analog scale (range very negative to very positive: 0-100).

The stimulus time presentation was 2.5s with an average inter-trial interval (ITI) of 4s. In order to achieve a good estimate of baseline activity, several longer ITIs (so-called null-events) were also included. This resulted in a slightly de-synchronized ("jittered") presentation of the stimuli as compared to the onset of volume acquisitions, thus increasing the effective sampling rate (Josephs *et al.*, 1997).

3.2.4. fMRI Acquisition

Scanning was performed on a 1.5 Tesla Siemens Sonata system at the Montreal Neurological Institute (MNI). The experiment was run using E-PRIME. Functional T2*-weighted images were acquired using blood oxygenation level-dependent (BOLD)

contrast (TR=2540 ms, TE=50 ms, Flip angle=90°, FOV=256 mm, Matrix=64x64), covering the entire brain (30 interleaved slices parallel to the anterior-posterior commissural plane; voxel size 4x4x4mm). Two functional runs of 350 volumes each were acquired (encoding and recognition). An anatomical volume was also acquired (voxel size $1x1x1mm^3$).

3.2.5. Data Analysis

3.2.5.1. Behavioral data

Memory performance was calculated according to the Two-High Threshold Model (Snodgrass & Corwin, 1988) by means of the discrimination index Pr

$$\Pr = H - FA$$

and the response bias Br

$$Br = \frac{FA}{[1-(H-FA)]},$$

where H and FA represent hit and false alarm rates, respectively. The former provides an unbiased estimate of the accuracy in the response to old and new items, where higher values correspond to better (more accurate) memory. The response bias, in contrast, is an index of the overall tendency to respond "old" or "new" regardless of accuracy. In this case, positive values indicate a tendency to say "old" (i.e., a familiarity bias), whereas the negative side of the scale represents a novelty bias (that is, a propensity to say "new"). Importantly, the Pr and Br measures are independent (Snodgrass & Corwin, 1988).

3.2.5.2. Neuroimaging

fMRI data was pre-processed and analyzed with SPM2 using standard procedures as we have previously done (Sergerie et al., 2006). For the recognition run, twelve event types based on facial expression (sad, happy, neutral), presentation (old and new) and accuracy (correct and incorrect) were defined, based on each subjects' performance. We also included the six covariates corresponding to the movement parameters obtained from the realignment procedure. Linear contrasts of subject-specific parameter estimates for conditions of interest were calculated and taken to a second-level random effects model. Main effects were calculated with a one-sample t-test, whereas correlations with behavioral measures (response bias) were entered in a simple regression model, using a threshold of $p<0.0005$ (uncorrected). To identify regions commonly activated for happy and sad faces, we used a conjunction analysis according to the Minimum Statistic compared to the Conjunction Null Hypothesis (MS/CN; (Nichols *et al.*, 2005)), by setting a threshold of 0.005 for each contrast separately and combining the resulting statistical maps with the logical AND function, thus yielding an overall threshold of significance of $p<0.005^2$. We then identified those voxels from this analysis that also exhibited a significant ($p<0.05$ uncorrected) main effect of subjective old vs. subjective new for either happy of sad expressions.

3.2.5.3. Eigenface Analysis

We assessed whether potential differences in memory performance for the different facial expressions could have been influenced by the intrinsic physical properties of the stimuli used. Specifically, we determined the degree of similarity among the faces belonging to each emotional category using the "eigenface" method based on a principal component

analysis (PCA) technique (Turk & Pentland, 1991). We first divided each face image in a grid of 289x190 pixels, with the intensity of the pixel (0-255) as the value for each point. The resulting matrices were submitted to a PCA, from which a set of eigenvectors (*eigenfaces*) were obtained. Each face could then be fully represented by the weights associated with each eigenface. That is, each original face could be thought of as a point in a multi-dimensional space defined by the eigenfaces. Therefore, an expression-specific distance (or similarity) matrix can be built by calculating the Euclidean distance between all pairs of faces for each category. Furthermore, for each face, we calculated a mean distance to all the other faces in the group. We then tested whether there were any significant differences among these distances between the three expressions either in terms of medians or overall distributions.

3.3. RESULTS

3.3.1. Behavioral Results

There was a significant effect of expression on accuracy, as measured by Pr ($F(2,36)=9.4$, $p=0.001$). Post-hoc comparisons revealed that this effect was due to a worse performance for sad faces (Pr: Mean=0.41, SD=0.12), compared to both happy (Pr: Mean=0.54, SD=0.11; $p<0.001$) and neutral (Pr: Mean=0.51, SD=0.13; $p<0.05$) expressions. No difference in accuracy between happy and neutral faces was observed ($p>0.4$). Interestingly, separate analyses for old and new stimuli revealed, however, that memory for old sad faces (78%) was in fact better than for neutral (73%; $t(18)=2.12$, $p<0.05$) or happy (72%; $t(18)=2.63$, $p<0.02$) expressions. In contrast, memory for new sad expressions (63%) was much lower than happy (82%; $t(18)=7.59$, $p<0.0001$) or neutral (79%; $t(18)=4.21$, $p<0.001$) faces, suggesting an influence of expression on response

criteria. Consistent with this, we observed a significantly positive response bias for sad expressions (Br: Mean=0.12, SD=0.14; $p<0.001$), reflecting a familiarity bias. Notably, happy expressions were associated with a negative (novelty) response bias (Br: Mean=-0.11, SD= 0.13; $p<0.001$). In contrast, there was no significant bias for neutral expressions, as the corresponding Br was not statistically different from zero (Br: Mean=-0.07, SD= 0.20; $p>0.2$). As expected, Pr and Br values were not significantly correlated (0.01, $p>0.9$).

A repeated-measures ANOVA for reaction times (RTs) for new faces with accuracy and emotion as within-subject factors revealed a significant effect of accuracy ($F(1,18)=21.3$, $p<0.001$) and an interaction between expression and accuracy ($F(2,36)=10.6$, $p<0.001$). These effects were due to an overall faster RTs for correct than incorrect responses and a significantly slower RTs for correct new responses for sad faces, respectively, as shown in Figure 1. That is, whereas subjects were faster to correctly identify new neutral and happy faces, they took longer to correctly decide that a sad face was new. This slower RT for correctly identified new sad faces provides further support for the familiarity bias, as subjects had to overcome their tendency to say old to respond correctly, thus taking longer to do so.

An ANOVA with category as main factor and rating as the dependent variable confirmed the a priori assignment of each face to the sad, neutral or happy category ($p<0.001$).

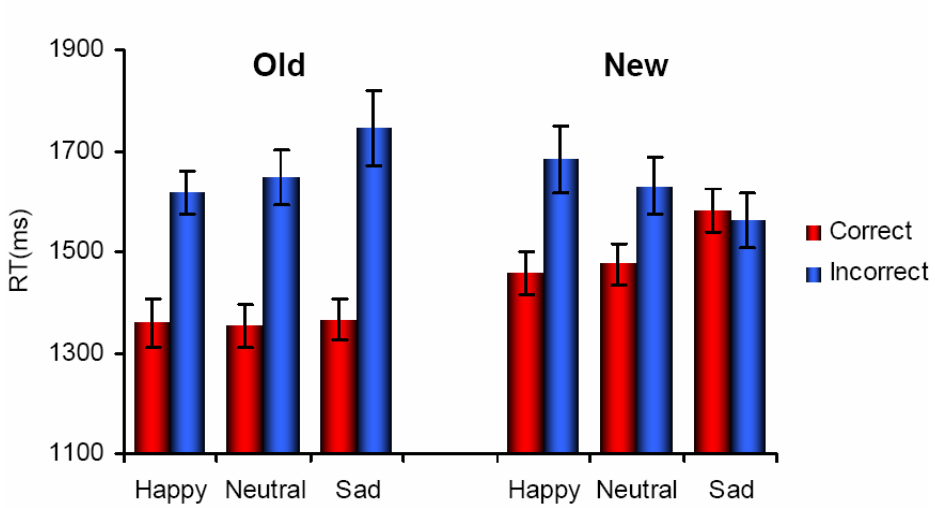

Figure 1. Reaction Times for old and new responses for each facial expression (happy, neutral and sad) as a function of accuracy. Error bars represent one standard deviation of the mean.

3.3.2. Eigenface Analysis

Similarity matrices for the three facial expressions are shown in Figure 2. A Kruskal-Wallis test revealed no significant differences in the median of the within-category mean distance between expressions ($\chi^2(2)=3.53$, $p>0.1$). Furthermore, pairwise comparisons using a Kolmogorov-Smirnov statistic confirmed that there were no significant differences in the mean-distance distributions between expressions (all $p>0.3$). Thus, these results suggest that any modulation of memory performance by emotion was unlikely to be due to differences in the degree of similarity among faces for the three expressions.

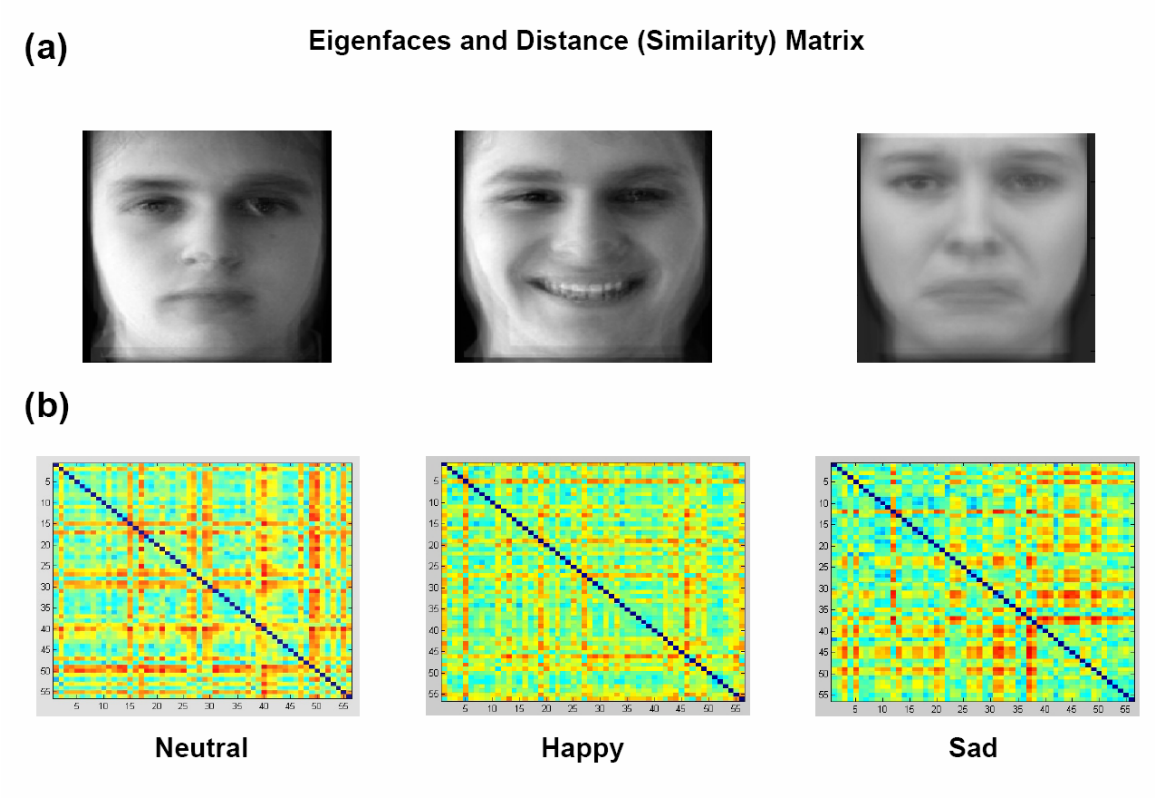

Figure 2. (a) Examples of eigenfaces and **(b)** distance matrices for each facial expression.

3.3.3. fMRI results

In order to investigate the neural correlates of the observed memory bias for emotional faces, we conducted a random-effects analysis in which the contrast *subjective old* (i.e., hits and false alarms) minus *subjective new* (correct rejections and misses) was correlated with the behavioral memory bias response (Br) for each subject, for each expression. These are shown in Table 1.

Table 1. Significant activations associated with the correlation between behavioral response bias (Br) and the contrast subjective old (hits and false alarms) minus subjective new (misses and correct rejections).

Region	Coordinates						Z-score
	Left			Right			
	x	y	z	x	y	z	
Sad							
Middle Frontal Gyrus	-20	24	36				3.54
Superior Temporal Gyrus	-38	-50	26				3.88
Amygdala				22	-8	-28	3.71
Happy							
Superior Frontal Gyrus				8	60	-6	4.14
	-16	22	46				4.04
	-12	34	50				3.91
Inferior Frontal Gyrus	-34	24	-18				3.93
Insula	-32	-20	24				4.06
Cingulate Gyrus	-16	-16	40				3.90
				18	-48	24	4.24
Lingual Gyrus	-4	-90	-10				4.09
Superior Parietal Lobule	-30	-58	38				4.22
Inferior Parietal Lobule				44	-36	34	4.29
Superior Temporal Gyrus	-54	-8	12				3.95
Middle Temporal Gyrus	-60	-38	-14				4.36
	-56	-8	-12				4.10
				50	0	-22	4.51
				44	-14	-16	4.20
Inferior Temporal Gyrus				62	-14	-24	4.15
Parahippocampal Gyrus				30	-36	-8	3.68
Cuneus				0	-94	-2	4.08
Amygdala	-26	2	-26				3.98
Amygdala	-24	0	-24				3.86
Amygdala				22	-2	-24	3.51
Hippocampus	-26	-14	-22				3.99
Neutral							
Superior Frontal Gyrus				36	-44	-6	3.99
Superior Temporal Gyrus				42	16	-46	4.13
Middle Temporal Gyrus				40	14	-48	4.11

Note: Coordinates of local maxima ($p < 0.0005$ uncorrected) are in MNI space.

We then isolated those regions common to both sad and happy expression by performing a conjunction analysis (see Methods). Results are shown in Table 2 and Figure 3. Table 2 also shows the main effect of the contrast subjective old vs. new for each expression for the peak voxels obtained in the correlation analysis. These show that the amygdala and the superior frontal gyrus were significantly more active for those

happy faces judged to be new than those thought to have been previously seen. No voxel was significant in the opposite contrast. In the case of sad faces, the only significant effect was in the STG, which exhibited stronger responses to subjective old than new stimuli.

Table 2. Significant activations for the correlation between the behavioral response bias (Br) and the conjunction of the contrasts subjective old minus new for sad and happy faces. The last two columns show the z scores for the main effect of subjective old minus new for each emotion (a negative score indicates that the effect is in the opposite direction)

Region	**Coordinates**						**Min Z-score**	**Main Effect sad z-score**	**Main Effect happy z-score**
	Left			**Right**					
	x	**y**	**z**	**x**	**y**	**z**			
Superior Frontal Gyrus				12	36	50	2.63	0.10	**-2.31***
Middle Frontal Gyrus	-26	28	44				2.64	0.45	-0.37
Middle Frontal Gyrus	-20	24	40				3.25	0.88	-0.37
Middle Frontal Gyrus	-24	20	48				2.63	1.22	-0.24
Insula	-26	-24	24				2.90	1.10	-0.95
Posterior Cingulate Gyrus				14	-50	24	3.14	1.01	-0.97
Superior Temporal Gyrus	-42	0	-18				2.83	**3.31***	-0.09
Superior Temporal Gyrus	-38	-48	24				2.61	-1.15	-0.39
Angular Gyrus	-38	-54	26				2.76	-0.89	-1.59
Superior Temporal Gyrus				46	-62	20	3.20	-0.14	-1.58
Parahippocampal Gyrus				18	-34	-2	3.01	-0.26	-1.09
Amygdala				22	-6	-26	2.89	0.83	**-2.23***

Note: Coordinates of local maxima ($p<0.005^2$ uncorrected) are in MNI space.
*$p < 0.05$ (uncorrected)

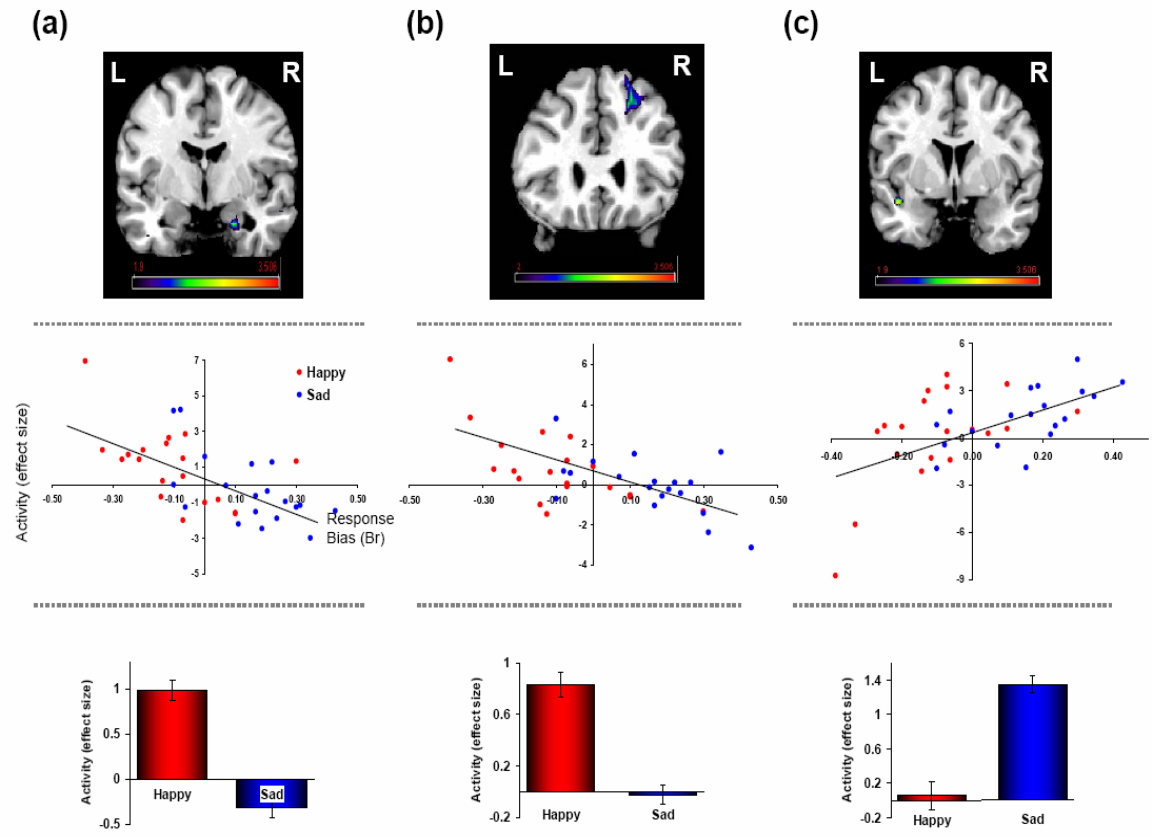

Figure 3. ***Top*** Statistical parametric maps showing the activations associated with the correlation between the response bias and the conjunction, for happy and sad expressions, of the contrast subjective new minus subjective old in **(a)** amygdala and **(b)** Superior Frontal Gyrus (SFG) and for the contrast subjective old minus subjective new in **(c)** the Superior Temporal Gyrus (STG). The activations were rendered onto the subject-averaged anatomical image, normalized to Talairach space using the MNI template, and thresholded at $p<0.005^2$; ***Middle*** Scatterplots of the correlations at the peak voxel of each of these regions. ***Bottom*** Effect sizes for the contrast subjective new minus old for sad and happy expressions at the peak voxel for each region.

3.4. DISCUSSION

Emotion can enhance memory, especially when the stimuli used have a negative valence. Our results show that emotion can also lead to a decrease in memory performance, as participants performed worse for sad faces, compared to both happy and neutral expressions. Critically, this detrimental effect of emotion on memory was due to a difference in response bias; that is, subjects were more likely to believe that they had

previously seen a sad face before, regardless of whether this was the case or not, resulting in a significant familiarity bias.

In contrast, happy faces were associated with a novelty response bias without any significant differences in accuracy when compared to neutral faces. Importantly, reanalysis of our data from a recent study, using the same paradigm (Sergerie et al., 2006), also revealed a significant novelty bias for happy faces (Br: Mean=-0.11, SD=0.22; $t(17)=2.2$, $p<0.05$). In contrast, in that study, fearful faces were associated with a net enhancement of memory without a significant response bias (Br: Mean=-0.04, SD=0.25; $t(17)=0.76$, $p>0.4$). Thus, taken together, results from this and our previous study (Sergerie et al., 2006) suggest that memory for faces is differentially modulated by the expression, both in terms of accuracy and response bias. Notably, our eigenface analysis of the stimuli suggests that this emotion-dependent response bias is unlikely to be due to simple perceptual features (for example, sad faces being more similar to each other and thus resulting in a higher confusion between old and new stimuli). The differential effects of expression on memory for fearful and sad faces are particularly interesting, as these two emotions are associated with similar negative valence but different levels of arousal (Posner *et al.*, 2005). This is consistent with studies suggesting that the enhancement of memory for emotional material only occurs, or at least is stronger, for high-arousal stimuli (Canli et al., 2000; Florin Dolcos *et al.*, 2004a). Alternatively, sad faces could elicit a strong empathic emotional reaction, making participants focus more on the feeling elicited by the faces. This would then lead to a sense of familiarity during recognition, based on the emotion rather than identity.

3.4.1. Neural correlates of emotional response bias

3.4.1.1. Novelty bias

The observed correlation of amygdala activity and novelty bias for emotional faces is consistent with the postulated role of this structure in the detection of emotional stimuli (Dubois *et al.*, 1999) and its rapid habituation to repeating occurrences of the same event (Breiter *et al.*, 1996; Fischer *et al.*, 2000; Wright *et al.*, 2001). Our results suggest that the amygdala response may influence the decision to consider a stimulus as novel or not. In addition, this observed amygdala involvement in the shift of response towards a novelty bias brings a new light in its traditional role in the detection of objective new emotional stimuli, that is the amygdala can also play a role in the "subjective feeling of novelty" for emotional material, regardless of the valence.

Although it is generally agreed that the dorsal prefrontal cortex (dPFC) is involved in memory retrieval (Buchel *et al.*, 1998; Fletcher *et al.*, 1997; E. Tulving *et al.*, 1994), its specific function appears to be more related to a controlled evaluation of the retrieval product, rather than to a simple familiarity-based assessment (Schacter et al 1996; Ranganath et al 2000). In particular, activity of this region has been associated with the detection of novel stimuli, including faces (Wiser *et al.*, 2000), especially when there is ambiguity in the information, such as when a familiar but new stimulus is encountered. For example, Van Petten at al. (Van Petten *et al.*, 2002) found prefrontal activity associated with the presentation of rearranged pairs of old words, regardless of accuracy. Similarly, Duzel and colleagues (Duzel *et al.*, 2004) reported significant activation of right dPFC when contrasting rearranged pairs of old pictures of faces and tools with the original arrangements. Interestingly, the opposite contrast resulted in anterolateral temporal activation (see below). Because performance in this previous study was almost

perfect, it would not be possible to distinguish whether this activity was associated with the subjective or the objective new responses. The correlation between dPFC activation and novelty bias observed in our study provides further support for the hypothesis that dPFC may be involved in novelty detection of stimuli that have a certain degree of familiarity (e.g., new arrangement of old stimuli). Indeed, subjects had to ignore the feeling of familiarity elicited by the reoccurrence of sad or happy expressions in order to judge a face as new.

3.4.1.2. Familiarity bias

The activation cluster involved in the subjective old responses (i.e., familiarity) was located in the anterolateral superior temporal gyrus. Lesion studies have suggested that this region may be critical for memory for people, as patients with lesions encompassing this part of the brain are impaired in famous faces recognition tests (Damasio *et al.*, 1996). Furthermore, electrophysiological recordings show that some neurons in the anterior temporal cortex respond selectively to familiar faces (Seeck *et al.*, 1995). Functional neuroimaging studies have also provided evidence for a role of this region in the recognition of familiar faces (Leveroni *et al.*, 2000; Nakamura *et al.*, 2000; Sergent *et al.*, 1992; Sugiura *et al.*, 2001; Tempini *et al.*, 1998). For example, Gorno-Tempini and colleagues (Tempini et al., 1998) found a significant activation in left anterior temporal gyrus for the contrast of famous vs. nonfamous faces.

The STG, including its anterior aspect, has been also implicated in the processing of sad stimuli. Gross and colleagues (Goldin *et al.*, 2005; Hutcherson *et al.*, 2005) found that this region was significantly activated when participants were viewing sad films. In

addition, Britton et al. (Britton *et al.*, 2006) observed activation in STG for sad faces, compared to neutral expressions.

Thus, our findings and those of previous studies suggest that this brain region may be involved not only in the perception of emotional stimuli, especially those associated with sadness, but also in the retrieval of contextual information related to the stimulus, in particular in terms of their perceived familiarity.

3.4.2. Clinical Implications

Our findings show that an apparent emotional memory deficit in terms of accuracy, such as the one obtained here for sad faces, may be better characterized as a difference in the criterion used to decide on the history of a stimulus. This observation is particularly relevant in the context of studies reporting abnormal patterns of emotional memory in patients suffering from psychiatric disorders (Calev & Edelist, 1993; Exner et al., 2004; Gilboa-Schechtman et al., 2002; Moritz et al., 2004; Neumann et al., In press; Pine et al., 2004; Watkins et al., 1992; Watkins et al., 1996; Weniger et al., 2006). Indeed, our findings strongly suggest that some of these observations may not simply reflect a difference in the ability to encode or retrieve this information but, rather, to a difference in the response bias. Future studies in clinical populations are necessary to directly test this hypothesis and, more importantly, to assess whether these putative difference in emotional memory bias are associated with current symptomatology or, instead, they represent a trait-like, perhaps even premorbid, disposition. This latter issue is of particular interest given that several of the brain regions often reported to be dysfunctional in patients overlap with those we found to be involved in the emotional influence of

response bias, such as the amygdala and prefrontal cortex (Beyer & Krishnan, 2002; Cannon *et al.*, 1998; Exner et al., 2004; Molina *et al.*, 2004; Volk & Lewis, 2002; Weniger et al., 2006).

3.4.3. Limitations

One potential limitation of our study is that we used an old/new paradigm, rather than other, more complex designs such as those including a remember/know response (Endel. Tulving, 1985) or a confidence rating for each old judgment. By comparing remember vs. know responses or the degree of confidence attributed to each response, these paradigms are useful to isolate the "feeling of remembering" independently of accuracy. While our paradigm did not allow us to perform such comparisons, it had the advantage that, the response bias measure we used did not rely on subjects' introspective evaluation of the strength of their memory trace but, rather, on their (arguably more ecologically relevant) judgment of whether they thought they have previously encountered a particular person or not.

Another potential limitation of our study is that we did not differentiate between valence and arousal due to the significant correlation between these two dimensions in facial expressions (Sergerie et al., 2006). Thus, it remains a possibility that the difference in response bias observed for happy and sad faces could be due to differences in intensity or arousal in addition to valence. Our results from this and our previous study involving fearful faces suggests that in fact there may be an interaction between valence and arousal in the influence of facial expressions on memory accuracy and response bias (see above). Future studies are necessary to further explore these questions.

ACKNOWLEDGMENTS

This study was supported by the Canadian Institutes of Health Research (MOP 53280 to M. L. and MOP 57724 to J. L. A.). J. L. A. is supported by the Canada Research Chairs Program. The authors declare no conflict of interest.

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Our previous study demonstrated that different negative emotions can have an effect of memory and that, critically, this effect can be observed not only at the level of accuracy (as was the case with fearful expressions) but also in terms of response bias.

The study of emotional memory has important implications not only for our understanding of the workings of the healthy emotional brain, but it can also have clinical relevance. Indeed, several psychiatric disorders are associated with deficits in emotional perception and memory. In particular, schizophrenia is characterized, as much by the more thoroughly studied cognitive deficits (e.g., memory, executive functions, attention, etc) as it is by a variety of emotional and social disturbances. Critically, these impairments have a substantial negative impact in the patients' quality of life. Thus, it becomes crucial to gain a better understanding of the emotional deficits associated with this disorder. In particular, studying the influence of emotional expressions, particularly those with a social relevance, on perception and memory can contribute to a better understanding of the aetiology of some of the symptoms associated with this disorder. I thus conducted an fMRI study of the influence of facial expressions memory in this population. Specifically, I used the same paradigm as in healthy controls in order to directly compare the two groups both at the behavioral and neural levels. That is, participants performed a recognition memory task on faces depicting sad, happy and neutral expressions during scanning. Patients with DSM-IV–defined schizophrenia were recruited from the outpatient clinics of the Douglas Institute, whereas matched healthy controls were recruited in the community through advertisements.

Behavioral memory accuracy (Pr) and response bias (Br) were measured during memory recognition. Brain activity associated with the contrast subjective old minus

subjective new responses was correlated with the behavioral response bias for happy and sad expressions and with symptom severity.

Chapter 4

Influence of Emotional Expression on Memory Recognition Bias in Schizophrenia as revealed by fMRI

"Schizophrenia will continue to be a mystery so long as we fail to understand the forces and the organization which make for the wholeness of the personality"
Anthony Storr

4.1. INTRODUCTION

Since early last century (Bleuler, 1950), emotional dysfunction has been considered a hallmark of schizophrenia. This deficit can have significant consequences for many aspects of an individual's daily life. In particular, they may interfere with the successful formation of associations between relevant environmental cues and their proper emotional significance or salience (Kapur, 2003). Indeed, it is now generally accepted that emotion can help cognition by prioritizing biologically-relevant information (Damasio, 1994). Specifically, when the information is appropriately associated with its emotional context, it can influence our motivation and regulation of emotional states, as well as guide our future behavioral responses by referring to these learned associations in memory. Incorrect or aberrant associations could, however, lead an individual to assign inappropriate emotional significance to environmental information, resulting in severe impairments in his/her social interactions.

A few studies have directly investigated the influence of emotion on memory performance in schizophrenia, but have so far yielded conflicting findings. Namely, whereas some have reported group differences in the modulation of memory accuracy by emotion (Hall *et al.*, 2007; Herbener *et al.*, 2007; Neumann *et al.*, 2007), others found that, despite an overall lower performance in patients, the effect of emotion on accuracy was similar for both groups (Danion *et al.*, 2003; Mathews & Barch, 2004). Given the differences in the task (e.g., recognition vs. recall), response type (old/new vs. remember/know), time of testing (e.g., immediate vs. delayed) and material (e.g., words

vs. pictures), it is difficult to draw any definite conclusions in terms of memory deficits associated with emotional stimuli. Furthermore, while most of the studies that found a group difference observed a lack or reduction of memory enhancement, others have reported a stronger influence of emotion on memory in the schizophrenia group than in healthy controls (Herbener et al., 2007; Neumann et al., 2007).

Importantly, emotion can modulate recognition memory not only in terms of accuracy but also in relation to response bias, that is, the overall tendency to judge stimuli as previously seen or not, regardless of whether that was the case or not (Dougal & Rotello, 2007; Windmann & Kutas, 2001; Windmann *et al.*, 2002). For instance, in a recent series of experiments, we observed that whereas a memory enhancement, in terms of accuracy, was observed for fearful faces, compared to neutral ones (K. Sergerie *et al.*, 2005; Karine Sergerie *et al.*, 2006), a significant increase in the proportion of false alarms (familiarity bias) was obtained for sad expressions (K. Sergerie *et al.*, 2007). In contrast, a tendency to classify faces as never seen before (novelty bias), in the absence of any changes in accuracy, was observed for happy expressions. Notably, amygdala activity was associated with the behavioral novelty bias for both happy and sad expressions, consistent with the proposed role of this region in emotional processing and novelty detection.

Interestingly, the few studies that have directly assessed the effects of emotion on response bias in schizophrenia reported a similar response bias in patients and controls, independently of recognition accuracy (Hall et al., 2007; Herbener et al., 2007). However, both studies used emotional pictures combining several negative emotions, including fear and sadness. Given the differential effects of these emotions on accuracy and response

bias in healthy individuals, it remains unknown to what extent the emotion-specific response bias patterns are similar in healthy controls and in people with schizophrenia.

We have therefore conducted an fMRI study to directly investigate the influence of individual emotions, namely happiness and sadness, on memory for faces in individuals with schizophrenia and healthy matched controls, using our previously validated paradigm (Karine Sergerie et al., 2006; K. Sergerie et al., 2007). This paradigm is particularly well-suited for investigating emotional memory in schizophrenia, given the independent effects of the different expressions on memory accuracy and response bias, and the engagement of the amygdala, a region which has been shown to exhibit abnormal functioning in schizophrenia (Aleman & Kahn, 2005; Brunet-Gouet & Decety, 2006; Raquel E. Gur *et al.*, 2007; Raquel E. Gur *et al.*, 2002). Furthermore, facial expressions are critical for conveying socially-relevant information, and, as such, have been shown to be an important component of the social dysfunction associated with schizophrenia (for reviews see (Edwards *et al.*, 2002; Kohler & Martin, 2006; Mandal *et al.*, 1998; Trémeau, 2006)). Finally, the use of face stimuli allowed us to derive an objective measure of stimulus similarity for each emotion, through the use of the eigenface method based on a principal component analysis technique (Turk & Pentland, 1991), and thus rule out the possibility that the results could be attributed to differences in the degree of physical similarity among stimuli for each emotional expression (K. Sergerie et al., 2007).

Our main objective was to assess whether, despite a predicted overall reduced memory accuracy, people with schizophrenia would exhibit the same influence of emotion on memory response bias as we previously observed in healthy individuals. We explored this question both at behavioral and neural levels. We performed a whole-brain analysis with particular emphasis on regions within the prefrontal cortex and medial

temporal lobes (amygdala, hippocampus and parahippocampal gyrus), given their established role in memory in the healthy brain, and the involvement of the amygdala in emotional novelty detection. In addition, several studies have highlighted these regions as exhibiting abnormal activation patterns in schizophrenia people while performing memory tasks, particularly in those distinguishing between conscious recollection and familiarity-based recognition (Achim & Lepage, 2005).

A secondary objective was to explore whether positive or negative symptoms influenced the neural correlates of this bias. Although the influence of symptom severity on emotional memory response bias has not been investigated, several studies have shown that positive and negative symptoms can modulate response bias to neutral items. For instance, it has been shown that hallucinations and delusions significantly correlated with false alarms or intrusions (Bentall & Slade, 1985; Brebion *et al.*, 2000; Brebion *et al.*, 2005; Brebion *et al.*, 1998; Ragland *et al.*, 2003). In contrast, a significant correlation was observed between a propensity towards a more conservative response bias in source memory tasks and some negative symptoms (Brebion et al., 2000; Brebion *et al.*, 1999). However, conflicting results have also been obtained (Ragland et al., 2003; Thoma *et al.*, 2006).

4.2. METHODS

4.2.1. Subjects

Thirty outpatients with DSM-IV-defined schizophrenia participated in the study. Ten participants were excluded from the final analysis due to excessive movement during the scan, poor behavioral performance or inability to complete the session. Demographic and

clinical characteristics of the patients included in the final analysis are shown in Table 1. Patients were recruited from the various outpatient clinics of the Douglas Institute. Diagnoses were made by the treating psychiatrist. All diagnoses were confirmed on the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P) and by medical records. All patients were administered the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989). In addition, patients completed the Wechsler Abbreviated Scale of Intelligence. The mean illness duration was 8.6 (SD=7.0). At the time of assessment, all patients had been clinically stable for at least 4 weeks and had been on a fixed medication regimen for at least 6 weeks.

Of the twenty patients included in the analysis, eighteen were taking antipsychotic medication (13 on second-generation antipsychotics, 5 taking a combination of second-generation and conventional antipsychotics) and two were neuroleptic free. None of the patients were taking an anticholinergic medication. The mean dose of antipsychotic medication was equivalent to 1019 mg/day of chlorpromazine, and medication was not withdrawn for the purposes of the study. None of the patients had a concurrent mood disorder at the time of the study, though 7 patients were receiving concomitant antidepressant medication and two patients were taking anticonvulsive medication.

Table 1. Demographic and clinical characteristics of the groups.

	Schizophrenia Group			Control Group			p-value (2-tailed)
	Mean	SD	Range	Mean	SD	Range	
Age	31.8	7.4	19-45	28.5	6.0	18-42	0.14
	N	**%**		**N**	**%**		
Sex							0.72
Female	9	45		10	50		
Male	11	55		10	50		
Parental Socioeconomic Status							0.26
Upper	2	10		3	15		
Upper-middle	4	20		8	40		
Middle	8	40		4	20		
Lower-middle	2	10		3	15		
Lower	4	20		2	10		
Handedness Categories							0.39
Right handed	15	75		18	90		
Moderately right handed	1	5		0	0		
Ambidextrous handed	2	10		1	5		
Moderately left handed	1	5		0	0		
Left handed	1	5		1	5		
SAPS*	8.7	8.7	0-33	--	--	--	
SANS*	16	7.2	2-26	--	--	--	

*SAPS: Scale for the Assessment of Positive Symptoms; SANS: Scale for the Assessment of Negative Symptoms

4.2.2. Stimuli

We used a previously validated set of 168 photographs of different individuals depicting sad, happy or neutral facial expressions (Karine Sergerie et al., 2006). Two equivalent subsets of stimuli were made from this set, each including 28 sad, happy and neutral faces (half male).

4.2.3. Task Procedure

The experiment consisted of two runs, *encoding* and *recognition*. During the *encoding* phase, one stimulus subset was presented twice, in a pseudo-random order (counterbalanced across subjects). Subjects were asked to perform a gender decision on the faces and also try to remember them.

During the *recognition* phase, subjects were presented with the same stimuli together with the other set, never seen before. Subjects were instructed to determine if a face had been previously seen or not (old/new judgment). Following the scanning session, subjects rated all the faces in terms of valence using a visual-analog scale (data from 6 controls and 5 patients was not available due to technical problems).

Stimulus duration was 2.5s with a mean stimulus onset asynchrony (SOA) of 4s. Longer SOAs (null events) were interspersed in a pseudo-random fashion to obtain an estimate of baseline. Stimulus presentations were de-synchronized with respect to the onsets of volume acquisitions to increase the effective sampling rate and thus get a better estimate of the hemodynamic response (Josephs *et al.*, 1997).

4.2.4. fMRI Acquisition

Scanning took place at the Montreal Neurological Institute (MNI), using a 1.5 Tesla Siemens Sonata. Functional T2*-weighted echoplanar images were acquired using blood oxygenation level-dependent (BOLD) contrast (TR=2540 ms, TE=50 ms, Flip angle=90°, FOV=256 mm, Matrix=64x64), covering the entire brain (30 interleaved slices parallel to the anterior-posterior commissural plane; voxel size 4x4x4mm). Two functional runs of 350 volumes each were acquired (*encoding* and *recognition*). An anatomical volume was also acquired (voxel size 1x1x1mm^3). Stimulus presentation and subjects response recording was done with a PC laptop running E-PRIME.

4.2.5. Data Analysis

4.2.5.1. Behavioral data

Memory performance was calculated according to the Two-High Threshold Model (Snodgrass & Corwin, 1988) by means of the discrimination index Pr

$$\Pr = H - FA$$

and the response bias Br

$$Br = \frac{FA}{[1-(H-FA)]} - 0.5,$$

where H and FA represent hit and false alarm rates, respectively. Notably, Pr and Br measures are independent (Snodgrass & Corwin, 1988). Whereas the former provides an unbiased estimate of memory accuracy, the latter is an index of the overall tendency to respond "old" or "new" regardless of accuracy. In this case, positive values indicate a familiarity bias (i.e., a tendency to say "old"), whereas the negative ones correspond to a novelty bias (that is, a propensity to say "new").

4.2.5.2. Neuroimaging

Functional data was analyzed using SPM2, as described elsewhere (K. Sergerie et al., 2007). We defined twelve event types based on facial expression (sad, happy, neutral), presentation (old and new) and accuracy (correct and incorrect, based on each subjects' performance). We also included the six covariates corresponding to the movement parameters obtained from the realignment procedure. Linear contrasts of subject-specific parameter estimates for conditions of interest were taken to a second-level random-effects model. Main effects for the schizophrenia group were calculated using a one-sample t-test and correlations with the response bias. Areas commonly activated by patients and controls were identified using a conjunction procedure according to the Minimum Statistic compared to the Conjunction Null Hypothesis (Nichols *et al.*, 2005), by setting a

threshold of 0.005 for each contrast separately, thus yielding an overall threshold of $p<0.005^2$. Differences between patients and controls were calculated with a two-sample t-test for the contrasts of interest. We then identified those voxels from this analysis that also exhibited a significant ($p<0.05$ uncorrected) main effect of subjective old vs. subjective new for either happy of sad expressions.

In addition, we examined the relation between activation maps between patients and controls by computing the Tanimoto coefficient, *T* (Tanimoto, 1957)

$$T(A,B) = \frac{A \cdot B}{\|A\|^2 + \|B\|^2 - A \cdot B}$$

This coefficient is an extension of the Jaccard index (Jaccard, 1901), which provides the ratio between the number of voxels commonly activated (i.e., the size of the intersection) and the total number of voxels activated by both groups (i.e., the size of union). However, whereas this value depends on the threshold of statistical significance and is similar to a vote-counting approach, the Tanimoto index takes into account not only whether a voxel is activated or not, but also the magnitude (and direction) of the effect.

4.3. RESULTS

4.3.1. Behavior

People with schizophrenia had an overall lower memory performance (Pr: Mean=0.33, SD=0.11) than healthy subjects (Pr: Mean=0.47, SD=0.10; $t(18)=4.75$, $p<0.0001$). There was a significant effect of expression on accuracy, as measured by Pr ($F(2, 38)=3.5$, $p< 0.05$), with the same pattern as that for healthy individuals. However, post-hoc comparisons showed that the effect was statistically driven by the happy faces, as accuracy for them was higher compared to both neutral ($t(19)=2.7$, $p<0.05$) and sad

(t(19)=2.3, p<0.05) expressions. Interestingly, separate analyses for old and new stimuli revealed that memory for old sad faces (74%) was in fact better than for neutral (66%; t(19)=3.56, p=0.002) or happy expressions (66%; t(19)=2.46, p=0.02), similar to the healthy group (Figure 1).

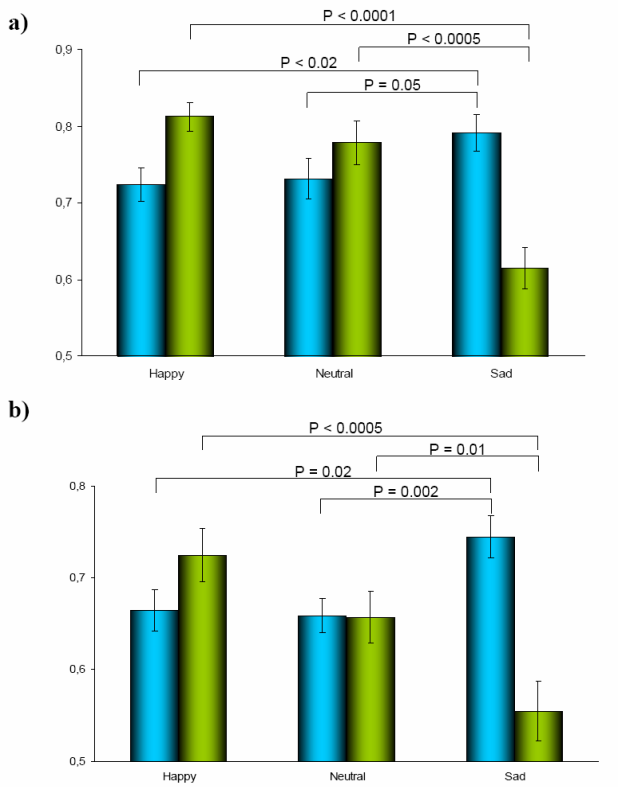

Figure 1. Mean memory recognition accuracy rates for old and new responses for each facial expression (happy, neutral and sad) for ***(a)*** healthy subjects and ***(b)*** individuals with schizophrenia. Error bars represent one standard error of the mean.

Thus, in both groups the differential effects of emotional expression on memory could be partly accounted for by a significant familiarity bias for sad faces (Br: Mean=0.12, SD=0.19; p=0.01). Although a novelty bias was observed for happy faces, this did not reach statistical significance (Br: Mean=-0.06, SD=0.20; p=0.2, see Figure 2). Finally, and similar to controls, patients did not show a significant bias for neutral expressions (Br: Mean=-0.01, SD= 0.14; p>0.5).

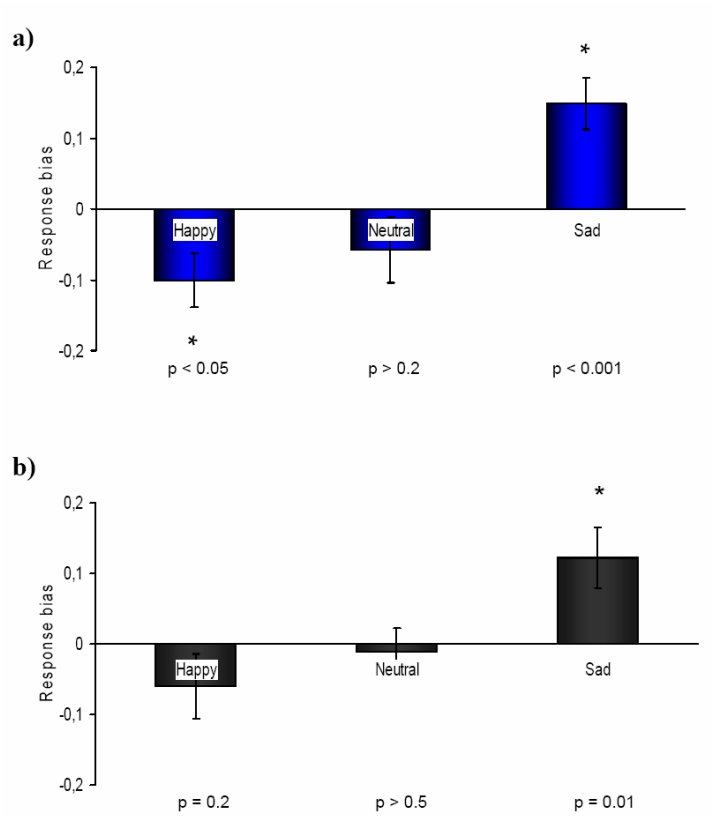

Figure 2. Memory response bias (Br) for each facial expression (happy, neutral and sad) for ***(a)*** healthy subjects and ***(b)*** individuals with schizophrenia. Error bars represent one standard error of the mean.

We also conducted a repeated-measures analysis of variance (ANOVA) with RTs as the dependent variable and subjective old (hits and false alarms)/new (correct rejections and misses) and accuracy as within-subject factors and group as a between-subjects factor. We obtained a significant main effect of accuracy [$F(1,37)=8.4$, $p=0.006$] and subjective old/new [$F(1,37)=12.3$, $p=0.001$], as well as an interaction between subjective old/new-by-accuracy [$F(1,37)=123.4$, $p<0.0001$]. These effects were due to an overall faster RT for correct than incorrect responses and for subjective old compared to subjective new. In addition, there was a triple interaction between subjective old/new-by-accuracy-by-group [$F(1,37)=8.7$, $p=0.005$]. Post-hoc analyses revealed that this effect was due to the fact that, whereas controls showed a faster RT for correct than incorrect new responses (i.e.,

correct rejections vs. false alarms), no significant difference was present in the schizophrenia group.

When including facial expression as a within-subject factor, the only new significant effect was a significant triple interaction between subjective old/new-by-facial expression-by-accuracy [$F(1,37)=9.6$, $p<0.0001$], driven by an overall slower RT for subjective new responses to sad faces.

A repeated-measures ANOVA of the ratings yielded a significant main effect of expression ($F(2,54)=335.8$, $p<0.0001$) but no main effect of group ($F<1$) or interaction between expression and group ($F(2,54)=1.1$, $p>0.3$). In addition, ratings by patients and controls for each stimulus were highly correlated ($r=0.98$, $p<0.0001$), confirming that both groups rated all the faces equally in terms of their emotional value.

Including IQ measures (WAISI full scale) and antipsychotic medication (equivalent chlorpromazine dose) did not have a significant effect on any of the behavioral results.

4.3.2. fMRI

In order to identify the brain regions associated with memory recognition bias, we conducted a correlation analysis between *subjective old* (i.e., hits and false alarms) minus *subjective new* (correct rejections and misses) with the behavioral memory bias response for each subject, for each expression (see (K. Sergerie et al., 2007)).

4.3.2.1. Individuals with schizophrenia

Results are shown in Table 2. Particularly noteworthy was the significant activation in the right amygdala for sad faces, corresponding to a positive correlation between the novelty bias and the subjective new minus subjective old contrast associated with this expression.

Table 2. Correlation between behavioral response bias and the contrast subjective old minus subjective new for the schizophrenia group.

Region	Coordinates						Z-score	
	Left			Right				
	x	y	z	x	y	z	r	M Effect
Sad								
Superior Frontal Gyrus	-30	30	54				3.56	-0.07
Inferior Frontal Gyrus	-50	34	12				3.39	-0.20
				26	28	-24	3.56	1.32
Precentral Gyrus	-42	-2	30				3.64	1.44
Anterior Cingulate	-6	46	2				3.38	1.93
Cingulate Gyrus	-8	-38	36				3.49	2.28
	-24	-42	24				4.23	-0.05
Posterior Cingulate				6	-30	22	4.48	0.25
Caudate				6	2	4	4.43	2.10
Putamen				28	-10	-4	4.39	2.29
Angular Gyrus				48	-64	32	3.53	1.65
Uncus				34	-10	-28	3.53	0.76
Parahippocampal Gyrus				22	-32	-4	3.84	0.33
Amygdala	-34	0	-26				3.32	2.47
				20	0	-20	3.13	-0.18
Happy								
Caudate				22	-32	24	3.75	0.01
	-10	-24	24				3.65	-0.53
Parahippocampal Gyrus	-30	-28	-28				3.51	-0.70
Neutral								
Superior Frontal Gyrus				32	54	32	4.29	4.03
	-2	36	54				3.56	-2.54
Middle Frontal Gyrus				32	36	50	3.65	0.88
Postcentral Gyrus				68	-12	14	4.13	-1.53
				20	-46	70	3.85	1.83
Posterior Cingulate	-8	-40	20				4.19	-2.43
Caudate				4	6	8	3.35	-1.58
Superior Temporal Gyrus	-40	-50	24				3.74	1.36
Inferior Temporal Gyrus				44	-4	-20	3.45	-0.39
Fusiform Gyrus	-40	-4	-28				4.31	2.18
Precuneus				26	-40	28	3.63	-0.24
Lingual Gyrus				14	-54	-4	3.75	-0.84
	-10	-54	-6				3.70	0.62
	-14	-80	-8				3.54	-1.33
Cuneus				2	-90	12	3.71	-2.44
Amygdala				32	0	-16	3.14	0.89

Note: Coordinates of local maxima ($p < 0.001$ uncorrected) are in MNI space.
r: Pearson's correlation coefficient
M Effect: main effect

In addition, activations within the frontal lobes and throughout the cingulate gyrus were observed. In contrast, a smaller network of regions was activated for the happy condition and, critically, these did not include the amygdala. Significant activations were observed in the caudate and parahippocampal regions for both happy and sad expressions, although these were located in non-overlapping voxels. In fact, a conjunction analysis did not yield

any significant voxels commonly activated in both cases, even when using a lower threshold ($p=0.01^2$).

4.3.2.2. Comparison between patients and controls

In order to directly identify the similarities and differences in the neural correlates of the memory recognition bias between schizophrenia patients and healthy individuals, we conducted conjunction and interaction analyses using the same contrast as mentioned above.

4.3.2.2.1. Conjunction

Table 3 shows areas commonly activated by both groups for the correlation between behavioral bias and the *subjective old* minus *subjective new* contrast for happy and sad expressions. Consistent with the individual group analysis, the conjunction for sad faces revealed a significant right amygdala and a bilateral parahippocampal gyrus, both corresponding to a novelty bias, as determined by the simple main effect contrasts. In addition, we found a right middle temporal gyrus activation correlating with the response bias in both groups, although exhibiting opposite directions for the corresponding main effect, namely a novelty bias in the control group and a familiarity one for patients. In the case of happy expressions, significant activations were observed in the caudate, parahipocampal gyrus, and hippocampus.

Table 3. Significant activations for the correlation between the behavioral response bias and the conjunction of the control and schizophrenia groups for the contrast subjective old minus new for both sad and happy faces.

Region	Coordinates						Min Z-score	Main Effect Controls z-score	Main Effect Patients z-score
	Left			Right					
	x	y	z	x	y	z			
Happy									
Caudate	-12	-26	24				3.35	-4.21*	0.73
				24	-30	20	3.45	-4.64*	-1.09
Parahippocampal Gyrus	-34	-26	-18				3.67	-4.86*	-4.87*
				28	-58	20	3.98	-5.42*	-1.02
Hippocampus				24	-16	-16	2.06	-1.81*	0.99
Sad									
Middle Temporal Gyrus				46	-66	20	4.22	-5.79*	2.40*
Parahippocampal Gyrus				22	-36	-6	2.69	-2.75*	0.70
	-32	-36	-12				3.01	-2.96*	-0.21
Amygdala				24	-6	-26	2.19	-1.99*	-0.71

Note: Coordinates of local maxima ($p<0.005^2$ uncorrected) are in MNI space.
The last two columns show the z scores for the main effect of subjective old minus new for each group (a negative score indicates that the effect is in the opposite direction), *p < 0.05 (uncorrected)

4.3.2.2.2. Interaction

As shown in Table 4 and Figures 3 and 4, only a few regions exhibited significant differential activations between groups for sad faces confirming the similar patterns associated with memory bias for both groups. Critically, no amygdala activation was observed even when lowering the statistical threshold (p=0.05 uncorrected). In contrast, in the case of happy faces, schizophrenia patients showed significantly less activations than healthy individuals over a widespread network, especially within the frontal lobes, as well as temporal regions, including the amygdala, hippocampus and parahipocampal gyrus (Figure 3 and 5a).

Table 4. Significant activations for the correlation between the behavioral response bias and the interaction between the control and schizophrenia groups for the contrast subjective old minus new for both sad and happy faces.

Region	Coordinates							Main Effect		Partial Correlation	
	Left			Right				Controls	Patients	SANS	SAPS
	x	y	z	x	y	z	Z-score	z-score	z-score	z-score	z-score
Controls > Patients											
Happy											
Superior Frontal Gyrus	-26	62	16				3.26	3.46*	0.00		
	-4	26	60				3.29	3.45*	-1.58		-2.51
				22	10	58	3.57	2.37	-3.46*		
Middle Frontal Gyrus	-44	38	0				3.87	2.91	-3.49*		
				36	36	-12	3.65	3.04	-2.76	-1.73	
				54	32	20	4.34	3.59*	-3.61*		
	-36	0	46				4.24	4.30*	-2.05		
Inferior Frontal Gyrus	-20	36	-8				3.29	2.44	-2.68		
				46	28	-10	3.55	2.78	-2.80		
	-44	28	-8				3.53	2.66	-3.00		-1.66
	-40	24	6				4.29	2.80	-4.54*		
				56	22	20	3.87	3.28*	-2.59		
	-32	22	-16				4.00	3.41*	-3.29*	-1.85	
				48	16	26	3.30	1.85	-3.52*		
Precentral Gyrus	-32	4	32				4.58	7.07*	-1.36		
Caudate	-12	8	16				3.93	2.79	-3.69*		
Insula	-28	-22	24				3.41	3.83*	-0.43		
Superior Parietal Lobule	-30	-60	54				3.25	4.17*	-1.17		
Inferior Parietal Lobule				48	-40	36	3.95	4.26*	-1.28		
Middle Temporal Gyrus				52	0	-20	4.09	4.59*	-1.96		
	-54	-4	-18				3.38	3.58*	-0.89		
	-64	-36	-2				3.59	3.54*	-1.45		
				42	-70	18	3.54	2.78	-2.83		
	-54	-70	8				3.46	3.44*	-1.14		
Inferior Temporal Gyrus				48	-8	-22	3.69	4.03*	-1.08		
				62	-14	-22	4.15	4.30*	-2.50		
Fusiform Gyrus	-48	-54	-16				3.74	3.39*	-2.17		
	-40	-60	-18				3.58	3.31*	-1.66		
Uncus	-30	-16	-34				3.99	3.59*	-2.63		
Precuneus				10	-54	26	3.31	4.08*	-0.10		
Middle Occipital Gyrus	-54	-70	-8				3.32	3.57*	-1.54		
Inferior Occipital Gyrus	-38	-84	-10				3.44	3.23*	-1.86		
Hippocampus	-28	-14	-24				4.06	4.43*	-1.49		
Parahippocampal Gyrus				22	-36	-6	3.38	2.79	-2.21		
Amygdala	-28	0	-26				3.65	3.23*	-2.02		
				24	-2	-26	3.13	2.61	-2.21		-1.74
				32	-4	-14	3.16	2.69	-2.12		
Sad											
Precuneus				24	-52	48	4.38	2.84	-4.76*		
Patients > Controls											
Happy											
Parahippocampal Gyrus	-30	-50	8				3.61	-3.36*	2.50		1.80
Sad											
Inferior Frontal Gyrus	26	26	-22				3.62	-1.57	4.26*		
Insula	40	-22	26				3.52	-1.03	3.71*		
Postcentral Gyrus	-36	-26	34				4.09	-3.41*	3.29*	1.74	
	-60	-32	40				3.80	-4.67*	1.76		
Inferior Parietal Lobule	-50	-34	42				4.00	-3.30*	3.27*		
	46	-36	34				3.51	-3.13*	2.46		
Posterior Cingulate	10	-30	22				3.81	-1.02	5.25*		

Note: Coordinates of local maxima ($p<0.001$ uncorrected) are in MNI space.
The last two columns show the z scores for the main effect of subjective old minus new for each emotion (a negative score indicates that the effect is in the opposite direction), *$p < 0.001$ (uncorrected).

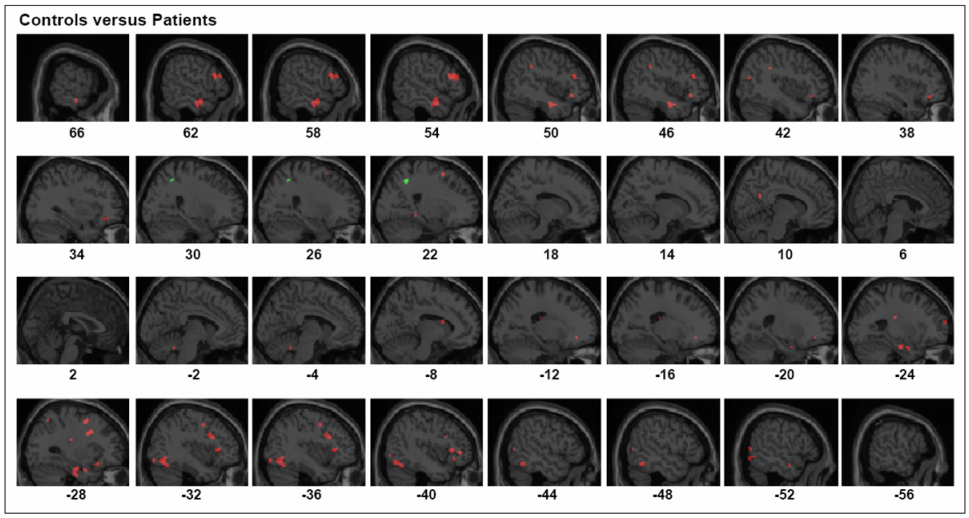

Figure 3. Between-group comparisons (Control>Schizophrenia) of the correlation between brain activity associated with subjective old minus subjective new response and the behavioral response bias for sad (green) and happy (red) expressions. The statistical parametric map was thresholded at $p<0.001$ and overlaid on the canonical MRI of SPM.

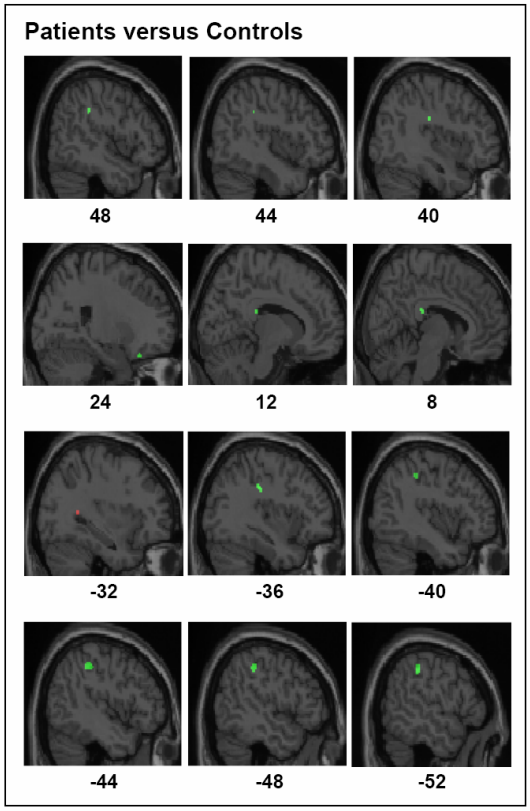

Figure 4. Between-group comparisons (Schizophrenia>Control) of the correlation between brain activity associated with subjective old minus subjective new response and the behavioral response bias for sad (green) and happy (red) expressions. The statistical parametric map was thresholded at $p<0.001$ and overlaid on the canonical MRI of SPM.

Interestingly, as revealed by the correlation analyses for each group separately, several regions including the amygdala exhibited opposite patterns for controls and patients, namely significant positive and negative correlations with behavioral bias, respectively (figure 5b).

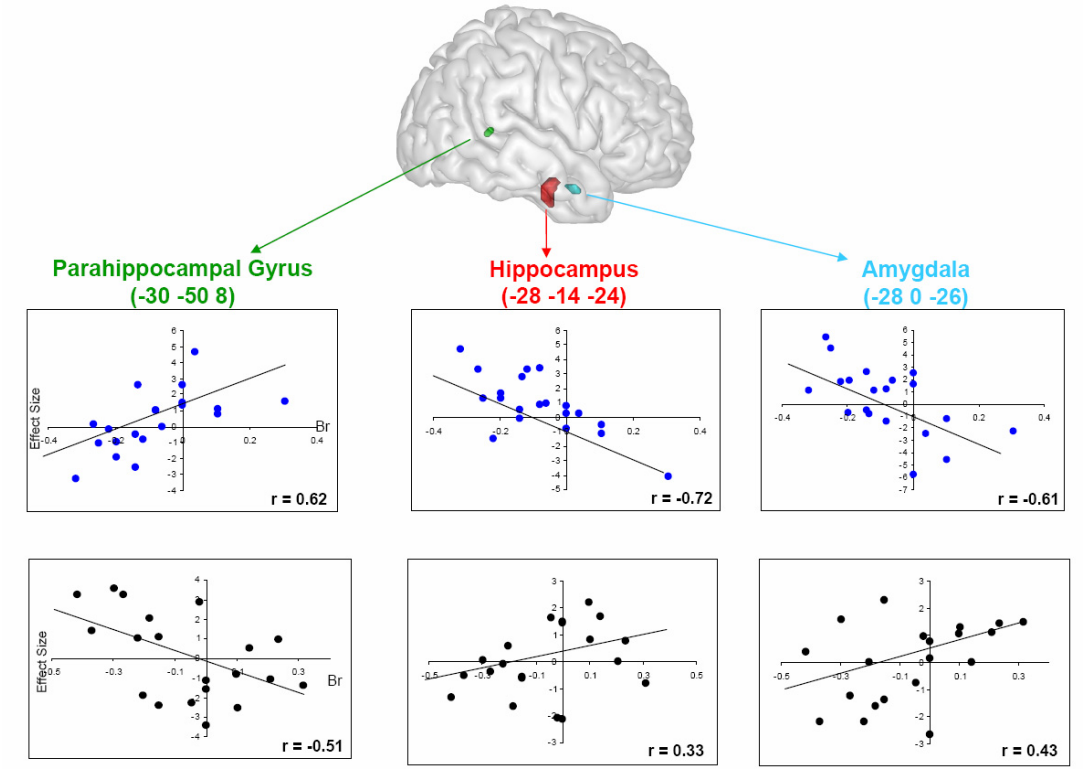

Figure 5. (a) Three dimensional rendering of the clusters for the amygdala (blue), hippocampal (red) and parahippocampal (green) activations from the between-group comparisons for and happy expressions. **(b)** Scatterplots of the correlation between brain activity associated with subjective old minus subjective new response and the behavioral response bias for the control (top) and schizophrenia (bottom) groups.

To further quantify the similarities and differences in the overall pattern of activations between patients and controls, associated with the response bias, we computed the Tanimoto index for the activation maps corresponding to this contrast. Consistent with the conjunction and interaction analyses, the index for sad faces was 0.162, indicating overlaps between activations from both groups, whereas the index for happy faces was -0.006. This small and negative value highlights the lack of a consistent overlap

in the areas activated by each group. Furthermore, it shows the overall tendency for some regions to exhibit opposite patterns of correlation between brain activity and behavioral bias for patients and controls, namely a positive and negative one, respectively. For reference purposes, the Tanimoto index for neutral faces associated with the bias contrast was 0.095.

In order to assess whether the observed differences in activations in patients, as compared to controls, were modulated by symptomatology, we regressed the peak voxels arising from the interaction analysis with negative and positive symptoms (SANS and SAPS) (see Table 4) using partial correlations to isolate the unique contribution of each symptom cluster to the effects. For happy expressions, SANS scores correlated negatively with activations in MFG and IFG, whereas voxels in the SFG, IFG and the amygdala correlated with the SAPS scores. That is, the reduced activity observed in patients in these areas was more pronounced in those exhibiting more severe symptoms. In addition, there was a positive correlation between SAPS and activity in the parahippocampal gyrus.

In the case of sad expressions, only the voxel in the postcentral gyrus correlated positively with SANS.

4.4. DISCUSSION

4.4.1. Behavior

As expected, schizophrenia patients exhibited a significantly lower overall recognition memory performance than controls. Critically, however, the modulation of memory by emotion was similar for both groups, across a variety of behavioral measures, namely accuracy, response bias and reaction times. All these indices pointed towards a tendency

in all participants to classify sad faces as previously seen, regardless of whether this had been the case or not, together with a trend for a novelty bias for happy expressions.

These results are consistent with previous studies showing an intact modulation of emotion on accuracy (Danion et al., 2003; Mathews & Barch, 2004) and response bias (Hall et al., 2007; Herbener et al., 2007) in schizophrenia. However, as mentioned in the Introduction, conflicting findings have also been reported.

4.4.2. Neural Correlates

Brain activity associated with the response bias for sad faces was in agreement with the behavioral findings. Indeed, patients and controls showed little difference in their activations, as determined by the conjunction and interaction analyses. The presence of a common network of activated regions, with similar magnitudes was further confirmed by the Tanimoto index, which quantifies the degree of overlap between groups, in terms of location and effect size.

In stark contrast to the case of sad faces, response bias for happy faces in patients was associated with a substantially different network from that observed in control subjects. This difference in activation patterns was reflected in the small number of significant voxels obtained in the conjunction analysis and the large areas showing a significantly bigger activation in controls than patients. Furthermore, the Tanimoto index for happy faces was very small in magnitude and negative.

The absence of group differences in accuracy or bias for both happy and sad expressions, together with the large differences in brain activations only for happy faces, is particularly intriguing. One possible interpretation for this effect relies on differences in terms of the mechanisms or strategies employed by the two groups, specifically with

regards to familiarity vs. recollection, depending on the emotional expression of the face being processed.

In general, "old" responses can be based on familiarity or recollection, the latter involving the retrieval of contextual details associated with the stimulus (Curran & Hintzman, 1995; Mandler, 1980; Yonelinas, 2001). We have previously argued (K. Sergerie et al., 2007) that the tendency to classify sad faces as previously seen is mostly based on a sense of familiarity elicited by an empathic response to these stimuli, which would bias subjects to focus more on the emotional expression and the feeling generated by them, rather than on their physical attributes. According to this hypothesis, both groups should rely on familiarity to decide whether sad faces were new or old. Thus, given that it has been shown that individuals with schizophrenia are not impaired in familiarity-based memory (Huron & Danion, 2002; Huron *et al.*, 1995; Sonntag *et al.*, 2003; Stark & Squire, 2000; Tendolkar *et al.*, 2002; Thoma et al., 2006; van Erp *et al.*, 2007), it would be expected that both groups should exhibit similar behavioral and neural patterns associated with the response bias for sad faces, as observed in our study. Indeed, the between-group conjunction analysis for sad faces yielded a significant activation in the parahippocampal gyrus, a region typically considered to be involved in familiarity-based memory (Yonelinas, 2002). Further support for this hypothesis comes from the reaction times to sad faces: both groups responded significantly faster to those sad faces they believed to have seen before (subjective old) than to those judged to be new. This difference in reaction time, together with the familiarity response bias, suggests a more liberal criterion associated with recognition memory for sad faces in both patients and controls.

In contrast, even though happy faces were associated with a novelty bias in both groups, albeit to a lesser extent in patients, they elicited different brain activation patterns. Specifically, control subjects engaged a larger neural network than patients for subjective old compared to subjective new happy faces, as a function of their individual response bias. Interestingly, several of these regions, more active in controls than patients, are thought to be important for processes associated with recollection-based retrieval. For example, the anterior frontal cortex and inferior parietal cortex have been proposed to be associated with recollection (Henson *et al.*, 2005; J. S. Simons & Spiers, 2003; Vincent *et al.*, 2006; Wheeler & Buckner, 2004; Woodruff *et al.*, 2005), as well as with the postretrieval monitoring and the evaluation of the retrieved information (Ranganath *et al.*, 2004; J. S. Simons & Spiers, 2003; Yonelinas *et al.*, 2005). In addition, activation in the superior parietal lobule has been posited to depend on the amount of information being retrieved (Vilberg & Rugg, 2007), which is typically larger during recollection than familiarity-based memory retrieval. Consistent with the hypothesized increased reliance of patients in familiarity-based retrieval, the group comparison revealed that the parahippocampal gyrus was significantly more activated in patients than controls for happy faces.

Finally, the reduced hippocampal activation observed in patients is in agreement with a recent meta-analysis of neuroimaging studies of episodic memory in schizophrenia (Achim & Lepage, 2005) in which a deactivation of this region, shown to be involved in conscious recollection (Aggleton & Brown, 1999; Eldridge *et al.*, 2000; Montaldi *et al.*, 2006; Wheeler & Buckner, 2004; Yonelinas et al., 2005), was observed when comparing high vs. low retrieval conditions. Importantly, although these findings have been interpreted as representing a functional deficit of this structure, the reduced activation

could also reflect structural differences between patients and controls. Indeed, several studies have reported a smaller hippocampal volume (Gothelf *et al.*, 2000; R. E. Gur *et al.*, 2000; Nelson *et al.*, 1998; Steen *et al.*, 2006) and an alteration in shape (Casanova & Rothberg, 2002; Csernansky *et al.*, 2002; Shenton *et al.*, 2002) in schizophrenia compared to matched healthy controls.

Alternatively, the reduced activation in patients in the hippocampus and other previously mentioned regions involved in recollection, as well as the increased one in the parahippocampal gyrus, could be a consequence, rather than a cause, of their behavior. For instance, it has been suggested that schizophrenia patients are more confident in their responses than controls, even if this does not always lead to increased errors (Moritz *et al.*, 2006). Thus, it is possible that patients made their decisions based simply on a feeling of familiarity and therefore did not need to resort to more elaborate processing (i.e., recollection) to obtain the necessary level of confidence to make their response (Danion *et al.*, 1999; Huron et al., 1995; Rushe *et al.*, 1999; Thoma et al., 2006; Weiss *et al.*, 2003). Our behavioral data supports this hypothesis: whereas control subjects were significantly faster for correct than incorrect responses, suggesting a higher level of confidence for the former, patients did not show a significant difference in response times between correct and incorrect new responses.

Importantly, although we hypothesize that control subjects relied more on recollection to assess whether a happy face was previously presented, they likely used familiarity judgments as well. Interestingly, the conjunction analyses for both happy and sad faces revealed a common activation in patients and controls of the parahippocampal gyrus, in accord with this hypothesis.

Finally, the finding related to the amygdala also provides support for the differential effect of happy and sad expressions on response bias in schizophrenia patients compared to controls. Indeed, patients exhibited a significant amygdala activation associated with novelty bias for sad faces, similar to that previously reported in healthy controls and consistent with a role of this structure in the detection of novel stimuli, particularly those with biological or emotional relevance (Sander *et al.*, 2003). In contrast, no amygdala activation was found for happy faces in patients, whereas a significant one was present in controls, leading to a significant interaction (see Table 4 and Figures 3-5). This lack of activation could underlie the somewhat reduced novelty bias observed in patients for happy expressions. Importantly, the emotion-specific abnormal amygdala activation pattern argues against a generalized structural or functional deficit of this structure in schizophrenia and may partly explain the inconsistencies reported in the literature (Aleman & Kahn, 2005).

4.4.3. Influence of symptomatology

The abnormal activation patterns observed in patients, in particular those within the superior and inferior frontal gyri and amygdala, as well as parahippocampal gyrus, appear to be modulated by positive symptoms scores (SAPS), as a negative correlation was observed for the former three regions and a positive one for the latter. Previous studies have shown that positive symptoms are associated with a more liberal response criterion, that is, with a higher tendency for false alarms (i.e., incorrect subjective old responses) (Bentall & Slade, 1985; Brebion et al., 2000; Brebion et al., 2005; Brebion et al., 1998; Ragland et al., 2003). Although we did not observed a significant correlation between SAPS and behavioral response bias for any of the expressions, the correlations with brain

activity suggest that patients with more severe positive symptoms will preferentially engage regions associated with familiarity-based memory retrieval and less so those involved in recollection or novelty detection (e.g., amygdala).

Activation in other frontal areas, such as the middle and inferior frontal gyri, was modulated by SANS scores. Although the influence of negative symptoms on memory in general and response bias in particular have not been thoroughly explored, these findings seem to raise the possibility that highly symptomatic patients make less use of areas that are important for an efficient elaborative and deeper processing or monitoring (Dougal & Rotello, 2007; Raquel E. Gur et al., 2007; Lang *et al.*, 2001; Ragland *et al.*, 2001; Ragland et al., 2003; Windmann et al., 2002), as well as the correct attribution and integration of information from various sources, including those that are self-generated (Achim & Lepage, 2005; Allen *et al.*, 2007; Brebion et al., 2000; Brebion et al., 2005; Jon S. Simons *et al.*, 2006).

4.4.4. Conclusion

Our results have several implications for the understanding of emotional processing in schizophrenia. In particular, we have shown that differences in neural processing of emotional information between schizophrenia patients and healthy individuals can occur in the absence of behavioral differences. Therefore, reduced activations in patients in brain areas linked to emotion and/or memory should not be automatically interpreted as representing a deficit or inability to recruit these regions, but instead, they may indicate different strategies or approaches (e.g., familiarity vs. recollection) being used to solve the task. Importantly, different strategies can be used depending on the particular characteristics of the stimuli being processed, in this case, their emotional expression.

Acknowledgments

This study was supported by the Canadian Institutes of Health Research. We thank Drs Joober, Lal, Malla and Debruille for help with patient recruitment.

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In this final study, we sought to further explore the issue of amygdala lateralization in emotional memory. Specifically, we decided to test the proposed model of sex-dependent amygdala lateralization in memory encoding of negative stimuli and to assess whether this proposed lateralization was modulated by other, stimulus-specific factors, such as the sex of the emotional faces being presented. To do that, we performed a novel reanalysis of my M.Sc. fearful memory study where the sex of the participants as well as that of the face stimuli was taken into account.

Chapter 5

Own-sex effects in emotional memory for faces

"Women always worry about the things that men forget;
men always worry about the things women remember"
Author Unknown

It is generally accepted that emotionally charged stimuli, especially those with a negative content, are better remembered than neutral material. A wealth of lesion and functional neuroimaging studies has identified the amygdala as a critical structure for this emotion-induced memory enhancement (Hamann, 2001; LaBar & Cabeza, 2006; Phelps, 2004). Interestingly, individual differences in emotional memory have been reported (Hamann & Canli, 2004). In particular, several studies have suggested that women have a better memory for emotional stimuli than men (Cahill, 2003; Hamann, 2005), although some studies have failed to find any sex differences (Bremner *et al.*, 2001; Piefke *et al.*, 2005) or even found better memory in men (Burton *et al.*, 2004). A neural interpretation of this sex difference in memory for emotional items has been proposed by Cahill and colleagues (Cahill, 2003; Cahill *et al.*, 2001; Cahill *et al.*, 2004). This sex-specific lateralization hypothesis posits that whereas the right amygdala is involved in the enhancement of memory for emotional stimuli in men, it is the left amygdala that plays this role in women. This hypothesis has received some support from neuroimaging studies conducted by other groups (Canli *et al.*, 2002; Mackiewicz *et al.*, 2006; van Stegeren *et al.*, 2005).

However, all these studies used pictures as the emotional material to be remembered, leaving open the question of whether these putative sex differences in the neural correlates of emotional memory can also be observed for other types of stimuli. One class of stimuli that is of particular interest is facial expressions. Indeed, emotional expressions are powerful emotional stimuli that play a critical role in social interactions. The ability to quickly and accurately decode emotional expressions in other people is

essential for an individual's successful functioning in a social environment. We have recently shown (K. Sergerie *et al.*, 2006) an enhancement of memory for fearful faces, compared to happy and neutral ones, which is amygdala mediated. Interestingly, there were no sex-related differences in this memory advantage for fearful faces either in terms of behaviour or brain activity. Yet, several studies have suggested that women exhibit a same-sex advantage for memory of neutral faces; that is, they remember female faces better than males ones (Lewin & Herlitz, 2002; Rehnman & Herlitz, 2006; Wright & Sladden, 2003). In contrast, men do not appear to show this own-sex memory bias, although the findings are less consistent (Rehnman & Herlitz, 2006; Wright & Sladden, 2003).

Therefore, it is conceivable that emotional expressions could influence memory in a different fashion, at the behavioural and neural levels, depending on whether the faces being encoded are of the same sex of the perceiver or not. In other words, an interaction between emotional expression, sex of the perceiver and sex of the face may exist. Such an interaction would then explain the lack of sex differences in memory for emotional faces previously mentioned, where the sex of the face stimulus was not taken into account. If such an own-sex memory bias for fearful faces does exist, it would be of interest to investigate its neural correlates, in particular in terms of amygdala lateralization.

Here we explored this question using the subsequent memory paradigm for faces with fearful, happy and neutral expressions, within the context of an event-related functional magnetic resonance imaging (fMRI) experiment. At a behavioural level, we predicted a same-sex enhancement of recognition memory for fearful faces, especially for females. At the neural level, we focused on the role of the amygdala on the successful

encoding of emotional faces, as a function of the sex of the participants and of the faces, to assess whether any sex-specific laterality effects were present.

Eighteen healthy individuals (9 men and 9 women, mean age 27 years) participated in this study. Data from two men were discarded from the final analysis due to insufficient number of trials for one of the conditions of interest. All participants were right handed, had normal or corrected-to-normal vision and no history of neurological or psychiatric disorders. None of the subjects was taking psychotropic medication at the time of the study. The study was approved by the Research Ethics Board of the Montreal Neurological Hospital and Institute and written informed consent was provided by all participants.

During the encoding session, eighty-four pictures of different individuals (half male and half female), each depicting a fearful, happy or neutral expression were presented twice, in a pseudo-random order, using E-PRIME. Each stimulus was shown for 2500ms, with average stimulus onset asynchrony of 4000ms. Participants were instructed to determine the sex of the face presented and to remember the stimuli for later questioning. During the recognition session, the original 84 pictures were presented again, together with an equal number of new faces, also depicting fearful, happy and neutral expressions, in equal proportions in terms of expression and sex. Subjects performed an old/new judgment. At the end of the experiment, subjects rated the valence of all the previously presented faces on a seven-point scale. Further details of the stimuli and overall procedure are given in (K. Sergerie *et al.*, 2005; K. Sergerie et al., 2006).

The experiment was performed on a 1.5T Siemens Sonata whole-body scanner (Siemens, Erlangen, Germany), equipped with a standard head coil, at the Montreal Neurological Institute (MNI). Details of the fMRI acquisition parameters and procedure

are described elsewhere (K. Sergerie et al., 2005; K. Sergerie et al., 2006). Briefly, volumes of 30 interleaved slices parallel to the anterior-posterior commissural plane, covering the whole brain, were acquired during the encoding and recognition sessions (TR = 2450ms, TE = 50ms, FOV = 256mm). A high resolution ($1mm^3$ voxel size) anatomical scan was also obtained for each subject. Only the data from the encoding session is reported here.

Functional images were time-corrected to account for differences in acquisition times for the different slices, coregistered to the first scan to correct for head movements, normalized to the standard space of Talairach and Tournoux (Talairach & Tournoux, 1988) according to the MNI template (Evans *et al.*, 1994) and spatially smoothed (8mm FWHM isotropic kernel). Statistical analysis was conducted using SPM2 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm), using a mixed-effects linear mode. For each subject, 12 trial types were defined based on the facial expression and sex of the stimuli, as well as whether the subjects had correctly identified the face as old or not during recognition (i.e., the subsequent memory paradigm (Buckner *et al.*, 1999)). On average, there were 20 trials for the subsequently remembered condition and 8 for the forgotten one. Critically, as all our comparisons involved higher order interactions of the remembered minus forgotten contrast (see below), our results were not statistically biased by the difference in the number of events for these two conditions. Linear contrasts of the parameter estimates of interest for male and female participants were subsequently taken to second-level one-sample t-tests. For the current analysis, we were specifically interested in the triple interaction between memory success (remembered vs. forgotten), emotional expression (fearful vs. neutral) and stimulus sex

(male vs. female). Moreover, we focused our analysis on the amygdala, where we used a threshold of statistical significance of $p < 0.005$ (uncorrected).

Memory performance results for men and women, calculated as hit minus false alarm rates, are shown in Figure 1. A repeated-measures ANOVA for accuracy for fearful faces with stimulus and participants' sex as within- and between-subjects factors, respectively, yielded a significant interaction ($F(1,16)=7.2$, $p = 0.017$). Post-hoc analyses revealed that this effect was due to the female participants, who exhibited a better memory for female fearful faces than for male ones ($p = 0.03$). In contrast, there was no significant difference on memory performance as a function of the sex of the face for men ($p = 0.4$). Critically, this own-sex memory bias was specific to fearful expressions, as no significant sex effects were observed for either neutral ($p > 0.8$) or happy ($p > 0.7$) faces.

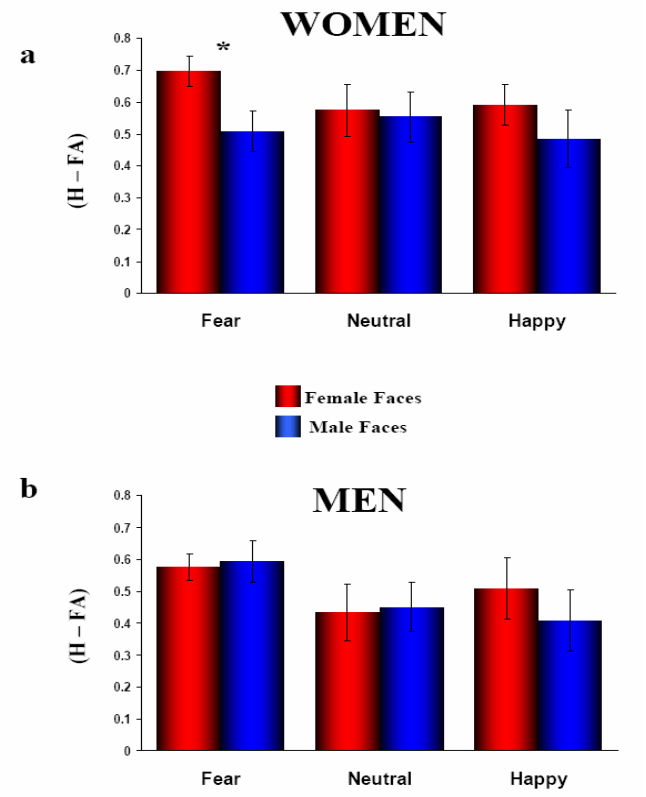

Figure 1: Memory performance (hit minus false alarm rate) in (a) women and (b) men for fearful, neutral and happy facial expressions as a function of the sex of the faces. Error bars represent standard error of the mean (SEM). *$p < 0.05$

Analysis of reaction times during encoding and recognition did not yield any significant main effects of participants' or stimulus sex, nor an interaction. Likewise, valence ratings were similar between men and women and between male and female faces for each emotional expression (all $p > 0.1$).

In females, a stimulus-sex (female vs. male) by memory success (remembered vs. forgotten) by expression (fearful vs. neutral) interaction for the subsequent memory contrast revealed a significant activation within the left amygdala (MNI coordinates (Evans et al., 1994) $x\ y\ z$ = -16 0 -28, $z = 2.72$, $p < 0.005$), as shown in Figure 2a. This interaction represented a stronger amygdala activation associated with successfully remembered female fearful faces (Figure 2c). No sex differences were observed for male participants in this voxel ($p > 0.3$). A similar interaction analysis for men showed, in contrast, significant activation within the right amygdala (Figure 2b; $x\ y\ z$ = 16 -2 -24, $z = 3.58$, $p < 0.001$), which was associated with stronger activity for successful memory for male, compared to female, fearful faces (Figure 2d).

To directly test for possible differences between left and right amygdala responses as a function of the sex of the faces, we conducted post-hoc ANOVAs on the parameter estimates obtained in these regions for the different conditions. These analyses yielded a significant hemisphere-by-sex interaction for both women ($F(1,8)=18.6$, $p < 0.005$) and men ($F(1,6)=6.1$, $p < 0.05$), confirming the amygdala lateralization pattern observed in the whole-brain analysis. No significant sex effects were observed for happy expressions in either the left ($p < 0.3$) or right ($p > 0.2$) amygdala.

The behavioral findings from this study show an own-sex effect on memory accuracy for fearful faces in women, as they remembered female fearful faces better than male ones. In contrast, and consistent with previous studies using neutral faces (Lewin &

Herlitz, 2002; Rehnman & Herlitz, 2006), no own-sex bias for memory was observed in men.

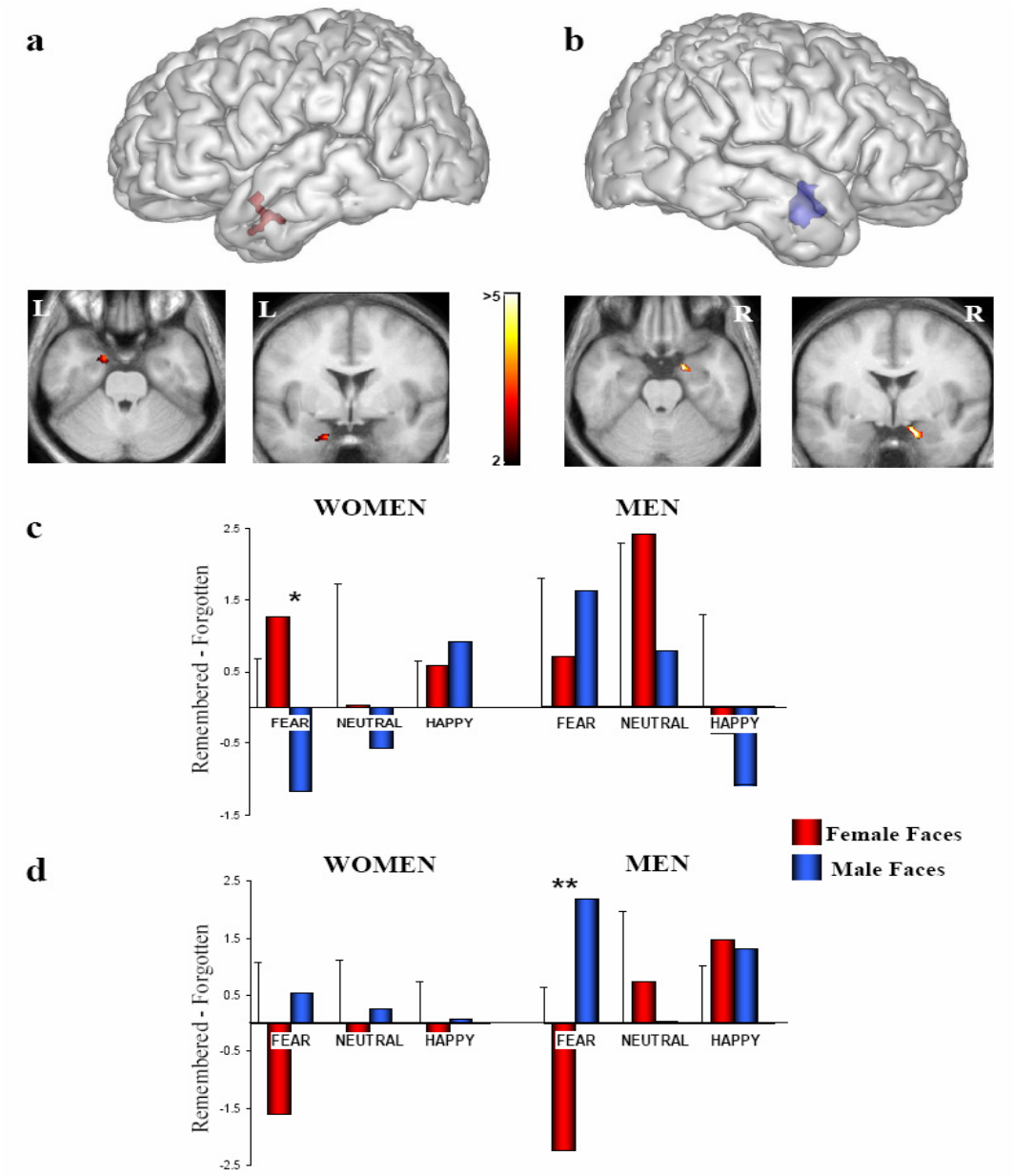

Figure 2: Three-dimensional reconstruction and two-dimensional renderings of the amygdala activations for the interaction of memory success (remembered vs. forgotten), facial expression (fearful vs. neutral) and face sex (female vs. male) in (a) the left hemisphere (MNI coordinates *x y z* = -16, 0, -28) for women and (b) in the right (MNI coordinates *x y z* = 16, -2, -24) for men. Bar graphs with the values of the subsequently remembered minus forgotten contrasts for the (c) left and (d) right amygdala, for each condition (expression and stimulus sex), are shown as a function of the sex of the participants. Error bars represent the standard error for each of the paired t-tests. *p < 0.01; **p < 0.001.

Our fMRI results confirmed the presence of sex differences in emotional memory at a neural level. Specifically, we found a stronger left amygdala activation in women and enhanced activity in the right amygdala in men. Thus, these findings can be considered to provide further support to the amygdala lateralization hypothesis proposed by Cahill and colleagues (Cahill, 2003; Cahill et al., 2001; Cahill et al., 2004), showing that it may also apply to facial expressions. However, our critical finding is that this sex-dependent hemispheric specialization in emotional memory was stimulus specific. Namely, the left amygdala in women was preferentially involved in the successful encoding of fearful female faces, compared to male ones, whereas the right amygdala in men was more strongly activated for the encoding of male than female fearful faces.

It has been argued that the emotion-induced memory enhancement and associated sex-related amygdala lateralization only occur for highly arousing stimuli (LaBar & Cabeza, 2006; McGaugh, 2004). Thus, one possible alternative interpretation for our sex-by-sex interaction could be that men and women perceived male and female fearful faces, respectively, as more negative. However, this is unlikely, as we did not observed any differences in ratings as a function of the sex of the participants or of the faces. Similarly, the lack of any differences in reaction times rules out differential degrees of attention or interest allocated to own-sex faces (A. G. Goldstein & Chance, 1974) as potential explanation for the observed effects. None the less, it is important to keep in mind that, due to the relatively small sample size used in this study, we cannot discard the possibility that other, yet to be determined, differences among groups may have contributed to the results reported here.

Our results suggest that the involvement of the amygdala on emotional memory may depend not only on the valence or intensity of the stimulus per se, but also on the relation

it has with the perceiver. In particular, memory for fearful faces appears to be modulated by a same-sex effect, which can be considered as a special case of a more general own-group bias ((Shapiro & Penrod, 1986), but see (Rudman & Goodwin, 2004)). For instance, although women may perceive male and female faces equally in terms of their emotional value, female fearful faces are likely to have a greater relevance, either in terms of biological significance (e.g., survival) or the degree to which they can relate to them (e.g., empathy or closeness). Thus, in addition to valence and arousal (LaBar & Cabeza, 2006), a third dimension may influence memory for emotional material, namely stimulus relevance (Ochsner, 2004). This biological/social-relevance hypothesis (Sander *et al.*, 2003) has also received support by a recent study showing that men are faster at detecting angry male faces ((Williams & Mattingley, 2006), but see (Becker *et al.*, 2007)). Interestingly, an opposite-sex memory advantage for neutral faces has been shown when the face stimuli were shown in a three-quarter view with straight gaze and when they were presented in front view but with their gaze averted (Vuilleumier *et al.*, 2005), further highlighting the importance of the relation between stimulus and observer in memory. Future studies could help further characterize these effects by combining different factors, such as expression and gaze direction, as well as including other measures of stimulus evaluation, such as closeness.

An outstanding question remains regarding the functional significance of the right amygdala activation associated with the successful memory encoding for fearful male, compared to female, faces, in the absence of any significant behavioral differences. Differential brain activations in the absence of significant behavioral effects have been often reported in the literature (Wilkinson & Halligan, 2004). Such activations may reflect different strategies employed, or different degrees of attention or effort required to

perform the task at the same level for the different conditions. A more sensitive paradigm, such as the remember/know judgment or the use of confidence ratings, could capture these putative, more subtle, differences in performance in a way that it was not possible with our simpler old/new design. Further studies are necessary to clarify this question and allow for a more definitive and comprehensive model of sex differences in emotional memory.

Our study has a number of limitations, in addition to those already pointed out. Each face was presented twice to increase memory performance. As we have no way of determining at which presentation each stimulus was encoded, we collapsed them in the analysis. Thus, it is possible that (automatic) stimulus retrieval, or priming effects, could have contributed to the observed amygdala activation. In addition, we did not take into account the possible effects of the known sex differences in amygdala anatomy (J. M. Goldstein *et al.*, 2001) on the observed activations. Studies combining functional and structural information could shed issue on this potential confound.

In summary, we have demonstrated that emotional memory for faces is subject to an own-sex effect, both in terms of memory accuracy and, more critically, with respect to amygdala lateralization. Further studies should investigate whether this observed stimulus-specificity of memory for threat-related material also applies to other emotions, such as anger or sadness, as well as to other types of stimuli, including words and pictures. Of particular interest would be to explore these issues using positive stimuli, which have so far yielded inconsistent results in terms of their effects on memory performance (K. Sergerie et al., 2006, 2007; Shimamura *et al.*, 2006).

ACKNOWLEDGMENTS

We are grateful to Dr. Martin Lepage for sharing the data with us. This study was funded by the Canadian Institutes of Health Research (CIHR; MOP 53280 & MOP 57724) and the Natural Sciences and Engineering Research Council of Canada (262439-04). J.L.A. was supported by the Canada Research Chairs Program. K.S. was supported by a CIHR Doctoral Fellowship.

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Chapter 6

General Discussion and Conclusion

"Je comprends mais je ne vois pas pourquoi je comprends.
Je comprends ce que vous dites, mais ce que vous voulez dire
en disant ce que vous dites, ça je ne le comprends pas"
Marguerite Duras

6.1. DISCUSSION

6.1.1. Amygdala lateralization

Results from the meta-analysis support an amygdala lateralization based on the temporal dynamics of their response to emotional stimuli. Namely, the right amygdala would be involved in the initial rapid and transient response to the presence of an emotional stimulus, followed by a slower and more sustained activation by the left amygdala. Indeed, our findings showed that whereas no difference between hemispheres was observed in the number of activations for event-related studies, significantly more activations were reported in the left than in the right amygdala for experiments using a block design, where the averaging of the activity over a block would lead to a lower right amygdala activity due to its faster habituation. In contrast, the randomization of stimulus presentation in event-related design would prevent habituation and therefore both left and right amygdala activity would be significantly activated, compared to the control conditions.

Direct support for this temporal dynamics model comes from studies investigating the habituation of the amygdala response to emotional material. For example, Wright and colleagues (Wright *et al.*, 2001) have found that whereas there is a greater habituation of the right amygdala to emotional stimuli, the left amygdala exhibits a sustained activity. Similar findings have been reported by other researchers (Phillips *et al.*, 2001; Whalen *et al.*, 1998; Williams *et al.*, 2006; Wright et al., 2001).

At a cognitive level, this hemispheric difference in response dynamics has been proposed to be associated with a differential, and complementary, involvement of the right and left amygdala in the processing of emotional stimuli (Glascher & Adolphs, 2003; Wright et al., 2001). Specifically, it has been suggested, as briefly mentioned in the Introduction (Chapter 1), that the right amygdala underlies the initial, undifferentiated and most likely automatic response, providing an overall level of autonomic activation triggered by any type of emotional arousing stimulus. This initial right amygdala response would be followed by a more distinct and emotion-specific reaction by the left amygdala that discriminates or decodes the difference in arousal magnitude signaled by the specific stimulus and provides a more elaborate evaluation of the stimulus. Along similar lines, Markowitsch (Markowitsch, 1998) suggested that the right amygdala is mainly engaged in a faster, more implicit, shallow or crude general processing of emotional information, whereas the left one is involved in more explicit, or feature-extracting processes. Consistent with this, the left amygdala has been shown to be is preferentially involved in associative learning for paired faces (Killgore *et al.*, 2000), a function requiring sustained neural representations.

In addition, according to this model, a brief emotional stimulus that does not reach awareness should only, or preferentially, engage the rapid, automatic right amygdala response, as it has been reported in some studies (Costafreda *et al.*, 2007; Morris *et al.*, 1998). In contrast, a more cognitively-based emotional response would preferentially be mediated by the left amygdala (Phelps *et al.*, 2001).

This origin of this lateralization remains unknown. However, I can provide some speculative explanations. A first possibility is a top-down modulation of the amygdala by other, possibly cortical, regions. For example, the recruitment of language-related areas

in the left hemisphere required for the processing of semantic and/or more elaborate information would influence activity within the left amygdala. This in turn, would result in a more sustained response in this structure. Studies examining hemispheric differences in amygdala responses in individuals exhibiting right-lateralized or bilateral language could be used to test this hypothesis.

Alternatively, the hemispheric specialization could be due to intrinsic physiological and/or anatomical differences. Indeed, it has been show that the size of the right amygdala is significantly larger than the left one (Brierley *et al.*, 2002; De Olmos, 2004; Filipek *et al.*, 1994; Pedraza *et al.*, 2004; Szabo *et al.*, 2001), although the functional implications of this volume difference remain unknown. Interestingly, in a conditioning study with rats, it has been shown that different types of neuronal cells exist within the dorsal subnucleus of the lateral amygdala (LAd) and that they present different habituation characteristics (Repa *et al.*, 2001). One group, the transiently plastic neurons, located in the dorsal tip of LAd, had short-latency responses (<20 ms) and exhibited only transient responses. Another type, most frequently observed in ventral regions of LAd, had longer latency responses, but showed a sustained increase of activity throughout both acquisition and extinction sessions. Although, the authors did not report whether there was any hemispheric differentiation in terms of these populations, their existence may provide a means through which the temporal dynamics of the amygdala response could be modulated by selectively facilitating or inhibiting the activity of either population of neurons. A direct comparison in the proportion of transiently plastic and long-lasting plastic neurons in the right and left amygdala in animal studies could shed light on this issue.

6.1.2. Emotion specificity

The findings from the study on emotional memory for sad faces, when taken together with those from the previous one using fearful faces (M.Sc. thesis) (Sergerie *et al.*, 2005, 2006), raise some noteworthy points regarding the valence vs. arousal debate in emotional memory (Hamann *et al.*, 1999; Kensinger, 2004; Kensinger & Corkin, 2004). Indeed, the enhancement and decrease in memory accuracy for fearful and sad faces, respectively, suggests that valence alone cannot explain the influence of emotion on memory performance. Importantly, this difference is unlikely to be due to artifactual differences between studies given that, as mentioned earlier, they were both conducted using the exact same paradigm. On the other hand, the lack of significant difference in memory performance for happy faces, compared to neutral ones, points against a purely arousal-based memory modulation. Thus, our results can be interpreted as supporting an emotion-specific modulation of memory (i.e., different effects for different discrete emotions) or, alternatively, a specific combination between arousal and valence. In other words, the former interpretation would be more along the lines of the basic discrete emotion hypothesis, whereas the latter would mean that emotions lying in different subspaces within the emotion space, as described in the circumplex model, have different effects on memory. In this respect, the use of morhphed stimuli (e.g., (Young *et al.*, 1997)) and computational models (e.g., (Susskind *et al.*, 2007)) can provide critical insights on this issue. In addition, further studies using other emotions could also shed light on this question. Of particular interest would be to study anger which, like fear, is a negative valence and high arousal emotion. In contrast to the latter, however, anger has been associated with an approach, rather than withdrawal, response (Harmon-Jones, 2004).

6.1.3. From perception to memory: A long and winding road

Interestingly, although fear, happy and sad stimuli had very different effects on memory, they all activate the amygdala in perception studies, as shown in our meta-analysis. In fact, the strongest activation was observed for positive stimuli, including happy faces, even though this was the one expression that did not have a significant influence on episodic memory (a result obtained in both our studies). In addition, despite the absence of a significant difference in the magnitude of activation in the perception of fear and sad stimuli (including faces), these two emotions had opposite effects on memory. Thus, the precise relation between amygdala activation to the presence of emotional stimuli and their influence on subsequent memory is not straightforward and needs to be further investigated.

The results from the schizophrenia study provide an example of the opposite case. Namely, although emotion had the same relative influence on memory for both patients and controls, these two groups exhibited different neural activation patterns in the case of happy faces. As described in the Discussion of Chapter 4, this finding may reflect different strategies employed by schizophrenia patients and controls which, although subserved by different neural networks, resulted in the same behavioral response (Fletcher, 2004; Wilkinson & Halligan, 2004).

6.1.4. Individual differences

The results from the schizophrenia study highlight the role of individual differences in emotional processing. That is, emotion can influence a particular cognitive process, such as memory, through different routes, representing distinct strategies or mechanisms, and engaging different neural regions. In such a case, if one were to combine both groups in

the analysis, many of the activations associated with the observed behavior would "wash out" and thus not come out as significant. This was indeed the case in our first emotional memory experiment, involving fearful faces, where an amygdala lateralization effect as a function of memory success was only observed when the sex of both the stimuli and participants were taken into account (Chapter 5). Interestingly, a dissociation between behavior and brain activation was observed for men. Specifically, whereas the predominance of a left amygdala involvement in successful memory for female fearful faces in women was accompanied by an increase in memory accuracy for those stimuli, male participants exhibited a larger right amygdala activation for male fearful faces in the absence of any stimulus-sex effects on behavior. That is, like in the case of the schizophrenia study, this study provides further evidence that significant group differences in brain activity can be obtained with or without concomitant differences in behavioral responses. The challenge remains to provide a theoretical interpretation of this mismatch between brain activity and behavioral measures. In addition to the already mentioned possibility of their reflecting trait- and state-dependent non-specific confounds (e.g., task difficulty, attention, motivation, medication, etc), they could also indicate an insensitivity of the behavioral indices to capture different cognitive processes or strategies. Finally, it is possible that the same cognitive processes are implemented through different neural systems (redundancy) or that an alternative circuit is engaged when the default one is not available (compensatory mechanisms).

6.1.5. Literature update

Since the acceptance of the meta-analysis paper (Sergerie *et al.*, 2008), another article on this subject has been published (Costafreda et al., 2007). In this meta-analysis of 385

functional neuroimaging studies, from 1990 to July 2006, Costafreda and colleagues investigated the potential influence of experimental factors on the probability of detecting amygdala activity. Briefly, they included as experimental characteristics basic emotions (fear, disgust, anger, sadness, happiness) as well as sex, humor and more social ones (guilt, embarrassment, shame, abandonment, pride, admiration, attachment, friendship, love and moral), experimental task instructions (passive viewing, explicit processing and incidental processing), modality of presentation of stimuli (visual, auditory, audio-visual, gustatory/olfactory, internal and external), use of language in the emotional stimuli, masking, conditioning, baseline or control task (emotional, neutral, low level), technique (PET or fMRI), magnet strength for fMRI and finally the type of analysis. They used the ALE method (Turkeltaub *et al.*, 2002) with all the fixed factors previously mentioned. Essentially, this method is an extension of the traditional vote-counting approach in which each activation peak reported is represented in the brain by a Gaussian probability distribution centered in that voxel, weighted by the number of subjects in the study. The union of all the probability distributions constitutes an activation probability map with the value at each voxel representing the "activation likelihood estimate" (ALE) for that particular location. Statistical significance can be calculated through a permutation approach in which many ALE maps are generated using the same number of peaks as in the original map but in random positions within the region of interest. In agreement with our findings and the temporal-dynamics model, Costafreda et al. observed that a larger proportion of amygdala activation peaks were reported in studies using fMRI (both block and event-related designs combined) than PET (which only allows for block designs), although no lateralization interaction was reported. In addition, more right amygdala activations were associated with masked stimuli (i.e., presented below awareness),

whereas a larger proportion of left amygdala peaks was observed in studies using semantic material. Consistent with the previous vote-counting meta-analyses, they observed a larger proportion of amygdala activation reports for fear and disgust than for happy stimuli. As mentioned earlier, this finding does not necessarily conflict with ours (i.e., a stronger magnitude for happy than negative emotions, including fear), as it did not take into account the magnitude of the activation or the statistical threshold used (i.e., p-value) to determine whether an activation was present or not.

In terms of emotional memory, Sharot et al (Sharot *et al.*, 2007) have recently reported findings from an emotional memory study in amnesic patients which has particular relevance to our schizophrenia study. Specifically, they observed that, in healthy individuals, time enhanced emotional memory in terms of recollection rather than familiarity-based judgments. In contrast, individuals with hippocampal lesions, who therefore had recollection impairments, exhibited an increased familiarity-based memory for emotional stimuli. Thus, these findings are consistent with our hypothesis that, when the hippocampal-mediated recollection processes are inaccessible, a reliance on familiarity can still lead to a similar modulation of memory performance for emotional material. This latter mechanism or strategy is likely to be mediated by different neural structures, including parahippocampal and/or rhinal cortices.

6.1.6. Limitations and future studies

The specific limitations pertaining to each study have been already discussed in the respective chapters, with the exception of the schizophrenia study. Here, I therefore highlight some of the potential confounds associated with this study, as well as some general ones that could apply to all the experiments described in this thesis. In addition, I

propose a few future directions that could partly address these limitations and, where applicable, I present some very preliminary results for them.

In general, differences at the neural level associated with similar behavioral performance could simply reflect differences between groups that are unrelated to the processes of interest, such as task difficulty, motivation, level of attention, etc. These are important potential confounding factor in studies involving psychiatric populations. Our schizophrenia study is no exception and therefore a possible influence of these variables on the behavioral and fMRI results cannot be completely ruled out. However, it is unlikely that they could explain the main findings of this study, namely the intact modulation of behavioral memory accuracy and response bias by emotion, associated with differences in brain activation only in the case of happy expressions.

Similarly, although I cannot rule the possibility that medication, as well as other illness-related variables, such as its duration, may have influenced overall memory performance, it is unlikely that they could explain the observed emotion-specific modulation of memory observed in our study.

One general potential limitation of the emotional memory studies is that I used an old/new paradigm rather than other more complex designs, such as those including a remember/know response (Tulving, 1985) or a confidence rating for each judgment. This is particularly relevant when investigating emotional memory in individual with schizophrenia. Specifically, one could argue that although our results suggest a difference between patients and controls in terms of strategies, processes or confidence levels associated with the response bias for happy faces, our paradigm did not allow us to directly measure the relative contributions of recollection and familiarity processes underlying participants' old/new judgments. Indeed, it is typically assumed that these

processes are better isolated by using a remember/know paradigm, although this has been recently put into question (Dougal & Rotello, 2007; Dunn, 2004; Goldberg & Weinberger, 1996; Wixted & Stretch, 2004). On the other hand, the simple old/new recognition task used in our two studies has a number of advantages, in particular when comparing clinical populations to healthy controls. For instance, old/new responses do not require subjects to decide how good their memory is for a particular stimulus (i.e. they do not need to do an introspective evaluation of the strength of their memory trace) but, rather, they are asked to simply state whether they think the item has been previously presented or not. This may be a particularly important issue here, as patients with schizophrenia have been shown to have difficulties in the appropriate use of self-generated information to make decisions about the source and characteristics of external stimuli (Achim & Lepage, 2005; Allen *et al.*, 2007; Brebion *et al.*, 2000; Simons *et al.*, 2006). Furthermore, constraints in terms of (i) the minimum number of trials per condition required in an event-related fMRI analysis to achieve a proper estimation of the model parameters (i.e., adequate statistical power), (ii) the maximal duration of the scan that subjects tolerate well (i.e., without excessive movement, fatigue, etc) and (iii) the need to have an above-chance memory performance, impose a limit in the number of conditions that can be individually modeled. Our current design already has a considerable number of event types (emotion: 3, memory success: 2 and old/new: 2), thus making the inclusion of further variables (e.g., remember/know or confidence values) statistically problematic. Finally, the use an old/new recognition measure allowed us to integrate our findings to previous studies assessing the influence of emotion on memory (Dougal & Rotello, 2007; Sergerie et al., 2006, 2007; Windmann & Kutas, 2001; Windmann *et al.*, 2002).

Although the eigenface analysis suggests that the observed emotion-specific modulation of response bias is unlikely to be simply due to the physical characteristics of the stimuli, I cannot completely rule out this potential confound. Indeed, despite the advantage of using facial expression as emotional stimuli, their very nature does not allow for the complete isolation of the emotional value of the stimulus from its physical properties, which are characteristic of the particular expression being studied (e.g., wider eyes in fear, open mouths in happy expressions). One way to circumvent this confounding factor would be to assign an arbitrary value to neutral faces through an association with a sentence comprising an action performed by the individual in the picture, which can have a positive, negative or neutral emotional connotation for the observer. Indeed, this paradigm has been recently used to study emotional source memory (Somerville *et al.*, 2006; Todorov *et al.*, 2007). However, in the scanning session, one study used an incidental 1-back task (Todorov et al., 2007), whereas in the other, extensive practice had led to a possible ceiling effect in performance (~95% correct for both new and old items). Thus, the direct influence of emotion on memory success (i.e., remembered vs. forgotten) using this paradigm remains to be explored. In addition, including more complex and ambiguous emotional actions could also allow us to explore both what is consistent across people (it is likely that most if not all participants will judge a serial killer as negative) but also the individual variability (e.g., cheating on one's partner is likely to have a negative valence, although less consistent in its intensity; see Figure 1 for some examples of individual variability in ratings).

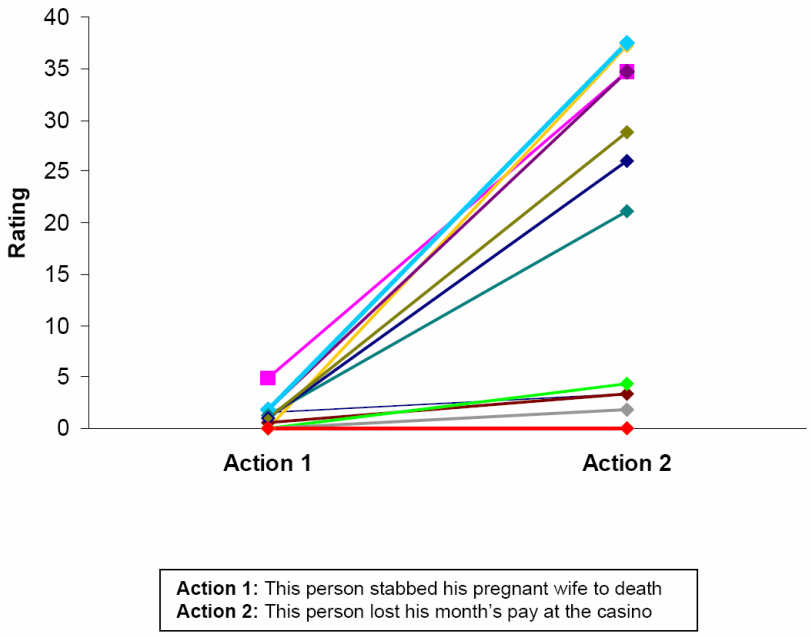

Figure 1. Examples of scripts and their valence ratings performed by twelve subjects. Whereas all participants judged the person who performed Action 1 very negatively, there was more variability in the judgment of the person for Action 2. Each color corresponds to one subject. As shown in the figure, some subjects rated both actions similarly, whereas others found the second less negative. Rating were performed on a visual analog scale (0-100)

Critically, as the association between a given individual and an emotion is arbitrary, I would be able, by counterbalancing these association across participants, to eliminate any unwanted effects due to the intrinsic value that some of these faces may have (i.e., mildly positive or negative expression, attractive or not, etc).

A variation of this approach would be to directly associate each neutral face with an intrinsically emotional stimulus, belonging to the same (Depue *et al.*, 2007; Kensinger & Schacter, 2005a, 2005b, 2006; Smith *et al.*, 2004; Smith *et al.*, 2005; Smith *et al.*, 2006; Somerville et al., 2006; Todorov et al., 2007) or different modality. For instance, we conducted a pilot behavioural recognition memory experiment combining neutral faces with happy (laughter), fearful (scream) or neutral (yawning) vocalizations in healthy individuals and patients with schizophrenia. Interestingly, whereas no modulation of

memory was observed for healthy participants, individuals with schizophrenia exhibited a significantly reduced memory accuracy for neutral faces previously paired with either positive or negative vocalizations, compared to those that had been associated with neutral ones. Thus, this paradigm appears to be promising for further exploring the influence of emotion on memory in schizophrenia, especially given the importance of auditory information processing (e.g., auditory hallucinations) in this population.

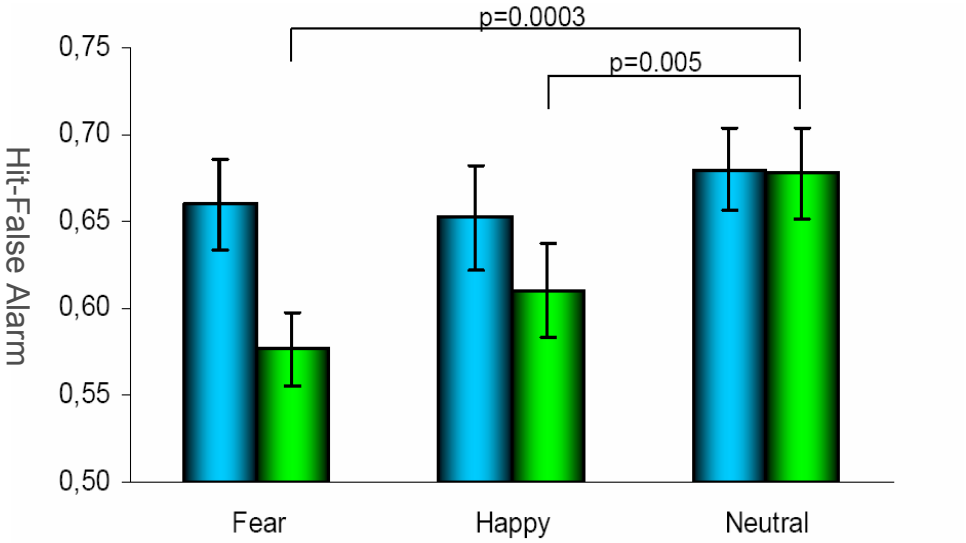

Figure 2. Mean memory recognition accuracy rates for responses for neutral faces associated with each emotional vocalization (happy, fearful and neutral) for healthy subjects (blue) and individuals with schizophrenia (green). Error bars represent one standard error of the mean.

Finally, it is worth highlighting that in the emotional memory studies, I only explored immediate recognition memory (i.e., with a delay of the order of minutes). Previous studies have shown that emotion can have a long-lasting influence on memory (Dolcos *et al.*, 2005) and that this effect may be different for familiarity- and recollection-based retrieval (Sharot et al., 2007). Thus, it would be interesting, given the results reported in this thesis, to explore the behavioural and neural effects of emotion on memory recognition bias at longer delays, in both healthy individuals and patients with

schizophrenia. This would perhaps further clarify the suggested differential strategies employed by these two groups during emotional face memory recognition.

6.2. CONCLUSION

Taken together, the results from these studies confirm the important role of the amygdala in emotional perception and memory. However, our findings suggest that the specific function of this structure in emotion may be more complex than previously thought, as its response, and hemispheric lateralization, appears to be modulated by several factors. These include not only experimental parameters, such as design, stimulus type, control condition and stimulus valence, but also the characteristics of the participants being tested (i.e., their sex). Our results are consistent with the amygdala being a "relevance detector" (see Chapter 1), as it was found to respond to both positively and negatively valenced stimuli. In addition, our meta-analysis also provide strong support for the temporal dynamics model of amygdala lateralization, namely a fast and transient right response followed by a slower and more sustained activity in the left hemisphere.

The work presented here also corroborates and further refines the generally accepted modulation of episodic memory by emotion. Importantly, this effect appears to be emotion-specific, and it can lead to enhanced as well as decreased memory accuracy, in addition to differences in response bias. Interestingly, this differential influence of emotion on memory cannot be solely explained in terms of either valence or arousal.

Finally, there are some potentially important clinical implications of this research. The study of emotional memory in individuals with schizophrenia demonstrated that, despite an overall reduced performance, the influence of emotion on memory is similar to that of healthy controls. However, this similar behavioral pattern appears to be achieved

by strategies or mechanisms, subserved by different neural circuits. A better understanding of these alternative strategies could lead to improvements of treatment approaches, particularly in terms of cognitive-behavioral and social therapies, by helping patients find their own way to integrate emotional and perceptual information to better cope with their social environment.

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Appendix A

Sergerie, K., Chochol, C., Armony, JL. (2008) The role of the amygdala in emotional processing: A quantitative metaanalysis of functional neuroimaging studies. Neurosci. Biobeh. Rev., 32(4):811-30.

Available online at www.sciencedirect.com
ScienceDirect
Neuroscience and Biobehavioral Reviews 32 (2008) 811 830
NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS
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Review

The role of the amygdala in emotional processing: A quantitative meta-analysis of functional neuroimaging studies

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Received 28 August 2007; received in revised form 14 December 2007; accepted 15 December 2007

Abstract

Functional neuroimaging studies have provided strong support for a critical role of the amygdala in emotional processing. However, several controversies remain in terms of whether different factors such as sex, valence and stimulus type have an effect on the magnitude and lateralization of amygdala responses. To address these issues, we conducted a meta analysis of functional neuroimaging studies of visual emotional perception that reported amygdala activation. Critically, unlike previous neuroimaging meta analyses, we took into account the magnitude (effect size) and reliability (variance) associated with each of the activations. Our results confirm that the amygdala responds to both positive and negative stimuli, with a preference for faces depicting emotional expressions. We did not find evidence for amygdala lateralization as a function of sex or valence. Instead, our findings provide strong support for a functional dissociation between left and right amygdala in terms of temporal dynamics. Taken together, results from this meta analysis shed new light on several of the models proposed in the literature regarding the neural basis of emotional processing.

Keywords: Amygdala; Functional magnetic resonance imaging; Positron emission tomography; Emotion; Fear; Happy; Sad; Anger; Disgust; Facial expressions; Meta analysis; Effect size

Contents

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0149 7634/$ see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.neubiorev.2007.12.002

1. Introduction

The field of human affective neuroscience has greatly benefited from the use of functional neuroimaging techniques. In particular, results from several hundred studies in healthy participants have helped delineate the neural circuitry involved in emotional processing, as well as the interactions between emotion and other cognitive processes, such as attention, memory and decision-making. Overall, these studies have confirmed the critical role of the amygdala in emotion, in agreement with findings from research on experimental animals (LeDoux, 2000) and neurological patients (Adolphs and Spezio, 2006). Furthermore, these studies have allowed researchers to test and refine existing models of amygdala function, and to develop new ones.

For instance, a widely held view is that the amygdala is a key component of a neural system specialized for the rapid and automatic evaluation of stimuli that signal potential threat or danger in the immediate environment (Adolphs et al., 1999). However, other researchers have proposed a more general role of this structure in the processing of signals of distress (Blair et al., 1999), including other negative emotions such as sadness, or in the processing of signals that indicate potentially important environmental information that must be disambiguated (Whalen et al., 2001) (e.g., facial expressions of surprise (Kim et al., 2003)). Finally, a recent model postulates that the human amygdala acts as a "relevance detector," involved in the processing of biologically relevant stimuli, regardless of their valence (Sander et al., 2003).

In addition, several theories have been proposed regarding possible hemispheric differences in emotion, thus raising the possibility of a differential involvement of the left and right amygdala in emotional processing. One of the oldest models of emotion lateralization, first proposed by Luys in 1881, posits that the right hemisphere is more involved than the left in emotional processing in general, including both positive and negative emotions (Sackeim and Gur, 1978; Schwartz et al., 1975). Another one suggests a hemispheric dissociation based on emotional valence, namely preferential processing of positive and negative information by the left and right hemispheres, respectively (e.g., Sackeim et al., 1982). This lateralization theory, especially in relation to the role of prefrontal cortex, has been refined by Davidson and colleagues, who proposed a hemispheric differentiation in terms of approach and withdrawal behavior, rather than valence (Davidson, 1984; Davidson et al., 1990; Sackeim et al., 1982).

More specific to the amygdala, a lateralization model has been proposed based on the established hemispheric differences associated with language. Namely, left amygdala would be involved in the processing of semantic material (e.g., scripts, sentences or words), whereas non-semantic information (e.g., faces, pictures) would engage the right amygdala (Markowitsch, 1998; Phelps et al., 2001).

Finally, more recent models have been proposed in terms of the temporal dynamics of the amygdala in response to emotional stimuli, based on its differential patterns of habituation (Phillips et al., 2001; Whalen et al., 1998; Wright et al., 2001). For instance, Wright et al. (2003) have proposed that whereas the right amygdala is involved in the rapid detection of emotional stimuli, the left amygdala plays a role in the more elaborate stimulus evaluation (see also Markowitsch, 1998). In a similar vein, Glascher and Adolphs (2003) suggested that the right amygdala is engaged in the initial, possibly automatic detection of an emotional stimulus, followed by a more detailed and specific analysis of variations in the magnitude of arousal associated with the stimulus mediated by the left amygdala.

In addition, sex differences in amygdala responses to emotional stimuli have also been proposed, specifically, a stronger and more bilateral amygdala activity in women than in men (Hamann, 2005; Killgore and Yurgelun-Todd, 2001). These putative neural differences are thought to underlie the often reported enhanced emotional reactivity in women (Hall and Matsumoto, 2004).

Although all these theories have received considerable support from the neuroimaging literature, many other studies have yielded contradictory results. The reasons for these discrepancies remain to be determined, especially given the large differences in methodology, paradigms, population, stimuli, and other experimental parameters across studies. One way to avoid these potential confounds and draw conclusions from disparate studies is through the use of meta-analytical approaches. This "analysis of analyses" (Glass, 1976) combines the findings of many studies investigating a common topic within a unifying framework. This technique is particularly well-suited for functional neuroimaging studies, where different paradigms are used and the number of statistical results typically reported (i.e., voxels activated in a particular contrast) can be quite large, making it difficult to interpret without the aid of a quantitative instrument.

A few meta-analyses of neuroimaging studies on emotion have been published in recent years. In the first one, which included 55 studies, Phan et al. (2002) investigated brain responses to emotional stimuli as a function of emotion type (happiness, fear, anger, sadness, disgust), valence (positive and negative), induction method (visual, auditory, recall/imagery) and cognitive load or demand. They focused their analysis on 20 *a priori* defined regions, including the amygdala. They concluded that fear specifically recruits the amygdala since out of the 8 studies investigating fear, 6 reported activations in this region. Interestingly, 50% of studies using visual induction activated the amygdala, compared to only 7% and 0% for recall and auditory induction methods, respectively. Finally, cognitive demand did not appear to significantly influence the proportion of studies reporting amygdala activation.

In a follow-up meta-analysis, Wager et al. (2003) increased the number of studies to 65 and specifically focused on the effects of sex, valence (as well as withdrawal/approach), and lateralization of the different patterns of activations. As with the previous study, they used a region-of-interest analysis (11 regions) and, in addition, calculated peak density maps based on the coordinates reported for each activation. Their main findings regarding the amygdala were: (1) more peaks were reported on the left than the right hemisphere, (2) the amygdala was more often activated for withdrawal than approach conditions (though no differences were observed for the positive vs. negative contrast), and (3) no significant sex main effects or interactions were observed in the proportion of activation peaks. However, density-map analyses revealed a more left-lateralized activation density for women and a right-lateralized one for men in the sublenticular area, partly extending into the amygdala/hippocampus region. Similar results, namely a larger proportion of activation peaks in the left hemisphere, albeit with no differences in terms of valence, was reported by Murphy et al. (2003) in their meta-analysis including 106 studies. Finally, a meta-analysis of 54 neuroimaging studies focusing on the amygdala confirmed the left lateralization of amygdala activation (Baas et al., 2004). Importantly, no interaction between laterality and stimulus type, task instructions or stimulus novelty was found.

Although these meta-analyses have provided critical insights into the neuroanatomy of emotion, they all used the so-called vote-counting technique, which may have given rise to potential confounds in the conclusions drawn. Indeed, in this approach each study has an equal weight in the overall counting; therefore the degree of statistical significance of individual activation peaks, either in terms of the magnitude of the observed effect (e.g., effect size) or its reliability (e.g., variance, sample size), is not taken into account (Deeks, 2001). However, modified vote-counting methods, including the sample size as an estimation of the study variance have been recently applied to neuroimaging (Etkin and Wager, 2007). Perhaps more importantly, vote-counting methods test whether a difference in the number of significant effects is itself significant, but do not provide an estimate of the magnitude of that difference. In the case of neuroimaging, this means that the vote-counting technique can tell us whether a particular condition results in more activations than another one, but gives no information regarding whether the activations themselves are different or not. This can be particularly problematic as the threshold for statistical significance can vary widely across studies, depending on factors such as the use of *a priori* regions of interest or the different methods employed, if any, for correcting for multiple comparisons (Genovese et al., 2002; Worsley et al., 1996).

One way to circumvent the problems associated with simple vote counting is to take into account not only whether each result is significant or not, but also how strong it is. This can be done by including the effect size corresponding to each activation in the statistical comparison across experimental conditions. Here, we conducted such a meta-analysis. Specifically, we investigated whether different experimental parameters and manipulations, such as participants' sex, stimulus type, experimental design and technique, had a significant influence on the strength of amygdala activation and its lateralization during the perception of emotional visual stimuli.

2. General methods

2.1. Literature search

We performed a search on Medline for articles of fMRI and PET studies referring to emotion in their title and/or abstract, written in English and published within the years 1993 and 2006. We used the following combination of key words: (1) Emotion and (fMRI or functional magnetic resonance imaging) and (2) Emotion and (PET or positron emission tomography). We also used similar search criteria for each of the basic emotions, namely fear, sadness, happiness, anger and disgust (and their related terms). This initial search covered all the articles included in the four previous neuroimaging meta-analyses of emotion (Baas et al., 2004; Murphy et al., 2003; Phan et al., 2002; Wager et al., 2003) and yielded 1505 studies. Data sets that were used in several different publications were included only once in the meta-analysis.

2.2. Inclusion criteria

The initial sample was then restricted to studies that met the following inclusion criteria: (1) included contrasts involving healthy adults (placebo groups in pharmacological manipulations or controls for clinical populations were also included); (2) investigated perceptual processes using visual stimuli (in studies investigating other processes, such as memory or attention, we only included the contrasts involving perception); (3) measured regional cerebral blood flow (PET) or BOLD signal (fMRI); (4) coordinates were

reported in the standardized Montreal Neurological Institute (MNI) or Talairach space (Talairach and Tournoux, 1988) (i.e., ROIs without indication of the location of the peak activation were excluded); and (5) sufficient information was provided so that an effect size could be derived for each activation (see below). This initial selection resulted in 444 studies.

We then kept only those studies which reported an activation in the amygdala. We included all the peaks that were referred to in the original studies as being in the amygdala or related areas (i.e., amygdala, extended amygdala, amygdaloid complex/region, amygdala hippocampal junction, periamygdala and periamygdaloid complex/region). Peaks whose effect size or distance to the center of gravity were larger than 3 times the interquartile range (IQR), a measure of statistical dispersion of the data, were considered outliers and thus removed from the final analysis.

2.3. Effect size

The standardized effect size is a dimensionless number that permits summarizing results across studies that use different types of measurements. Concretely, it is the magnitude of an effect divided by the variance (Glass, 1976). Although neuroimaging articles do not usually report the magnitude of the effect or the standard deviation, they often provide the z-score associated with a given significant activation, from which an effect size can be derived. Effect sizes can also be obtained from t-scores (and degrees of freedom) as well as from (exact) p-values. In those studies in which only an upper limit of the p-value was given (e.g., $p<0.001$), this number was used to calculate a minimum effect size.

Because the usual effect size g is slightly biased, especially for small sample sizes, an unbiased estimator d of the effect size was used instead (Hedges and Olkins, 1985):

$$d_{ij} \cong \left(1-\frac{3}{4N_{ij}-9}\right) g_{ij},$$

where N_{ij} is the sample size (typically subjects or scans) of study j included in the factor of interest i (e.g., left/right, male/female).

The reliability of each effect size was included by calculating the weighted mean unbiased estimator of the effect size for each factor i:

$$d_{i+} \sum_j \frac{d_{ij}}{\hat{\sigma}^2(d_{ij})} \Big/ \sum_j \frac{1}{\hat{\sigma}^2(d_{ij})},$$

where

$$\hat{\sigma}^2(d_{ij}) = \frac{1+d_{ij}^2/2}{N_{ij}}$$

is an estimate of the variance associated with each effect size d_{ij}.

These values can then be used to construct the goodness-of-fit statistics

$$Q_T \sum_i \sum_j \frac{(d_{ij}-d_{++})^2}{\hat{\sigma}^2(d_{ij})},$$

where

$$d_{++} = \sum_i \sum_j \frac{d_{ij}}{\hat{\sigma}^2(d_{ij})} \Big/ \sum_i \sum_j \frac{1}{\hat{\sigma}^2(d_{ij})}$$

is the grand mean.

The total weighted sum of squares Q_T can be partitioned into Q_W and Q_B:

$$Q_T = Q_W + Q_B$$

with

$$Q_W = \sum_i \sum_j \frac{(d_{ij}-d_{i+})^2}{\hat{\sigma}^2(d_{ij})}$$

and

$$Q_B = \sum_i \sum_j \frac{(d_{i+}-d_{++})^2}{\hat{\sigma}^2(d_{ij})}.$$

Q_W and Q_B follow a χ^2 distribution of $(k-p)$ and $(p-1)$ degrees of freedom, respectively, with k being the total number of observations (activation peaks in our case) and p is the number of factors (typically two). They can be interpreted as representing the within- and between-factors fit, respectively (similar to the partitioning of the sum of squares in an ANOVA). Therefore, Q_B can be used to test whether a significant amount of the total variance can be explained by taking into account that the observations belong to different factors or groups. In other words, a significantly non-zero Q_B means that the effect sizes for the different factors are significantly different from each other. For a more detailed discussion of the methods, the reader is referred to Hedges and Olkins (1985).

In those cases where there was a large difference in the number of activation peaks between conditions, we also conducted a modified version of the standard jackknife analysis (Miller, 1974) to confirm the results obtained with the χ^2-test described above. Briefly, this analysis consisted of randomly selecting a subset of data points from the larger group of the same size as the smaller one, and computing the difference in effects size between the groups. We repeated this procedure 10,000 times and calculated the proportion of instances in which the mean effect size for one condition was larger than the other one, thus obtaining an exact p-value (p_{jk}) associated with the effect of interest.

3. Results

3.1. Number of activations

Our search yielded a total of 365 activation peaks in the amygdala (Fig. 1). Five values were removed as their

associated effect sizes were considered outliers ($d > 3.65$). Another 6 peaks (3 in the left and 3 in the right hemisphere) were also removed, as their distance to the center of gravity of the all the data points (left: −21, −5, −16; right: 22, −4, −15) was larger than the cut-off for outliers (3*IQR; left: 26 mm, right: 22 mm). Thus, the final analysis was performed on data from 354 peaks, derived from 148 different studies. A list of these studies, depicting their main characteristics, is shown in Table 1 (the full references are provided in Appendix A).

3.2. Control condition

The contrasts involving a comparison between emotional and control stimuli were assigned to two categories, depending on whether the control condition was the same type of stimulus but of neutral emotional value (e.g., neutral faces, pictures or words), called the "neutral" condition, or whether a lower-level condition was used, such as scrambled pictures, fixation cross or a blank screen (the "baseline" condition). As expected, effect sizes were larger ($Q_B = 14.1$, $p = 0.0002$; see Fig. 2 and Table 2) for the comparison of emotional stimuli to low-level controls (E > B) than when using a similar but neutral stimulus (E > N). A jackknife analysis (see Methods) confirmed this result ($p_{jk} = 0.0002$), ruling out the possibility of a bias due to the different number of peaks included in each condition.

3.3. Sex

A comparison between studies testing only male or female participants revealed a main effect of sex ($Q_B = 15.1$, $p = 0.0001$), due to a larger effect size for men than for women. This sex effect was confirmed by a positive correlation between effect size and the relative proportion of male participants for studies with participants of both sexes ($r = 0.12$, $z = 3.62$, $p < 0.001$). In terms of proportion of reported peaks within the amygdala, relative to all brain activations, across studies involving only male or female participants, no significant differences were observed (male = 64%, female = 67%, $p = 0.8$).

3.4. Stimulus type

A significantly stronger effect size was observed for faces compared to pictures ($Q_B = 6.3$, $p = 0.01$). In addition, there was a trend for a larger effect size for semantic stimuli than for pictures in the left amygdala ($p = 0.08$). No differences between films and any of the other stimulus types were observed ($p > 0.3$).

3.5. Valence and individual emotions

We observed an influence of stimulus valence on mean effect sizes ($Q_B = 9.7$, $p = 0.002$; $p_{jk} = 0.0075$), although it was in the opposite direction of what is commonly assumed: the effect size was larger for positive than negative material. In order to exclude the possibility that the effect was due to differences between studies unrelated to the valence of the stimuli, we conducted the same analysis on the subset of experiments ($N = 13$) that used both negative and positive material and reported amygdala activation for both conditions, relative to control. A similar valence effect was obtained, namely larger magnitude for positive than negative stimuli ($Q_B = 6.1$, $p = 0.01$), as illustrated by the effect size histograms shown in Fig. 3.

We directly tested the valence lateralization model, which postulates a right hemisphere advantage for positive

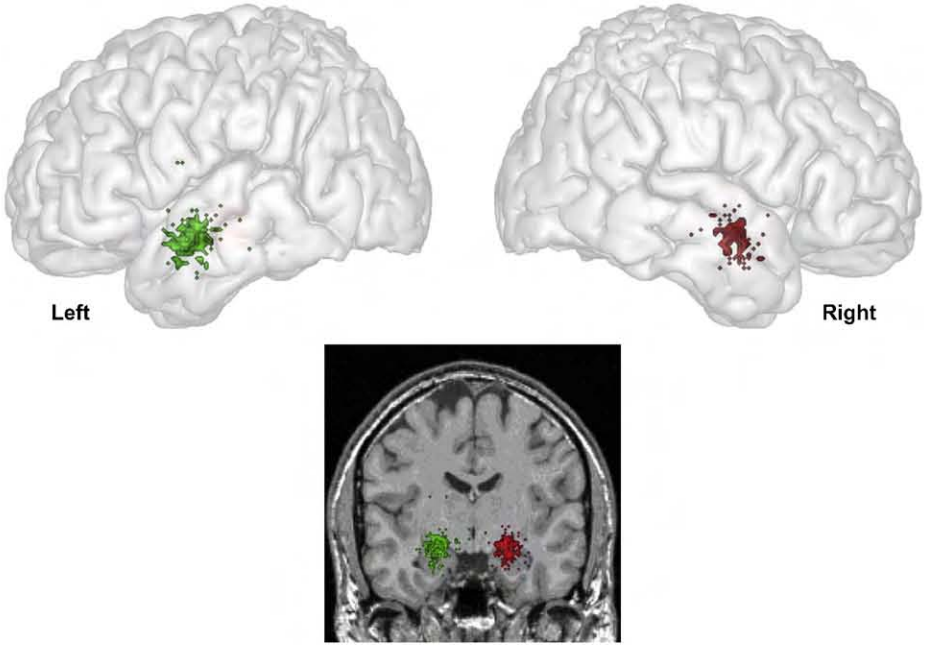

Fig. 1. Three dimensional rendering of all the amygdala peaks included in the meta analysis.

Table 1
Main characteristics of the studies included in the meta-analysis

#	First author	Year	Journal	Ss	M	W	Age	Tech	Emotional stimulus type	F	H	S	Su	D	A	N	Valence		
																	+	−	N
1	Breiter	1996	Neuron	10	10	0	27 1	fMRI	Face	x						x		x	x
2	Lane	1997	Neuropsychologia	12	0	12	18–45[a]	PET	Picture							x	x	x	x
3	Phillips	1997	Nature	7	2	5	27 0	fMRI	Face	x				x		x		x	x
4	Reiman	1997	Am J Psychiatry	12	0	12	23 3	PET	Picture		x	x		x		x	x	x	x
5	Morris	1998	Brain	5	4	1	42 8	PET	Picture	x	x					x	x	x	x
6	Phillips	1998	Proc Biol Sci	6	6	0	37 0	fMRI	Face	x				x		x		x	x
7	Taylor	1998	NeuroImage	8	0	8	27 9	PET	Picture	x				x		x		x	x
8	Whalen	1998	J Neurosci	10	10	0	23 8	fMRI	Picture	x	x						x	x	
9	Blair	1999	Brain	13	13	0	25 3	PET	Face			x			x	x		x	x
10	Isenberg	1999	Proc Natl Acad Sci	6	2	4	26 4	PET	Semantic							x		x	x
11	Paradiso	1999	Am J Psychiatry	17	7	10	31 2	PET	Picture							x	x	x	x
12	Canli	2000	J Neurosci	10	0	10		fMRI	Picture							x		x	x
13	Critchley	2000	Hum Brain Mapp	9	9	0	27 0	fMRI	Face		x				x	x	x	x	x
14	Hariri	2000	NeuroReport	16	8	8	25 3	fMRI	Face	x					x			x	
15	Simpson	2000	J Cogn Neurosci	18	9	9	24 9	fMRI	Picture							x		x	x
16	Taylor	2000	NeuroPsychologia	14	9	5	32 1	PET	Picture							x		x	x
17	Gorno-Tempini	2001	NeroImage	10	5	5	25–30[a]	fMRI	Face		x			x		x	x	x	x
18	Iidaka	2001	J Cogn Neurosci	12	6	6	25 1	fMRI	Face							x	x	x	x
19	Maratos	2001	Neuropsychologia	12	5	7	18–30[a]	fMRI	Semantic							x	x	x	x
20	Vuilleumier	2001	Neuron	12	6	6	27 7	fMRI	Face	x						x		x	x
21	Whalen	2001	Emotion	8	4	4	25 0	fMRI	Face	x					x	x		x	x
22	Williams	2001	NeuroImage	11	11	0	30 0	fMRI	Face	x						x		x	x
23	Wright	2001	NeuroReport	8	8	0	28 0	fMRI	Face	x	x						x	x	
24	Canli	2002	Science	15	4	11		fMRI	Face	x	x						x	x	
25	Gur	2002	Am J Psychiatry	14	10	4	27 4	fMRI	Face	x	x	x		x	x	x	x	x	x
26	Hamann	2002	NeuroReport	14	14	0	20–31[a]	fMRI	Semantic							x	x	x	x
27	Hamann	2002	Psychol Sci	10	10	0	22 8	PET	Picture							x	x	x	x
28	Hariri	2002	NeuroImage	12	6	6	28 0	fMRI	Face	x					x	x		x	x
29	Hariri	2002	Neuropsychopharmacology	12	5	7	33 0	fMRI	Face	x					x	x		x	x
30	Kosaka	2002	Schizophr Res	12	6	6	24 4	fMRI	Face		x	x		x	x	x	x	x	x
31	Liberzon	2002	PNAS	12	12	0	45 8	PET	Picture							x		x	x
32	Schienle	2002	NeuroReport	12	0	12	26 3	fMRI	Picture	x				x		x		x	x
33	Tessitore	2002	J Neurosci	10	7	3	61 0	fMRI	Face	x					x	x		x	x
34	Wright	2002	NeuroReport	16	8	8	30 0	fMRI	Face		x				x	x	x	x	x
35	Yang	2002	NeuroReport	17	6	11	23 0	fMRI	Face	x	x	x			x	x	x	x	x
36	Abel	2003	NeuroReport	8	8	0	28 8	fMRI	Face	x						x		x	x
37	Anderson	2003	J Neurosci	12	3	9	22 1	fMRI	Face	x				x		x		x	x
38	Carr	2003	PNAS	11	7	4	29 0	fMRI	Face	x	x	x	x	x	x		x	x	
39	Compton	2003	Cogn Affect Behav Neurosci	12	8	4	25 2	fMRI	Semantic							x	x	x	x
40	Erk	2003	Neuroimage	10	7	3	27 1	fMRI	Picture							x	x	x	x
41	Eugène	2003	NeuroImage	20	0	20	24 3[b]	fMRI	Film			x				x		x	x
42	Gunning-Dixon	2003	Neurobiol Aging	8	4	4	25 8	fMRI	Face	x	x	x		x	x	x	x	x	x
43	Hadjikhani	2003	Curr Biol	7	4	3		fMRI	Film	x	x	x			x	x	x	x	x
44	Hariri	2003	Biol Psychiatry	11	5	6	32 0	fMRI	Picture							x		x	x
45	Hendler	2003	NeuroImage	11	11	0	33 0	fMRI	Picture							x		x	x
46	Kim	2003	NeuroReport	15	8	7	22 3	fMRI	Face				x			x		x	x
47	Klein	2003	Pharmacopsychiatry	20	10	10	41 6[b]	fMRI	Picture							x	x	x	x
48	Lange	2003	Biol Psychiatry	9	9	0	29 0	fMRI	Face	x						x		x	x

49	Lévesque	2003	Biol Psychiatry	20	0	20	24 3	fMRI	Film			x				x		x	x
50	Liberzon	2003	Neuropsychopharmacology	10	6	4	27 5	PET	Picture							x	x	x	x
51	Maddock	2003	Hum Brain Mapp	8	2	6	24–45[a]	fMRI	Semantic							x	x	x	x
52	Mataix-Cols	2003	Biol Psychiatry	10	5	5	27 6	fMRI	Picture							x		x	x
53	Phan	2003	Neuropsychopharmacology	8	3	5	24 4	fMRI	Picture							x		x	x
54	Shirao	2003	Neuropsychobiology	15	0	15	25 0	fMRI	Semantic							x		x	x
55	Stark	2003	Int J Psychophysiol	19	9	10	27 2	fMRI	Picture	x				x		x		x	x
56	Surguladze	2003	NeuroImage	9	5	4	39 6	fMRI	Face	x	x	x		x		x	x	x	x
57	Taylor	2003	NeuroImage	10	6	4	21 2	PET	Picture							x		x	x
58	Vuilleumier	2003	Nat Neurosci	13	6	7	27 0	fMRI	Face	x						x		x	x
59	Winston	2003	Current Biol	14	6	8	30 0	fMRI	Face	x						x		x	x
60	Winston	2003	NeuroImage	11	6	5	26 0	fMRI	Face	x	x	x		x		x	x	x	x
61	Benuzzi	2004	Brain Res Bull	14	7	7	21–27[a]	fMRI	Face	x						x		x	x
62	Bishop	2004	J Neurosci	27	7	20	18–38[a]	fMRI	Face	x						x		x	x
63	Cannistraro	2004	Biol Psychiatry	10	4	6	24 9	fMRI	Face	x	x					x	x	x	x
64	Cunningham	2004	J Cogn Neurosci	20				fMRI	Face							x	x	x	x
65	de Gelder	2004	PNAS	7	4	3		fMRI	Film	x	x					x	x	x	x
66	Etkin	2004	Neuron	17	9	8	20–33[a]	fMRI	Face	x						x		x	x
67	Fichtenholtz	2004	Brain Res Cogn Brain Res	22	13	9	20–47[a]	fMRI	Picture							x	x	x	x
68	Gläscher	2004	BMC Neurosci	11	3	8	25 6	fMRI	Face	x	x					x	x	x	x
69	Kensinger	2004	PNAS	28	14	14		fMRI	Semantic							x		x	x
70	Killgore	2004	NeuroImage	12	0	12	23 7	fMRI	Face		x	x				x	x	x	x
71	Lee	2004	Cogn Behav Neurol	10	5	5	29 5	fMRI	Picture							x	x	x	x
72	Mathews	2004	J Cogn Neurosci	22	6	16		fMRI	Picture	x						x		x	x
73	Nomura	2004	NeuroImage	10	5	5	23 5	fMRI	Face		x				x	x	x	x	x
74	Ochsner	2004	NeuroImage	24	0	24	20 6	fMRI	Picture							x		x	x
75	Phan	2004	NeuroImage	12	6	6	22 7	fMRI	Picture							x	x	x	x
76	Phillips	2004	NeuroImage	8	8	0	31 9	fMRI	Face	x				x		x		x	x
77	Sato	2004	Brain Res Cogn Brain Res	22	10	12	26 5	fMRI	Face	x	x					x	x	x	x
78	Sato	2004	NeuroImage	10	5	5	24 4	fMRI	Face						x	x		x	x
79	Stark	2004	Neuropsychobiology	24	24	0	25 5	fMRI	Face	x				x		x		x	x
80	Takahashi	2004	NeuroImage	15	9	6	29 1	fMRI	Picture							x	x	x	x
81	Vuilleumier	2004	Nat Neurosci	13	7	6	35 8[b]	fMRI	Face	x						x		x	x
82	Wang	2004	J Am Acad Child Adolesc Psychiatry	12	12	0	11 8	fMRI	Face	x					x	x		x	x
83	Whalen	2004	Science	20	20	0	21 9	fMRI	Picture	x	x					x	x	x	x
84	Williams	2004	Am J Psychiatry	22	14	8	27 2	fMRI	Face	x						x		x	x
85	Williams	2004	Brain Res Cogn Brain Res	22	15	7	27 5	fMRI	Face	x						x		x	x
86	Anand	2005	Biol Psychiatry	15	4	11	28 0	fMRI	Picture							x		x	x
87	Das	2005	NeuroImage	28	14	14	30 1	fMRI	Face	x						x		x	x
88	Erk	2005	NeuroImage	10	7	3	24 3	fMRI	Picture								x	x	
89	Ferstl	2005	J Cogn Neurosci	20	8	12	25 0	fMRI	Semantic							x	x	x	x
90	Fischer	2005	Neurosci Lett	24	12	12	24 7	fMRI	Face						x	x		x	x
91	Goldin	2005	NeuroImage	13	0	13	19 7	fMRI	Film		x	x				x	x	x	x
92	Habel	2005	NeuroImage	26	26	0	33 4	fMRI	Face		x	x					x	x	
93	Hennenlotter	2005	NeuroImage	12	6	6	24 5	fMRI	Face		x					x	x		x
94	Hutcherson	2005	NeuroImage	28	0	28	18–21[a]	fMRI	Film		x	x				x	x	x	x
95	Johnston	2005	Eur J Neurosci	10	8	2	31 2	fMRI	Face	x	x	x	x	x	x	x	x	x	x
96	Kensinger	2005	NeuroImage	16	8	8	18–30[a]	fMRI	Picture, semantic							x	x	x	x
97	Kensinger	2005	Neuropsychologia	16	7	9	18–30[a]	fMRI	Picture, semantic							x	x	x	x
98	Liddell	2005	NeuroImage	22	11	11	32 0	fMRI	Face	x						x		x	x
99	Moll	2005	Cogn Behav Neurol	13	7	6	25 5	fMRI	Semantic					x		x		x	x
100	Noesselt	2005	Curr Biol	12	7	5	22 6	fMRI	Face	x						x		x	x
101	Phan	2005	Biol Psychiatry	14	6	8	27 6	fMRI	Face									x	
102	Protopopescu	2005	Biol Psychiatry	14	7	7	27 0	fMRI	Semantic							x	x	x	x
103	Ray	2005	Cogn Affect Behav Neurosci	24	0	24	20 6	fMRI	Picture							x		x	x

Table 1 (*continued*)

#	First author	Year	Journal	Ss	M	W	Age	Tech	Emotional stimulus type	F	H	S	Su	D	A	N	Valence		
																	+	–	N
104	Reinders	2005	Eur J Neurosci	15	7	8	25 8	fMRI	Face	x						x		x	x
105	Schienle	2005	Neuropsychobiology	63	0	63	27 3	fMRI	Picture					x		x		x	x
106	Schienle	2005	Neurosci Letters	13	0	13	23 9	fMRI	Picture	x				x		x		x	x
107	Shäfer (b)	2005	Int J Psychophysiol	40	20	20	23 9	fMRI	Face, picture	x				x		x		x	x
108	Shin	2005	Arch Gen Psychiatry	13	13	0	49 7	fMRI	Face	x	x						x	x	x
109	Skuse	2005	Brain	12	0	12	25 6	fMRI	Face	x						x		x	x
110	Smith	2005	Learn Mem	18	10	8	21 0	fMRI	Picture							x	x	x	x
111	Stark	2005	Biol Psychol	12	6	6	28 2	fMRI	Picture					x		x		x	x
112	Straube	2005	Neuropsychobiology	9	4	5	22 7	fMRI	Face		x				x	x	x	x	x
113	Strauss	2005	NeuroImage	8	8	0	26 5	fMRI	Face						x	x		x	x
114	Takahashi	2005	NeuroImage	13	13	0	29 2	fMRI	Picture							x		x	x
115	Tessitore	2005	Psychiatry Res Neuroimaging	12	6	6	25 0	fMRI	Face	x					x			x	
116	van Stegeren	2005	NeuroImage	30	15	15	20 9	fMRI	Picture							x		x	x
117	Wang	2005	Emotion	12	5	7	25 9	fMRI	Picture			x				x		x	x
118	Williams	2005	NeuroReport	13	5	8	24 0	fMRI	Face	x				x	x	x		x	x
119	Ashwin	2006	Neuropsychologia	13	13	0	25 6	fMRI	Face	x						x		x	x
120	Bermpohl	2006	Hum Brain Mapp	17	8	9	21–37[a]	fMRI	Picture							x	x	x	x
121	Britton	2006	NeuroImage	12	6	6	21 4	fMRI	Face, picture	x	x	x			x	x	x	x	x
122	Erk	2006	Eur J Neurosci	14	0	14	21–25[a]	fMRI	Picture							x		x	x
123	Fitzgerald	2006	NeuroImage	20	10	10	26 0	fMRI	Face	x	x	x		x	x	x	x	x	x
124	Garrett	2006	NeuroImage	9	4	5	38 7	fMRI	Picture							x		x	x
125	Grosbras	2006	Cereb Cortex	20	10	10	28 6	fMRI	Film						x	x		x	x
126	Harenski	2006	NeuroImage	10	0	10	18–29[a]	fMRI	Picture							x		x	x
127	Herwig	2006	NeuroImage	16	6	10	23–26[a]	fMRI	Picture							x	x	x	x
128	Holt	2006	Schizophrenia Res	16	16	0	48 2	fMRI	Face	x	x					x	x	x	x
129	Kensinger	2006	Cogn Affect Behav Neurosci	21	11	10	18–35[a]	fMRI	Picture, semantic							x	x	x	x
130	Lewis	2006	Cereb Cortex	19	10	9	30 0	fMRI	Semantic								x	x	
131	Lobaugh	2006	NeuroReport	10	6	4	10 3	fMRI	Face	x	x	x	x	x	x	x	x	x	x
132	Mackiewicz	2006	PNAS	40	22	18	20 7	fMRI	Picture							x		x	x
133	Mobbs	2006	Soc Cogn Affect Neurosci	14	6	8	27 5	fMRI	Face, picture	x	x					x	x	x	x
134	Moser	2006	J Neurosci Methods	12	7	5	27 7	fMRI	Face, picture	x	x	x		x	x	x	x	x	x
135	Nakic	2006	NeuroImage	13	5	8	32 0	fMRI	Semantic							x		x	x
136	Ogino	2006	Cereb Cortex	10	10	0	26 3	fMRI	Picture							x		x	x
137	Pessoa	2006	Cereb Cortex	37	19	18	28 1	fMRI	Face	x	x					x	x	x	x
138	Reinders	2006	NeuroImage	15	7	8	25 8	fMRI	Face	x						x		x	x
139	Sambataro	2006	Eur J Neurosci	24	11	13	26 8	fMRI	Face					x		x		x	x
140	Schienle	2006	Neurosci Lett	12	0	12	19–41[a]	fMRI	Picture							x		x	x
141	Simon	2006	Pain	17	8	9	23 1	fMRI	Face						x	x		x	x
142	Smith	2006	Neuron	16	8	8		fMRI	Picture							x		x	x
143	Taylor	2006	Biol Psychiatry	30	12	18		fMRI	Face	x					x	x		x	x
144	Williams	2006	Hum Brain Mapp	15	7	8	35 8	fMRI	Face	x						x		x	x
145	Williams	2006	NeuroImage	13	7	6	34 8	fMRI	Face	x						x		x	x
146	Williams	2006	J Neurosci	15	7	8	35 8	fMRI	Face	x						x		x	x
147	Wright	2006	Neurobiol Aging	18	6	12	24 0	fMRI	Face	x						x		x	x
148	Wright	2006	NeuroImage	12	6	6	29 0	fMRI	Face	x	x				x	x	x	x	x

[a]Age range. No mean age was reported.

[b]Represents the mean age of all the participants from the two groups tested (control and experimental), although only the control group was included in the meta-analysis.

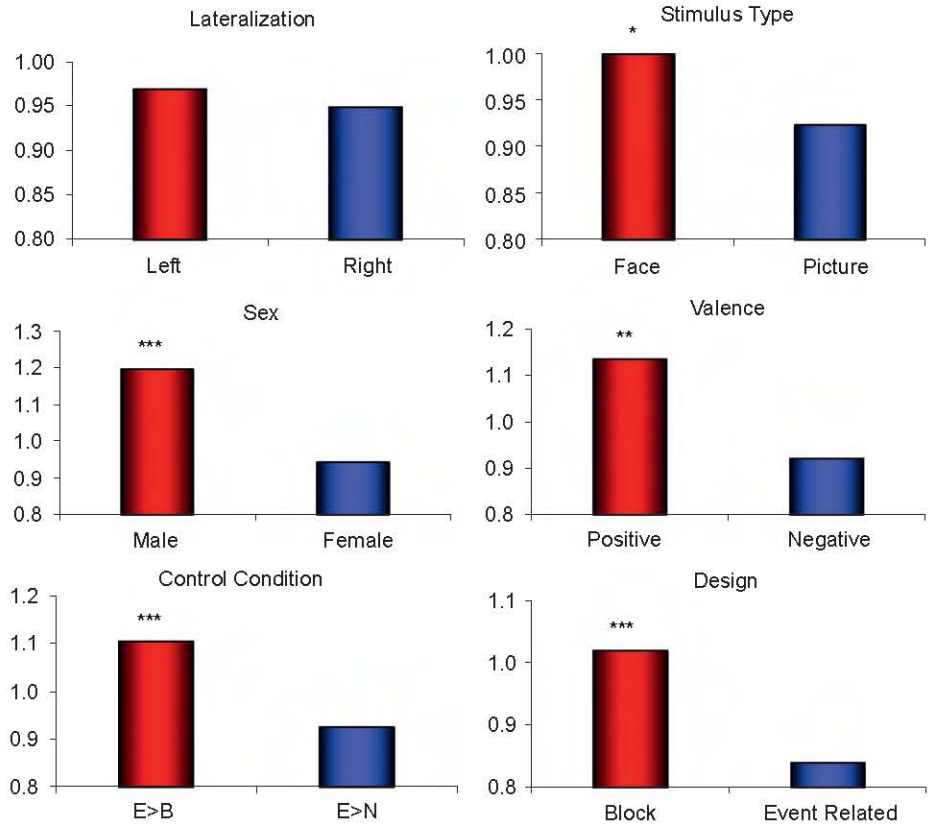

Fig. 2. Mean effect sizes associated with the amygdala activation for the different conditions of interest. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

material and a left one for negative, by performing an interaction analysis between valence and hemisphere. No significant effect was observed ($p = 0.6$).

A further emotion-specific analysis including happiness, fear, sad, disgust and anger revealed that happy stimuli consistently elicited stronger effect sizes compared to all negative emotions, although it only reached statistical significance for comparisons with fear ($Q_B = 6.1$, $p = 0.01$) and disgust ($Q_B = 6.0$, $p = 0.01$). No pairwise differences between negative emotions were observed (all $p > 0.3$). Other emotions (e.g., surprise, contempt) could not be separately analyzed due to insufficient number of studies.

3.6. Laterality

Consistent with previous meta-analyses, a significantly larger number of activation peaks across studies were reported in the left than in the right amygdala ($\chi^2 = 5.46$, $p = 0.02$; see Fig. 1). In contrast, no difference in terms of mean value or distribution of the effect sizes of these activation was observed ($Q_B = 0.4$, $p = 0.5$).

3.7. Experimental design and technique

When comparing studies using PET and fMRI, a trend for a larger magnitude in the PET activations was observed ($Q_B = 3.1$, $p = 0.08$; $p_{jk} = 0.08$). Further analyses revealed that this difference was driven by stronger effect sizes associated with block designs compared to those using an event-related analysis (only possible in fMRI). Indeed, the comparison between block and event-related designs for fMRI studies was significant ($Q_B = 17.8$, $p < 0.00005$; $p_{jk} < 0.00001$), while there was no significant difference between PET and fMRI studies when only considering block designs ($Q_B = 1.4$, $p = 0.24$; $p_{jk} = 0.26$), as shown in Fig. 4.

3.8. Interaction between experimental design and laterality

Because of the previously hypothesized differential habituation rates of left and right amygdala (Phillips et al., 2001; Whalen et al., 1998; Wright et al., 2001), we explored the interaction between hemispheric lateralization and experimental design. Specifically, we compared the number of activations in left and right amygdala for block and event-related designs separately. Whereas no difference between hemispheres in the number of activations was observed for event-related studies ($p > 0.5$), significantly more activations were reported in the left than in the right amygdala for experiments using a block design ($p = 0.007$). Notably, no significant differences in mean effect size between hemispheres were observed for either type of paradigm.

Table 2
Mean effect size and number of peaks and studies for the different factors included in the analysis

Factors	Effect size	Number of peaks	Number of studies
Lateralization			
Left	0.97	199	122
Right	0.95	155	112
Sex[a]			
Male	1.20	53	24
Female	0.92	40	20
Control condition			
E>B	1.11	63	24
E>N	0.92	220	107
Stimulus type			
Face	1.01	191	76
Picture	0.92	123	55
Film	1.02	12	6
Semantic	1.02	23	14
Valence[b]			
Positive	1.14	28	16
Negative	0.92	227	109
Emotion			
Happy	1.11	19	9
Fear	0.89	84	46
Disgust	0.85	22	13
Angry	0.99	15	10
Sad	0.93	12	10
Technique			
PET	1.10	27	12
fMRI	0.95	327	136
Design[c]			
Block	1.01	266	111
Event related	0.85	88	38

[a]Studies including only male or female participants.
[b]Indicates studies in which a positive or negative condition was contrasted to a control one.
[c]One study (Schafer et al., 2005) conducted both block and event related experiments.

4. Discussion

The main goal of this study was to examine the influence of specific experimental parameters on the magnitude and laterality of amygdala activations across functional neuroimaging studies of emotional perception within the visual modality. Unlike previous meta-analyses of emotion using vote-counting approaches, each activation peak was represented by its effect size and weighted by the corresponding estimated variance. Taking into account the strength and reliability of each activation reported in the literature allowed us to derive an index of the strength of amygdala activation associated with the different conditions of interest and, critically, to compare them in a quantitative fashion.

4.1. Experimental design

The results from this meta-analysis confirm the importance of the control condition when assessing neural responses to emotional stimuli using neuroimaging techniques (Gusnard et al., 2001). Indeed, a stronger amygdala activation was associated with those contrasts in which the emotional stimuli were compared to a low-level baseline condition, such as fixation cross or scrambled images, than when a neutral stimulus (of the same type as the emotional one) was used. This difference is likely due to the fact that the amygdala also responds, albeit more weakly, to neutral stimuli, such as faces or pictures (Holt et al., 2006; Iidaka et al., 2002; Kesler/West et al., 2001; Liberzon et al., 2002; Taylor et al., 2000, 2002, 2005). This would result in a smaller difference between the two stimulus categories than when using low-level baseline conditions, which are less effective in driving the amygdala.

The stronger effect size associated with experiments using a block design compared to those using an event-related one supports the notion that the former are more efficient from a statistical point of view (Josephs and Henson, 1999). Notably, our findings show that such an increase in efficiency holds even for a structure such as the amygdala, which has been proposed to be particularly susceptible to habituation effects following the repeated presentation of stimuli belonging to the same category (see below). Interestingly, despite the possibility of signal loss in the amygdala in fMRI due to susceptibility artefacts, the mean effect sizes obtained in blocked fMRI and PET designs were not significantly different.

4.2. Valence models

Contrary to the traditional view of the amygdala as a structure specialized in the detection of negative information, presentation of positive stimuli appeared to consistently elicit activation in this structure. This finding is in accord with some of the previous meta-analyses of emotion (Murphy et al., 2003; Wager et al., 2003) and provides further support for the notion of the amygdala as being involved in the processing of biologically relevant information, regardless of valence (Sander et al., 2003).

In fact, the mean effect size associated with amygdala response to positive stimuli was significantly larger than for negative ones. Because of the usual *a priori* expectation of an amygdala involvement in the processing of negative stimuli, it was critical to rule out the possibility that the observed difference in mean effect size as a function of valence could be due to a bias in the accepted statistical threshold between positive and negative stimuli. In other-words, studies using negative material could have adopted a more liberal statistical threshold for the amygdala than those using positive stimuli, therefore resulting in a larger proportion of reported activations for negative valences with smaller effect sizes. This explanation was explicitly tested by selectively comparing the effect sizes associated

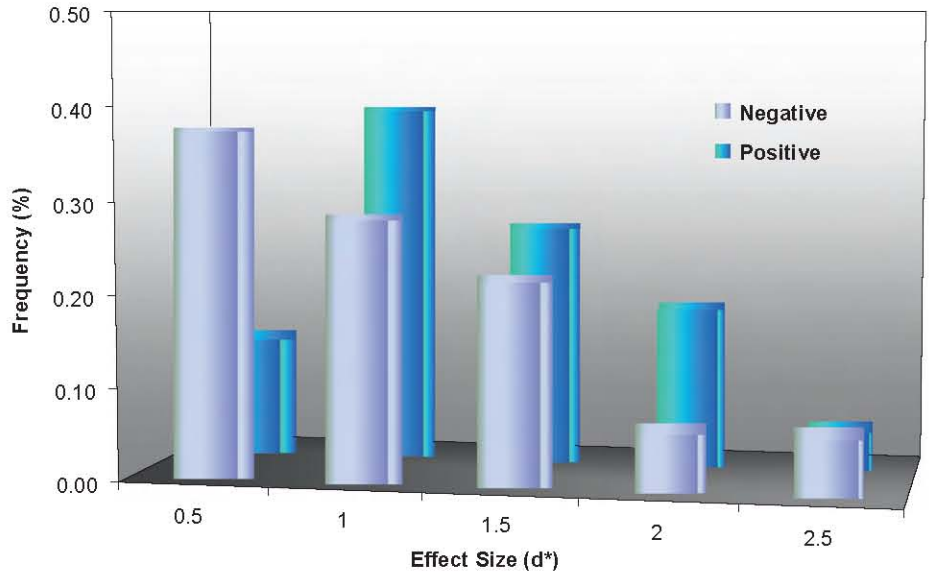

Fig. 3. Histogram of the effect sizes for the amygdala activations associated with the presentation of positive and negative stimuli for the studies in which both types of material were used ($N = 13$).

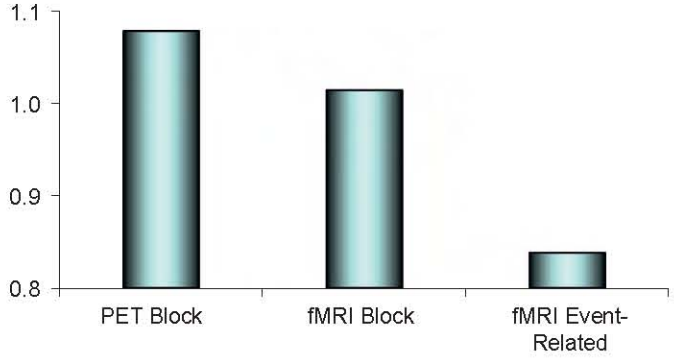

Fig. 4. Mean effect sizes associated with the amygdala activation as a function of technique (fMRI/PET) and experimental design (block/event related).

with positive and negative stimuli in those studies in which both types of material were presented (and thus the same thresholds used for both conditions). Similar results i.e., larger magnitude for positive than negative material were obtained as when analyzing the entire data set. Although this valence effect was unexpected and somewhat counter-intuitive, it is consistent with electrophysiological recordings in monkeys showing not only that amygdala neurons respond to both positive and negative material (Nishijo et al., 1988), but that there in fact is a larger proportion of cells that respond to positive than negative stimuli (Paton et al., 2006).

When contrasting individual emotions separately, similar valence effects were observed; namely, happy stimuli elicited larger activations than each of the negative emotions included in the analysis (fear, angry, sad and disgust), indicating that the general valence effects described above were not driven by any single negative emotion. Unfortunately, there were not enough data points to test whether the results observed also applied to other positive emotions (e.g., pleasure), as the majority of studies did not analyze separately the various positive emotions contained in their stimulus set (e.g., affective pictures from IAPS).

The stronger amygdala response to faces compared to pictures is in agreement with studies comparing both types of material (e.g., (Hariri et al., 2002)), and it may reflect the key role of this structure in our evolutionarily shaped ability to rapidly and efficiently decode conspecifics' emotional expressions. The trend for a larger response in the left amygdala to semantic material is in line with the proposed hemispheric specialization for processing of this type of information.

4.3. Sex differences

Our findings do not support the sometimes hypothesized (Hamann, 2005) stronger amygdala response in women than in men, as no significant difference in the proportion of amygdala activations between male- and female-only studies was observed, in agreement with results from the previous meta-analysis that examined this issue (Wager et al., 2003). Notably, our results show a significantly larger mean amygdala effect size in studies involving only men than in those testing only women, as well as a correlation between effect size and relative proportion of male participants in studies with participants from both sexes. This sex effect may be partly explained by the established anatomical and physiological dimorphism in the amygdala. Specifically, MRI studies have reported a larger amygdala volume and/or gray matter density in men, even after controlling for overall brain size (Goldstein et al., 2001). Furthermore, animal studies have demonstrated that the male amygdala has a greater dendritic density, putatively

associated with a larger number of excitatory synapses (Cooke and Woolley, 2005).

Alternatively, the smaller effect size observed in female participants could be due to a larger amygdala response to neutral stimuli. Such an enhanced baseline activity would then result in a reduced difference between emotional and control stimuli in women, as compared to men.

Finally, another, more speculative explanation could be based on the variability in anxiety-like behavior and amygdala responsivity throughout the menstrual cycle in women. Indeed, it has often been reported that female rats exhibit less fear than males, although this difference varies with the estrous cycle (Toufexis et al., 2006). Specifically, female rats exhibit reduced anxiety-like behaviors, compared to males, during their proestrous (follicular) phase, when progesterone is at its peak level, but they show similar levels during the other phases (Frye et al., 2000). Consistent with findings in experimental animals, amygdala response to positive and negative stimuli in women are largest during their follicular phase (Dreher et al., 2007; Goldstein et al., 2005). Thus, it is possible that the observed sex differences in amygdala activation were due to the fact that most neuroimaging studies do not take into account the phase of the menstrual cycle of the female participants at the time of testing, and therefore the response reported represents an average across all phases, leading to an overall reduced activation.

4.4. Laterality

The larger proportion of activation foci in the left amygdala than in the right is consistent with findings from previous meta-analyses (Baas et al., 2004; Murphy et al., 2003; Wager et al., 2003). However, there was no difference in terms of effect sizes between hemispheres, either in the mean values or their distributions. Taken together, these results suggest that when amygdala activations were reported, the magnitude of the effect was similar, regardless of the hemisphere, but that activations were reported more often in the left than in the right amygdala. Critically, further analysis that took into account the design used in the studies showed that the difference in the proportion of activation peaks between hemispheres was only apparent in experiments using a block design, and not when an event-related paradigm was employed.

This finding supports the often observed hemispheric differences in temporal dynamics and/or habituation rates, namely a short-duration response in the right amygdala and a more sustained one in the left. Indeed, block designs typically involve the repeated presentation of stimuli of the same category (e.g., positive, negative or neutral) for relatively long periods of time (the mean block duration for studies included in this meta-analysis was 107 s). Therefore, averaging the activity over a block would result in a lower, below significance magnitude in the right amygdala due to its rapid return to baseline levels. In contrast, the pseudo-random stimulus presentation order used in event-related designs would prevent such a habituation from taking place and therefore both left and right amygdala responses would be consistently stronger than baseline/control conditions. In other words, our analysis leads to the prediction that a difference in the likelihood of observing significant amygdala activation between hemispheres (more on the left than on the right) should only be expected in experiments using a block design.

4.5. Limitations

A number of limitations of this study need to be highlighted. First, we only examined contrasts involving the perception of emotional stimuli. Therefore, our conclusions may not apply to the expression or experience of emotions, which have been proposed to engage different neural systems, particularly in term of hemispheric lateralization (Lanteaume et al., 2007).

As shown in Table 2, the number of activation peaks for some of the conditions was substantially smaller than for others, which may have introduced a bias in some of the comparisons. Unfortunately, this was unavoidable as this relative difference in number of studies across conditions reflects the predominance of some methodological approaches (e.g., block vs. event-related designs), as well as theoretical assumptions (e.g., amygdala preferential role in negative emotions) in the existing literature. However, as we confirmed our results using the jackknife method, which minimizes this potential problem, we can be fairly confident that the main conclusions are not confounded by relative differences in sample sizes across conditions.

As mentioned in the Methods section, we included all activations that were labeled as being in the amygdala by the authors themselves, even if they fell outside the traditional anatomical borders of this structure (Mai et al., 2004). We chose this approach rather than only including the peaks falling within an *a priori* anatomical mask because of the likely inter-study differences in spatial localization and resolution caused by spatial smoothing and subject normalization. Additionally, the Authors' assignment of an activation to the amygdala may have relied not only on the location of the voxel with the most significant *p*-value (the "peak voxel" typically reported in tables), but also on the entire activation cluster, of which the coordinates are very rarely provided. Nonetheless, a few points that were clearly outliers were removed based on their distance to the center of gravity of the data.

Finally, an inherent limitation of all meta-analytical techniques relates to the so-called file drawer problem (Rosenthal, 1979), that is, the potential bias introduced by the non-significant results that are not published. It is important to emphasize that this issue was less of a problem in our study than in other meta-analyses which use the vote-counting method, as our goal was not to assess the presence or absence of amygdala activation under different conditions but, rather, to determine whether the magnitude of the activation depended on a set of specific *a*

priori experimental factors. Nevertheless, it is possible that other variables not included in the present analysis may have also a significant influence on the magnitude and/or lateralization of amygdala responses to emotional stimuli. For instance, a growing literature suggests that individual differences beyond sex, such as personality (e.g., trait anxiety (Bishop, 2007)) or genotype (e.g., the serotonin transporter gene (Hariri and Holmes, 2006)), modulate amygdala activity. To date, there is not a sufficient number of studies to include these individual-differences in a meta-analysis, although, based on the rapid expansion of this field of research, this is likely to change in the near future.

4.6. Summary and conclusions

The findings from our study show that the amygdala responds to all visual emotional stimuli, regardless of valence, with a stronger activation for faces, thus providing strong support for the relevance detector model, which posits a general role of this structure in the detection of innate, biologically and socially relevant information. In contrast, our results do not support a stronger right amygdala involvement in emotional processing, nor a hemispheric lateralization based on valence or sex. Instead, our results are in agreement with the hemispheric lateralization models based on temporal dynamics (Glascher and Adolphs, 2003; Wright et al., 2001), although our analysis cannot be used to provide a mechanistic explanation of this difference, especially as to whether it represent a physiological or psychological process.

In practical terms of the concrete implementation of neuroimaging studies of emotional perception, our findings suggest that a block design will be statistically more efficient, and thus result in stronger effect sizes, but at the potential cost of losing significant activations due to habituation, especially in the right amygdala. In addition, stronger responses would be expected when using a low-level control condition, although such contrasts may lead to significant activations within the amygdala that are not directly related to the emotional properties of the target stimuli.

In conclusion, we have shown that through the use of a novel quantitative meta-analytical approach to functional neuroimaging, findings from previous studies can be integrated to generate new results which can, in turn, be used to directly test some of the existing hypotheses regarding the role of the amygdala on visual emotional processing, as well as refine theoretical models. Critically, our conclusions give rise to specific predictions which can be tested in future functional neuroimaging studies.

Acknowledgments

This study was funded by the Canadian Institutes of Health Research and the Natural Sciences and Engineering Research Council of Canada. J.L.A. was supported by the Canada Research Chairs Program. K.S. was supported by a CIHR Doctoral Fellowship.

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Appendix B

Sergerie, K., Lepage, M., Armony, JL. (2007) Influence of Emotional Expression on Memory Recognition Bias: A Functional Magnetic Resonance Imaging Study. Biol. Psychiatry, 62(10):1126-33.

Influence of Emotional Expression on Memory Recognition Bias: A Functional Magnetic Resonance Imaging Study

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Background: Most studies of the influence of emotion on memory performance have focused on accuracy. However, there is evidence that emotion can influence other aspects of memory, in particular response bias (overall tendency to classify items as new or old regardless of the accuracy of the response). Here we investigated the behavioral and neural-related modulation of response bias by emotion.

Methods: Nineteen healthy individuals performed a recognition memory task on faces with happy, sad, and neutral expressions while undergoing functional magnetic resonance imaging (fMRI).

Results: We observed a familiarity (tendency to say "old") and novelty (tendency to say "new") bias for sad and happy faces, respectively. Novelty response bias was associated with amygdala and prefrontal cortex activity, whereas familiarity bias correlated with superior temporal gyrus activation.

Conclusions: These results show that emotional expressions can have an influence on memory beyond simple accuracy and that this effect is in part mediated by the amygdala, a region previously implicated in emotional perception and memory. Our findings might have important clinical relevance, because they could help explain some of the inconsistencies in the literature regarding emotional memory deficits in psychiatric populations.

Key Words: Emotion, faces, fMRI, memory, response bias, sadness

Research into the modulation of memory performance by emotion and its neural underpinnings in healthy individuals has significantly contributed to our understanding of the abnormal patterns of emotional memory observed in psychiatric populations, such as schizophrenia (Calev and Edelist 1993; Exner *et al.* 2004; Moritz *et al.* 2004; Neumann *et al.* in press), anxiety disorders (Gilboa-Schechtman *et al.* 2002), and depression (Pine *et al.* 2004; Watkins *et al.* 1992, 1996; Weniger *et al.* 2006). Numerous studies have shown an enhancement of memory for emotional (Canli *et al.* 1999; Dolcos *et al.* 2004b; Hamann 2001; Hamann *et al.* 1999), especially negative (Cahill *et al.* 1996; Canli *et al.* 2000; Heuer and Reisberg 1990; Kensinger and Corkin 2004; Sergerie *et al.* 2005, 2006), stimuli in healthy individuals. They have also made significant progress in delineating the neural network involved in this modulation of memory accuracy by emotion. Yet, there is some evidence supporting the idea that emotion can also influence other aspects of memory. For example, some authors have found that negative stimuli are more likely to be classified as old (Maratos *et al.* 2001; Windmann and Kutas 2001), independently of whether they are actually old or new, although the opposite effect (i.e., tendency to classify them as new) has also been reported (Phaf and Rotteveel 2005). Furthermore, an increased rate of false recognition errors or intrusions for emotional items has been shown to partly explain some of the enhanced mood-congruency effects of memory found in patients with anxiety disorders (Mogg and Mathews 1990) and major depression (Moritz *et al.* 2005; Ridout *et al.* 2003) as well as in high–trait-anxiety individuals (Dowens and Calvo 2003). These findings suggest that some of the observed effects of emotion on memory in healthy individuals and the corresponding abnormal patterns reported in psychiatric groups might not only be due to differences in the formation or retrieval of true memories. For instance, these patterns could also reflect an influence of emotional valence on the relative number of false memories or in the willingness to endorse ambiguous stimuli as previously seen.

In a memory recognition paradigm, this tendency to judge items as previously seen, regardless of whether it is the case, can be dissociated from true memory success and operationalized in terms of the response bias (Snodgrass and Corwin 1988). Specifically, whereas accuracy is measured by the rate of hits minus false alarms, false memories are assessed by the response bias, which measures the tendency to incorrectly classify a new item as previously seen (corrected for overall accuracy). Importantly, these two aspects of memory are largely independent (Snodgrass and Corwin 1988). For example, completely random responses would correspond to chance accuracy and no response bias, whereas a classification of all stimuli as previously seen (saying always "old") would also result in a chance level for accuracy but would correspond to an extreme value of familiarity bias.

In terms of neural substrates of the memory-related response bias, several studies have highlighted the role of prefrontal cortex. Patients with frontal damage show a higher false alarm rate (Curran *et al.* 1997; Swick and Knight 1999) while having comparable hit rates to control subjects (Swick and Knight 1999). Consistent with this, Windmann *et al.* (2002) observed differences in the early event-related potential components (ca. 300 msec) of the response in prefrontal cortex sites for the subjective old (hits and false alarms) versus new (misses and correct rejections) responses as a function of the participants' overall behavioral familiarity bias, without any differences for the objective old/new comparison. Furthermore, this early prefrontal

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Received September 22, 2006; revised December 22, 2006; accepted December 29, 2006.

0006-3223/07/$32.00
doi:10.1016/j.biopsych.2006.12.024

signal difference between subjective old and new was modulated by the emotional valence of the stimuli, possibly reflecting an automatic, preattentive influence of emotion on recognition bias (Windmann and Kutas 2001).

Another structure that is likely to be involved in the emotional modulation of response bias is the amygdala. Indeed, this region has been implicated not only in the enhancement of memory for emotional stimuli (Dolan *et al.* 2000; Dolcos *et al.* 2004b, 2005; Hamann 2001; Kensinger and Schacter 2005; Maratos *et al.* 2001; Phelps 2004; Sergerie *et al.* 2006; Strange and Dolan 2004; Tabert *et al.* 2001) but also in the subjective feeling of remembering negative stimuli (Sharot *et al.* 2004).

Here, we conducted a functional magnetic resonance imaging (fMRI) study to directly investigate the behavioral and neural correlates of response bias in recognition memory for emotional stimuli in healthy volunteers. We used faces depicting different emotional expressions, because these are powerful stimuli that convey crucial information used for social interactions and have been extensively employed to examine the neural correlates of emotional processing in healthy individuals (Haxby *et al.* 2002; Pessoa and Ungerleider 2004; Pessoa *et al.* 2002; Posamentier and Abdi 2003) as well as in psychiatric populations (Leppanen 2006; Mandal *et al.* 1998; Mogg and Bradley 1998). We specifically chose sad and happy expressions, because these are basic emotions that are encountered in everyday life and are easily decoded, even in clinical groups (Heimberg *et al.* 1992; Kohler *et al.* 2003; Leppanen 2006; Mogg *et al.* 2000).

Another important advantage of using facial expressions as emotional stimuli is that they do not suffer from the potential confounds due to the overlap between stimulus emotionality and complexity and/or unusualness that are often encountered with words or pictures (Adolphs *et al.* 2001; Ochsner 2000; Talmi and Moscovitch 2004). Furthermore, because of the nature of face stimuli, it is possible to objectively determine the degree of physical similarity among stimuli within and between emotional categories. This latter point is critical when investigating the potential expression-induced modulation of memory performance, although it has not been taken into account in the previous research. Here, we directly addressed this issue by performing an eigenface analysis (Turk and Pentland 1991) of the stimuli and calculating similarity matrices for the three emotional categories.

Methods and Materials

Subjects

Twenty healthy right-handed volunteers (10 male) participated in the study (age 26.9 ± 3.4 years). None of the participants had a history of neurological conditions, psychiatric disorders, or substance abuse, on the basis of self report; nor were they taking any psychotropic medications at the time of study. All procedures were approved by the Research Ethics Committee of the Montreal Neurological Hospital and Institute. One subject (female) was removed from the final analysis owing to excessive movement.

Stimuli

Photographs of individuals depicting sad, happy, or neutral facial expressions were selected from four databases (Sergerie *et al.* 2006). A total of 168 stimuli were used, each corresponding to a different individual. Stimuli were converted to gray-scale and adjusted for face size, contrast, and resolution. Stimuli were divided into two subsets, each with 28 sad, happy, and neutral faces (one-half male).

Task Procedure

The experiment consisted of two runs, encoding and recognition. During the encoding phase, 84 faces taken from one subset (counterbalanced across subjects) were presented twice, in a pseudo-random order. Subjects were instructed to make a gender judgment by clicking on a mouse and to remember the stimuli.

During the recognition phase, the same stimuli were presented with a same number of new faces never seen before. Subjects were asked to judge whether each face had been previously presented (old/new judgment). After the scanning session, subjects were asked to rate all the faces in terms of valence with a visual-analog scale (range very negative to very positive: 0–100).

The stimulus time presentation was 2.5 sec with an average inter-trial interval (ITI) of 4 sec. To achieve a good estimate of baseline activity, several longer ITIs (so-called null-events) were also included. This resulted in a slightly de-synchronized ("jittered") presentation of the stimuli as compared with the onset of volume acquisitions, thus increasing the effective sampling rate (Josephs *et al.* 1997).

fMRI Acquisition

Scanning was performed on a 1.5 Tesla Siemens Sonata system (Siemens, Malvern, Pennsylvania) at the Montreal Neurological Institute (MNI). The experiment was run with E-PRIME (Psychology Software Tools, Pittsburgh, Pennsylvania). Functional T2*-weighted images were acquired with blood oxygenation level-dependent (BOLD) contrast (repetition time = 2540 msec, echo time = 50 msec, Flip angle = 90°, field-of-view = 256 mm, Matrix = 64 × 64), covering the entire brain (30 interleaved slices parallel to the anterior-posterior commissural plane; voxel size 4 × 4 × 4mm). Two functional runs of 350 volumes each were acquired (encoding and recognition). An anatomical volume was also acquired (voxel size 1 × 1 × 1 mm^3).

Data Analysis

Behavioral Data. Memory performance was calculated according to the Two-High Threshold Model (Snodgrass and Corwin 1988) by means of the discrimination index Pr

$$\mathrm{Pr} = H - FA$$

and the response bias Br

$$Br = \frac{FA}{[1 - (H - FA)]} - 0.5$$

where H and FA represent hit and false alarm rates, respectively. The former provides an unbiased estimate of the accuracy in the response to old and new items, where higher values correspond to better (more accurate) memory. The response bias, in contrast, is an index of the overall tendency to respond "old" or "new" regardless of accuracy. In this case, positive values indicate a tendency to say "old" (i.e., a familiarity bias), whereas the negative side of the scale represents a novelty bias (that is, a propensity to say "new"). Importantly, the Pr and Br measures are independent (Snodgrass and Corwin 1988).

Neuroimaging. The fMRI data were pre-processed and analyzed with SPM2 with standard procedures as we have previously done (Sergerie *et al.* 2006). For the recognition run, 12

event types based on facial expression (sad, happy, neutral), presentation (old and new), and accuracy (correct and incorrect) were defined, on the basis of each subjects' performance. We also included the six covariates corresponding to the movement parameters obtained from the realignment procedure. Linear contrasts of subject-specific parameter estimates for conditions of interest were calculated and taken to a second-level random effects model. Main effects were calculated with a one-sample *t* test, whereas correlations with behavioral measures (response bias) were entered in a simple regression model, with a threshold of $p < .0005$ (uncorrected). To identify regions commonly activated for happy and sad faces, we used a conjunction analysis according to the Minimum Statistic compared with the Conjunction Null Hypothesis (MS/CN; (Nichols *et al.* 2005) by setting a threshold of .005 for each contrast separately and combining the resulting statistical maps with the logical AND function, thus yielding an overall threshold of significance of $p < .005^2$. We then identified those voxels from this analysis that also exhibited a significant ($p < .05$ uncorrected) main effect of subjective old versus subjective new for either happy of sad expressions.

Eigenface Analysis

We assessed whether potential differences in memory performance for the different facial expressions could have been influenced by the intrinsic physical properties of the stimuli used. Specifically, we determined the degree of similarity among the faces belonging to each emotional category with the "eigenface" method on the basis of a principal component analysis (PCA) technique (Turk and Pentland 1991). We first divided each face image in a grid of 289 × 190 pixels, with the intensity of the pixel (0–255) as the value for each point. The resulting matrices were submitted to a PCA, from which a set of eigenvectors (eigenfaces) were obtained. Each face could then be fully represented by the weights associated with each eigenface. That is, each original face could be thought of as a point in a multi-dimensional space defined by the eigenfaces. Therefore, an expression-specific distance (or similarity) matrix can be built by calculating the Euclidean distance between all pairs of faces for each category. Furthermore, for each face, we calculated a mean distance to all the other faces in the group. We then tested whether there were any significant differences among these distances between the three expressions either in terms of medians or overall distributions.

Results

Behavioral Results

There was a significant effect of expression on accuracy, as measured by Pr [$F(2,36) = 9.4$, $p = .001$]. Post hoc comparisons revealed that this effect was due to a worse performance for sad faces (Pr: mean = .41, SD = .12), compared with both happy (Pr: mean = .54, SD = .11; $p < .001$) and neutral (Pr: mean = .51, SD = .13; $p < .05$) expressions. No difference in accuracy between happy and neutral faces was observed ($p > .4$). Interestingly, separate analyses for old and new stimuli revealed, however, that memory for old sad faces (78%) was in fact better than for neutral [73%; $t(18) = 2.12$, $p < .05$] or happy [72%; $t(18) = 2.63$, $p < .02$] expressions. In contrast, memory for new sad expressions (63%) was much lower than happy [82%; $t(18) = 7.59$, $p < .0001$] or neutral [79%; $t(18) = 4.21$, $p < .001$] faces, suggesting an influence of expression on response criteria. We observed, consistent with this, a significantly positive response bias for sad expressions (Br: mean = .12, SD = .14; $p < .001$), reflecting a familiarity bias. Notably, happy expressions were associated with a negative (novelty) response bias (Br: mean = −.11, SD = .13; $p < .001$). In contrast, there was no significant bias for neutral expressions, because the corresponding Br was not statistically different from zero (Br: mean = −.07, SD = .20; $p > .2$). As expected, Pr and Br values were not significantly correlated (.01, $p > .9$).

A repeated-measures analysis of variance (ANOVA) for reaction times (RTs) for new faces with accuracy and emotion as within-subject factors revealed a significant effect of accuracy [$F(1,18) = 21.3$, $p < .001$] and an interaction between expression and accuracy [$F(2,36) = 10.6$, $p < .001$]. These effects were due to an overall faster RT for correct than incorrect responses and a significantly slower RT for correct new responses for sad faces, respectively, as shown in Figure 1. That is, whereas subjects were faster to correctly identify new neutral and happy faces, they took longer to correctly decide that a sad face was new. This slower RT for correctly identified new sad faces provides further support for the familiarity bias, because subjects had to overcome their tendency to say old to respond correctly, thus taking longer to do so.

An ANOVA with category as main factor and rating as the dependent variable confirmed the a priori assignment of each face to the sad, neutral, or happy category ($p < .001$).

Eigenface Analysis

Similarity matrices for the three facial expressions are shown in Figure 2. A Kruskal-Wallis test revealed no significant differ-

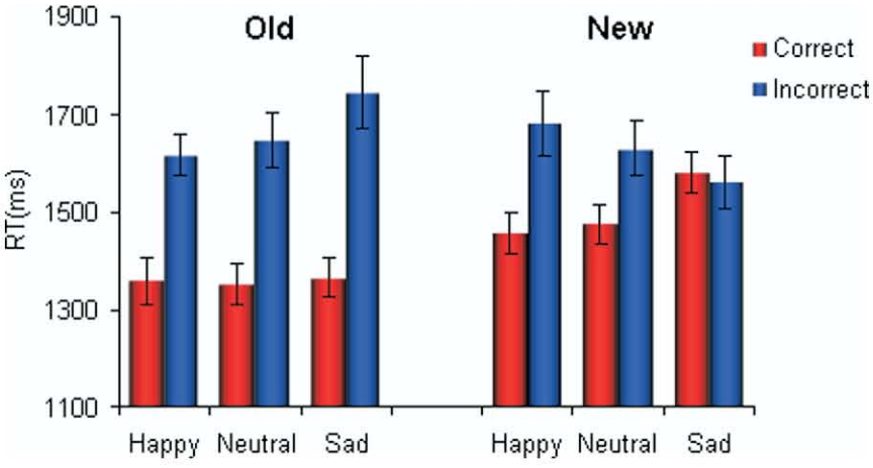

Figure 1. Reaction times for old and new responses for each facial expression (happy, neutral, and sad) as a function of accuracy. Error bars represent 1 SD of the mean.

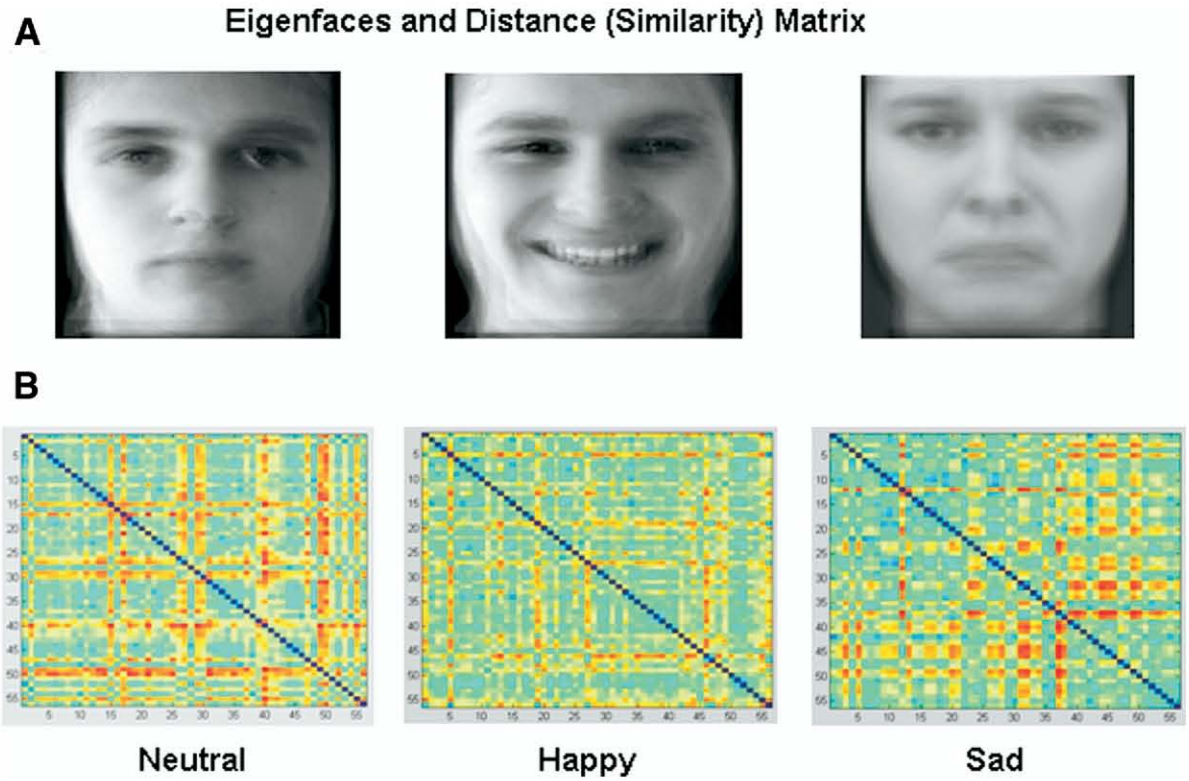

Figure 2. Examples of **(A)** eigenfaces and **(B)** distance matrices for each facial expression.

ences in the median of the within-category mean distance between expressions [$\chi^2(2) = 3.53$, $p > .1$]. Furthermore, pairwise comparisons with a Kolmogorov-Smirnov statistic confirmed that there were no significant differences in the mean-distance distributions between expressions (all $p > .3$). Thus, these results suggest that any modulation of memory performance by emotion was unlikely to be due to differences in the degree of similarity among faces for the three expressions.

fMRI Results

To investigate the neural correlates of the observed memory bias for emotional faces, we conducted a random-effects analysis in which the contrast "subjective old" (i.e., hits and false alarms) minus "subjective new" (correct rejections and misses) was correlated with the behavioral memory bias response (Br) for each subject, for each expression. These are shown in Table 1. We then isolated those regions common to both sad and happy expression by performing a conjunction analysis (see Methods). Results are shown in Table 2 and Figure 3. Table 2 also shows the main effect of the contrast subjective old versus new for each expression for the peak voxels obtained in the correlation analysis. These show that the amygdala and the superior frontal gyrus were significantly more active for those happy faces judged to be new than those thought to have been previously seen. No voxel was significant in the opposite contrast. In the case of sad faces, the only significant effect was in the superior temporal gyrus (STG), which exhibited stronger responses to subjective old than new stimuli.

Discussion

Emotion can enhance memory, especially when the stimuli used have a negative valence. Our results show that emotion can also lead to a decrease in memory performance, because participants performed worse for sad faces, compared with both happy and neutral expressions. Critically, this detrimental effect of emotion on memory was due to a difference in response bias; that is, subjects were more likely to believe that they had previously seen a sad face before, regardless of whether this was the case, resulting in a significant familiarity bias. In contrast, happy faces were associated with a novelty response bias without any significant differences in accuracy when compared with neutral faces. Importantly, reanalysis of our data from a recent study with the same paradigm (Sergerie *et al.* 2006) also revealed a significant novelty bias for happy faces [Br: mean = −.11, SD = .22; $t(17) = 2.2$, $p < .05$]. In contrast, in that study, fearful faces were associated with a net enhancement of memory without a significant response bias [Br: mean = −.04, SD = .25; $t(17) = .76$, $p > .4$]. Thus, taken together, results from this and our previous study (Sergerie *et al.* 2006) suggest that memory for faces is differentially modulated by the expression, both in terms of accuracy and response bias. Notably, our eigenface analysis of the stimuli suggests that this emotion-dependent response bias is unlikely to be due to simple perceptual features (e.g., sad faces being more similar to each other and thus resulting in a higher confusion between old and new stimuli). The differential effects of expression on memory for fearful and sad faces are particularly interesting, because these two emotions are associated with similar negative valence but different levels of arousal (Posner *et al.* 2005). This is consistent with studies suggesting that the enhancement of memory for emotional material only occurs or at least is stronger for high-arousal stimuli (Canli *et al.* 2000; Dolcos *et al.* 2004a). Alternatively, sad faces could elicit a strong empathic emotional reaction, making participants focus more on the feeling elicited by the faces. This would then lead to a sense

Table 1. Significant Activations Associated With the Correlation Between Behavioral Response Bias (Br) and the Contrast Subjective Old (hits and false alarms) Minus Subjective New (misses and correct rejections)

	Coordinates						
	Left			Right			*Z*
Region	x	y	z	x	y	z	Score
Sad							
Middle frontal gyrus	−20	24	36				3.54
Superior temporal gyrus	−38	−50	26				3.88
Amygdala				22	−8	−28	3.71
Happy							
Superior frontal gyrus				8	60	−6	4.14
	−16	22	46				4.04
	−12	34	50				3.91
Inferior frontal gyrus	−34	24	−18				3.93
Insula	−32	−20	24				4.06
Cingulate gyrus	−16	−16	40				3.90
				18	−48	24	4.24
Lingual gyrus	−4	−90	−10				4.09
Superior parietal lobule	−30	−58	38				4.22
Inferior parietal lobule				44	−36	34	4.29
Superior temporal gyrus	−54	−8	12				3.95
Middle temporal gyrus	−60	−38	−14				4.36
	−56	−8	−12				4.10
				50	0	−22	4.51
				44	−14	−16	4.20
Inferior temporal gyrus				62	−14	−24	4.15
Parahippocampal gyrus				30	−36	−8	3.68
Cuneus				0	−94	−2	4.08
Amygdala	−26	2	−26				3.98
Amygdala	−24	0	−24				3.86
Amygdala				22	−2	−24	3.51
Hippocampus	−26	−14	−22				3.99
Neutral							
Superior frontal gyrus				36	−44	−6	3.99
Superior temporal gyrus				42	16	−46	4.13
Middle temporal gyrus				40	14	−48	4.11

Coordinates of local maxima ($p < .0005$ uncorrected) are in Montreal Neurological Institute (MNI) space.

of familiarity during recognition, on the basis of the emotion rather than identity.

Neural Correlates of Emotional Response Bias

Novelty Bias. The observed correlation of amygdala activity and novelty bias for emotional faces is consistent with the postulated role of this structure in the detection of emotional stimuli (Dubois *et al.* 1999) and its rapid habituation to repeating occurrences of the same event (Breiter *et al.* 1996; Fischer *et al.* 2000; Wright *et al.* 2001). Our results suggest that the amygdala response might influence the decision to consider a stimulus as novel or not. In addition, this observed amygdala involvement in the shift of response toward a novelty bias brings a new light in its traditional role in the detection of objective new emotional stimuli (i.e., the amygdala can also play a role in the "subjective feeling of novelty" for emotional material, regardless of valence).

Although it is generally agreed that the dorsal prefrontal cortex (dPFC) is involved in memory retrieval (Buchel *et al.* 1998; Fletcher *et al.* 1997; Lepage *et al.* 2000; Tulving *et al.* 1994), its specific function seems to be more related to a controlled evaluation of the retrieval product rather than to a simple familiarity-based assessment (Ranganath *et al.* 2000; Schacter *et al.* 1996). In particular, activity of this region has been associated with the detection of novel stimuli, including faces (Wiser *et al.* 2000), especially when there is ambiguity in the information, such as when a familiar but new stimulus is encountered. For example, Van Petten at al (2002) found prefrontal activity associated with the presentation of rearranged pairs of old words, regardless of accuracy. Similarly, Duzel *et al.* (2004) reported significant activation of right dPFC when contrasting rearranged pairs of old pictures of faces and tools with the original arrangements. Interestingly, the opposite contrast resulted in anterolateral temporal activation (see following text). Because performance in this previous study was almost perfect, it would not be possible to distinguish whether this activity was associated with the subjective or the objective new responses. The correlation between dPFC activation and novelty bias observed in our study provides further support for the hypothesis that dPFC might be involved in novelty detection of stimuli that have a certain degree of familiarity (e.g., new arrangement of old stimuli). Indeed, subjects had to ignore the feeling of familiarity elicited by the reoccurrence of sad or happy expressions in order to judge a face as new.

Familiarity Bias. The activation cluster involved in the subjective old responses (i.e., familiarity) was located in the anterolateral STG. Lesion studies have suggested that this region might be critical for memory for people, because patients with lesions encompassing this part of the brain are impaired in famous faces recognition tests (Damasio *et al.* 1996). Furthermore, electrophysiological recordings show that some neurons in the anterior temporal cortex respond selectively to familiar faces (Seeck *et al.* 1995). Functional neuroimaging studies have also provided evidence for a role of this region in the recognition of familiar faces (Gorno-Tempini *et al.* 1998; Leveroni *et al.* 2000; Nakamura *et al.* 2000; Sergent *et al.* 1992; Sugiura *et al.* 2001). For example, Gorno-Tempini *et al.* (1998) found a significant activation in left anterior temporal gyrus for the contrast of famous versus nonfamous faces.

The STG, including its anterior aspect, has been also implicated in the processing of sad stimuli. Gross *et al.* (Goldin *et al.* 2005; Hutcherson *et al.* 2005) found that this region was significantly activated when participants were viewing sad films. In addition, Britton *et al.* (2006) observed activation in STG for sad faces, compared with neutral expressions.

Thus, our findings and those of previous studies suggest that this brain region might be involved not only in the perception of emotional stimuli, especially those associated with sadness, but also in the retrieval of contextual information related to the stimulus, in particular in terms of their perceived familiarity.

Clinical Implications

Our findings show that an apparent emotional memory deficit in terms of accuracy, such as the one obtained here for sad faces, might be better characterized as a difference in the criterion used to decide on the history of a stimulus. This observation is particularly relevant in the context of studies reporting abnormal patterns of emotional memory in patients suffering from psychiatric disorders (Calev and Edelist 1993; Exner *et al.* 2004; Gilboa-Schechtman *et al.* 2002; Moritz *et al.* 2004; Neumann *et al.* in press; Pine *et al.* 2004; Watkins *et al.* 1992, 1996; Weniger *et al.* 2006). Indeed, our findings strongly suggest that some of these observations might not simply reflect a difference in the ability to encode or retrieve this information but, rather, to a difference in the response bias. Future studies in clinical populations are

Table 2. Significant Activations for the Correlation Between the Behavioral Response Bias (Br) and the Conjunction of the Contrasts Subjective Old Minus New for Sad and Happy Faces

Region	Coordinates						Min *Z* Score	Main Effect Sad *Z* Score	Main Effect Happy *Z* Score
	Left			Right					
	x	y	z	x	y	z			
Superior Frontal Gyrus				12	36	50	2.63	.10	−2.31[a]
Middle Frontal Gyrus	−26	28	44				2.64	.45	−.37
Middle Frontal Gyrus	−20	24	40				3.25	.88	−.37
Middle Frontal Gyrus	−24	20	48				2.63	1.22	−.24
Insula	−26	−24	24				2.90	1.10	−.95
Posterior Cingulate Gyrus				14	−50	24	3.14	1.01	−.97
Superior Temporal Gyrus	−42	0	−18				2.83	3.31[a]	−.09
Superior Temporal Gyrus	−38	−48	24				2.61	−1.15	−.39
Angular Gyrus	−38	−54	26				2.76	−.89	−1.59
Superior Temporal Gyrus				46	−62	20	3.20	−.14	−1.58
Parahippocampal Gyrus				18	−34	−2	3.01	−.26	−1.09
Amygdala				22	−6	−26	2.89	.83	−2.23[a]

The last two columns show the *Z* scores for the main effect of subjective old minus new for each emotion (a negative score indicates that the effect is in the opposite direction). Coordinates of local maxima ($p < .005^2$ uncorrected) are in MNI space.

[a] $p < .05$ (uncorrected).

necessary to directly test this hypothesis and, more importantly, to assess whether these putative difference in emotional memory bias are associated with current symptomatology or instead represent a trait-like, perhaps even premorbid, disposition. This latter issue is of particular interest, given that several of the brain regions often reported to be dysfunctional

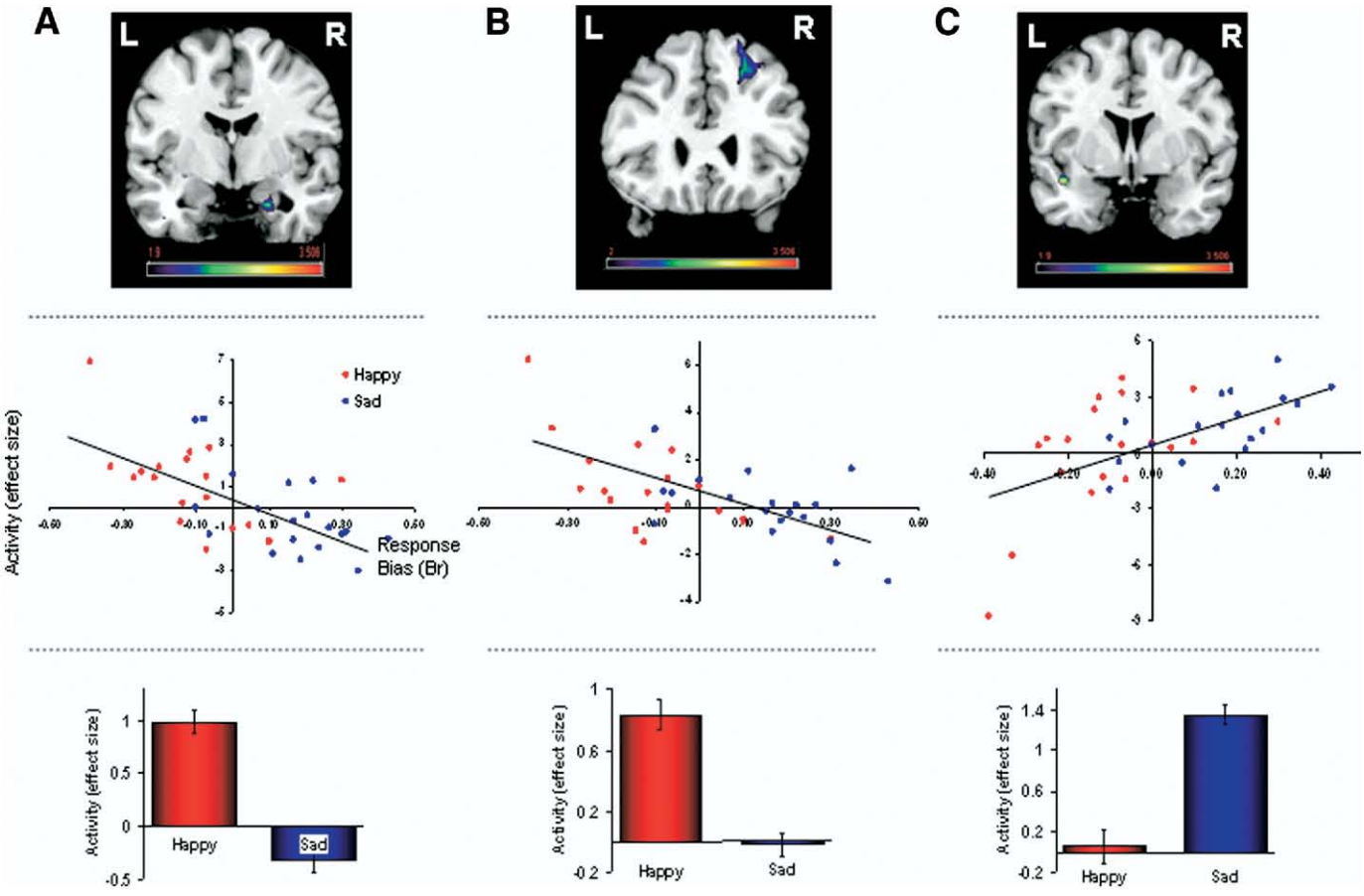

Figure 3. (Top) Statistical parametric maps showing the activations associated with the correlation between the response bias and the conjunction, for happy and sad expressions, of the contrast subjective new minus subjective old in **(A)** amygdala and **(B)** superior frontal gyrus (SFG) and for the contrast subjective old minus subjective new in **(C)** the superior temporal gyrus (STG). The activations were rendered onto the subject-averaged anatomical image, normalized to Talairach space with the Montreal Neurological Institute (MNI) template, and thresholded at $p < .005^2$; (Middle) scatterplots of the correlations at the peak voxel of each of these regions; (Bottom) effect sizes for the contrast subjective new minus old for sad and happy expressions at the peak voxel for each region.

in patients overlap with those we found to be involved in the emotional influence of response bias, such as the amygdala and prefrontal cortex (Beyer and Krishnan 2002; Cannon *et al.* 1998; Exner *et al.* 2004; Molina *et al.* 2004; Volk and Lewis 2002; Weniger *et al.* 2006).

Limitations

One potential limitation of our study is that we used an old/new paradigm rather than other more complex designs such as those including a remember/know response (Tulving 1985) or a confidence rating for each old judgment. These paradigms, by comparing remember versus know responses or the degree of confidence attributed to each response, are useful for isolating the "feeling of remembering" independently of accuracy. Although our paradigm did not allow us to perform such comparisons, it had the advantage that the response bias measure we used did not rely on subjects' introspective evaluation of the strength of their memory trace but, rather, on their (arguably more ecologically relevant) judgment of whether they thought they have previously encountered a particular person.

Another potential limitation of our study is that we did not differentiate between valence and arousal due to the significant correlation between these two dimensions in facial expressions (Sergerie *et al.* 2006). Thus, it remains a possibility that the difference in response bias observed for happy and sad faces could be due to differences in intensity or arousal in addition to valence. Our results from this and our previous study involving fearful faces suggests that in fact there might be an interaction between valence and arousal in the influence of facial expressions on memory accuracy and response bias (see previous text). Future studies are necessary to further explore these questions.

This study was supported by the Canadian Institutes of Health Research (MOP 53280 to ML, and MOP 57724 to JLA); JLA is supported by the Canada Research Chairs Program.

The authors declare no conflict of interest.

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Appendix C

Armony, JL. & Sergerie, K. (2007) Own-sex effects in emotional memory for faces. Neurosci. Lett., 426(1):1-5

Available online at www.sciencedirect.com
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Neuroscience Letters
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Own-sex effects in emotional memory for faces

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Received 6 February 2007; received in revised form 7 May 2007; accepted 10 August 2007

Abstract

The amygdala is known to be critical for the enhancement of memory for emotional, especially negative, material. Importantly, some researchers have suggested a sex-specific hemispheric lateralization in this process. In the case of facial expressions, another important factor that could influence memory success is the sex of the face, which could interact with the emotion depicted as well as with the sex of the perceiver. Whether this is the case remains unknown, as all previous studies of sex difference in emotional memory have employed affective pictures. Here we directly explored this question using functional magnetic resonance imaging in a subsequent memory paradigm for facial expressions (fearful, happy and neutral). Consistent with our hypothesis, we found that the hemispheric laterality of the amygdala involvement in successful memory for emotional material was influenced not only by the sex of the subjects, as previously proposed, but also by the sex of the faces being remembered. Namely, the left amygdala was more active for successfully remembered female fearful faces in women, whereas in men the right amygdala was more involved in memory for male fearful faces. These results confirm the existence of sex differences in amygdala lateralization in emotional memory but also demonstrate a subtle relationship between the observer and the stimulus in this process.

Keywords: Amygdala; Hemispheric lateralization; Gender; Neuroimaging; Functional magnetic resonance imaging; fMRI

It is generally accepted that emotionally charged stimuli, especially those with a negative content, are better remembered than neutral material. A wealth of lesion and functional neuroimaging studies has identified the amygdala as a critical structure for this emotion-induced memory enhancement [12,15,20]. Interestingly, individual differences in emotional memory have been reported [14]. In particular, several studies have suggested that women have a better memory for emotional stimuli than men [5,13], although some studies have failed to find any sex differences [2,21] or even found better memory in men [4]. A neural interpretation of this sex difference in memory for emotional items has been proposed by Cahill and colleagues [5–7]. This sex-specific lateralization hypothesis posits that whereas the right amygdala is involved in the enhancement of memory for emotional stimuli in men, it is the left amygdala that plays this role in women. This hypothesis has received some support from neuroimaging studies conducted by other groups [8,17,31].

However, all these studies used pictures as the emotional material to be remembered, leaving open the question of whether these putative sex differences in the neural correlates of emotional memory can also be observed for other types of stimuli. One class of stimuli that is of particular interest is facial expressions. Indeed, emotional expressions are powerful emotional stimuli that play a critical role in social interactions. The ability to quickly and accurately decode emotional expressions in other people is essential for an individual's successful functioning in a social environment. We have recently shown [27] an enhancement of memory for fearful faces, compared to happy and neutral ones, which is amygdala mediated. Interestingly, there were no sex-related differences in this memory advantage for fearful faces either in terms of behavior or brain activity. Yet, several studies have suggested that women exhibit a same-sex advantage for memory of neutral faces; that is, they remember female faces better than males ones [16,22,35]. In contrast, men do not appear to show this own-sex memory bias, although the findings are less consistent [22,35].

Therefore, it is conceivable that emotional expressions could influence memory in a different fashion, at the behavioral and neural levels, depending on whether the faces being encoded are of the same sex of the perceiver or not. In other words, an interaction between emotional expression, sex of the perceiver and sex of the face may exist. Such an interaction would then explain the lack of sex differences in memory for emotional faces

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doi:10.1016/j.neulet.2007.08.032

previously mentioned, where the sex of the face stimulus was not taken into account. If such an own-sex memory bias for fearful faces does exist, it would be of interest to investigate its neural correlates, in particular in terms of amygdala lateralization.

Here we explored this question using the subsequent memory paradigm for faces with fearful, happy and neutral expressions, within the context of an event-related functional magnetic resonance imaging (fMRI) experiment. At a behavioral level, we predicted a same-sex enhancement of recognition memory for fearful faces, especially for females. At the neural level, we focused on the role of the amygdala on the successful encoding of emotional faces, as a function of the sex of the participants and of the faces, to assess whether any sex-specific laterality effects were present.

Eighteen healthy individuals (nine men and nine women, mean age 27 years) participated in this study. Data from two men were discarded from the final analysis due to insufficient number of trials for one of the conditions of interest. All participants were right handed, had normal or corrected-to-normal vision and no history of neurological or psychiatric disorders. None of the subjects was taking psychotropic medication at the time of the study. The study was approved by the Research Ethics Board of the Montreal Neurological Hospital and Institute and written informed consent was provided by all participants.

During the encoding session, 84 pictures of different individuals (half male and half female), each depicting a fearful, happy or neutral expression were presented twice, in a pseudo-random order, using E-PRIME. Each stimulus was shown for 2500 ms, with average stimulus onset asynchrony of 4000 ms. Participants were instructed to determine the sex of the face presented and to remember the stimuli for later questioning. During the recognition session, the original 84 pictures were presented again, together with an equal number of new faces, also depicting fearful, happy and neutral expressions, in equal proportions in terms of expression and sex. Subjects performed an old/new judgment. At the end of the experiment, subjects rated the valence of all the previously presented faces on a seven-point scale. Further details of the stimuli and overall procedure are given in [25,27].

The experiment was performed on a 1.5T Siemens Sonata whole-body scanner (Siemens, Erlangen, Germany), equipped with a standard head coil, at the Montreal Neurological Institute (MNI). Details of the fMRI acquisition parameters and procedure are described elsewhere [25,27]. Briefly, volumes of 30 interleaved slices parallel to the anterior-posterior commissural plane, covering the whole brain, were acquired during the encoding and recognition sessions (TR = 2450 ms, TE = 50 ms, FOV = 256 mm). A high resolution (1 mm^3 voxel size) anatomical scan was also obtained for each subject. Only the data from the encoding session is reported here.

Functional images were time-corrected to account for differences in acquisition times for the different slices, coregistered to the first scan to correct for head movements, normalized to the standard space of Talairach and Tournoux [30] according to the MNI template [9] and spatially smoothed (8 mm FWHM isotropic kernel). Statistical analysis was conducted using SPM2 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm), using a mixed-effects linear mode. For each subject, 12 trial types were defined based on the facial expression and sex of the stimuli, as well as whether the subjects had correctly identified the face as old or not during recognition (i.e., the subsequent memory paradigm [3]). On average, there were 20 trials for the subsequently remembered condition and eight for the forgotten one. Critically, as all our comparisons involved higher order interactions of the remembered minus forgotten contrast (see below), our results were not statistically biased by the difference in the number of events for these two conditions. Linear contrasts of the parameter estimates of interest for male and female participants were subsequently taken to second-level one-sample *t*-tests. For the current analysis, we were specifically interested in the triple interaction between memory success (remembered versus forgotten), emotional expression (fearful versus neutral) and stimulus sex (male versus female). Moreover, we focused our analysis on the amygdala, where we used a threshold of statistical significance of $p < 0.005$ (uncorrected).

Memory performance results for men and women, calculated as hit minus false alarm rates, are shown in Fig. 1. A repeated-measures ANOVA for accuracy for fearful faces with stimulus and participants' sex as within- and between-subjects factors, respectively, yielded a significant interaction ($F(1, 16) = 7.2$, $p = 0.017$). Post-hoc analyses revealed that this effect was due

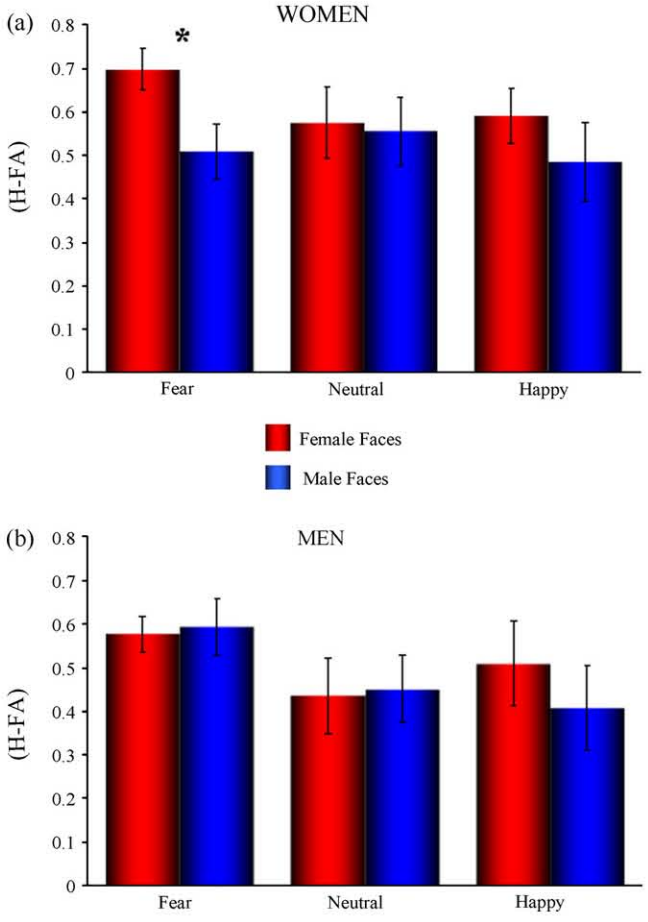

Fig. 1. Memory performance (hit minus false alarm rate) in (a) women and (b) men for fearful, neutral and happy facial expressions as a function of the sex of the faces. Error bars represent standard error of the mean (S.E.M.). *$p < 0.05$.

to the female participants, who exhibited a better memory for female fearful faces than for male ones ($p = 0.03$). In contrast, there was no significant difference on memory performance as a function of the sex of the face for men ($p = 0.4$). Critically, this own-sex memory bias was specific to fearful expressions, as no significant sex effects were observed for either neutral ($p > 0.8$) or happy ($p > 0.7$) faces.

Analysis of reaction times during encoding and recognition did not yield any significant main effects of participants' or stimulus sex, nor an interaction. Likewise, valence ratings were similar between men and women and between male and female faces for each emotional expression (all $p > 0.1$).

In females, a stimulus-sex (female versus male) by memory success (remembered versus forgotten) by expression (fearful versus neutral) interaction for the subsequent memory contrast revealed a significant activation within the left amygdala (MNI coordinates [9] $x\ y\ z = -16\ 0\ -28$, $z = 2.72$, $p < 0.005$), as shown in Fig. 2a. This interaction represented a stronger amygdala activation associated with successfully remembered female fearful faces (Fig. 2c). No sex differences were observed for male participants in this voxel ($p > 0.3$). A similar interaction analysis for men showed, in contrast, significant activation within the right amygdala (Fig. 2b; $x\ y\ z = 16\ -2\ -24$, $z = 3.58$, $p < 0.001$), which was associated with stronger activity for successful memory for male, compared to female, fearful faces (Fig. 2d).

To directly test for possible differences between left and right amygdala responses as a function of the sex of the faces, we conducted post-hoc ANOVAs on the parameter estimates obtained in these regions for the different conditions. These analyses yielded a significant hemisphere-by-sex interaction for both women ($F(1, 8) = 18.6$, $p < 0.005$) and men ($F(1, 6) = 6.1$, $p < 0.05$), confirming the amygdala lateralization pattern observed in the whole-brain analysis. No significant sex effects were observed for happy expressions in either the left ($p < 0.3$) or right ($p > 0.2$) amygdala.

The behavioral findings from this study show an own-sex effect on memory accuracy for fearful faces in women, as they remembered female fearful faces better than male ones. In contrast, and consistent with previous studies using neutral faces [16,22], no own-sex bias for memory was observed in men.

Our fMRI results confirmed the presence of sex differences in emotional memory at a neural level. Specifically, we found a

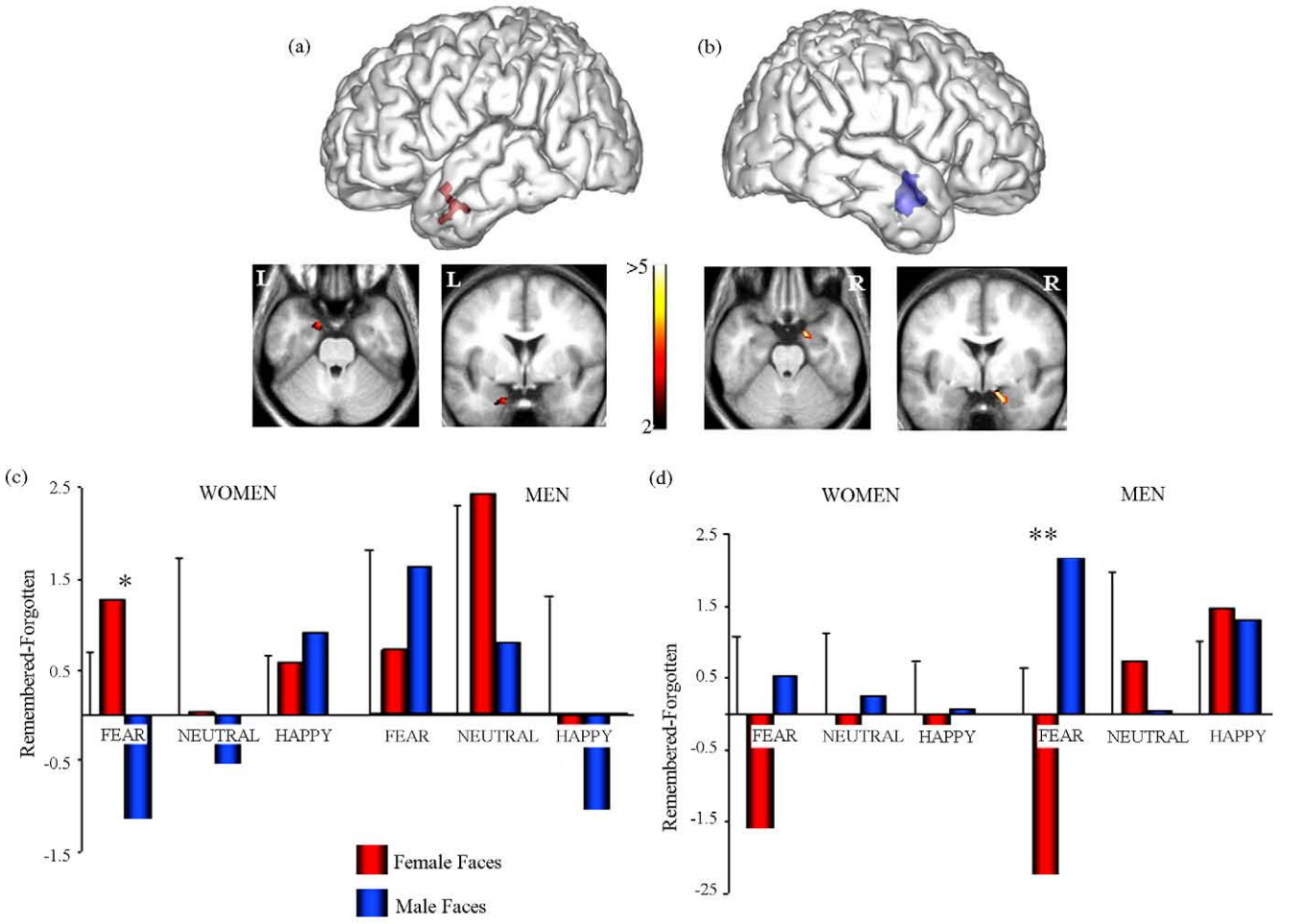

Fig. 2. Three-dimensional reconstruction and two-dimensional renderings of the amygdala activations for the interaction of memory success (remembered vs. forgotten), facial expression (fearful vs. neutral) and face sex (female vs. male) in (a) the left hemisphere (MNI coordinates $x\ y\ z = -16, 0, -28$) for women and (b) in the right (MNI coordinates $x\ y\ z = 16, -2, -24$) for men. Bar graphs with the values of the subsequently remembered minus forgotten contrasts for the (c) left and (d) right amygdala, for each condition (expression and stimulus sex), are shown as a function of the sex of the participants. Error bars represent the standard error for each of the paired t-tests. *$p < 0.01$; **$p < 0.001$.

stronger left amygdala activation in women and enhanced activity in the right amygdala in men. Thus, these findings can be considered to provide further support to the amygdala lateralization hypothesis proposed by Cahill and colleagues [5–7], showing that it may also apply to facial expressions. However, our critical finding is that this sex-dependent hemispheric specialization in emotional memory was stimulus specific. Namely, the left amygdala in women was preferentially involved in the successful encoding of fearful female faces, compared to male ones, whereas the right amygdala in men was more strongly activated for the encoding of male than female fearful faces.

It has been argued that the emotion-induced memory enhancement and associated sex-related amygdala lateralization only occur for highly arousing stimuli [15,18]. Thus, one possible alternative interpretation for our sex-by-sex interaction could be that men and women perceived male and female fearful faces, respectively, as more negative. However, this is unlikely, as we did not observed any differences in ratings as a function of the sex of the participants or of the faces. Similarly, the lack of any differences in reaction times rules out differential degrees of attention or interest allocated to own-sex faces [10] as potential explanation for the observed effects. None the less, it is important to keep in mind that, due to the relatively small sample size used in this study, we cannot discard the possibility that other, yet to be determined, differences among groups may have contributed to the results reported here.

Our results suggest that the involvement of the amygdala on emotional memory may depend not only on the valence or intensity of the stimulus per se, but also on the relation it has with the perceiver. In particular, memory for fearful faces appears to be modulated by a same-sex effect, which can be considered as a special case of a more general own-group bias ([28], but see [23]). For instance, although women may perceive male and female faces equally in terms of their emotional value, female fearful faces are likely to have a greater relevance, either in terms of biological significance (e.g., survival) or the degree to which they can relate to them (e.g., empathy or closeness). Thus, in addition to valence and arousal [15], a third dimension may influence memory for emotional material, namely stimulus relevance [19]. This biological/social-relevance hypothesis [24] has also received support by a recent study showing that men are faster at detecting angry male faces ([34], but see [1]). Interestingly, an opposite-sex memory advantage for neutral faces has been shown when the face stimuli were shown in a three-quarter view with straight gaze and when they were presented in front view but with their gaze averted [32], further highlighting the importance of the relation between stimulus and observer in memory. Future studies could help further characterize these effects by combining different factors, such as expression and gaze direction, as well as including other measures of stimulus evaluation, such as closeness.

An outstanding question remains regarding the functional significance of the right amygdala activation associated with the successful memory encoding for fearful male, compared to female, faces, in the absence of any significant behavioral differences. Differential brain activations in the absence of significant behavioral effects have been often reported in the literature [33]. Such activations may reflect different strategies employed, or different degrees of attention or effort required to perform the task at the same level for the different conditions. A more sensitive paradigm, such as the remember/know judgment or the use of confidence ratings, could capture these putative, more subtle, differences in performance in a way that it was not possible with our simpler old/new design. Further studies are necessary to clarify this question and allow for a more definitive and comprehensive model of sex differences in emotional memory.

Our study has a number of limitations, in addition to those already pointed out. Each face was presented twice to increase memory performance. As we have no way of determining at which presentation each stimulus was encoded, we collapsed them in the analysis. Thus, it is possible that (automatic) stimulus retrieval, or priming effects, could have contributed to the observed amygdala activation. In addition, we did not take into account the possible effects of the known sex differences in amygdala anatomy [11] on the observed activations. Studies combining functional and structural information could shed issue on this potential confound.

In summary, we have demonstrated that emotional memory for faces is subject to an own-sex effect, both in terms of memory accuracy and, more critically, with respect to amygdala lateralization. Further studies should investigate whether this observed stimulus-specificity of memory for threat-related material also applies to other emotions, such as anger or sadness, as well as to other types of stimuli, including words and pictures. Of particular interest would be to explore these issues using positive stimuli, which have so far yielded inconsistent results in terms of their effects on memory performance [26,27,29].

Acknowledgments

We are grateful to Dr. Martin Lepage for sharing the data with us. This study was funded by the Canadian Institutes of Health Research (CIHR; MOP 53280 & MOP 57724) and the Natural Sciences and Engineering Research Council of Canada (262439-04). J.L.A. was supported by the Canada Research Chairs Program. K.S. was supported by a CIHR Doctoral Fellowship.

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Appendix D

Ethics Certificates

Centre universitaire de santé McGill
McGill University Health Centre

20 August 2004

Jorge Armony, PhD
Department of Psychiatry
Douglas Hospital Research Centre

4.m./5.c. NEU–4-033 **Neural Bases of Emotional Memory: An Event-related fMRI Study** (NSERC RGPIN 262439)
Application for Initial Review dated 2004.08.18, Approval letter from MRRC dated 2004.06.07, Grant application to NSERC or 2003.10.22, English and French consent documents dated 2004.06.10, English and French ads

The above submission, reviewed by the full board at the 2004.08.09 REB meeting was found, upon receipt of a satisfactory revision of Application for Initial Review, consent documents in response to our letter of 2004.08.10, to be within the McGill University Health Centre's ethical guidelines and was entered accordingly into the minutes of the REB meeting. At the MUHC, sponsored research activities that require US federal assurance are conducted under Federal Wide Assurance (FWA) 00000840.

We are pleased to inform you that final approval for the above submission was provided on 2004.08.20.

All research involving human subjects requires review at a recurring interval and the current study approval is in effect until 2005.08.19. It is the responsibility of the principal investigator to submit an Application for Continuing Review to the REB prior to the expiration of approval to comply with the regulation for continuing review of "at least once per year".

It is important to note that validation for the translated version of the consent document has been certified by an MUHC translator. As the translated text was potentially modified, the document must be reviewed by the study sponsor prior to its use. Any further modification to the REB-approved and certified consent document must be identified by a 'revised date' in the document footer, and resubmitted for review prior to its use.

The Research Ethics Boards (REBs) of the McGill University Health Centre are registered REBs working under the published guidelines of the Tri-Council Policy Statement, in compliance with the "Plan d'action ministériel en éthique de la recherche et en intégrité scientifique" (MSSS, 1998) and the Food and Drugs Act (2001.06.07), acting in conformity with standards set forth in the (US) Code of Federal Regulations governing human subjects research and functioning in a manner consistent with internationally accepted principles of good clinical practice.

We wish to advise you that this document completely satisfies the requirement for Research Ethics Board Attestation as stipulated by Health Canada.

The project was assigned MUHC Study #NEU-04-033, which is required as MUHC reference when communicating about the research. Should any revision to the study or other development occur prior to the next required review, you must advise the REB without delay. Regulation does not permit initiation of a proposed study modification prior to REB approval for the amendment.

We trust this will meet with your complete satisfaction.

Yours very truly,

for Dr Bereza

Eugene Bereza, MD CM, CCFP, Chair
MNH/I Research Ethics Board
/ve

Cc: MUHC Study #NEU-04-033

Centre universitaire de santé McGill
McGill University Health Centre

4 June 2004

Martin Lepage, PhD
Brain Imaging Group
Douglas Hospital Research Centre
6875 LaSalle Blvd
MONTREAL H4H 1R3

4.b. NEU-04-002 **The Influence of Emotional Expressions on Face Recognition Memory in Healthy Subjects and Patients with Schizophrenia: An fMRI Study (CIHR #53280)**
Application for Initial Review dated 2004.03.08, Special Populations Guidelines of 2004.03.08, English and French consent documents dated 2004.05.28, Letter dated 2003.01.12 of commitment from A Montoya, English and French ads, grant application

The above submission, reviewed by the full board at the 2004.04.19 REB meeting, was found, upon receipt of a satisfactory revision of Application for Initial Review and consent documents as indicated above in response to our letter of 2004.04.20, to be within the McGill University Health Centre's ethical guidelines and was entered accordingly into the minutes of the REB meeting.

We are pleased to inform you that final approval for the above submission was provided on 2004.06.04.

All research involving human subjects requires review at a recurring interval and the current study approval is in effect until 2005.06.03. It is the responsibility of the principal investigator to submit an Application for Continuing Review to the REB prior to the expiration of approval to comply with the regulation for continuing review of "at least once per year".

It is important to note that validation for the translated version of the consent document has been certified by an MUHC translator. As the translated text was potentially modified, the document must be reviewed by the study sponsor prior to its use. Any further modification to the REB-approved and certified consent document must be identified by a 'revised date' in the document footer, and resubmitted for review prior to its use.

The Research Ethics Boards (REBs) of the McGill University Health Centre are registered REBs working under the published guidelines of the Tri-Council Policy Statement, in compliance with the "Plan d'action ministériel en éthique de la recherche et en intégrité scientifique" (MSSS, 1998) and the Food and Drugs Act (2001.06.07), acting in conformity with standards set forth in the (US) Code of Federal Regulations governing human subjects research and functioning in a manner consistent with internationally accepted principles of good clinical practice.

We wish to advise you that this document completely satisfies the requirement for Research Ethics Board Attestation as stipulated by Health Canada.

The project was assigned MUHC Study #NEU-04-002, which is required as MUHC reference when communicating about the research. Should any revision to the study or other development occur prior to the next required review, you must advise the REB without delay. Regulation does not permit initiation of a proposed study modification prior to REB approval for the amendment.

We trust this will meet with your complete satisfaction.

Yours very truly,

Hanna M Pappius, PhD, Co-Chair
MNH/I Research Ethics Board
/ve

Cc: MUHC Study #NEU-04-002

Appendix E

Consent Forms

CONSENT FORM
MONTREAL NEUROLOGICAL INSTITUTE AND HOSPITAL
McConnell Brain Imaging Centre

1. TITLE OF PROJECT: Neural Bases of Emotional Memory: An event-related fMRI study.

INVESTIGATORS: Jorge Armony, Ph.D., Martin Lepage, Ph.D., Karine Sergerie, M.Sc., Bruce Pike, Ph.D.

2. REASON FOR THE STUDY

The purpose of the study is to understand the functioning of memory and particularly what happens in the brain when people try to encode and retrieve some emotional information. To identify brain regions engaged in memory encoding and retrieval for emotional information, functional Magnetic Resonance Imaging (fMRI) technique will be used.

3. PROCEDURES

Your participation in this study will consist in a single session lasting about an hour. During this session, you will undergo structural (MRI) and functional Magnetic Resonance Imaging (fMRI). They are non-invasive techniques that use a magnetic field and radiofrequency waves to visualize brain tissues (MRI) and to identify regions involved in performing a task (fMRI).

During the structural run, we will ask you to close your eyes, stay as still as possible and be relaxed. This run will last for about 15 minutes.

For the functional part, the experiment will be divided into two successive tasks. For the first task, you will have to look at 100 faces and determine if the attended face is a man or a woman (gender judgment). You will respond by clicking on a mouse with your right hand. You will also have to remember the faces. For the second task, 100 faces with will be presented and you will have to evaluate if the person has been shown in the first part or not, regardless of whether their facial expression is the same or not.

The fMRI machine will be quite noisy. To reduce the noise, you will be given earplugs. You will be asked to remain absolutely still during the examination, and your head will be held in place with restraints that can be disengaged at any time. You will be in constant communication with the operator throughout the experiment.

4. CONTRAINDICATIONS

The following are contraindications for a magnetic resonance study:

- Pacemaker
- Aneurysm Clip
- Heart/Vascular Clip
- Prosthetic Valve
- Metal Prosthesis
- Pregnancy
- Claustrophobia
- Metal fragments in body

Please note that transdermal patches must be removed prior to scanning. You are advised to bring an additional patch to reapply post scanning.

5. ADVANTAGES OF THE PROPOSED STUDY

Functional Magnetic Resonance Imaging (fMRI) is a test, not a treatment. It is hoped that the information obtained in this study will help to clarify what happens in the brain during memory encoding and retrieval tasks for emotional information.

6. DISADVANTAGES OF THE PROPOSED STUDY

During this study, you will be exposed to a strong magnetic field and radio waves. However, no long-term negative side effects have been observed from this type of examination. As mentioned above, the MR machine is very noisy and you will be given earplugs to reduce this effect. Metallic objects can be attracted with great force by the magnetic field. You will be asked to remove all such objects from your person and clothing prior to the test.

7. EFFECTS OF PARTICIPATION IN THIS STUDY

Magnetic Resonance Imaging does not interfere with any treatment or other diagnostic tests.

8. CONFIDENTIAL NATURE OF THIS STUDY

The results of the testing will be kept confidential. No personal information will be released to third parties without your written approval. You should be aware that the Research Ethics Board or Quality Assurance Officers duly authorized by it may access study data.

9. INCIDENTAL FINDINGS

Research scans are not subject to clinical review. However, any incidental finding regarding your health will be communicated to you and, upon your request, to your physician.

10. DISCONTINUATION OF THE STUDY BY THE INVESTIGATOR

At any time during the testing, the investigators have the right to terminate the study for any reason.

11. WITHDRAWAL FROM THE STUDY

Your participation in this research study is voluntary and you may withdraw at any time, including during the procedure.

12. COMPENSATION

Upon completion of the study, you will receive $50 as compensation for your time and inconvenience

13. CONTACT INFORMATION

Should you have any questions regarding your rights as a research subject in this project, you should contact the MNH Patient's Committee (a group established to protect the rights of patients and research subjects), Room 354, tel. 514-398-5358.

DECLARATION OF CONSENT

I, _____, have reviewed the project with one of the investigators, _____.

I fully understand the procedures, advantages and disadvantages of the study which have been explained to me. I freely and voluntarily consent to participate in this study.

Further, I understand that I may seek information about each test either before or after it is given, that I am free to withdraw from the testing at any time if I desire, and that my personal information will be kept confidential.

SIGNATURE _____ _____ _____

SUBJECT **DATE** **CONTACT NO.**

SIGNATURE _____ _____ _____

INVESTIGATOR **DATE** **CONTACT NO.**

Neural Bases of Emotional Memory: An event-related fMRI study.

Magnetic Resonance Imaging QUESTIONNAIRE

McConnell Brain Imaging Centre

It is **essential** for the participant that this questionnaire be completed by the **participant and investigator**.

1. Previous surgery (type and date)

_____
_____.

2. Does the subject have any of the following?	**YES**	**NO**
Cardiac pacemaker	____	____
Surgical clip on an aneurysm or other vessel	____	____
Surgical clip or valve on the heart	____	____
Prostheses (please specify type and location) _____	____	____
Implants (please specify type and location) _____	____	____
Metal or metallic fragments in any part of the body (please specify) _____	____	____
3. Is the subject pregnant?	____	____

SIGNATURE _____ _____ _____
SUBJECT *DATE* *CONTACT NO.*

SIGNATURE _____ _____ _____
INVESTIGATOR *DATE* *CONTACT NO.*

FORMULAIRE DE CONSENTEMENT
INSTITUT ET HÔPITAL NEUROLOGIQUE DE MONTREAL
Centre d'imagerie cérébrale McConnell

1. TITRE DU PROJET: Bases neuronales de la mémoire émotionnelle: Une étude en IRMf événementiel.

CHERCHEURS: Jorge Armony, Ph.D., Martin Lepage, Ph.D., Karine Sergerie, M.Sc., Bruce Pike, Ph.D.

2. MOTIFS DE L'ÉTUDE

La présente étude est menée afin de mieux comprendre le fonctionnement de la mémoire et plus particulièrement ce qui se passe dans le cerveau quand une personne encode et essaie de retrouver de l'information relative à des émotions. Afin d'identifier les régions du cerveau impliquées dans l'encodage et la récupération en mémoire pour de l'information émotionnelle, la technique d'Imagerie par Résonance Magnétique fonctionelle (IRMf) sera utilisée.

3. PROCÉDURE

Votre participation dans cette étude consistera en une seule session d'une durée approximative d'une heure. Durant cette session, vous passerez une Imagerie par Résonance Magnétique structurelle (IRM) et fonctionnelle (IRMf). Ce sont des techniques non-invasives qui utilisent un champ magnétique et des ondes de fréquence radio pour visualiser les tissus du cerveau (IRM) et identifier les régions impliquées dans la réalisation de différentes tâches (IRMf).

L'expérimentation fonctionnelle sera divisée en deux tâches successives. Dans la première tâche, vous aurez à regarder 100 visages et déterminer si le visage présenté est un homme ou une femme (jugement de genre). Vous devrez répondre en cliquant sur une souris avec votre main droite. Vous devrez également tenter de vous souvenir de ces visages. Dans la deuxième tâche, une autre série de 100 visages vous sera présentée et vous aurez à déterminer si l'individu a déjà été observé lors de la première partie ou non, et ce peu importe si leur expression faciale est différente.

Durant la phase structurelle de l'imagerie, on vous demandera de fermer les yeux et de rester aussi immobile et détendu que possible. Cette phase prendra environ 15 minutes. La phase fonctionnelle sera par la suite répétée une seconde fois.

La machine à IRMf est très bruyante. Pour réduire le bruit, vous recevrez des bouchons pour les oreilles. On vous demandera de rester parfaitement immobile durant l'expérimentation et votre tête sera immobilisée par un système qui peut être désengagé en tout temps. Vous serez en constante communication avec l'opérateur tout au long de l'expérimentation.

4. CONTRE-INDICATIONS

Les éléments suivants sont des contre-indications pour les études en Résonance Magnétique:

- Stimulateur cardiaque
- Clip d'anévrisme
- Clip cardiaque ou vasculaire

- Valve artificielle
- Prothèses métalliques
- Grossesse
- Claustrophobie
- Fragments de métaux dans le corps

S.V.P. veuillez noter que les timbres transdermaux doivent être retirés avant d'entrer dans le scanneur. Il serait donc avisé d'apporter avec vous un timbre additionnel afin de l'appliquer après le scan.

5. AVANTAGES DE L'ÉTUDE PROPOSÉE

L'Imagerie par Résonance Magnétique fonctionnelle (IRMf) est un test, pas un traitement. Nous espérons que l'information obtenue par la présente étude permettra de clarifier ce qui se passe dans le cerveau lors de l'encodage et de la récupération en mémoire de l'information relative à des émotions.

6. DÉSAVANTAGES DE L'ÉTUDE PROPOSÉE

Durant cette étude, vous serez exposé à un puissant champ magnétique et à des ondes radio. Toutefois, aucun effet à long terme n'a été observé à ce jour pour ce type de protocole. Comme mentionné précédemment, la résonance magnétique est très bruyante et vous recevrez des bouchons pour les oreilles pour réduire cet effet. Les objets métalliques peuvent être attirés avec force par le champ magnétique. On vous demandra d'enlever ces objets de votre corps et de vos vêtements avant le test.

7. EFFETS DE VOTRE PARTICIPATION

L'Imagerie par Résonance Magnétique ne nuit à aucun traitement ou autre test diagnostique.

8. CARACTÈRE CONFIDENTIEL DE L'ÉTUDE

Les résultats de l'étude resteront confidentiels. Aucune information personnelle ne sera dévoilée à une tierce personne sans votre autorisation écrite. Toutefois, vous devez être avisé que le Comité d'Éthique en Recherche ou les Officiers de Contrôle de la Qualité dûment autorisés peuvent avoir accès aux données relatives à cette étude.

9. CONSTATATIONS FORTUITES

Les scans effectués à des fins de recherche ne seront pas examinés de façon clinique. Cependant, toutes découvertes accidentelles concernant votre santé vous seront communiquées et, à votre demande, seront aussi communiquées à votre médecin.

10. INTERRUPTION DE L'ÉTUDE PAR L'EXPÉRIMENTATEUR

À tout moment durant l'étude, l'expérimentateur a le droit d'y mettre fin pour des raisons scientifiques ou autres.

11. DÉCLARATION DES PARTICIPANTS QUI SOUHAITENT SE DÉSISTER

Votre participation à cette étude se fait sur une base volontaire et vous pouvez vous désister à tout moment, y compris durant son déroulement.

12. COMPENSATION

Après la réalisation de l'étude, vous recevrez 50$ en dédommagement pour votre temps et déplacement.

13. CONTACTS

Si vous avez des questions relatives à vos droits en tant que participant de recherche dans ce projet, vous pouvez contacter le Comité des Patients du INM (Institut Neurologique de Montréal), un groupe créé dans le but de protéger les droits des patients et des participants de recherche. (Salle 354, tél. 514-398-5358).

DÉCLARATION DE CONSENTEMENT

Je soussigné(e) _____ ai pris connaissance du projet en présence de l'un des chercheurs suivants _____.

J'ai parfaitement compris les procédures, les avantages et les inconvénients de cette étude, lesquels m'ont été expliqués. Je consens volontairement et librement à participer à la présente étude.

Il est entendu par ailleurs que je peux demander des renseignements à propos de chaque examen avant ou après son déroulement, que je suis libre de me désister de ce protocole à tout moment si je le souhaite et que toute donnée me concernant restera confidentielle.

SIGNATURE _____ _____ _____
SUJET **DATE** **N° DE CONTACT**

SIGNATURE _____ _____ _____
CHERCHEUR **DATE** **N° DE CONTACT**

Bases neuronales de la mémoire émotionnelle: Une étude en IRMf événementiel

Imagerie par Resonance Magnétique
QUESTIONNAIRE
McConnel Brain Imaging Centre

Il est **essentiel** pour le participant que ce questionnaire soit rempli par le **participant ainsi que par le chercheur.**

1. Chirurgies antérieures (type et date)

_____
_____.

2. Le participant porte-t-il l'un ou plusieurs des éléments suivants?

	OUI	**NON**
Stimulateur cardiaque	_____	_____
Clip d'anévrisme ou clip sur un autre vaisseau	_____	_____
Clip chirurgical ou valve cardiaque	_____	_____
Prothèse (veuillez préciser le type et l'organe) _____	_____	_____
Implants (veuillez préciser le type et l'organe) _____	_____	_____
Métal ou fragments métalliques dans le corps (veuillez préciser) _____	_____	_____

3. Le sujet est-elle enceinte? _____ _____

SIGNATURE _____ _____ _____
PARTICIPANT DATE N^{O} DE CONTACT

SIGNATURE _____ _____ _____
EXPÉRIMENTATEUR DATE N^{O} DE CONTACT

MAGNETIC RESONANCE IMAGING (MRI)
CONSENT FORM
MONTREAL NEUROLOGICAL INSTITUTE AND HOSPITAL
McConnell Brain Imaging Centre

1. TITLE OF PROJECT: The influence of emotional expressions on face recognition memory in healthy subjects and patients with schizophrenia: An fMRI study.

INVESTIGATORS: Martin Lepage, Ph.D., Alonso Montoya, M.D., Samarthji Lal, M.D., Bruce Pike, Ph.D.

2. REASON FOR THE STUDY

The purpose of the study is to understand the functioning of memory and particularly what happens in the brain when people try to encode and retrieve some emotional information. To identify brain regions engaged in memory encoding and retrieval for emotional information, a technique called functional Magnetic Resonance Imaging (fMRI) will be used. We also want to examine differences in brain activity between a group of healthy control subjects and a group of subjects with schizophrenia. The hypothesis is that schizophrenia could be associated with abnormal activity in specific portions of the brain.

3. PROCEDURES

Your participation in this study will consist of a single session lasting about an hour. During this session, you will undergo structural (MRI) and functional Magnetic Resonance Imaging (fMRI). They are non-invasive techniques that use a magnetic field and radiofrequency waves to visualize brain tissues (MRI) and to identify regions involved in performing a task (fMRI).

For the functional part, the experiment will be divided into two successive tasks. For the first task, you will have to look at 100 faces with emotional or neutral expressions and determine if the attended face is a man or a woman (gender judgment). You will respond by clicking on a mouse with your right hand. You will also have to remember the faces. For the second task, 100 faces with emotional or neutral expressions will be presented and you will have to evaluate if they have been presented in the first part or not. During the structural run, we will ask you to close your eyes, stay as still as possible and be relaxed. This run will last for about 15 minutes. The functional part will be repeated.

The fMRI machine will be quite noisy. To reduce the noise, you will be given earplugs. You will be asked to remain absolutely still during the examination, and your head will be held in place with restraints that can be disengaged at any time. You will be in constant communication with the operator throughout the experiment.

4. CONTRAINDICATIONS

The following are contraindications for a magnetic resonance study:

- Pacemaker
- Aneurysm Clip
- Heart/Vascular Clip
- Prosthetic Valve
- Metal Prosthesis
- Pregnancy
- Claustrophobia
- Metal fragments in body

5. ADVANTAGES OF THE PROPOSED STUDY

Functional Magnetic Resonance Imaging (fMRI) is a test, not a treatment. It is hoped that the information obtained in this study will help to clarify what happens in the brain during memory encoding and retrieval tasks for emotional information.

6. DISADVANTAGES OF THE PROPOSED STUDY

During this study, you will be exposed to a strong magnetic field and radio waves. However, no long-term negative side effects have been observed from this type of examination. As mentioned above, the MR machine is very noisy and you will be given earplugs to reduce this effect. Metallic objects can be attracted with great force by the magnetic field. You will be asked to remove all such objects from your person and clothing prior to the test.

7. EFFECTS OF PARTICIPATION IN THIS STUDY

Magnetic Resonance Imaging does not interfere with any treatment or other diagnostic tests.

8. CONFIDENTIAL NATURE OF THIS STUDY

The results of the testing will be kept confidential. No personal information will be released to third parties without your written approval.

9. INCIDENTAL FINDINGS

Research scans are not subject to clinical review. However, any incidental finding by the researcher regarding your health will be communicated to you and, upon your request, to your physician.

10. DISCONTINUATION OF THE STUDY BY THE INVESTIGATOR

At any time during the testing, the investigators have the right to terminate the study for any reason.

11. SUBJECT'S STATEMENT CONCERNING WITHDRAWAL FROM THE STUDY

Your participation in this research study is voluntary and you may withdraw at any time, including during the procedure.

12. COMPENSATION FOR PARTICIPATION IN THE STUDY

Upon completion of the study, patients will receive $75 and control subjects $60 as compensation for their time and inconvenience.

The influence of emotional expressions on face recognition memory
in healthy subjects and patients with schizophrenia: An fMRI study.

Magnetic Resonance Imaging
DECLARATION OF CONSENT

McConnell Brain Imaging Centre

I, _____, have reviewed the project with one of the investigators, _____.

I fully understand the procedures, advantages and disadvantages of the study which have been explained to me. I freely and voluntarily consent to participate in this study.

Further, I understand that I may seek information about each test either before or after it is given, that I am free to withdraw from the testing at any time if I desire, and that my personal information will be kept confidential.

SIGNATURE _____ _____ _____
SUBJECT **DATE** **CONTACT NO.**

SIGNATURE _____ _____ _____
INVESTIGATOR **DATE** **CONTACT NO.**

The influence of emotional expressions on face recognition memory in healthy subjects and patients with schizophrenia: An fMRI study.

Magnetic Resonance Imaging
QUESTIONNAIRE AND DECLARATION OF CONSENT
McConnell Brain Imaging Centre

It is of the **utmost importance** for the participant that this questionnaire be completed by the **participant and investigator**.

1. Previous surgery (type and date)

_____
_____.

2. Does the subject have any of the following?	**YES**	**NO**
Cardiac pacemaker	____	____
Surgical clip on an aneurysm or other vessel	____	____
Surgical clip or valve on the heart	____	____
Prostheses (please specify type and location) _____	____	____
Implants (please specify type and location) _____	____	____
Metal or metallic fragments in any part of the body (please specify) _____	____	____
3. Is the subject pregnant?	____	____

I, _____, have read the above description with one of the above investigators, _____.

SIGNATURE _____ _____ _____
SUBJECT *DATE* *CONTACT NO.*

SIGNATURE _____ _____ _____
INVESTIGATOR *DATE* *CONTACT NO.*

Imagerie Par Résonance Magnétique (IRM)
FORMULAIRE DE CONSENTEMENT
INSTITUT ET HÔPITAL NEUROLOGIQUES DE MONTREAL
Centre d'imagerie cérébrale McConnell

1. TITRE DU PROJET: L'influence de l'expression émotionnelle sur la mémoire de reconnaissance des visages chez les sujets sains et chez les schizophrènes : Une étude en IRMf.

CHERCHEURS: Martin Lepage, Ph.D., Alonso Montoya, M.D., Samarthji Lal, M.D., Bruce Pike, Ph.D.

2. MOTIFS DE L'ÉTUDE

La présente étude est menée afin de mieux comprendre le fonctionnement de la mémoire et plus particulièrement ce qui se passe dans le cerveau quand une personne essaie d'encoder et de retrouver de l'information relative à des émotions. Afin d'identifier les régions du cerveau impliquées dans l'encodage et la récupération en mémoire pour de l'information émotionnelle, la technique d'Imagerie par Résonance Magnétique fonctionelle (IRMf) sera utilisée. Les différences au niveau de l'activité cérébrale entre les sujets contrôles et les sujets atteints de schizophrénie seront également examinées. L'hypothèse est que la schizophrénie pourrait être associée à une activation anormale de régions spécifiques du cerveau.

3. PROCÉDURE

Votre participation dans cette étude consistera en une seule session d'une durée approximative d'une heure. Durant cette session, vous passerez une Imagerie par Résonance Magnétique structurelle (IRM) et fonctionnelle (IRMf). Ce sont des techniques non-invasives qui utilisent un champ magnétique et des ondes de fréquence radio pour visualiser les tissus du cerveau (IRM) et identifier les régions impliquées dans la réalisation de différentes tâches (IRMf).

L'expérimentation fonctionnelle sera divisée en deux tâches successives. Dans la première tâche, vous aurez à regarder 100 visages neutres ou avec une expression émotionnelle et à déterminer si le visage présenté est un homme ou une femme (jugement de genre). Vous devrez répondre en cliquant sur une souris avec votre main droite. Vous devrez également vous souvenir de ces visages. Dans la deuxième tâche, une autre série de 100 visages neutres ou avec une expression émotionnelle vous sera présentée et vous aurez à déterminer si le visage a déjà été présenté dans la première partie ou non.
Durant la phase structurelle de l'imagerie, on vous demandera de fermer les yeux et de rester aussi immobile et détendu que possible. Cette phase prendra environ 15 minutes. La phase fonctionnelle sera par la suite répétée une seconde fois.

La machine à IRMf est très bruyante. Pour réduire le bruit, vous recevrez des bouchons pour les oreilles. On vous demandera de rester parfaitement immobile durant l'expérimentation et votre tête sera immobilisée par un système qui peut être désengagé en tout temps. Vous serez en constante communication avec le technicien tout au long de l'expérimentation.

4. CONTRE-INDICATIONS

Les éléments suivants sont des contre-indications pour les études en Résonance Magnétique:

- Stimulateur cardiaque
- Clip d'anévrisme
- Clip cardiaque ou vasculaire
- Valve artificielle
- Prothèses métalliques
- Grossesse
- Claustrophobie
- Fragments de métal dans le corps

5. AVANTAGES DE L'ÉTUDE PROPOSÉE

L'Imagerie par Résonance Magnétique fonctionnelle (IRMf) est un test, pas un traitement. Nous espérons que l'information obtenue par la présente étude permettra de clarifier ce qui se passe dans le cerveau lors de l'encodage et de la récupération en mémoire de l'information relative à des émotions.

6. DÉSAVANTAGES DE L'ÉTUDE PROPOSÉE

Durant cette étude, vous serez exposé à un puissant champ magnétique et à des ondes radio. Toutefois, aucun effet à long terme n'a été observé à ce jour pour ce type de protocole. Comme mentionné précédemment, la résonance magnétique est très bruyante et vous recevrez des bouchons pour les oreilles pour réduire cet effet. Les objets métalliques peuvent être attirés avec force par le champ magnétique. On vous demandra d'enlever ces objets de votre corps et de vos vêtements avant le test.

7. EFFETS DE VOTRE PARTICIPATION

L'Imagerie par Résonance Magnétique ne nuit à aucun traitement ou autre test diagnostique.

8. CARACTÈRE CONFIDENTIEL DE L'ÉTUDE

Les résultats de l'étude resteront confidentiels. Aucune information personnelle ne sera dévoilée à une tierce personne sans votre autorisation écrite.

9. CONSTATATIONS FORTUITES

Les scans effectués à des fins de recherche ne seront pas examinés de façon clinique. Cependant, toute découverte accidentelle faite par le chercheur concernant votre santé vous sera communiquée et, à votre demande, sera aussi communiquée à votre médecin.

10. INTERRUPTION DE L'ÉTUDE PAR L'EXPÉRIMENTATEUR

À tout moment durant l'étude, l'expérimentateur a le droit d'y mettre fin pour quelque raison que ce soit.

11. DÉCLARATION DES PARTICIPANTS QUI SOUHAITENT SE DÉSISTER

Votre participation à cette étude est volontaire et vous pouvez vous désister à tout moment, y compris durant son déroulement.

12. COMPENSATION POUR PARTICIPATION À L'ÉTUDE

Après la réalisation de l'étude, les patients recevront 75$ et les sujets contrôles 60$ en dédommagement pour leurs temps et déplacement.

L'influence de l'expression émotionnelle sur la mémoire de reconnaissance des visages chez les sujets sains et chez les schizophrènes : Une étude en IRMf.

Imagerie par Resonance Magnétique
DÉCLARATION DE CONSENTEMENT

Centre d'Imagerie Cérébrale McConnell

Je soussigné(e) _____ ai pris connaissance du projet en présence de l'un des chercheurs suivants _____.

J'ai parfaitement compris les procédures, les avantages et les inconvénients de cette étude tels qu'ils m'ont été expliqués. Je consens volontairement et librement à participer à la présente étude.

Il est entendu par ailleurs que je peux demander des renseignements à propos de chaque examen avant ou après son déroulement, que je suis libre de me désister de ce protocole à tout moment si je le souhaite et que toute donnée me concernant restera confidentielle.

SIGNATURE _____ _____ _____

SUJET **DATE** **N^{O} DE CONTACT**

SIGNATURE _____ _____ _____

CHERCHEUR **DATE** **N^{O} DE CONTACT**

L'influence de l'expression émotionnelle sur la mémoire de reconnaissance des visages chez les sujets sains et chez les schizophrènes : Une étude en IRMf.

Imagerie par Resonance Magnétique
QUESTIONNAIRE
Centre d'Imagerie Cérébrale McConnell

Il est **essentiel** pour le participant que ce questionnaire soit rempli par le **participant ainsi que par le chercheur.**

1. Chirurgies antérieures (type et date)

_____

_____.

2. Le participant porte-t-il l'un ou plusieurs des éléments suivants?

	OUI	**NON**
Stimulateur cardiaque	_____	_____
Clip d'anévrisme ou clip sur un autre vaisseau	_____	_____
Clip chirurgical ou valve cardiaque	_____	_____
Prothèse (veuillez préciser le type et l'organe) _____	_____	_____
Implants (veuillez préciser le type et l'organe) _____	_____	_____
Métal ou fragments métalliques dans le corps (veuillez préciser) _____	_____	_____

3. Pour sujet féminin, est-elle enceinte? _____ _____

Je soussigné(e) _____ ai pris connaissance de ce qui précède en présence de l'un des chercheurs suivants _____.

SIGNATURE _____ _____ _____
PARTICIPANT DATE N^{O} DE CONTACT

SIGNATURE _____ _____ _____
EXPÉRIMENTATEUR DATE N^{O} DE CONTACT