Université de Montréal

Étude neuroanatomique fonctionnelle de l'émoussement affectif dans la schizophrénie: les implications du traitement à la quetiapine

Présenté par
Cherine Fahim

Vice-décanat à la recherche et aux études supérieures
Faculté de médecine

Thèse présentée à la Faculté des études supérieures
en vue de l'obtention du grade de
Philosophae Doctor (Ph. D.)
en sciences neurologiques

Mars, 2005

Université de Montréal
Faculté des études supérieures

Cette thèse intitulée:

Étude neuroanatomique fonctionnelle de l'émoussement affectif dans la schizophrénie: les implications du traitement à la quetiapine

présentée par :
Cherine Fahim

a été évaluée par un jury composé des personnes suivantes :

Louis-Éric Trudeau, président-rapporteur
Emmanuel Stip, directeur de recherche
Mario Beauregard, co-directeur
Pierre Rainville, membre du jury
Robin Murray, examinateur externe
Louis-Éric Trudeau, représentant du Doyen

AVANT-PROPOS

Cette thèse de Doctorat est présentée sous forme d'articles et a été autorisée par le vice doyen de la faculté des études supérieures Monsieur Fernand Roberge. Trois articles scientifiques composent cette thèse, un est publié, le 2ème et le 3ème sont en révision. L'auteur de cette thèse est également le premier auteur des 3 articles.

Le premier article intitulé «Negative socio-emotional resonance in schizophrenia: a functional magnetic resonance imaging hypothesis» a été publié dans la revue Medical hypotheses, 2004; 63 :467-475.

Le deuxième article intitulé «Brain activity during emotionally negative pictures in schizophrenia with and without flat affect: An fMRI study» est en révision dans le journal Psychiatry Research: Neuroimaging .

Le troisième article intitulé «Differential hemodynamic brain activity in schizophrenia patients with blunted affect during quetiapine treatment» est en révision dans le journal Journal of Clinical Psychopharmacology, 2005 Aug;25(4):367-371.

Résumé

L'objectif de ce travail doctoral est d'examiner des mécanismes cérébraux impliqués dans le traitement d'informations d'ordre émotionnel chez des patients atteints de schizophrénie avec un regard plus particulier sur une éventuelle différence entre ceux qui présentent un émoussement affectif (FA+) et ceux qui en sont dépourvus (FA-). En second lieu, la thèse propose d'évaluer si la quetiapine (un antipsychotique atypique) peut normaliser ou modifier les modes d'activation cérébrale impliqués dans ces processus de traitement d'information émotionnelle. L'affect émoussé peut être défini en tant que déficit de la spontanéité et de la réactivité affectives; phénomène qui peut être observé et, parfois, subjectivement ressenti. Il constitue un symptôme cardinal de la schizophrénie. De plus, l'affect émoussé fait partie des symptômes négatifs dont l'ensemble constitue le syndrome déficitaire de la schizophrénie, ainsi que le facteur le plus valide de l'évaluation des symptômes négatifs. À l'aide de l'imagerie par résonance magnétique nucléaire fonctionnelle (IRMf), nous avons mené trois études.

Première étude: Le but de cette étude est d'examiner les mécanismes soutenant la résonance émotive dans deux groupes de patients schizophrènes (FA+ N= 13 et FA- N= 11). Nous tentons d'éclairer ces mécanismes en nous référant aux théories des neurosciences sur le fonctionnement du cerveau basé sur ce que l'on désigne comme les neurones miroirs (MN). Nous prévoyons que le groupe FA+ ne va pas activer les régions préfrontales impliquées dans le traitement émotionnel. Par contre, le groupe FA- va activer ces régions, ce qui témoigne de l'existence d'un système fonctionnel de miroir pour la résonance émotive confirmée par une activation du cortex pré-frontal. Nous avons ainsi comparé les deux groupes en utilisant une banque d'images (IAPS= International Affective Picture System) à l'aide de l'IRMf. Une analyse de type *random-effects*, pour les patients FA- a mis en évidence des régions significatives dans le cortex pré-frontal médian. Les analyses de corrélation effectuées entre les estimations individuelles des sentiments négatifs

et des changements du signal BOLD "Blood Oxygenated Level Dependent" ont révélé l'existence d'une corrélation positive dans le cortex pré-frontal médian. Réciproquement, on n'a pas noté d'activation significative dans le cortex pré-frontal dans le groupe FA+. Nous proposons ainsi que la résonance émotive négative induite en regardant passivement des images négatives puisse être une forme de *mirroring*. Ainsi que l'on pourrait saisir et interprèter les sentiments négatifs par l'intermédiaire d'un mécanisme miroir «empathie émotive en se mettant à la place de l'autre ». Avec les neurones miroirs, l'évolution humaine a franchi un pas de plus dans le monde de la représentation, en facilitant une représentation plus abstraite de l'état interne des autres. Par conséquent, nous proposons que les sujet FA-, relativement au système MN émotionnel (Comportement de résonance) puissent ressentir des images négatives. Inversement, nous proposons que le dysfonctionnement objectivé dans le groupe FA+ soit le résultat d'un échec ou d'une anomalie dans le développement du système MN. Ceci pourrait être dû à des causes génétiques ou d'autres causes endogènes ayant affecté le système MN du cortex pré-frontal impliqué dans la résonance émotive.

Deuxième étude: pour tenter de comprendre les différences neurobiologiques entre les patients schizophrènes avec (FA+ N= 13) et sans (FA-= 11) émoussement affectif (même patients que la 1ère étude), nous avons scanné pendant un état négatif (neg) puis neutre (neut) au cours d'un visionnement d'images IAPS, en utilisant l'IRMf. Sur une échelle de 0 à 8 correspondant au sentiment négatif ressenti pendant la séance d'imagerie, le groupe de sujets FA+ a exprimé une moyenne de 1±1.52 et le groupe FA- 5.9 ±1.22 ($P<0.0001$). Ainsi, une analyse de *test T à un échantillon* (neg – neutre pour FA+ - FA- et vice-versa) a montré une activation significative pour le groupe FA- dans le cortex visuel, visuo-temporal, cunéus, pré-frontal médian, orbito-frontal, le cortex cingulaire antérieur, l'amygdale, l'insula, le mésencéphale et la protubérance . Quant à lui, le groupe FA+ a activé de manière significative le cortex visuel, la protubérance et le mésencéphale. L'inactivation relative des régions pré-frontales, orbito-frontales, cingulaires antérieures,

l'amygdale et l'insula pourraient expliquer le fonctionnement émotif altéré dans le groupe FA+. Inversement, l'activation significative de ces mêmes régions chez les parents FA- pourrait signifier que l'altération du fonctionnement émotif soit non pas le symptôme fondamental de la schizophrénie mais plutôt celui du sous-groupe des patients atteints de schizophrénie avec émoussement affectif. Nous proposons que les patients FA+ utilisent une stratégie passive dans la réaction au stimulus négatif en n'activant conséquemment que la région du mésencéphale. Au contraire, les sujets FA- mettent en œuvre une stratégie active permettant la propagation de l'information au cortex pré-frontal.

Troisième étude: L'objectif de cette étude en IRMf était de mesurer l'impact d'un traitement à la Quetiapine sur le fonctionnement de la circuiterie neuronale sous-tendant l'expérience de la tristesse chez les sujets schizophrènes souffrant d'un émoussement affectif. Pendant le visionnement passif des extraits tristes et neutres des films, nous avons scanné 12 patients (12 des 13 patients des études 1 et 2) avant et après le traitement à la quetiapine (une médiane de 5,5 mois de traitement avec la quetiapine). Les analyses 'random-effects' d'activation de cerveau avant la quetiapine ont indiqué une activation significative dans le tronc cérébral (protubérance). Après une durée suffisamment longue de traitement avec la quetiapine, le même contraste a montré une activation prefrontale (Broadmann "BA" 32, 46) et temporale (BA 38 et l'amygdale) significative. L'activation des régions prefrontales principales impliquées dans le traitement de l'émotion, de plus, l'amélioration, significative de symptômes, mesureé par l'échelle d'évaluation subjective et le PANSS "Positive and Negative Symptoms Scale" suggèrent un effet potentiel de la quetiapine dans l'amélioration des symptômes relatifs à l'émoussement affectif (c-à-d., retrait passif, retrait émotif, évitement) dans la schizophrénie.

L'ensemble des resultats de cette thèse propose que les mécanismes neuronaux sous jacent au traitement de l'information émotionnelle soient différents entre les deux groupes (FA+

et FA-). De plus, la quetiapine joue un role dans l'amélioration de l'affect émoussé dans le groupe FA+ en agissant sur le circuit mésocortical.

Mots-clés : schizophrénie, symptomes négatifs, émoussement affectif, émotion, antipsychotique atypique, quetiapine, résonance magnétique nucléaire fonctionnelle RMNf.

Abstract

Research suggests emotion abnormalities to be a highly prevalent symptom of schizophrenia. Such studies argue for a "unitary" based model for schizophrenia. However, we advocate that no "unitary" model is likely to account for the multiplicity of schizophrenia symptomatology. Our study attempts to further test this by comparing schizophrenia patients with (FA+) to without (FA-) flat affect, thus investigating the true neurobiologically based heterogeneity that goes beyond any one dysfunctional circuit (model). Furthermore, we investigate quetiapine as a potential treatment for schizophrenia patients (FA+). To that end, we conducted the following three studies using functional magnetic resonance imaging (fMRI). *First study:* The aim of this study was to use neuroscience theories about brain function (mirror-neurons MN) to draw inferences about the mechanisms supporting emotional resonance in two different groups of schizophrenia patients (FA+ n=13 and FA- n=11). We hypothesize that FA+ will not activate key brain areas involved in emotional processing. Conversely, FA- will have a functional mirror system for emotional resonance confirmed by activation of the prefrontal cortex and behavioral results. To test this hypothesis, we compared the 2 groups using blood oxygenation level dependent (BOLD) fMRI during a passive visual task (44 negative IAPS pictures and 44 neutral pictures). A random-effects analysis, for schizophrenia patients FA-, revealed significant loci of activation in the left medial prefrontal (LMPFC), right orbitofrontal (ROFC) and left anterior cingulate cortices (LACC). Correlational analyses carried out between self-report ratings of negative feelings and BOLD signal changes revealed the existence of positive correlation in the LACC, LMPFC and ROFC. Conversely, FA+ did not show significant activation in the prefrontal cortex. We propose that negative emotional resonance induced by passively viewing negative pictures may be a form of "mirroring" that grounds negative feelings via an experiential mechanism. Hence, it could be argued that FA- were able to 'feel' emotions through this resonance behavior.

Conversely, we suggest that the dysfunction seen in the FA+ group is a failure or distortion in the development of the MN system. This could be due to genetic or other endogenous causes, which affected prefrontal cortex MN involved in emotional resonance. *The second study:* The aim of this fMRI study was to compare regional brain activity in schizophrenia subjects with (FA+) and without (FA-) flat affect during the viewing of emotionally negative pictures. Thirteen FA+ subjects and eleven FA- subjects were scanned while being presented with series of emotionally negative and neutral pictures. Experientially, the viewing of the negative pictures induced a negative emotional state whose intensity was significantly greater in the FA- group than in the FA+ group. Neurally, the Negative minus Neutral contrast revealed, in the FA- group, significant loci of activation in the midbrain, pons, anterior cingulate cortex, insula, ventrolateral orbitofrontal cortex, anterior temporal pole, amygdala, medial prefrontal cortex, and extrastriate visual cortex. In the FA+ group, this contrast produced significant loci of activation in the midbrain, pons, anterior temporal pole, and extrastriate visual cortex. When the brain activity measured in the FA+ group was subtracted from that measured in the FA- group, only the lingual gyrus was significantly activated. Perhaps in FA+ subjects an amygdaloid malfunction rendered the amygdala unable to correctly evaluate the emotional meaning of the pictures presented, thus preventing effective connectivity linking the amygdala to the brain regions implicated in the physiological and experiential dimensions of emotion. Alternatively, a disturbance of effective connectivity in the neural networks linking the midbrain and the medial prefrontal system could be responsible for the quasi absence of emotional reaction in FA+ subjects, and the abnormal functioning of the medial prefrontal cortex and anterior cingulate cortex in the FA+ group. *The third study:* BOLD brain changes underlying response to quetiapine were examined using passive viewing of emotionally aversive and neutral stimuli. Twelve DSM-IV schizophrenia patients with flat affect/emotional withdrawal (FA+) (positive and negative symptoms scale + rating scale for emotional blunting) were scanned before and after 5.5 months of quetiapine treatment. Whole-brain, voxel-based methods were used to assess response-specific quetiapine effects. A post-hoc comparison to an independent group

of 11 schizophrenia patients without flat affect/social withdrawal (FA-) was also performed to interpret the specificity of identified quetiapine effects. A 5.5-month treatment with quetiapine resulted in significant clinical improvement in the 12 study completers (mean ±SD post-treatment PANSS flat affect score of 5.50 ±0.76 at baseline to 2.08 ±1.00 at end point ($t=7.78$, $df=11$, $p<0.0001$). Treatment response was associated with significant BOLD changes both in sub-cortical an cortical structures: increases in prefrontal cortex activation right dorsolateral prefrontal (DLPFC, BA 46) and the right anterior cingulate cortex (ACC, BA 32); left putamen, right anterior temporal pole (ATP) and right amygdala. Conversely, before quetiapine, the same subjects activated only sub-cortical structures: the midbrain bilaterally and the right pons. The post-hoc conjunctional analyses demonstrated that FA- subjects activated the left ACC, left insula, left ATP (BA 21), left ATP (BA 38), left amygdala and right medial prefrontal cortex. Quetiapine seems to affect clinical recovery by modulating the functioning of specific sites from subcortical to cortical regions (i.e., modulating the mesocortical pathway). Unique BOLD changes in the putamen and DLPFC with quetiapine, in the FA+ post-quetiapine, relative to other drugs (used by FA-) may reflect modality-specific effects with implications for understanding the neural correlates underlying different treatment mechanisms. In summary, it should be noted that we do not suggest that there are categorical subtypes of schizophrenia patients based on the with flat affect/without flat affect symptomatology. However, our findings, demonstrating differential haemodynamic flow between schizophrenia patients with and without flat affect, mean that the quest for the symptom-specific-neuropathology of schizophrenia could help explain the multiplicity of neuro-circuit dysfunction in this heterogeneous disorder. Furthermore, we suggest quetiapine could have a role in improving flat affect/emotional withdrawal symptoms in schizophrenia patients.

Keywords : schizophrenia, flat affect, emotions, functional magnetic resonance imaging, visual cortex, midbrain, amygdala, prefrontal cortex.

Table des matières

Page titre i
Identification du jury ii
AVANT-PROPOS iii
Accord des coauteurs des articles iv
Résumé vii
Abstract xi
Table des matières xiv
Liste des tableaux xvi
Liste des figures xvii
Liste des abréviations : xviii
Dédicace xx
Remerciements xxi

Introduction 1
1. Schizophrenia 1
2. Diagnosis of schizophrenia 3
3. Pathogenesis and pathophysiology: focus on abnormal brain circuits connectivity and neurodevelopmental theories 5
4. Schizophrenia sub-types and negative symptoms: focus on flat affect 11
4. Explanatory models of flat affect (affective deficits) in schizophrenia 15
5. Studies in support of affective deficits in schizophrenia 16
6. Studies contradicting affective deficits in schizophrenia 22
7. Psychopharmacological treatments and negative symptoms 26
8. An attempt to refute the homogeneity of emotion dysfunction in schizophrenia and the quest for a possible treatment 30

Article 1: Negative socio-emotional resonance in schizophrenia: a functional magnetic resonance imaging hypothesis..... 35
Article 2: Brain activity during emotionally negative pictures in schizophrenia with and without flat affect: an fMRI study..... 65
Article 3: Differential haemodynamic brain activity in schizophrenia patients with blunted affect during quetiapine treatment..... 112

Discussion..... 149
1. Neuroimaging emotional experience and potential treatment in schizophrenia: What we have found..... 149
1.1. The visual cortex..... 150
1.2. Midbrain..... 150
1.3. The Insula..... 153
1.4. The amygdala..... 155
1.5. The Prefrontal cortex..... 157
2. Clinical and Biological Implications..... 159
3. Discussing Methodological Issues..... 162
3.1. Why choosing the Rating Scale for Emotional Blunting (RSEB) and the Calgary Depression Scale (CDS)?..... 162
3.2. Why Choosing IAPS?..... 164
3.3. Why choosing a passive-viewing method?..... 165
3.4. Why choosing quetiapine?..... 166
4. Limitations..... 168
5. Conclusion..... 169

Liste des tableaux

Article 2

Table 1.....70
Table 2.....77
Table 3.....80
Table 4.....81

Article 3

Table 1.....114
Table 2.....121
Table 3.....122
Table 4.....123
Table 5.....125
Table 6.....126
Table 7.....127

Liste des figures

Article 1

Figure 1……..……..……..45

Aticle 2

Figure 1……...78
Figure 2……...79
Figure 3……...……...……...…82

Article 3

Figure 1……...……123

Discussion

Figure 1……...……159

Liste des abréviations :

ACC:	Anterior cingulate cortex
AC-PC:	Anterior commissure-Posterior commissure
ATP:	Anterior temporal pole
BA:	Brodmann's area
BOLD:	Blood oxygen level dependent
CA-CP :	Commissure antérieure-commissure postérieure
CDS:	Calgary depression scale
D2:	Dopamine-2
DSM IV:	Diagnostic and statistical manual of mental disorders, 4th edition
EMG:	Electromyography
EPI:	Echo planar imaging
FA+:	With flat affect
FA-:	Without flat affect
FG:	Fusiform gyrus
fMRI:	Functional magnetic resonance imaging
GOM:	Middle occipital gyrus
GOS:	Superior occipital gyrus
GTI:	Inferior temporal gyrus
IAPS:	International affective picture system
ICD:	International classification of disease
IRMf :	Imagerie par résonance magnétique fonctionnelle
L:	Left
LG:	Lingual gyrus
MEP:	Motor evoked potential
MN:	Mirror neurons

MNI:	Montreal neurological institute
MPFC:	Medial prefrontal cortex
OMACC:	Orbitofrontal, mesial prefrontal and anterior cingulate cortices
PANSS:	Positive and negative syndrome scale
PET:	Positron emission tomography
PFC:	Prefrontal cortex
OFC:	Orbitofrontal cortex
R:	Right
rCBF:	Regional cerebral blood flow
ROI:	Region of interest
RSEB:	Rating scale for emotional blunting
SANS:	Scale for Assessment of Negative Symptoms
SCID:	Structured Clinical Interview for DSM-IV
5-HT2A:	Serotonin 2A
SPECT:	Single single photon emission computed tomography
SPEM:	Smooth pursuit eye movement
SPM:	Statistical Parametric mapping
SVC:	Small volume correction
T:	Tesla
TE:	Echo time
TMS:	Transcranial magnetic stimulation

Dédicace

<u>À mes chères parents et famille Habachi et Fahim:</u>

Tous mes respects et ma reconnaissance vont à ma famille, source de ma motivation et de mes espoirs: votre amour, affection, soutien moral, et gentillesse m'ont donné le goût et l'enthousiasme de faire quelque chose qui ajoute à votre fierté. C'est pour moi un immense plaisir d'écrire vos noms ici, et de vous dédier cette thèse. Ce travail est la reconnaissance des multiples efforts consentis à mon éducation. Je vous dis tout simplement que c'est vous qui avez alimenté l'âme de ce travail de recherche.

<u>À mon cher époux Adham Mancini-Marïe et mon chèr fils Zein:</u>

Adham, tu as pu me supporter, m'encourager et me préparer les conditions parfaites pour mener à bien cette thèse de doctorat. Tu as été très généreux et aimable et tu as consenti beaucoup d'amour pendant des années. Permet-moi de te dédier cette thèse en gage de reconnaissance, d'amour et d'affection à toi et à notre fils Zein.

Remerciements

À mes directeurs de recherche, les docteurs Emmanuel Stip et Mario Beauregard :

A mes Professeurs Emmanuel Stip et Mario Beauregard, dont la rigueur de l'enseignement a nourri mon esprit. Je les remercie surtout pour la confiance qu'ils m'ont gracieusement accordée. Ils m'ont suivi pas à pas en m'ouvrant les portes de leurs laboratoires et m'ont recommandé pour obtenir la bourse de doctorat. Mes chers professeurs, j'ai pu, durant toutes ces années sous votre direction, apprécier vos qualités de chercheurs; vos qualités humaines et votre générosité scientifique. Veuillez me permettre de vous exprimer ici ma reconnaissance et vous dire merci pour tout.

À Messieurs Boualem Mensour et Jean-Maxime Leroux du laboratoire d'imagerie fonctionnelle de l'hôpital Notre-Dame, je vous remercie chaleureusement pour votre précieuse aide et disponibilité tout au long de ce travail.

Introduction

1. Schizophrenia

"*The singular indifference of the patients towards their former emotional relations, the extinction of affection for relatives and friends, of satisfaction in their works and vocation, in recreation and pleasures, is not seldom the first and most striking symptom of the onset of disease. The patients have no real joy of life, "no human feelings"; to them "nothing matters, everything is the same"; they feel "no grief and no joy", their heart is not in what they say* " (Kraepelin, 1919).

The above words emphasize the fact that schizophrenia is one of the most debilitating brain disease, damaging what we regard as specifically human. It is one of the most important public health problems. Among psychiatric disorders, the combined economic and social costs place schizophrenia among the world's top ten causes of disability-adjusted life-years (Murray and Lopez, 1996). Schizophrenia typically has its onset between the ages of 16 and 30 years. It usually has a gradual, insidious onset taking place over an average of 5 years (DSM IV). Outcomes are currently of interest in health-economics research; probably no other chronic illness parallels schizophrenia in the potential for poor functional outcome in the absence of a measurable decrease in lifespan, which is a substantial burden of morbidity. Noteworthy, approximately 10-15% commit suicide (Ho et al., 1997; Lewis and Lieberman, 2000).

Schizophrenia is a life-long disorder characterized by three broad types of symptoms: (i) Psychotic/positive symptoms involving the loss of contact with reality, including false beliefs (delusions), perceptual experiences not shared with others (visual, auditory, tactile and gustatory hallucinations), hostility, paranoid ideation. (ii) Negative symptoms including flat affect, emotional withdrawal, passive/apathetic social withdrawal, anhedonia (lack of pleasure), avolition/apathy (diminished ability to initiate and follow through on plans), and alogia (reduced speech). (iii) Cognitive symptoms including unusual thought content, poor attention, lack of judgment and insight, difficulties in abstract thinking, memory and problem solving (based on the DSM-IV description). Of particular relevance to our study, these various symptoms are present in schizophrenia patients in patterns that may not overlap at all. One person may have delusions without presenting any flat affect symptoms, while another may have hallucinations and anhedonia. From a pathophysiological view, this non-overlapping pattern of symptoms raises some questions: is there a core or single brain circuit that unites schizophrenia as a single disease or different brain circuits depending on the symptom(s) present? In other words, could the brain circuit dysfunction vary according to symptoms? What is the relationship, on a neural circuit level, between a patient who had poor premorbid socioemotional adjustment, then develops schizophrenia with a marked flat affect symptom and a patient who had normal socioemotional adjustment, then develops schizophrenia with bouts of positive psychotic symptoms without any trace of flat affect?

2. Diagnosis of schizophrenia

From a criterion-based view, schizophrenia symptoms are grouped into a single disease using a purely descriptive approach using clustering of symptoms. Criterion-based systems have been developed to decrease the complexity and improve the reliability of diagnosis. These systems include the International Classification of Diseases, tenth edition (ICD-10) (1994), and the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (1994), which describe characteristic symptoms of schizophrenia (it is the most widely used). In ICD-10, severe symptoms should have been present for 1 month, whereas in DSM-IV, 6 months' duration is required (ie, including less severe prodromal and residual symptoms). The DSM-IV criteria also require deterioration in social and occupational functioning, specified as dysfunction in work, interpersonal relations, or self-care. Other diagnoses, such as mood disorders with psychotic features, must be ruled out and symptoms must be shown to be due to no other medical disorder or drug effect, such as steroid-induced or amphetamine-induced psychosis. Noteworthy, diagnostic criteria improve reliability, enable standardization across centers, nationally and internationally, improve clinical communication, and facilitate research. However, these criteria should not discourage innovative thinking about the neural mechanisms of schizophrenia. Rather, they should be combined with symptom-rating scales, clinical experience and new techniques to better define features of this disorder that may respond to various therapeutic interventions.

Unfortunately, with their emphasis on psychotic symptoms (delusions, hallucinations, etc…), criterion-based approaches may have neglected other symptoms. For example, social deterioration commonly becomes prominent before and persists after the more severe symptoms (positive symptoms) have been controlled with medication. These symptoms result in impaired functioning in interpersonal relationships. Most commonly, people who have schizophrenia are unable to continue in employment or education. Fortunately, presently psychosocial impairment is being studied as an important outcome measure, and is becoming the focus of treatment. In addition, psychiatrists are increasingly recognizing the correlation between negative symptoms and loss of social function among schizophrenia patients. Alogia, avolition, apathy, flat affect, etc… are among these negative symptoms, which lead to long-term social and economic burden because patients cannot maintain productive employment (Green, 1996). It should be noted that negative symptoms are the least likely to improve over the course of illness, and resulting cognitive dysfunction in the context of these symptoms is most likely to contribute to unemployment (Pogue-Geile and Harrow, 1985). Hence, a better understanding of negative symptoms and the development of effective treatments are required.

Moreover, negative symptoms are known to occur long before the onset of florid psychosis (positive symptoms) in schizophrenia patients (Strauss et al., 1973). However, the emphasis on psychosis as a hallmark of schizophrenia has led to conceptualizing the early impairments, i.e. negative symptoms, as premorbid. It is imperative to determine

whether such impairments are premorbid, early manifestations of the disease or a schizophrenia subtype, under-diagnosed until the manifestation of positive symptoms. Indeed, schizophrenia, simplistically, could be viewed as a whole-brain disease. However, with its extremely diverse but interlocking neural circuit pathologies and symptoms, more research is needed using a true neurobiologically symptom-based models.

3. Pathogenesis and Pathophysiology: focus on abnormal brain circuits connectivity and neurodevelopmental theories

" Of the thousands of associative threads that guide our thinking, this disease seems to interrupt, quite haphazardly, sometimes single threads, sometimes a whole group, and sometimes whole segments of them... the thousands of associations guiding our thought are interrupted by this disease...the thought processses, as a result, become strange and illogical, and the associations find new paths" Bleuler, 1911.

These words should humble the modern neuroscientists, neuropathologists and neuropsychiatrists investigating the relationship between brain circuits misconnectivity and/or dysfunction and the phenomenology of schizophrenia. Bleuler's prophetic words have currently their counterparts in modern neuropsychiatry, which have implicated aberrant functional connectivity (miswiring) between different brain regions as the pathophysiological mechanism of psychosis. However, although some insights into the etiology of schizophrenia have been developed, an understanding of the illness remains

elusive. One could say that Bleuler's (1950) use of the term "group of schizophrenias" was insightful and prophetic.

In an attempt to understand schizophrenia, Weinberger (1995) reviewed the possible causes including: rhesus (Rh) factor incompatibility, perinatal/prenatal viral infections, obstetrical complications, hypoxia at birth, famine and malnutrition, severe environmental stress, the epidemiologic risk factors of urban and winter birth and heritability as demonstrated by twin and adoption studies. A number of abnormalities have been identified and confirmed by meta-analysis, for example, ventricular enlargement, which is accompanied by decreased cortical and association neocortical (prefrontal and superior temporal) and hippocampal volumes (Harrison and Weinberger, 2005).

Noteworthy, these abnormalities are characteristic of schizophrenia as a whole, rather than being restricted to a subtype, and are present in first-episode, unmedicated patients. These morphometric changes are in turn suggestive of alterations in synaptic, dendritic and axonal organization. Generally, it is hypothesized that the interaction of genetic and early neurodevelopmental insults result in defective connectivity between a number of brain regions, including the midbrain, nucleus accumbens, thalamus, temporolimbic (hippocampus), and prefrontal cortices (Selemon and Goldman-Rakic, 1999) leading to schizophrenia symptomatology. In this context, combinations of genetic and environmental factors may affect various neural circuits within the brain leading to diverse symptoms. The

insult (genetic and/or environmental) may hit one site and then flow across several neural circuits.

These changes tend to link schizophrenia with connectivity and communication disruption within the neural circuitry (for a complete review McGlashan and Hoffman, 2000). This defective neural circuitry is then vulnerable to dysfunction when unmasked by the developmental processes and events of adolescence (myelination, synaptic pruning, and hormonal effects of puberty) and/or exposure to stressors as the individual moves through the age of risk (Lewis and Lieberman, 2000).

Relatedly, Jones (1995) proposed, based on neuroanatomical and gene expression studies, that a disturbance of migration or in the pattern of preprogrammed cell death in the subplate zone of the developing cerebral cortex causes a failure to establish normal patterns of connections in the overlying cortex. Consequently, this could lead to schizophrenia symptoms and activity-dependent manifestations of altered gene expression for neurotransmitter- and receptor-related molecules. Jones (1997) showed that the number of neurons in the cortical subplate (the white matter immediately below layer VI of the cortex, a transitional structure that plays a key role in the formation of connections in the cerebral cortex), is reduced in the prefrontal and temporal lobe cortices, whereas their number in the white matter deeper than 3 mm from the cortex is significantly greater compared with normal subjects. In addition, Jones (1997) further suggested that the loss of cells in the

thalamus may be primary or secondary to cortical or other subcortical pathology. Loss of thalamic cells and/or of corticothalamic inputs could lead to disintegration of thought processes by a failure in functional brain states dependent on collective oscillation of large ensembles of cortical and thalamic neurons. Structural or functional defects of the thalamus, because it is associated with filtering sensory information and gating mechanisms, may be particularly important in the pathogenesis of schizophrenia; indeed, problems of information filtering may underlie disturbed thought processes.

Evidence suggesting that schizophrenia symptoms are not caused by dysfunction of a single brain region came based on empirical data derived from both magnetic resonance and positron emission tomography. Andreasen et al., (1998), developed a model that implicates the cortico-cerebellar-thalamic-cortical circuit (CCTCC) connectivity in schizophrenia symptomatology. The authors concluded that a dysfunction in this circuitry produces "cognitive dysmetria", difficulty in prioritizing, processing, coordinating and responding to information, a disruption of the fluid, coordinated sequences of thought and action that are the hallmark of normal cognitive functions.

Furthermore, interesting morphometric findings in the dorsolateral prefrontal cortex (Broadmann areas 9 and 46) have uncovered a form of cortical pathology in schizophrenia in which poor neuronal activity/connectivity appears to correlate with cognitive dysfunction (Selemon and Rajkowska, 2003) and *the reduced neuropil hypothesis* (Selemon and

Goldman-Rakic, 1999). The reduced neuropil hypothesis advances a circuit based model of schizophrenia proposing that a reduction in interneuronal neuropil in the prefrontal cortex is a prominent feature of cortical pathology. The authors suggest that this neuropathology is of subtle changes in cellular architecture and brain circuitry that nonetheless have a devastating impact on cortical function. They report that the increased neuronal density seen on histological examination as reduced neuropil without neuronal loss, point towards loss of connections between neurons.

Recently, a review by McGlashan and Hoffman (2000) formulated a pathophysiological model of schizophrenia according to postmortem and neuroimaging findings. The authors proposed that schizophrenia results from developmentally reduced synaptic connectivity (DRSC). The model posits that schizophrenia arises from critically reduced synaptic connectivity as a result of developmental disturbances of synaptogenesis during gestation and early childhood and/or synaptic pruning during adolescence. The DRSC model identifies reduced synaptic density in prefrontal and other areas of association cortex as the "final common pathway" to the symptoms and course of schizophrenia.

However, before this "final common pathway" mild dysfunctions associated with these early neurobiological lesions occasionally emerge as vulnerability factors or risk markers for schizophrenia. For example, diminished expression of positive and negative emotions, passivity, social withdrawal, and poor relationships (Grimes and Walker, 1994;

Hans et al., 2000), neuromotor abnormalities in the form of poor coordination, poor perceptual motor integration, or abnormal speech (Olin and Mednick, 1996), as well as minor physical anomalies (Whitty et al., 2003), and neurocognitive deficits (Olin and Mednick, 1996). Noteworthy, such deficits are not sufficient to produce schizophrenia. Further evidence of neuronal circuit dysfunction in schizophrenia, has come from studies investigating eye tracking. Indeed, smooth pursuit eye movement (SPEM) abnormalities are associated with liability for schizophrenia (Ross et al., 2002). Relatedly, in a recent article by Hong et al., (2005), the authors stated that understanding the neurophysiologic mechanisms underlying SPEM deficits is likely to enhance our ability to refine them as endophenotypes for genetic studies. Hong and colleagues have compared pursuit-related brain activation in schizophrenia patients and healthy control subjects, matching subjects on average maintenance pursuit performance. Patients showed *decreased* activation compared with healthy subjects in the medial superior temporal cortex, frontal eye field, and suplementary eye field areas hypothesized to be involved in extraretinal motion processing. However, they have showed *increased* activation Brodmann areas 19 and 37. These correspond to posterior retinal motion regions and are consistent with the notion that a portion of the individuals who possess liability for schizophrenia rely more on retinal signals to maintain pursuit

Overall, rather than having a distinctive diagnostic neuropathology, schizophrenia seems to consist of quantitative alterations in various normal parameters of neural

microcircuitry. In this vein, because of a lack of definite neuropathology, schizophrenia remains a clinical diagnosis based on the presence of positive and negative symptoms. Therefore, and since schizophrenia is a heterogeneous brain disease, understanding the functional abnormalities of different brain circuits and relating this to symptomatology is of primordial importance in our quest to understand schizophrenia.

4. Schizophrenia sub-types and Negative symptoms: focus on Flat affect

In 1857, John Russell Reynolds stated "Many of the symptoms of disease are merely modified vital actions…some symptoms are negative, i.e., they consist in the negation of vital properties…other symptoms are positive, i.e., they consist in the excess of alteration of vital properties", hence introducing the concept of negative versus positive symptoms to schizophrenia (Berrios, 1985). Insightfully, John Hughlings Jackson (1875, 1889) described negative symptoms as the diminution or negation of normal processes, resulting from tissue destruction; and positive symptoms as the excess in normal brain processes as disinhibiting consequences of this tissue destruction. Going one step further, Kraepelin (1919), reported: "…there are apparently two principal groups of disorders which characterize the malady. On the one hand we observe a weakening of those emotional activities…The result of this part of the morbid process is emotional dullness. Bleuler (1911) considered negative symptoms to represent "fundamental" or core psychopathologies in schizophrenia. He defined schizophrenia as essentially a splitting of thoughts (cognition) from feelings (emotion). More recently, many attempts to subtyping schizophrenia have emanated. I will

briefly outline the main six. First, in 1974, Tsuang and Winokur proposed the paranoid (delusions, hallucinations) versus the nonparanoid (flat affect, disorganized thoughts) subtypes. Then, in 1980 the concept of Type I and Type II schizophrenia was introduced by Crow (1980a). This subdivision put greater emphasis on the presence or absence of negative symptoms, with poverty of speech and flat affect defining the presence of the negative syndrome (Type II) and the prominance of psychotic symptoms for the positive (Type I) syndrome. Third, came Andreasen and Olsen (1982), who conceptualized positive (delusions, hallucinations, hostility) and negative symptoms (affective flatting, alogia, avolition-apathy, anhedonia-asociality, and attentional impairment) as different ends of the same continuum and described patients as either predominantly positive or predominantly negative. Farmer and colleagues (1983) were fourth to propose the P type (delusions, late onset) versus the H type (flat affect, bizarre behavior, incoherent speech and early onset) distinction. Fifth, Liddle and collaborators (1987) introduced the concept of the three syndromes: psychomotor poverty (poverty of speech, lack of spontaneous movement and various aspects of blunting of affect); disorganisation (inappropriate affect, poverty of content of speech, and disturbances of the form of thought); and reality distortion (particular types of delusions and hallucinations). Sixth, in an effort to clarify the situation, the deficit/non-deficit distinction was put forth by Carpenter and colleagues (1988). They identified six negative symptoms (i.e., poverty of speech, diminished emotional range, flat affect, diminished sense of purpose, curbing of interests and diminished social drive) as the deficit syndrome. In this vein, Kirkpatrick and colleagues (2001), stated that the

deficit/non-deficit schizophrenia sub-groups differ in their signs and symptoms, course, biological correlates, treatment response, and etiologic factors.

In 1980, Crow hypothesized that negative symptoms (poverty of speech, flat affect) in schizophrenia represent a behavioral syndrome that was the manifestation of unspecified structural brain abnormalities. It should be noted that researchers seeking to establish different etiologies for the positive and negative subtypes struggled with the degree to which the sutypes are truly different because they have found overlap cross-sectionally and longitudinally. Other researchers made the attempt to delineate the defective brain circuits based on biochemical hypotheses. In this vein, the implications of several neurotransmitters have been proposed: GABA, glutamate, serotonin, achetylcholine, noradrenaline (for a full review see Stahl, 2002). However, the classical cornerstone theory to explain schizophrenia is the 'dopamine hypothesis', proposing that the positive symptoms of schizophrenia are related to dopamine neurons overactivity in the mesolimbic pathway, and that the negative symptoms are related to underactivity of dopamine input to the prefrontal cortex (Weinberger and Wyatt, 1982).

From the above, we should note the emphasis on the role flat affect plays in schizophrenia. Kraepelin (1919) conceptualized affective deficits as fundamental symptoms of schizophrenia. Importantly he gave particular emphasis to diminished emotional *experience*. More recently, numerous other authors have also advocated the role emotional

deficits play in schizophrenia. For example, Crow (1985) used poverty of speech and flat affect as the key symptoms for the definition of a negative symptom subtype because these are the symptoms that are both primary and enduring.

In support of Kraepelin's early observation on the role emotional dullness (flat affect) plays in schizophrenia, contemporary research has provided converging evidence about its diagnostic and prognostic importance (Abrams and Taylor, 1978; Sweet et al., 1998; Gur et al., 2002). Flat affect has also been shown to be a relatively enduring symptom that generally responds poorly to treatment (Pogue-Geile and Harrow, 1985). It is important to note that patients with schizophrenia exhibit impairments in emotional discrimination and experience across cultures (Habel et al., 2000). Furthermore, the presence of this symptom is related to poor clinical outcomes on several dimensions, including employment (Pogue-Geile and Harrow, 1985), social functioning (Breier et al., 1991), and severity of illness (Abrams and Taylor, 1978). Moreover, premorbid affective blunting is associated with an earlier onset of illness and poorer prognosis in schizophrenia (Grimes and Walker, 1994). A great body of evidence suggests that diminshed expression of positive and negative emotions, passivity, social maladjustments, anxiety, withdrawal and poor peer relationships are the clearest prodromal symptoms leading to the onset of psychosis (Watt, 1978; Done et al., 1994; Ingraham et al., 1995; Mirsky et al., 1995; Olin and Mednick, 1996). Although research has given greater insights into the impact of flat affect and the nature of the deficit, the pathophysiology and causes are still not clearly understood.

4. Explanatory models of flat affect (affective deficits) in schizophrenia

Explanatory models of flat affect have proposed various etiologies, invoking psychodynamic processes such as repression (Arieti, 1955; Pao, 1979), emphasizing the role of impaired social relations and social rejection (Roff and Knight, 1978). A recent hypothesis has suggested that flat affect is the manifestation of dysfunction in the right hemisphere (Mayer et al., 1985). The potential significance of right hemisphere dysfunction in flat affect derives from evidence obtained in neurologic populations with cortical lesions. These patients have been described as showing flat affect or emotional indifference that is strikingly similar to the clinical picture of flat affect seen in schizophrenia. Whittaker and colleagues (1985) reported associations between frontotemporal dysfunction and impaired perception of both facially expressed and vocally expressed emotion. Another more recent hypothesis proposed dysfunction of the frontal lobe areas (Gur et al., 2002; Weinberger, 1987; Buchsbaum, 1990; Weddell et al., 1990; Mega and Cummings, 2001), because of their afferent and efferent connections with limbic structures, which have been implicated in affective behavior. Interestinsly, Takahashi et al., (2004) proposed that schizophrenia patients might have relatively intact function of conscious processing of significant emotional information, leading to a categorization of emotional pictures similar to that of controls, however, they have impairment in the rapid, automatic processing of salient stimuli. In other words, patients could assign significance to stimuli through conscious processing, but they might have diminished automatic emotional response to external stimuli.

5. Studies in support of affective deficits in schizophrenia

Affective deficits in schizophrenia can be identified in three general domains (reviewed in Limpert and Amador, 2001): 1) deficits in the *perception* of emotion (i.e., difficulty judging and interpreting the emotional displays of others), 2) deficits in the e*xpression* of emotion (i.e., difficulty conveying one's emotional experience to others) and 3) deficits in the *experience* of emotion (i.e., difficulty with the subjective feeling of emotion). In this study, we have focused on the latter, with some involvement of the first (i.e., in order to feel we need first to perceive and interpret the emotional displays).

The greatest amount of empirical work, investigating emotion deficits in schizophrenia, has been conducted in the areas of emotion perception and emotion expression, with few studies investigating emotional experience. A number of studies examining interpersonal behaviors in flat affect have focused on either self-report of interpersonal behaviors (Habel et al., 2000; Sison et al., 1996) or have used a behavioral approach to study these behaviors, such as assessing eye contact, verbal comments, and body gestures (Sweet et al., 1998; Kohler et al., 2000; Alpert et al., 2000; Alper et al., 2002). Further evidence comes from studies reporting that schizophrenia patients are impaired in judging various facial expressions depicted in photographs (for example, Cutting, 1981; Heimberg et al., 1992). Several studies also provide evidence for a deficit in judging vocal expressions of emotion in schizophrenia patients (Borod et al., 1990; Haskins

et al., 1995). Of particular note, the deficits appear to be less consistent, across studies and populations, when using observer ratings. These equivocal findings may be due to the fact that flat affect schizophrenia patients tend to be negatively evaluated and/or negatively evaluate their social skills. Alternatively, the faulty interpersonal responses may be too subtle to be reliably detected using a behavioral approach, which usually involves videotaping social responses and later quantifying the responses using a coding system. This approach can be problematic because the behavioral coding systems may not be those behaviours that are most critical to the social/emotional interaction. Furthermore, social/emotional interactions consist of capturing nuanced behaviors (e.g. slight curve of the lip, subtle flare of the nostril) that may be difficult to capture using behavioral coding systems.

For this reason, a second approach to measuring social/emotional displays was put forth: to employ physiological indices, such as facial electromyography (EMG) (Sison et al., 1996; Iwase et al., 1999; Kring et al., 1999). The authors found that increased bluntedness of affect was associated with longer pauses and reduced dyadic interaction and less zygomatic (cheek) electromyogram activity. The flat affect patients unexpectedly showed more corrugator (brow) electromyogram activity compared with control groups, which perhaps reflects difficulty in self-expression. Furthermore, schizophrenia patients showed reduced zygomaticus activity (EMG) during both the happy film and the interview, suggesting a reduced ability to express happy facial expressions, such as smiling, in the

lower face (Mattes et al., 1995). However, there remains the question: what happens in the brain?

The answer of this question lies in the third and more recent approach, the one we will be focusing on: functional neuroimaging. Functional magnetic resonance imaging (fMRI) is a noninvasive technique for measuring changes in cerebral blood flow and oxygenation that reflect the underlying neuronal activity. This technology offers a powerful method for exploring three of the outstanding questions in schizophrenia research (1) neural circuits abnormalities in schizophrenia and their associated symptoms; (2) how these neural circuit dysfunction relate to the heterogeneity of schizophrenia; and (3) how could the widely accepted single unitary model for schizophrenia account for the widespread functional deficits. Thus, numerous researchers have also introduced, albeit with different methodology, neuroimaging techniques to investigate the neural process of emotional deficits in schizophrenia. Since 1981, more than 100 articles on functional brain imaging in schizophrenia have been published. Positron emission tomography (PET) and single photon emission computed tomography (SPECT), which measure regional cerebral blood flow (rCBF) and/or metabolism, reveal a number of abnormalities and deficiencies in people with schizophrenia, compared with healthy subjects. A consistent finding (in two-thirds of the published PET or SPECT studies) is a lower level of prefrontal cortical metabolism in schizophrenia subjects (reviewed by Wu et al., 2000). Furthermore, many studies have reported in schizophrenia patients structural and functional abnormalities in the medial

prefrontal cortex, orbitofrontal and anterior cingulate gyrus, regions important in the effortful regulation of affective states and emotional behavior (reviewed in Phillips et al 2003).

Consistent with the theory, these studies have suggested that individuals with schizophrenia may be disturbed not only in their experience and/or expression of affect, but also in their ability to recognize emotions expressed by others (Gur et al., 2002; Schneider et al., 1998; Johnston et al., 2001; Paradiso et al., 2003). In these studies, the main modality for receiving emotional information was visual, specifically facial expressions. For example, Schneider and colleagues (Schneider et al., 1998) found that unlike controls, schizophrenia patients have not demonstrated amygdala activation during sadness despite matched ratings to normal controls indicating a similar negative affect. At that time, their results provided new evidence of functional abnormalities in the limbic system of schizophrenia patients processing emotions. Crespo-Facorro and colleagues (Crespo-Facorro et al., 2001) PET study reveals an interesting paradox. Schizophrenia: patients appear to have a normal ability to experience unpleasant emotions, coupled with an impairment in the ability to experience pleasant ones, and the more psychotic they are, the greater the acuity of their ability to recognize unpleasantness. At the neural level, patients with schizophrenia who subjectively rated the unpleasant odor the same as did healthy volunteers failed to recruit the subcortical limbic and paralimbic structures that would normally be used for this task. Instead, their normal behavioral response was associated

with abnormally increased rCBF in a widely distributed group of frontal cortical regions. On the other hand, these patients had difficulty identifying the positive emotional valence of the pleasant odors, despite the fact that they gave intensity ratings within the normal range. Accordingly, the authors concluded that abnormalities in the complex functional interactions between mesolimbic and frontal regions may underlie emotional disturbances in schizophrenia. In a more recent fMRI study, Gur and colleagues (2002), found that schizophrenia patients failed to activate limbic regions during emotional valence discrimination tasks. Another fMRI study Kosaka and colleagues (Kosaka et al., 2002), reported that negative face discrimination activated the bilateral amygdalae in the schizophrenia group whereas the right amygdala alone in the control group. The authors argued that exaggerated amygdala activation during emotional intensity judgment found in the schizophrenia patients may reflect impaired gating of sensory input containing emotion.

More recently, Takahashi and colleagues (2004), instructed the subjects (15 schizophrenia/15 controls), to indicate how each of the presented pictures made them feel. Whole brain activities in response to the affective pictures were measured by fMRI. Controls recruited the neural circuit including amygdaloid-hippocampal region, prefrontal cortex, thalamus, basal ganglia, cerebellum, midbrain, and visual cortex while viewing unpleasant pictures. However, the patients showed less activation in the components of this circuit. Furthermore, an elegant study by Ioannides and collaborators (2004), provided

evidence for disturbances in functional connectivity in schizophrenia patients, while processing of facial information.

Together, these studies provide substantial support for a socio-emotional deficit in schizophrenia (Sweet et al., 1998; Sison et al., 1996; Kohler et al., 2000, Cutting, 1981; Feinberg et al., 1986; Gessler et al., 1998; Heimberg et al., 1992; Archer et al., 1992). Reduced facial expression during social interaction (Krause et al., 2003) and diminished expressiveness in response to emotional films (Berenbaum and Oltmanns, 1992) have also been reported. According to Lee and colleagues (Lee et al., 2004) disturbances in socio-emotional cognition may represent an abnormal interaction between frontal lobe and its functionally connected cortical and subcortical areas.

In summary, substantial evidence supports emotional deficits and, hence, advocates a unitary model to schizophrenia (present in all schizophrenia patients). However, from a clinical point of view, these symptoms are heterogeneous among schizophrenia patients. Thus, studies should seek to explore the heterogeneity of socio-emotional dysfunction within schizophrenia.

6. Studies contradicting affective deficits in schizophrenia

In the preceding section, we examined emotional deficits in schizophrenia and reported some of the data that have been published to support it. We now turn to the issue that gave rise to our study. Notwithstanding these studies (see previous section), emotional deficits appear to be inconsistent across studies and populations (Kring et al., 1999; Earnst and Kring 1999). Overall, studies to date have produced contradictory and inconclusive results (Edwards et al., 2002). In their review, Morrison and colleagues (1988) reported some conflicting observations among schizophrenia patients in emotion recognition and experience. They proposed that task or methodology differences, are likely to explain the inconsistent results.

First, many studies include chronic patients without the use of comparably ill psychiatric controls or no psychiatric controls at all. Participants have been hospitalized continuously for lengthy periods, thus being subject to social isolation. Hence, it would be worthwhile to study patients with first-episode psychosis to minimize the influence of variables such as institutionalization. In this vein, Edwards and colleagues (Edwards et al., 2002) demonstrated that the magnitude of the significant differences between first-episode psychosis, assessed as outpatients during the early recovery phase of illness, and non-patients in the recognition of emotion was relatively small, suggesting only a subtle deficit. There are several studies that demonstrate that phase of illness seems to have an

effect on emotion recognition, with remitted patients performing better than acute patients (Gessler et al., 1998).

Second, we should note the lack of attention paid to the long-term impact of antipsychotic and anticholinergic medications. Paradiso and colleagues (Paradiso et al., 2003) measured regional rCBF during performance of a task that required unmedicated patients to recognize the emotional valence of visual images and to determine whether they were pleasant or unpleasant. When patients consciously evaluated the unpleasant images, they did not activate the phylogenetically older fear-danger recognition circuit (e.g., the amygdala) used by the healthy volunteers, although they correctly rated them as unpleasant. Likewise, the patients showed no activation in areas of the prefrontal cortex normally used to recognize the images as pleasant and were unable to recognize them as such. Areas of decreased CBF were widely distributed and comprised subcortical regions such as the thalamus and cerebellum. Thus, the authors suggested failure of the neural system used to support emotional attribution consistent with pervasive problems in experiencing emotions.

Third, to our knowledge, very few researchers have attempted to determine whether their findings are indicative of schizophrenia patients with flat affect or manifestations of a more general psychotic process. Investigations would benefit from the inclusion of a psychotic control group (i.e. schizophrenia patients without flat affect), hence, investigating

if this 'subgroup' exhibits the same deficits. Especially, if we consider studies reporting that some schizophrenia patients experience emotions (Kring et al., 1999; Berenbaum and Oltmanns, 1992).

In this section, we summarize a series of investigations that separately reflect the heretogeneity of schizophrenia.

1) Evidence suggests that the paranoid subtype has more intact cognitive functioning (Morrison et al., 1988), a better premorbid history (Goldstein, 1970), and fewer social deficits (Strauss et al., 1973) than non-paranoid subtypes. These differences would suggest that paranoid patients would perform better on tasks of social perception than non-paranoid patients.
2) Patients with negative symptom schizophrenia have generally been characterized as having poor premorbid adjustment and lower overall social functioning (Andreasen and Olsen, 1982; Crow, 1987; Schuldberg et al., 1999) in comparison to patients with positive symptom schizophrenia. Consistent with this, two studies have found that paranoid schizophrenic subjects are more accurate than non-paranoid subjects in judging facial expression of emotion (Kline et al., 1992; Lewis and Garver, 1995).
3) Bryson et al. (1998) found that deficit patients performed more poorly on an affect recognition test than non-deficit patients, and within the deficit group, diminished sense of purpose was the deficit symptom most strongly associated with impaired affect

recognition. Interestingly, the deficit patients demonstrated poorer premorbid adjustment and worse social functioning than non-deficit patients.

4) Blanchard and colleagues (1998) reported less positive affect and significantly greater negative affect in patients with schizophrenia, compared with controls. The authors concluded that their findings indicate that schizophrenia is characterized by both low positive affect and elevated negative affect and that these affective characteristics are a stable feature of the illness.

5) A similar result was obtained by Earnst and colleagues (Earnst and Kring, 1999). In this article, the authors examined emotional responding in deficit patients, non-deficit patients, and controls, and investigated the importance of the deficit/non-deficit distinction for studies of emotional responding in schizophrenia. They showed that deficit patients exhibited fewer outward facial expressions to the films than both non-deficit patients and controls.

6) Noteworthy, in a preliminary report done by our group, we demonstrated no significant difference between schizophrenia patients without flat affect and normal controls in emotion processing, using fMRI (Fahim et al., 2003).

7) In a recent study, Cohen and Docherty (2004) examined affective reactivity in the natural speech of schizophrenia patients with and without the deficit syndrome. Nondeficit patients showed greater affective reactivity of speech than deficit patients. Conversely, deficit patients' speech was not more reactive to emotion than the speech of the control group. These results suggest that emotion-related variables mediate the

relationship between stress and language symptom exacerbations in *some* patients with schizophrenia.

Although only few studies investigated emotion deficits between two groups of schizophrenia patients, the results mentioned above nonetheless seem to indicate that whereas schizophrenia patients with severe negative symptoms (flat affect) may have diminished affective experience, those patients with positive symptoms "feel more". Although the latter group of patients may at times show diminished subjective feeling as a consequence of positive (delusions/hallucinations) or depressive symptoms, this lack of feeling is not a stable feature of the illness, as it is for the deficit patients. Overall, these findings are consistent with the idea that subgroups of schizophrenia patients may differ in terms of their affective functioning.

7. Psychopharmacological treatments and negative symptoms

The treatment of schizophrenia changed in the 1950s with the discovery of conventional antipsychotics (typical), such as chlorpromazine and haloperidol. However, patients still had incomplete or partial response, with significant negative, more than positive symptoms remaining despite optimal dosing. In the 1960s, clozapine was introduced as the first 'atypical' antipsychotic. Clozapine had a positive effect on both the negative and the positive symptoms. Nonetheless, it was removed from the market because of its agranulocytosis. Following this discovery, other atypical antipsychotics have been

discovered. However, the major goal of antipsychotic drug development until the 1980s was, still, the treatment of positive symptoms. Nonetheless, Crow's provocative suggestion (1980a) that chronic schizophrenia patients with negative symptoms were insensitive to neuroleptic treatment, raised interest in the issue of treating negative symptoms.

Treating positive symptoms mainly relied on the antipsychotics' ability to bind to dopamine-2 (D2) receptors. Indeed, in vitro studies (Seeman et al., 1976; Seeman et al., 1997) show that all antipsychotics bind to dopamine-2 (D2) receptors and that the affinity for the D2 receptor is inversely correlated with the clinical dosage. Although the principal brain target that all antipsychotic drugs attach to is the dopamine D2 receptor, traditional or typical antipsychotics, by attaching to it, induce extrapyramidal signs and symptoms (EPS). They also, by binding to the D2 receptor, elevate serum prolactin. Atypical antipsychotics given in dosages within the clinically effective range do not bring about these adverse clinical effects.

The typical antipsychotics such as trifluperazine, pimozide, chlorpromazine, fluphenazine, haloperidol, and flupenthixol bind more tightly than dopamine itself to the dopamine D2 receptor, with dissociation constants that are lower than that for dopamine. The newer, atypical antipsychotics such as quetiapine, remoxipride, clozapine, olanzapine, sertindole, ziprasidone, and amisulpride all bind more loosely than dopamine to the dopamine D2 receptor and have dissociation constants higher than that for dopamine (Kapur and Seeman,

2002; Seeman, 2002). Despite the introduction of these several new antipsychotics, quetiapine has several specificities not shared by other atypical antipsychotics, i.e., lower extrapyramidal symptoms and no hyperprolactinemia (Tauscher et al., 2002). The pharmacological basis of quetiapine's low propensity to induce extrapyramidal symptoms may be explained by its combined antagonism at 5-HT2A and D2 receptors or its fast dissociation from the D2 receptor (Kapur and Remington, 2001). In this vein, moderate occupancy of D2 receptors has been proposed to be clinically superior to a more complete D2 blockade (Meltzer and Gudelsky, 1992). Tauscher and colleagues (2002) reported, using PET, that in the striatum, the D2 occupancy ranges from 81% for risperidone to 30% for quetiapine, with the following rank order: risperidone > olanzapine > clozapine > quetiapine. Kapur et al., (2000) demonstrated, using PET, that quetiapine does give rise to transiently high (58%-64%) D2 occupancy 2 to 3 hours after a single dose that then decreases to minimal levels (< 30%) in 12 hours. In other words, quetiapine's pharmacology has aspects that are consistent with the atypical pharmacologic profile of an antipsychotic, yet, novel and distinct in its low D2 binding affinity and fast dissociation from the receptor. In vivo functional studies all provide evidence that quetiapine has a preferential effect on limbic as opposed to striatal D2 receptors. EPS are associated with D2 occupancy in the striatum, which therefore predicts a therapeutic effect with placebo levels of EPS for quetiapine (Arvanitis et al., 1997).

A recent review (Lublin et al., 2005) reported that clinical trials suggest that atypical agents improve negative and affective symptoms, and cognitive functioning more than typical antipsychotics. Of particular relevance to our study, quetiapine has a direct effect on the negative symptoms of schizophrenia (Tandon, 2004). In this study, the author evaluated, quetiapine's effect on negative symptoms, from four randomized, controlled clinical studies involving 1106 patients employing a path analysis model. The total effect of quetiapine on negative symptoms was measured using the Scale for Assessment of Negative Symptoms (SANS) total score. Indirect effects on negative symptoms via positive, depressive and EPS were assessed using appropriate instruments. Effect sizes were calculated by path analysis for the difference between treatment groups in change from baseline to endpoint in SANS total score. Analysis confirmed that quetiapine produced a greater overall improvement in negative symptoms than placebo (effect size 1.96); this was explained by a significant direct effect ($p = 0.001$; 44.2% of total improvement), and a secondary effect of improved positive symptoms ($p < 0.001$; 47.5% of total improvement), but was not a consequence of changes in depressive symptoms or EPS. Thus, the author concluded that quetiapine has a substantial direct effect on improving the negative symptoms of schizophrenia. In addition, in animal studies, quetiapine has been shown to reverse amphetamine-induced social isolation in monkeys (an animal model for the negative symptoms (Ellenbroek et al., 1996). In this vein, chronic administration of quetiapine reverses the inhibitory effects of amphetamine on midbrain dopamine neurons and produces depolarization inactivatioin of limbic-related A10 dopamine neurons (Goldstein et al., 1993).

Finally, worth mentioning, a fundamental problem in schizophrenia treatment is the traditional view of schizophrenia as a disease entity rather than a syndrome comprising several pathologic domains. This is what we will attempt to explain in the next section.

8. An attempt to refute the homogeneity of emotion dysfunction in schizophrenia and the quest for a possible treatment

At this point, we should have noted that despite extensive research for many years and many promising hypotheses, we do not, yet, have a clear understanding of either the causes of schizophrenia or how the causative factors lead to the clinical features. Previous research has demonstrated abnormalities in most of the brain regions in schizophrenia. However, these ultimately convincing findings have yielded disappointing conclusions in our quest to understand schizophrenia as a disease. Hence, instead of advocating a "Gestalt" approach (the whole equals the sum of its parts) to schizophrenia, researchers should investigate the parts (symptomatology) then put them together to understand the whole (schizophrenia). Thus, any attempts to understand it requires explanation of its various guises and components. Furthermore, although the general concept of negative symptoms has been of considerable heuristic value and was successful in generating research findings leading to six major theories of sub-typing (section 4 in the introduction), the time has come for abandoning its general construct and focus on its discrete components. This approach may yield findings that have potential significance for an understanding of etiologic and

developmental aspects of schizophrenia. Furthermore, from a neuropsychopharmacological view, the ideal treatment should not be a single drug with multireceptor blockade ("one-size-fits-all" polypharmacy) but should require several specific and targeted treatment strategies that are titrated to match the variable expression of illness in each patient.

To that end, we have decided to bring together clinical experience (Dr. Emmanuel Stip, Psychiatrist) and functional magnetic resonance imaging (Dr. Mario Beauregard), to focus on a specific and important symptom (flat affect) and to investigate potential treatment. It is perhaps valuable at this point to state our central hypotheses, which we have formulated in the following three studies (please note that, for theese studies, we have recruited 25 schizophrenia patients, divided into two groups: 14 with and 11 without flat affect. Out of the 14 with flat affect, 12 were treated with quetiapine for 22 weeks and then rescanned):

1) **Study I:** Investigating the heterogeneity of hypofrontality in schizophrenia patients with (FA+) and without (FA-) flat affect and the role of the prefrontal cortex in emotional experience through interpretation of emotional stimuli. The central hypothesis we focus on in this study is that while passively viewing pictures with negative emotional content, which entails neural activation of the prefrontal cortex (orbitofrontal, mesial prefrontal, and anterior cingulate cortices), schizophrenia patients FA+ would show relative decreased activity in these brain areas. Conversely,

schizophrenia patients without flat affect (FA-) would show significant activation of the same areas. To that end, we have used a directed search targeting the prefrontal cortex.

2) **Study II:** Since current thinking about the mechanisms of schizophrenia, based on fMRI, postulates a disruption in distributed functional circuits rather than a single abnormality in a single brain region such as prefrontal cortex, we have decided to go one step beyond the heterogeneity of hypofrontality, to investigate whole brain cortical and subcortical differential heamodynamic flow between schizophrenia FA+ and FA-. The aim of this second fMRI study was to compare regional brain activity in FA+ subjects and FA- subjects during the viewing of emotionally negative pictures. Experientially, we hypothesized that the viewing of the negative pictures would induce a greater negative emotional state in the FA- group compared to the FA+ group. Neurally, we predicted that, relative to the FA+ subjects, the FA- subjects would show significantly greater BOLD signal increases in the brain regions normally associated with emotion processing (from the visual cortex, midbrain, amygdala, to the prefrontal cortex) during the viewing of such stimuli. To that end, we have used a whole brain analysis (global search) targeting regions, according to the litterature, involved in emotion processing.

3) **Study III:** Could quetiapine (an atypical antipsychotic) play a role in "normalizing" brain processing of negative emotions in schizophrenia FA+? Based on the notions that

(i) stimuli with strong affective content modulates neural information processing both at the cortical and subcortical levels, (ii) quetiapine modulates the mesocortical pathway (from the midbrain to the prefrontal cortex) (iii) this pathway is involved in emotion recognition, experience and expression, we predicted that:

a) Pre-quetiapine: schizophrenia patients with flat affect would demonstrate an enhanced response only in subcortical regions (based on findings from Study II).
b) Post-quetiapine: schizophrenia patients with flat affect would demonstrate significant activity both within cortical and subcortical regions.
c) When using a conjunctional analysis (post-hoc) schizophrenia patients with flat affect post-quetiapine would not significantly differ from schizophrenia patients without flat affect: both groups would reveal subcortical and cortical activation. We used this analysis to show commonalities between the two groups (since FA-process emotions similar to normal controls (please refer to Study I and II).

In summary, the use of multiple criteria to define contrasting cohorts makes it difficult to identify the source of cohort differences. Although there were some conflicting observations, results about emotional deficits in schizophrenia remained unquestioned for several years. Furthermore, to date, research has focused on the *recognition* of emotions in schizophrenia, much less interest has been shown in the subjective *experience* of emotions in 'sub-groups' of schizophrenia patients (i.e., with flat affect versus without flat affect). The study of subjective experiences and strategy choice (either to be implicated and process

the emotional situation or choose avoidance) based on these experiences requires introspection and self-reports. Such research strategies are more difficult to implement and are often considered unreliable, particularly in patients with schizophrenia. Hence, this is what this study has attempted to overcome. The main goal of the present investigation was to identify the neural substrate associated with the passive viewing (experience, feelings and strategy choice) of negative pictures in schizophrenia patients with and without flat affect, using fMRI.

The results supported our *à priori* hypotheses. We hypothesized *à priori* that flat affect reflects failure of coordinated interaction between two streams (from subcortical to cortical). The hypothesis we tested in this study was guided by a theoretical framework, which proposes that emotions are part of a neural multisystem. The responses of this multisystem are represented both in subcortical regulatory structures (for example, brainstem, midbrain) and in the cerebral cortex (mesial prefrontal gyrus, orbitofrontal cortex and anterior cingulated). Hence, we predicted differential activation between FA+ and FA- patients in these areas.

Negative socio-emotional resonance in schizophrenia: a functional magnetic resonance imaging hypothesis.

C Fahim M.Sc, E Stip M.D., A Mancini-Marïe M.D., B Mensour Ph.D., D Malaspina M.D., M Beauregard Ph.D.

Centre de Recherche Fernand-Seguin, Hôpital Louis-Hippolyte Lafontaine, Université de Montréal, Montréal (Québec) Canada.

Correspondance should be addressed to: Cherine Fahim, Université de Montréal, Centre for reseearch on neurological sciences, Centre de Recherche Fernand-Seguin, 7331 rue Hochelaga, Montréal (Québec) Canada, H1N 3V2. Tel (514) 251-4015 # 3557; Fax (514) 251-2617; [redacted]

Acknowledgement: This work was supported by grants from AstraZeneca pharmaceuticals and the Fonds de la Recherche en Santé du Québec (FRSQ). We thank all the patients who participated in the study, and the staff of the Département de radiologie, Centre Hospitalier de l'Université de Montréal (CHUM), Hôpital Notre-Dame, for their skilful technical assistance.

Summary

The aim of the present study is to use neuroscience theories about brain function (mirror-neurons MN) to draw inferences about the mechanisms supporting emotional resonance in two different groups of schizophrenia patients (with flat affect FA+ n=13 and without flat affect FA- n=11). We hypothesize that FA+ will not activate key brain areas involved in emotional processing. Conversely, FA- will have a functional mirror system for emotional resonance confirmed by activation of the prefrontal cortex and behavioral results. To test this hypothesis, we compared the 2 groups using blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) displaying a passive visual task (44 negative IAPS pictures and 44 neutral pictures). A random-effects analysis, for schizophrenia patients FA-, revealed significant loci of activation in the left mesial prefrontal (MPFC), right orbitofrontal (OFC) and left anterior cingulate cortices (ACC). Correlational analyses carried out between self-report ratings of negative feelings and BOLD signal changes revealed the existence of positive correlation in the LACC, LMPFC and ROFC. Conversely, FA+ did not show significant activation in the prefrontal cortex. We propose that negative emotional resonance induced by passively viewing negative pictures may be a form of "mirroring" that grounds negative feelings via an experiential mechanism. Hence, it could be argued that FA- were able to 'feel' emotions through this resonance behavior. Conversely, we suggest that the dysfunction seen in the FA+ group is a failure or distortion in the development of the MN system. This could be due to genetic or other endogenous causes, which affected prefrontal cortex MN involved in emotional resonance.

Key words: mirror-neurons, emotional resonance, schizophrenia, flat affect, functional magnetic resonance imaging, prefrontal cortex.

INTRODUCTION

In the past decades, researchers have attempted to delineate the functional elements and associated brain regions important for socio-emotional processing. In this paper, we will be using neuroscience theories to address these questions, traditionally of interest to psychologists and psychiatrists.

Mirror neurons: from primates to humans

When a monkey passively observes others perform specific gestures or actions, premotor and motor cortical areas involved in the internal representation and actual execution of those actions exhibit neuronal activation (1,2). This mechanism matches observation, representation, and execution, facilitating internal motor rehearsal, imitation, recognition of actions by others, their meanings and social learning (1-3). The functional properties of these cells have led Rizzolatti, Gallese, and colleagues to coin the term "mirror neurons" (MN) (4). In other words, mirror-neurons are defined as neurons that discharge both when the monkey makes a particular action and when it observes another individual (monkey or human) making a similar action (5). With their latest study, Umilta and colleagues (6) further our knowledge about the function of "mirror neurons" significantly and provide now strong evidence for its capability to encode not only fully perceived but even visually inferred action.

On this theoretical grounds, it is conceivable to propose that neurons of this type became co-opted during evolution to serve the processing of internal representation and reaction to socio-emotional environmental stimuli through a mirror neuronal system (2,7,8). Four lines of evidence strongly suggest that an action/observation matching system similar to that demonstrated in monkeys also exists in humans. The first refers to a study by Fadiga et al. (9), in which the authors stimulated the motor cortex of normal subjects (transcranial magnetic stimulation) while they observed an experimenter grasping 3D-objects. Interestingly, they found that the motor evoked potentials (MEP) significantly increased during the conditions in which subjects observed movements. Moreover, The MEP pattern reflected the pattern of muscle activity recorded when the subjects executed the observed actions. This study provided for the first time evidence that humans have a mirror system similar to that in monkeys. Another more intriguing evidence is psychological studies using mental chronometry tasks. These studies have shown that there is a remarkable parallelism between motor imagery and motor execution (10,11,12). For example, vegetative responses (such as increasing heart rate and blood pressure) associated with physical effort vary in the same manner during both motor imagery (presentation of a motor stimulus) and motor performance (13). The third evidence, comes from a study where the authors demonstrate that, during speech listening, there is an increase of motor-evoked potentials recorded from the listeners' tongue muscles when the presented words strongly involve, when pronounced, tongue movements (14). The fourth evidence was demonstrated by (15) using functional magnetic resonance imaging.

The authors showed that when individuals observe an action, an internal replica of that action is automatically generated in their premotor cortex. In the case of object-related actions, a further object-related analysis is performed in the parietal lobe, as if the subjects were indeed using those objects. Buccino and colleagues (15), hence, argued that these results bring the previous concept of an action observation/execution matching system (mirror system) into a broader perspective: this system is not restricted to the ventral premotor cortex, but involves several somatotopically organized motor circuits. of particular relevance to our study, in an emotional situation, humans exhibit nonconscious mimicry of others' facial expressions, postures and mannerisms (*the chameleon effect*) (16). In other words, since emotional states are closely linked to certain facial expressions, observation of an emotional situation (e.g., murder) might result in a mirrored emotional state. In this article we call it emotional resonance, which is the ability to mentally-represent the emotional stimuli in ones environment. Such a process might help to explain the phenomenon of emotional contagion, in which people automatically mirror the postures and moods of others (17). Of particular relevance, there is direct electromyographic evidence that observers adopt facial muscle activity congruent with expressions witnessed even when this process is not at an overt level (18). Thus, in humans as in nonhuman primates, it seems that an internal replica of a perceived action is automatically generated, represented as if the subjects were themselves performing that action.

Socio-emotional impairment in schizophrenia

Imagine you are telling two persons a story about your child who witnessed a murder two days ago. As the story progresses, one person seems amused and displays an inappropriate laughter making you and the other person, who displayed empathy, uncomfortable. As a result, you terminate the interaction as quickly as possible. Most people learn early in life to display socially appropriate responses, and that displaying an inappropriate social response or no response, could lead a person to become socially alienated. For example, schizophrenia patients with flat affect (FA+) have deficits in processing emotions displayed by others, which likely relates to their poor social adaptation and functioning (19,20,21). Descriptively, flat affect refers to an absent, constricted, unvarying and sometimes unrelated or inappropriate affect. In this vein, patients exhibit an expressionless face, unvarying, monotonous voice, they are socially withdrawn, lack spontaneity and indifferent to the surrounding (19). Interestingly, in a recent preliminary report done by our group, we demonstrated no significant difference between schizophrenia patients without flat affect (FA-) and normal controls in processing emotions (22).

Hypothesis : socio-emotional resonance through a mirror system

The central hypothesis we focus on in this study is that while passively viewing pictures with negative emotional content, requiring neural activation of the prefrontal cortex (orbitofrontal, mesial prefrontal and anterior cingulate cortices (OMACC) (23,24,25,26,27,28), schizophrenia patients FA+ would show relative decreased activity in these brain areas. Conversely, schizophrenia patients without flat affect (FA-) would show significant activation of the same areas. On that account, we propose that the OMACC play a role in emotional resonance between individuals. We suggest that these areas, of the prefrontal cortex, have a similar role to the mirror neuron system demonstrated in primates and humans. A possible role for the mesial prefrontal (MPFC), orbitofrontal (OFC), and anterior cingulate cortices (ACC) in voluntary emotional self-regulation (26,27), social learning (8) and in the internal representation of emotional expressions (7) was previously investigated (for a complete review see 25). Therefore, we used functional magnetic resonance imaging (fMRI) in schizophrenia patients FA+ and FA to detect relative changes of blood flow in these cortical areas.

METHODS AND MATERIALS

Subjects

Fourteen DSM-IV schizophrenia patients with flat affect and eleven without flat affect participated in the study. In the flat affect group the mean age was 27.57 ±8.90, range: 20-46 and in the without flat affect 25.73 ±4.43, range 21-37. All subjects gave written informed consent after a detailed explanation. The local scientific and ethics committees approved the study.

Psychiatric assessment

Psychiatric assessments included the patient version of the Structured Clinical Interview for DSM-IV (SCID), and the Positive and Negative Symptoms Scale (PANSS) (29) (flat affect symptom (FA+=5.50 ±0.76; FA-=1.45 ±0.82, p=0.0001); emotional withdrawal (FA+=5.00 ±1.04; FA-=1.73 ±0.90, p=0.0001)). The Rating Scale for Emotional Blunting (RSEB) (19) (FA+=19.86 ±1.70; FA-=6.00 ±1.41, p=0.0001). Criteria for entry into the study were a diagnosis of DSM-IV schizophrenia, no concomitant axis I or axis II disorder, and no medical or neurological disease. Schizophrenia patients with flat affect had a score higher then 17 and schizophrenia patients without flat affect had a score lower then 10 on the RSEB. Patients were stabilized on antipsychotic medications: FA+ subjects received: Haloperidol (one subject) 10mg ± 0.0; zuclopentixol (two subjects) 150mg ± 0.0; risperidone (8 subjects) 3.3mg ± 1.4; olanzapine (four subjects) 21.2mg ±

6.2. FA- received: Haloperidol (three subjects) 6.7mg ± 2.9; zuclopentixol (two subjects) 125mg ± 35.0; risperidone (4 subjects) 5.5mg ± 3.5; olanzapine (two subjects) 17.5mg ± 3.5; quetiapine (two subjects) 300mg ± 353.

Experimental setup

Blood oxygen level dependent (BOLD) signal changes were measured during two experimental conditions, i.e., a *Negative condition* and a *Neutral condition*. Negative emotions (disgust, fear, anger, surprise) were induced during functional magnetic resonance imaging (fMRI) brain scanning using negative scenes from 44 colored visual pictures of faces and recollections of unhappy events (e.g., plane crash, snake, spider, shark, angry face, sad face, mutilation, accident, burn victim, dead body, dying man, aimed gun, electric chair). Another series of 44 neutral pictures (e.g., chess, tourist, rocks, boat, leaves, outlet, towel, spoon, mug, basket, fan, iron, shoes, fork, umbrella, lamp, plate, chair) were also presented. The order of presentation was: one block of negative pictures followed by one block of neutral ones (each condition repeated 4 times). All pictures were selected from the International Affective Picture System (IAPS) (30), to be similar in complexity and quality. The two primary dimensions are one of affective valence ranging from pleasant to unpleasant (negative: mean 2.66 ±1.58 versus neutral: mean 5.74 ±1.47), and one of arousal ranging from calm to excited (negative: mean 6.11 ±2.14 versus neutral: mean 2.97 ±2.08).

Both groups of schizophrenia patients (*FA+, n=14; FA-, n=11*) were instructed to react normally to the 88 pictures seen during scanning (that is to allow themselves to become emotional in response to these stimuli). The emotionally negative and neutral conditions corresponded to one functional run, where each picture was presented for a period of 2.88 seconds. Each block lasted 31.68sec. Blocks were separated by resting periods of 14.4s during which subjects viewed a blank cyan screen. Overall, the whole functional run lasted 6.144 min: (8 blocks: 4 negative and 4 neutral; 11 volumes per block; 5 volumes separating each block; each picture was presented for 2.88s). These stimuli have been carefully developed to ascertain how each negative/neutral slide makes an individual feel (i.e., the conscious experience of emotion). To assess the subjective responses of the subjects to the stimuli, immediately at the end of each run, they were asked to rate verbally on a subjective rating scale ranging from 0 (absence of any negative emotional reaction) to 8 (strongest emotion ever felt in one's lifetime) - the average intensity of negative emotions (felt during the viewing of negative IAPS pictures. The exact instruction was: "please rate how you actually felt while watching the pictures inside the fMRI machine".

Image acquisition and analysis

Echoplanar images (EPI) were acquired on a 1.5 Tesla system (Magnetom Vision, Siemens Electric, Erlangen, Germany). Twenty-eight slices (5 mm thick) were acquired every 2.65 s in an inclined axial plane, aligned with the AC-PC axis. These T2* weighted functional images were acquired using an EPI pulse sequence (TE = 44 ms, Flip =

90°,FOV = 215 mm, Matrix = 64 x 64). Following functional scanning, high-resolution data were acquired via a Tl-weighted three-dimensional volume acquisition obtained using a gradient echo pulse sequence (TE = 44 ms, Flip = 12° FOV = 250 mm, Matrix = 256 x 256). Data were analyzed using Statistical Parametric Mapping software (SPM99, Wellcome Department of Cognitive Neurology, London, UK). Images for all subjects were realigned to correct for artifacts due to small head movements. The gradient-recalled echo-planar sequence that we used is associated with large static magnetic field inhomogeneities commonly found near air/tissue interfaces (31). These inhomogeneities can create artifacts like signal loss and voxel shifts in the ventral frontal, medial temporal, and inferior temporal regions (32). To correct for such artifacts, a mask was applied to the slices of the mean EPI image which presented signal loss. This procedure was implemented for every subject. The images for all subjects were then spatially normalized (voxel size: 3 mm x 3 mm x 3 mm) into an MRI stereotactic space (33) using this masked mean image. Images were then convolved in space with a three-dimensional isotropic gaussian kernel (12 mm FWHM) to improve the signal-to-noise ratio and to accommodate for residual variations in functional neuroanatomy that usually persist between subjects after spatial normalization. For the statistical analysis, the time series of the images were convolved with the delayed box-car function which approximates the activation patterns. Effects at each and every voxel were estimated using the general linear model. Voxel values for the contrasts of interest yielded a statistical parametric map of the t statistic (SPM *t*), subsequently transformed to the unit normal distribution, (SPM Z).

A multisubject analysis was performed by using a random-effects approach, which takes into account intersubject variance permitting population-level inferences (34). Statistical parametric maps were generated by using the general linear model within SPM (35). First, the signal time course for each subject was modeled with a boxcar function convolved with a hemodynamic response function and hi-pass filtering. Each of the negative or neutral IAPS conditions was contrasted with each other and the baseline condition, thereby creating one contrast image per subject for each condition. These images were entered into a "one-sample *t* test" to investigate the significant activation during each condition. Significant signal changes for each contrast were assessed using *t* statistics on a voxel-by-voxel basis (34). The resulting areas of activation were characterized in terms of their peak height and spatial extent. Second, for the group analysis, within-group t tests were performed on subtractions of beta weights contrasting two conditions at each voxel. Subtractions were negative emotional activation minus the neutral condition (each block seperatly). Voxels showing significantly greater response were examined in the group contrasts between patients with flat affect and patients without. Both "patients FA+ minus patients FA-" and the opposite contrasts were performed.

An à priori search strategy was used, and a small volume correction was performed in the brain regions of interest (ROI) defined à priori. The search volume corresponding to the ROIs was defined à priori by tracing the neuroanatomic boundaries of these regions on the MR reference image (Montreal Neurological Institute (MNI) template), using small volume

correction (SVC) and box volume function in SPM99. For this à priori search, a probability threshold for multiple comparison of a corrected $P<0.05$ was used. Only clusters showing a spatial extent of at least five contiguous voxels were kept for image analysis. In the negative condition, the à priori search strategy encompassed the mesial frontal cortex, the orbitofrontal cortex, and the anterior cingulate cortex. These brain regions have been found activated on a more or less consistent basis in previous functional neuroimaging studies of emotions (as noted in the introduction).

RESULTS

Subjective ratings

Post-scan ratings (t-tests) of negative emotional feelings experienced during the scan revealed a group effect on the mean subjective ratings of negative emotions felt during the passive viewing of the negative pictures. On a scale of 0 to 8, the FA+ group averaged 1.00 ± 1.52, range: 0-5 and the FA- 5.9 ±1.22, range: 3-7 ($t=-8.71$, $df=23$, $p<0.0001$).

fMRI Data: Subtraction Approach

In the present study we concentrate on frontal lobe (MPFC, OFC, ACC) activations associated with emotion representation. Other activations will not be dealt with here, as our à priori hypothesis focused on potential changes of brain activity in prefrontal areas.

The "random-effects model (FA+ minus FA-) for negative minus neutral pictures did not reveal any significant locus of activation in the prefrontal cortex. Conversely, the FA- group showed significant loci of activation in the left ACC (BA 32) (coordinates of maximum = (-3, 16, 37); z= 4.62; $p \leq 0.002$, corrected; 68 voxels); the right OFC (BA 47) (coordinates of maximum = (45, 23, -6); z= 4.34; $p \leq 0.005$, corrected; 26 voxels); and the left MPFC (BA 10) (coordinates of maximum = (-3, 56, 17); z= 3.56; $p \leq 0.01$, corrected; 14 voxels).

Figure 1

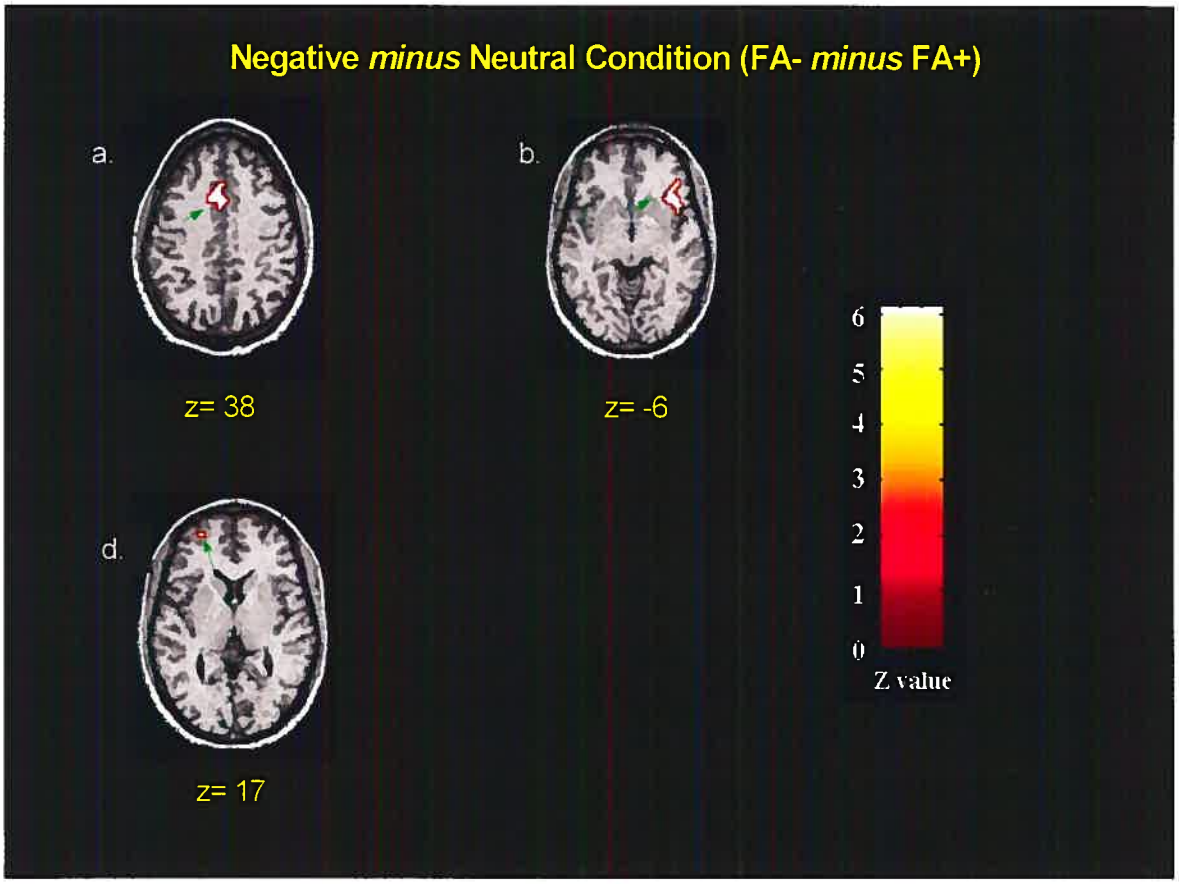


Figure 1. Cortical anatomy of emotional resonance. Significant increases of BOLD activation during passive viewing of the contrast negative minus neutral pictures. (a) activation in the left ACC (BA 32) (coordinates of maximum = (-3, 16, 38); z= 4.62; $p \leq 0.002$, corrected; 68 voxels); (b) the right OFC (BA 47) (coordinates of maximum = (45, 23, -6); z= 4.34; $p \leq 0.005$, corrected; 26 voxels) and (c) the left MPFC (BA 10)) (coordinates of maximum = (-3, 56, 17); z= 3.56; $p \leq 0.01$, corrected; 14 voxels).

fMRI Data: A Posteriori Correlational Analyses: Brain activation and self-report ratings

Correlational analyses were conducted between self-report ratings and BOLD signal increases found in the ROIs. These analyses revealed the existence of positive correlations in the left ACC (coordinates of maximum = (-6, 30, 35); $z= 3.81$; $p\leq0.001$, uncorrected; 21 voxels), the right OFC (BA 47) (coordinates of maximum = (42, 23, -9); $z= 3.66$; $p\leq0.001$, uncorrected; 5 voxels), and the left MPFC (coordinates of maximum = (-9, 53, 8); $z= 3.52$; $p\leq0.001$ uncorrected, 5 voxels). These results confirm the robustness and validity of our findings.

DISCUSSION

The aim of the present study was to use information about brain function to draw inferences about the mechanisms supporting emotional resonance in two different groups of schizophrenia patients. In this sense, it represents one example of a growing trend towards using neuroscience methods to address questions that traditionally have been of interest to social and personality psychologists. What is the function of a mirror-system? One possible function could be to internally reproduce the same action, thus creating a resonance behavior, which is at the basis of the understanding of actions made by others. Hence, humans may use mirror-system for more complicated social interactions (e.g., understanding others' emotions and intentions). In this article, we discussed this hypothesis using two groups of schizophrenia patients with and without flat affect. Noteworthy, in a previous study by our group (22), we did not find a significant difference between FA- patients and normal controls in processing emotions. The results of this study support our hypothesis on the role of OMACC mirror-system for representing emotions displayed in the pictures, thus making the FA- group feel them (as a result of the resonance behavior). This interpretation is supported by four facts. First, loci of activation of these areas were found only in the FA- group. Second, the positive correlation found between the subjective rating score and these areas. Third, inactivation of the same areas in the schizophrenia group FA+. Fourth, the latter group scored less on the subjective rating score and we found.

The above finding is very intriguing. Its interpretation, however, is not straightforward. In this study, we treated negative emotions as a single, unified entity. Recent literature has clearly shown that different emotions seem related to different neural systems. For example, disgust seems to activate preferentially the anterior insula (36), whereas fear seems to activate preferentially the amygdala (37,25), and sadness seems to activate the orbitofrontal cortex (22, 26, 27). We adopted this approach because our main goal was to investigate the negative emotional resonance through a mirror-system in the prefrontal cortex. Future studies may successfully employ further paradigms exploring the differential neural correlates of each emotional mirror-system. Furthermore, outstanding questions remain. First, is mirror-neuron activity innate or learned? Second, do they have a role in imitation and the theory of mind? Third, how do mirror-neurons relate to other social information processing neurons in performing social cognitive functions (e.g., remembering a sad event)? It is perhaps valuable at this point to ask why the prefrontal cortex? Both lesion and functional imaging studies in humans (38,25), as well as neurophysiological studies in nonhuman primates (39), demonstrate the importance of the prefrontal cortex in "representing" the emotional value of environmental stimuli. Of particular relevance to this study, Kawasaki and colleagues (40) investigated single-neuron responses to emotional stimuli in an awake person with normal intellect. Using recording from neurons within healthy tissue in ventral sites of the right prefrontal cortex, they found short-latency (120-160 ms) responses selective for aversive visual stimuli (IAPS pictures: same pictures shown in our study, see methods).

Furthermore, the authors argued that regions of the mesial aspects of the frontal cortex seem especially important in relating information about external sensory stimuli to introceptive information that represents emotional significance.

Where did the idea of "emotional-resonance" come from?

The results of this study were predicted on the basis of three models. The first is the evidence found by. Fadiga and colleagues (9). Using transcranial magnetic stimulation (TMS) experiments, the authors demonstrated that the human equivalent matching system facilitates in the observer the same muscle groups as those utilized by the target. This supports the idea that even when one is observing the action of another, one undergoes a neural event that triggers actual movement in the observed agent. The point is that mirror-neurons activity is not mere theoretical inference. It creates in the observer a state that matches that of the target. The second model is mirror neurons and the simulation theory of mind-reading (for a review please refer to 2), which suggests that subjects use their own mental mechanisms to calculate, attribute and predict both, the mental processes of others and environmental stimuli. Of relevance, the example used in this study: rating negative emotions felt during the scanning session. Hence, according to the simulation theory, each subject would have put himself in each of the pictures 'shoes' and imagined how he would have felt in their place (41). Overall, the simulation theory depicts 'mind-reading' as incorporating an attempt to replicate, mimic, or impersonate the mental life of the target

agent (42). The third model is resonance behaviors and mirror neurons (for a complete review see 5).

At the neurophysiological level, this model suggests that resonance behavior is characterized by the occurrence, at the observation of environmental stimuli, of a neural pattern, which, when internally generated, determines the making (feeling) of the observed action. In this type of resonance behavior the observed action is, typically, not repeated (overtly), but for example felt. This model argues that this resonance behavior is at the basis of the understanding of actions made by others. Furthermore, clinical evidence for a mirror system in humans is found in 'imitation behavior' (43). A group of patients with prefrontal lesions compulsively imitate gestures or even complex actions performed by the experimenter. This behavior is explained as an impairment of the inhibitory control normally governing motor plans. Hence, normal humans, when observing someone else perform an action, generate a plan to do the same action, conversely, this plan is inhibited so that it does not yield motor output. Such inhibition is impaired in the patient population in question. In addition, in a recent review by Williams and colleagues (44), the authors proposed that some dysfunction in the mirror-neuron system might be implicated in the generation of the constellation of clinical features which constitute the autistic syndrome, especially, socioemotional functions.

The most basic hypothesis for the dysfunction seen in the FA+ group would be that there is a failure or distortion in the development of the mirror neuron system. This could be due to genetic or other endogenous causes, to external conditions adverse to MN functioning, or some interaction between these. Such factors might have affected prefrontal cortex MN involved in emotional resonance. This in turn could explain the failure to develop reciprocal social abilities including emotion recognition.

Why some schizophrenia patients have flat affect?

Emotional experience occurs through a number of steps: activation of the mechanism of emotional recognition, comparing it to previous knowledge, representation of the emotion and finally the decision of transmitting this emotional representation to key brain areas involved in the experience emotion. Therefore, a process of emotion recognition and representation results in this representation becoming a trigger for the mechanism deciding upon the emotional experience. By requiring patients to passively view negative pictures, we create a situation in which patients will either have to choose an active response (i.e., be involved in the experience of negative emotions) or an avoidant response (deny/suppress experiencing negative emotions). Persistent recurrence of unwanted, upsetting thoughts, such as a history of childhood emotional invalidation (i.e., psychological abuse and parental punishment, minimization, and distress in response to negative emotion) or abuse and adult psychological distress could result in chronic emotional inhibition (45, 46, 47). Kraus et al. (48) demonstrated that individuals who recollect a pervasive history of emotional

invalidation in childhood are more likely to report the use of strategies designed to avoid or inhibit the experience and expression of emotion as an adult. Furthermore, Eisenberg, Cumberland and Spinard (49) reported that chronic emotional inhibition have long-term negative consequences for the inhibitor, such as avoidant regulatory strategies, absent, constricted, unvarying and sometimes unrelated or inappropriate affect and social withdrawal.

Going one step further, we could suggest that emotional numbing or flat affect could be the result of a long time (chronic) withholding of emotional expression. Based on our findings, we don't know if this emotional inhibition refers to conscious or subconscious attempts to suppress emotional experience, a possibility that awaits further experimental analyses. However, we do know that the emotional information was not transmitted from the midbrain to the prefrontal cortex. The most direct interpretation of this finding is that the schizophrenia patients FA+ "chose" the avoidant coping strategy: a response style in which the emotional impact of negative emotions is denied. This seems to be a simple observation, but it might reflect the operation of fundamentally different mechanisms. An alternative explanation might be that FA+ are not inhibiting emotional experience, but unable to mentally represent it in the first place. The appropriately developing child initially recognize and represents his own emotions through parental and social interactions (45). If this process is disturbed, then the mental representation and of his own and others' emotions is also disturbed.

Major theories of emotional development (50,51) suggest that young children acquire their emotional understanding from social interactions. Hence, they are highly vigilant to the emotional states displayed by caregivers and often use such affect displays as a way to cope with ambiguous or stressful situations (52). Such theories would also assert that if parents, in particular, are emotionally unavailable during stressful situations due to problems with emotion regulation, then children may ultimately develop coping styles that lead to avoidance of emotional experience.

Overall, our findings fit well with previously published imaging data on observation of emotional stimuli that report activation of the prefrontal cortex (for a review, see 25). We propose that negative emotional resonance induced by passively viewing negative pictures may be a form of "mirroring" that grounds negative feelings via an experiential mechanism providing a potential bridge between minds "standing in others mental shoes". If our proposal gains further empirical support, this may suggest important new avenues for both cognitive and pharmacological remediative strategies especially tailored to the prefrontal cortex pharmacology.

REFERENCES

1. Gallese, V., Goldman, A. Mirror neurons and the simulation theory of mind-reading. Trends Cogn Sci 1998; 2(12):493-501.
2. Gallese, V., Faddiga, L., Fogassi, L., Rizzolatti, G. Action recognition in the premotor cortex. Brain 1996;119:593-609.
3. Rizzolatti, G., Fogassi, L., Gallese V. Neurophysiological mechanisms underlying the understanding and imitation of action. Nat Rev Neurosci 2001; 2:661-670.
4. Rizzolatti, G., Fadiga, L., Matelli, M., et al. Localisation of grasp representation in humans by PET-1: observation vs execution. Exp Brain Res 1996; 111:246-252.
5. Rizzolatti, G., Fadiga, L., Fogassi, L., Gallese, V. Resonance behaviors and mirror neurons. Arch Ital Biol 1999; 137(2-3):85-100.
6. Umilta, M. A., Kohler, E., Gallese, V., Fogassi, L., Fadiga, L., Keysers, C., Rizzolatti, G. I know what you are doing. a neurophysiological study. Neuron 2001; 31(1):155-65.
7. Arbib, M. A., Billard, A., Iacoboni, M., Oztop, E. Synthetic brain imaging: grasping, mirror neurons and imitation. Neural Netw 2000; 13(8-9):975-97.
8. Carr, L., Iacoboni, M., Dubeau, M. C., Mazziotta, J. C., Lenzi, G. L. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. ProcNatl Acad Sci U S A 2001;100(9):5497-5502.

9. Fadiga, L., Fogassi, L., Pavesi, G. Motor facilitation during action observation: a magnetic stimulation study. J Neurophysiol 1995; 73:2608-2611.

10. Decety, J., Michel, F. Comparative analysis of actual and mental movements times in two graphic tasks. Brain Cogn 1989;11:87-97.

11. Jeannerod, M., Frak, V. Mental imaging of motor activity in humans. Curr Opin Neurobiol 1999; 9(6):735-739.

12. Gerardin, E., Sirigu, A., Lehericy, S., et al. Partially overlapping neural networks for real and imagined hand movements. Cereb Cortex 2000;10(11):1093-1104.

13. Decety, J., Jeannerod, M., Germain, M., Pastene, J. Vegetative response during imagined movement is proportional to mental effort. Behav Brain Res 1991; 3:1-5.

14. Fadiga, L., Craighero, L., Buccino, G., Rizzolatti, G. Speech listening specifically modulates the excitability of tongue muscles: a TMS study. Eur J Neurosci 2002;15(2):399-402.

15. Buccino, G., Binkofski, F., Fink, G. et al. Action observation activates premotor and parietal areas in a somatotopic manner. an fMRI study. Eur J Neurosci 2001; 13(2):400-404.

16. Chartrand, T. L., Bargh, J. A. The chameleon effect: the perception-behavior link and social interaction. J Pers Soc Psychol 1999; 76:893-910.

17. Hatfield, E., Caciopoo, J. T., Rapson, R. L. Emotional contagion. New York: Cambridge University Press, 1994.

18. Surakka, V., Hietnanen, J. K. Facial and emotional reactions to Duchenne and non-Duchene Smiles. Int J Psychophysiol 1998; 29:23-33.

19. Abrams, R., Taylor, M. A. A rating scale for emotional blunting. Am J Psychiatry 1978; 135: 226-229.

20. Pogue-Geile, M. F., Harrow, M. Negative symptoms in schizophrenia: Their longitudinal course and prognostic importance. Schizophr Bull 1985; 11:427-439.

21. Breier, A., Schreiber, J. L., Dyer, J., Pickar, D. National Institute of Mental Health longitudinal study of chronic schizophrenia: Prognosis and predictors of outcome. Arch Gen Psychiatry 1991; 48:239-246.

22. Fahim, C., Stip, E., Leroux, J. M., Boualem, M., Beaudoin, G. Cerebral mechanisms involved in implicit emotional processing in schizophrenia patients without flat affect and normal controls: a functional magnetic resonance imaging approach. Brain Cogn 2003; 51:193-195.

23. Price, J. L., Carmichael, S. T., Drevets, W. C. Networks related to the orbital and medial prefrontal cortex: A substrate for emotional behavior. Prog Brain Res 1996; 106:523-536.

24. Damasio, A. R., Grabowski, T. J., Bechara, A., et al. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nat Neurosci 2000; 3(10):1049-1056.

25. Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 2002; 16:331-348.

26. Beauregard, M., Levesque, J., & Bourgouin, P. Neural correlates of conscious self-regulation of emotion. J Neurosci 2003; 21:1-6.

27. Levesque, J., Eugene, F., Joanette, Y., et al. Neural circuitry underlying voluntary suppression of sadness. Biol Psychiatry 2003; 53:502-510.

28. Phillips, M. L. Understanding the neurobiology of emotion perception: implications for psychiatry. Br J Psychiatry 2003; 182:190-192.

29. Kay, SR., Opler, LA., Fiszbein, A. Manuel de cotation de la PANSS. 1986. traduction française LépineJP, 1988.

30. Lang, PJ., Öhman, A., Vaitl, D. The International Affective Picture System (photographic slides). Gainesville: Center for Research in Psychophysiology, University of Florida; 1988.

31. Cordes, D., Turski, PA,, Sorenson, JA.: Compensation of susceptibility-induced signal loss in echo-planar imaging for functional applications. Magn Reson Imaging 2000; 18:1055-1068.

32. Song, AW. Single-shot EPI with signal recovery from the susceptibility-induced losses. Magn Reson Med 2001; 46:407-411.

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

34. Friston, K. J., Frackowiak, R. S. Images of the future: a philosophical coda. In: R.S.J. Frackowiak, R.J Friston., et al. Eds.). Human brain function. San Diego, CA: Academic Press, 1997: 487-517.

35. Friston, K. J., Holmes, A. P., Price, C. J., Buchel, C. Worsely, K. J. Multisubject fMRI studies and conjunction analyses. Neuroimage, 1999; 10:385-396.

36. Phillips, M. L., Young, A. W., Senior, C. A specific neural substrate for perceiving facial expressions of disgust. Nat 1997; 389: 495-498.

37. Phillips, M. L., Young, A. W., Scott, S. K. Neural responses to facial and vocal expressions of fear and disgust. Proc R Soc Lond B Biol Sci 1998; 265(1408):1809-1817.

38. Damasio A R. (1994). Descartes' Error: Emotion, Reason, and the Human Brain. New York: Grosset/Putnam.

39. Rolls E T. The Brain and Emotion. New York: Oxford University Press, 1999.

40. Kawasaki, H., Kaufman, O., Damasio, H., et al. Single-neuron responses to emotional visual stimuli recorded in human ventral prefrontal cortex. Nat Neurosci 2001; 4(1):15-16.

41. Davis, M., Stone, T. Mental Simulation, Blackwell, 1995.

42. Goldman, A. In defence of the simulation theory. Mind Lang 1992; 7:104-119.

43. Lhermitte, F., Pillon, B., Serdaru, M. Human autonomy and the frontal lobes: I. imitation and utilization behavior: a neuropsychological study of 75 patients. Ann Neurol 1986; 19:326-334.

44. Williams, J., Whiten, A., Suddendorf, T., Perrett, D. Imitation, mirror neurons and autism. Neurosci Biobehav Rev 2001; 25:287-295.

45. Creasey, G., Ottlinger, K., Devico, K., Murray, T., Harvey, A., Hesson-McInnis, M. Children's affective responses, cognitive appraisals, and coping strategies in response to the negative affect of parents and peers. J Exp Child Psychol 1997; 67(1):39-56.

46. Harvey, A. G., Bryant, R. A. The effect of attempted thought suppression in acute stress disorder. Behav Res Ther 1998;36(6):583-590.

47. Purdon C. Thought suppression and psychopathology. Behav Res Ther 1999; 37(11):1029-54.

48. Krause, E. D., Mendelson, T., Lynch, T. R. Childhood emotional invalidation and adult psychological distress: the mediating role of emotional inhibition. Child Abuse Negl 2003; 27(2):199-213.

49. Eisenberg, N., Fabes, R. A., Schaller, M., Carlo, G., Miller, P. A. The relations of parental characteristics and practices to children's vicarious emotional responding. Child Dev 1991; 62(6):1393-1408.

50. Bowlby, J. Attachment and loss: Vol.1. Attachment (2nd ed.). New York: Basic, 1982.

51. Bretherton, I. The origins of attachment theory: John Bowlby and Mary Ainsworth. Dev Psychol 1992; 28:759-775.

52. Ainsworth, M., Blehar, M., Waters, E., Wall, S. Patterns of attachment: A psychological study of the strange situation. Hillsdale, New Jersey: Erlbaum, 1978.

Brain activity during emotionally negative pictures in schizophrenia with and without flat affect: An fMRI study

Cherine Fahim[1,3], Emmanuel Stip[2,3,5], Adham Mancini-Marïe[2,3], Boualem Mensour[5], Luc J Boulay[3], Jean-Maxime Leroux[5], Gilles Beaudoin[5,6], Pierre Bourgouin[5,6] and Mario Beauregard [1, 4, 6,7,8].

1- Department of Neurological Sciences, Faculty of medicine, University of Montreal.

2- Department of Psychiatry, Faculty of medicine, University of Montreal.

3- Centre de Recherche Fernand-Séguin, Hôpital Louis-Hippolyte Lafontaine.

4- Centre de Recherche, Institut universitaire de gériatrie de Montréal (CRIUGM).

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

6- Department of Radiology, Faculty of medicine, University of Montreal.

7- Department of Psychology, University of Montreal.

8- Centre de Recherche en Neuropsychologie Expérimentale et Cognition (CERNEC), Université de Montréal.

Correspondence should be addressed to: Emmanuel Stip, Centre de Recherche Fernand-Séguin, Hôpital Louis-Hippolyte Lafontaine. 7331 rue Hochelaga, Montréal, Québec, Canada H1N 3V2. Tel. (514) 251-4015, Fax (514) 251-2617, [redacted] : [redacted]

Abstract

The aim of this functional magnetic resonance imaging (fMRI) study was to compare regional brain activity in schizophrenia subjects with (FA+) and without (FA-) flat affect during the viewing of emotionally negative pictures. Thirteen FA+ subjects and eleven FA- subjects were scanned while being presented with series of emotionally negative and neutral pictures. Experientially, the viewing of the negative pictures induced a negative emotional state whose intensity was significantly greater in the FA- group than in the FA+ group. Neurally, the Negative minus Neutral contrast revealed, in the FA- group, significant loci of activation in the midbrain, pons, anterior cingulate cortex, insula, ventrolateral orbitofrontal cortex, anterior temporal pole, amygdala, medial prefrontal cortex, and extrastriate visual cortex. In the FA+ group, this contrast produced significant loci of activation in the midbrain, pons, anterior temporal pole, and extrastriate visual cortex. When the brain activity measured in the FA+ group was subtracted from that measured in the FA- group, only the lingual gyrus was significantly activated. Perhaps in FA+ subjects an amygdaloid malfunction rendered the amygdala unable to correctly evaluate the emotional meaning of the pictures presented, thus preventing effective connectivity linking the amygdala to the brain regions implicated in the physiological and experiential dimensions of emotion. Alternatively, a disturbance of effective connectivity in the neural networks linking the midbrain and the medial prefrontal system was maybe responsible for the quasi absence of emotional reaction in FA+ subjects, and the abnormal functioning of the medial prefrontal cortex and anterior cingulate cortex in the FA+ group.

Key Words: Schizophrenia, emotions, flat affect, functional magnetic resonance imaging.

1. Introduction

Although emotional blunting (also called "flat affect") has always been considered a core symptom of schizophrenia (Bleuler, 1911), it has been excluded from diagnostic criteria because of its alleged unreliability until 1978 when Abrams and Taylor developed the Rating Scale for Emotional Blunting (RSEB). These authors reviewed the literature for clinical descriptions of emotional blunting, starting with Pinel (1801) and ending with Kraepelin (1919). These descriptions included items such as lack of emotional depth, silly laughing, shallow emotional response, emotional dullness, absence of feelings and indifference towards relatives and friends. Abrams and Taylor (1978) organized these descriptions under three headings relating to affect, thought content and behavior.

Interpersonal behavioral studies using naturalistic behavioral measures of social functioning have shown that schizophrenia is associated with reduced facial expression during social interaction (Kause et al., 1989), diminished expressiveness in response to emotional films (Berenbaum and Oltmanns, 1992), and difficulties in everyday social experiences resulting from poor conversational skills and impairments in emotional

nonverbal expressiveness (i.e., body gestures, facial expression) (Alpert et al., 2000, 2002; Kohler et al., 2000; Mattes et al., 1995; Sweet et al., 1998). Furthermore, negative symptoms in schizophrenia are associated with difficulties in everyday social experiences, including fewer social contacts, poor work quality, lower scores on global assessments of functioning, and less ability to meet individual needs (Pogue-Geile et al., 1985; Breier et al., 1991). In line with this, electromyography (EMG) studies (Iwase et al., 1999; Kring et al., 1999; Sison et al., 1996) have shown that flatness of affect was associated, in schizophrenia, with less zygomatic (cheek) activity and reduced ability to express happy facial expressions, such as smiling. Moreover, Bryson and colleagues (1998) reported that patients with negative symptoms are especially subject to difficulties in correctly identifying and expressing the emotional content of both faces and scenes. In another study, Volz and collaborators (2003) investigated the temporal course of startle reflex modulation to emotional pictures in schizophrenia subjects and normal controls. Participants viewed pleasant, neutral and unpleasant pictures, which were presented for 6 s and acoustic startle probes were delivered at five different times after picture onset. Replicating previous findings schizophrenia subjects showed the same emotional modulation of the startle reflex as healthy controls when probes were presented later during the picture-viewing period (3800 ms). For the early probe times (300 ms and 800 ms), emotionally-laden pictures proved to be the effective pre-pulse stimuli resulting in a clear pre-pulse inhibition (PPI) effect in both groups. In contrast to previous findings, the PPI of startle response was not stronger during processing of emotional stimuli relative to neutral stimuli.

For control subjects, blink reflexes were larger for unpleasant pictures compared with neutral and pleasant pictures, representing an early activation of the motivational system. Volz and colleagues (2003) concluded that if it takes longer for the emotional system to encode the relevant information, it takes longer for the behavioral adjustment to occur in response to this encoding process. Since facial expression changes very quickly in response to different emotional stimuli, a deficit in encoding the emotional content of a cue might disturb an appropriate facial response to emotional stimuli.

There is mounting evidence that brain regions implicated in emotion processing/experience may be dysfunctional in individuals with schizophrenia. Using positron emission tomography (PET), Potkin and colleagues (2002) demonstrated lower glucose metabolic rate in the fusiform area in schizophrenia subjects with predominantly negative symptoms. Crespo-Facorro et al., (2001) demonstrated with PET that, relative to healthy volunteers, schizophrenia failed to activate limbic/paralimbic regions during the experience of unpleasant odors. Along the same lines, Paradiso and colleagues (2003) measured regional cerebral blood flow (rCBF) during performance of a task that required schizophrenia subjects and healthy volunteers to identify the emotional valence of visual images. When schizophrenia subjects consciously evaluated the unpleasant images, they did not activate the amygdala, unlike the healthy volunteers. Likewise, schizophrenia patients showed no activation in prefrontal cortical areas normally involved in the

evaluation of the emotional significance of visual stimuli. Paradiso and co-workers (2003) concluded that this failure of the neural systems implicated in emotional attribution is consistent with pervading problems in experiencing emotions by schizophrenia subjects. In another PET study, Schneider et al., (1998) found that unlike normal controls, schizophrenia did not show amygdala activation during sadness, despite matched ratings to normal controls indicating a comparable negative affect. More recently, Gur and colleagues (2002) showed in the left hemisphere a significantly greater blood-oxygen-level-dependent (BOLD) amygdalar signal increase in control subjects than in schizophrenia subjects during emotional valence discrimination tasks. Lastly, Takahashi et al. (2004) used functional magnetic resonance imaging (fMRI) to investigate the neural basis of impaired emotional processing in schizophrenia. Normal control and schizophrenia subjects were instructed to indicate how each of the presented pictures made them feel. In normal controls, BOLD signal increases were noted in the thalamus, basal ganglia, midbrain, hippocampal formation, amygdala, medial prefrontal cortex (MPFC), visual cortex and the cerebellum while viewing unpleasant pictures. In schizophrenia subjects, less activation was found in these brain regions.

Worth mentioning, in an elegant study by Stark and colleagues (2004), subjective and haemodynamic responses towards negative IAPS pictures (Lang et al., 1988) were investigated using fMRI. Within an interval of one week, 24 male subjects were scanned

twice in order to analyze possible response changes to repeated picture presentation (the same pictures were presented). Interestingly, during the retest the affective ratings hardly changed. However, most of the previously observed brain activations disappeared, with the exception of the temporo-occipital activation. The stability of the visual cortex activation over time suggests that the visual cortex is a very important component of the processing of emotional stimuli visually presented.

Explanatory models of flat affect have proposed various etiologies, invoking psychodynamic processes such as repression (Arieti, 1955) or emphasizing the role of impaired social relations and social rejection (Pao, 1979). More recently, it has been proposed that this negative symptom reflects a dysfunction in the right hemisphere (Mayer et al., 1985). This stance is based on clinical neuropsychological evidence obtained in individuals with cortical lesions located in the right hemisphere (Dolan, 1999; Critchley et al., 2001). These individuals show inappropriate emotional responses that are strikingly similar to those seen in schizophrenia with flat affect. It has also been postulated that emotional disturbances in schizophrenia results from a dysfunction of the medial prefrontal and anterior cingulate cortices (Weinberger, 1987; Mega et al 2001; Gur et al 2002). However, these studies did not differentiate between schizophrenia subjects with and without flat affect. Various lines of evidence indicate that these prefrontal cortical regions, which are heavily connected with limbic structures (e.g., hypothalamus and amygdala),

play a pivotal role in emotion processing (Beauregard et al., 2004). Of particular note, these prefrontal areas have been consistently seen activated during the induction of transient emotional states in healthy individuals (for a review see Phan et al., 2002).

The aim of the current fMRI study was to compare regional brain activity in schizophrenia subjects with (FA+) and without (FA-) flat affect during the viewing of emotionally negative pictures. Experientially, we hypothesized that the viewing of the negative pictures would induce a greater negative emotional state in the FA- group compared to the FA+ group. Neurally, we predicted that, relative to the FA+ subjects, the FA- subjects would show significantly greater BOLD signal increases in the brain regions normally associated with emotion processing (midbrain, amygdala, MPFC, etc.) during the viewing of such stimuli.

2. Methods

2.1. Subjects

Thirteen FA+ subjects and eleven FA- subjects participated in the study. In the FA+ group, the mean age was 27.57 ±8.90 years (range: 20-46) whereas in the FA- group, the mean age was 25.73 ±4.43 years (range 21-37). In the FA+ group, the age of onset of schizophrenia was 22.07 ±4.5 years while in the FA- group, this age was 21.27 ±2.72 years.

The level of education was comparable in both groups of subjects (FA+ group: 10.50 ±3.65 years; FA- group: 10.36 ±2.58 years) (p=0.92). All subjects gave written informed consent after a detailed explanation. The local scientific and ethics committees (Hôpital Louis-Hippolyte Lafontaine and Centre hospitalier de l'Université de Montréal, Hôpital Notre-Dame) approved the study.

2.2. Psychiatric assessments

Subjects were investigated using the patient version of the Structured Clinical Interview for DSM-IV (1994), the Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1986), the Rating Scale for Emotional Blunting (RSEB) (Abrams and Taylor, 1978) and the Calgary Depression Rating Scale (CDS) (Addington et al., 1990) (Table 1). Criteria for entry into the study were a diagnosis of schizophrenia (based on the DSM-IV), no concomitant axis I or axis II disorder, and no medical or neurological disease. On the RSEB, FA- subjects had a score higher than 17 and FA+ subjects had a score lower than 10. Subjects were stabilized with various types of antipsychotic medications. Some of the subjects received two antipsychotic drugs. Thus, in the FA+ group, subjects received Haloperidol (one subject, 10 mg ± 0.0), Zuclopentixol (two subjects, 150 mg ± 0.0), Risperidone (8 subjects, 3.3 mg ± 1.4), Olanzapine (four subjects, 21.2 mg ± 6.2). In the FA- group, subjects received Haloperidol (three subjects, 6.7 mg ± 2.9), Zuclopentixol (two subjects, 125 mg ± 35.0), Risperidone (4 subjects, 5.5 mg ± 3.5), Olanzapine (two subjects, 17.5 mg ± 3.5), and/or Quetiapine (two subjects, 300 mg ± 353). Using SPSS we have

conducted a two-tailed independent sample t-test and found no significant difference (t= 1.74; df= 23; p≤0.17) between the two groups in dose equivalent estimation to 100 mg/day of chlorpromazine (Woods, 2003).

Table 1. Results of psychiatric assessment tests

	Mean score and SD FA+	Mean score and SD FA-	p value
RSEB	19.86 ±1.70	6.00 ±1.41	0.0001
PANSS: Blunted affect	5.50 ±0.76	1.45 ±0.82	0.0001
PANSS: Emotional withdrawal	5.00 ±1.04	1.73 ±0.90	0.0001
PANSS: positive symptoms	3.09 ±1.38	3.23 ±1.31	0.56
PANSS: negative symptoms	4.48 ±1.04	2.05 ±0.95	0.02
PANSS:general psychopathology	3.06 ±1.24	2.53 ±1.08	0.33
PANSS: total	3.40 ±1.23	2.59 ±1.10	0.31
CDRS	6.7 ±4.53	4.1 ±3.71	0.12

Table 1. CDRS: Calgary Depression Rating Scale; PANSS: Positive and Negative Symptoms Scale; RSEB: Rating Scale for Emotional Blunting.

2.3. Behavioral Procedures

BOLD signal changes were measured during two experimental conditions, i.e., a *Negative condition* and a *Neutral condition*. During the Negative condition, a series of 44 emotionally-laden negative pictures (e.g., plane crash, snake, spider, shark, angry face, sad face, mutilation, accident, burn victim, dead body, dying man, aimed gun, electric chair, etc.) were presented to the subjects whereas in the Neutral condition, subjects saw a series of 44 emotionally neutral pictures (e.g., tourist, rocks, boat, leaves, outlet, towel, spoon, mug, basket, fan, iron, shoes, fork, umbrella, lamp, plate, chair, etc.). The two categories of pictures were selected from the International Affective Picture System (IAPS, Lang et al 1988). They were matched as much as possible in terms of visual complexity. The mean valence was 2.66 ± 1.58 for the negative pictures and 5.74 ± 1.47 for the neutral pictures. The mean arousal level was 6.11 ± 2.14 for the negative pictures and 2.97 ± 2.08 for the neutral pictures. These mean valence and arousal scores are based on the valence and arousal ratings from Lang's normative groups. During the functional scan, four blocks of negative pictures and four blocks of neutral pictures were presented to the subjects in an alternating manner (negative, neutral, negative, neutral, negative, neutral, negative, neutral). Each picture was presented for a period of 2.88 s and each block – which lasted 31.68 sec - comprised 11 pictures. Blocks were separated by resting periods of 14.4 sec, during which subjects viewed a blank cyan screen. Subjects were instructed to look carefully at each of the 88 pictures presented to them during the run. To assess the

subjective responses of the subjects to the stimuli, immediately at the end of the run, subjects were asked to rate verbally on a subjective rating scale ranging from 0 (absence of any emotional reaction) to 8 (strongest emotional reaction ever felt in one's lifetime) the intensity of emotional reaction felt during the viewing of the negative pictures.

2.4. Image acquisition and Analysis

Echoplanar images (EPI) were acquired on a 1.5 Tesla system (Magnetom Vision, Siemens Electric, Erlangen, Germany). Twenty-eight slices (5 mm thick) were acquired every 2.65 s in an inclined axial plane, aligned with the AC-PC axis. These T2* weighted functional images were acquired using an EPI pulse sequence (Echo-space time = 0.8 ms, TE = 44 ms, Flip = 90°, FOV = 215 mm, Matrix = 64 x 64, Voxel size = 3.36 mm X 3.36 mm X 5 mm). Following functional scanning, high-resolution data were acquired via a Tl-weighted three-dimensional volume acquisition obtained using a gradient echo pulse sequence (TE = 44 ms, Flip = 12° FOV = 250 mm, Matrix = 256 x 256, Voxel size = 0.94 mm^3).

Data were analyzed using Statistical Parametric Mapping software (SPM99, Wellcome Department of Cognitive Neurology, London, UK). Images for all subjects were realigned to correct for artifacts due to small head movements. The gradient-recalled echo-planar sequence that we used is associated with large static magnetic field inhomogeneities commonly found near air/tissue interfaces (Cordes et al., 2000). These inhomogeneities can

create artifacts like signal loss and voxel shifts in the ventral frontal, medial temporal, and inferior temporal regions (Song et al., 2001). To correct for such artifacts, a mask was applied to the slices of the mean EPI image, which presented signal loss. This procedure was implemented for every subject. The images for all subjects were then spatially normalized into an MRI stereotactic space (Talairach and Tournoux, 1988) using this masked mean image. Images were then convolved in space with a three-dimensional isotropic gaussian kernel (12 mm FWHM) to improve the signal-to-noise ratio and to accommodate for residual variations in functional neuroanatomy that usually persist between subjects after spatial normalization.

For the statistical analysis, the time series of the images were convolved with the delayed box-car function which approximates the activation patterns. Effects at each and every voxel were estimated using the general linear model. Voxel values for the contrasts of interest yielded a statistical parametric map of the t statistic (SPM *t*), subsequently transformed to the unit normal distribution, (SPM Z).

A "fixed-effects model" was implemented to contrast the brain activity associated with the viewing of the negative pictures and that associated with the viewing of the emotionally neutral pictures (Negative minus Neutral). This "fixed-effects model" produced individual contrast images, which were used as raw data for the implementation of a "random-effects model". This procedure, which estimates the error variance for each

condition across the subjects, allows one to make inferences on the population which participants are deemed representative (Friston and Frackowiack, 1997). Contrast images were obtained from single-subject analysis and were entered into the group analysis. A one-sample *t* test was applied to determine group activation for the Negative minus Neutral contrast. Significant clusters of activation were determined using the conjoint expected probability distribution of the height and extent of *z* scores with the height and extent threshold. Only clusters showing a spatial extent of at least five contiguous voxels were kept for image analysis. In addition, we tested for relative differences in the pattern of neural activation by subtracting the Negative minus Neutral contrast of the FA+ group from that of the FA- group and vice versa. Between-group comparisons were performed with a two-sample *t* test. Coordinates of activation were converted from MNI coordinates to Talairach and Tournoux (1988) coordinates using the mni2tal algorithm (M. Brett, Cambridge, MA). Contrast images were overlaid onto a group mean anatomy image provided by SPM for viewing.

An à priori search strategy was used, and a small volume correction was performed in the brain regions of interest (ROI) defined à priori. The search volume corresponding to the ROIs was defined à priori, using small volume correction (SVC) and box volume function in SPM99, and based on the neuroanatomic boundaries of these regions noted in the MR reference image (Montreal Neurological Institute (MNI) template) and the Talairach and Tournoux (1988) atlas. For this à priori search, a probability threshold for multiple

comparison of a corrected $P<0.05$ was used. Only clusters showing a spatial extent of at least five contiguous voxels were kept for image analysis. The à priori search strategy encompassed the orbitofrontal cortex (OFC, Brodmann area (BA)47; box-center situated at 30,28,-16mm bilaterally; box-volume=44,25,16; and, BA 11; box-center situated at 25,42.5,-20 mm bilaterally; box-volume=44,45,16), the anterior cingulate cortex (ACC BA32; box-center situated at 4.5,22.5,29mm bilaterally; box-volume=13,40,53; and, BA 24; box-center situated at 4,9.5,20.5 mm bilaterally; box-volume=2,51,49), the medial prefrontal cortex (MPFC BA10; box-center situated at 2.5,50,22mm bilaterally; box-volume=5,10,32; and, BA 9; box-center situated at 2.5,42.5,25.5 mm bilaterally; box-volume=5,5,19), the anterior temporal pole (ATP BA21; box-center situated at 56,-23.5,-2mm bilaterally; box-volume=8,10,19; and, ATP BA38; box-center situated at 40,10,-22mm bilaterally; box-volume=20,12,34), the insula (box-center situated at 39,-2,-6mm bilaterally; box-volume=4,32,2), the amygdala (box-center situated at 21,-2,-14mm bilaterally; box-volume= 8,10,11), the pons (box-center situated at 0,-22.5,-33.5mm; box-volume=32,25,29), and the midbrain (box-center situated at 6.5,8,-6.5mm bilaterally; box-volume=10,25,12). These brain regions have been found activated on a more or less consistent basis in previous functional neuroimaging studies of aversive emotional states (for a complete review please refer to Phan et al., 2002). In addition to our à priori ROIs, we have also investigated differential activity in the visual cortex between the two groups because of its involvement in emotional perception (Lang et al., 1998; Stark et al., 2004).

3. Results

3.1. Self-Report Data

Experientially, the viewing of the negative pictures induced a negative emotional state whose intensity was significantly greater in the FA- group (5.9 ± 1.22, range: 3-7) than in the FA+ group (1.00 ± 1.52, range: 0-5) ($t = -8.71$, $df = 23$, $p<0.0001$).

3.2. fMRI Data: Subtraction Approach (Negative minus Neutral contrast)

FA- group. The Negative minus Neutral contrast revealed significant loci of activation in the midbrain, bilaterally, as well as in the right pons, left ACC (BA 32), left insula, left OFC (BA 47), left ATP (BA 38), left amygdala, and right MPFC; BA 10). Other loci of activation were found in the left lingual gyrus (LG, BA 17/18), left superior occipital gyrus (GOS, BA 19), right cuneus, right inferior temporal gyrus (GTI, BA 37), and left fusiform gyrus (FG, BA 37) (Table 2 and Figure 1).

Table 2. Stereotaxic coordinates are derived from the human atlas of Talairach and Tournoux (1988) and refer to medial - lateral position (x) relative to medline (positive = right), anterior - posterior position (y) relative to the anterior commissure (positive = anterior), and superior – inferior position (z) relative to the commissural line (positive = superior). Designation of Brodmann areas for cortical areas are also based on this atlas. ACC: anterior cingulate cortex, ATP: anterior temporal pole, GOS: superior occipital gyrus, GTI: inferior temporal gyrus, LG: lingual gyrus, MPFC: medial prefrontal cortex, OFC: orbitofrontal cortex. L, left; R, right.

Table 2. Regional brain activity in FA- subjects (Negative minus Neutral)

Brain region	Brodmann Area	Talairach Coordinates (mm) x	y	z	Number of voxels	Z Statistic	Corrected p value
L LG	17/18	-12	-88	-8	48	5.44	0.001
L GOS	19	-24	-72	17	12	5.23	0.004
R cuneus		15	-87	10	10	5.07	0.01
R GTI	37	47	-50	-15	9	4.95	0.01
L ACC	32	-8	16	37	22	4.13	0.01
L Insula		-36	8	-13	12	4.11	0.01
L ATP	38	-45	8	-23	13	4.04	0.01
L OFC	47	-39	19	-19	12	3.49	0.01
R Midbrain		12	-24	-15	32	4.02	0.01
L Amygdala		-25	-7	-11	9	3.72	0.003
R MPFC	10	3	56	19	7	3.57	0.01
L Midbrain		-12	-26	-9	32	3.17	0.01
R pons		9	-23	-29	6	3.17	0.01

Figure 1

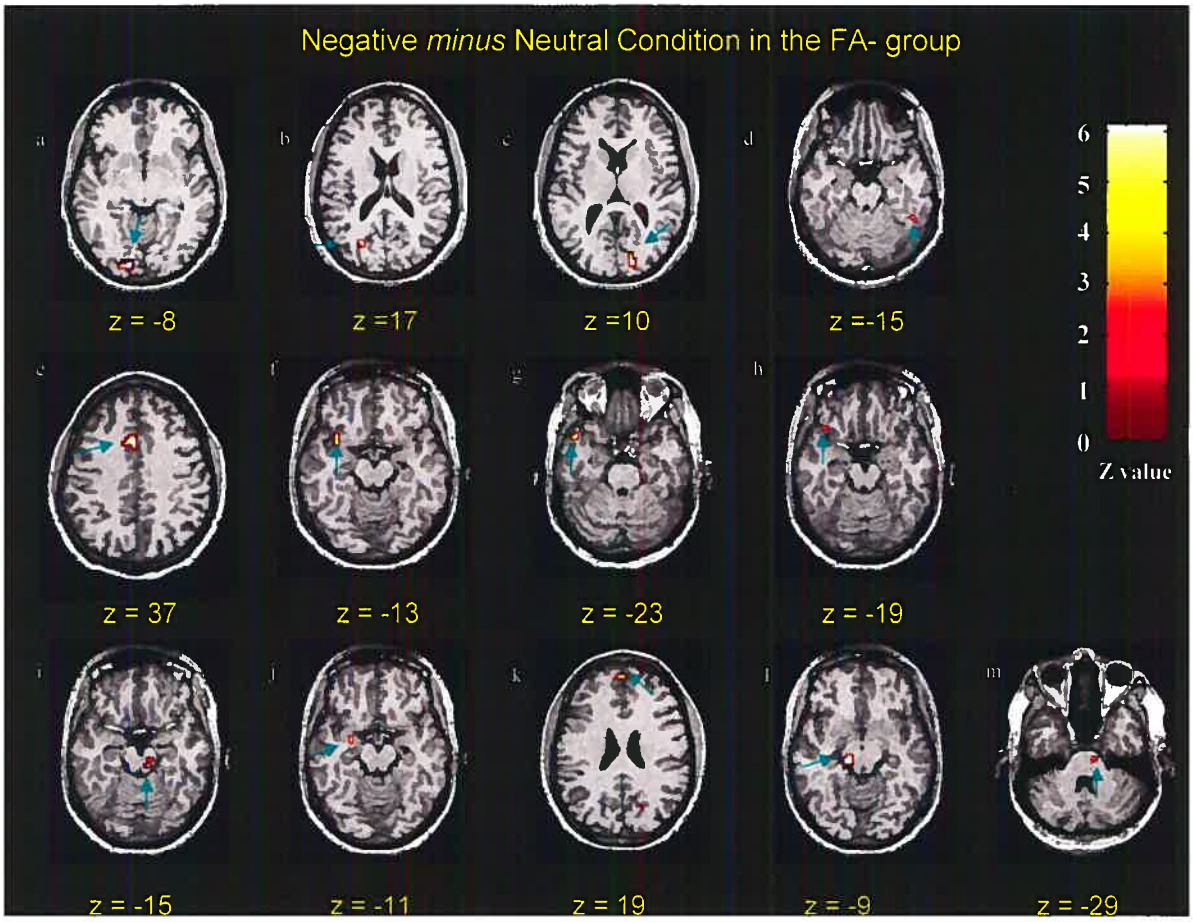


Figure 1. Statistical activation maps in the FA- group for the Negative minus Neutral contrast: (a) left LG (BA 17/18; z= 5.44, p≤0.001 corrected), (b) left GOS (BA 19; z= 5.23, p≤0.004 corrected), (c) right cuneus (z= 5.07, p≤0.01 corrected), (d) right GTI (BA 37; z= 4.95, p≤0.01 corrected), (e) left ACC (BA 32; z= 4.13, p≤0.01 corrected), (f) left insula (z=4.11, p≤0.01 corrected), (g) left ATP (BA 21; z=4.04, p≤0.01 corrected), (h) left OFC (BA 47; z=3.49, p≤0.01 corrected), (i) right midbrain (z=4.02, p≤0.01 corrected), (j) left

amygdala (z=3.72, p≤0.003 corrected), (k) right MPFC (BA 10; z=3.57, p≤0.01 corrected), (l) left midbrain (z=3.17, p≤0.01 corrected), and (m) right pons (z=3.17, p≤0.01 corrected). ACC: anterior cingulate cortex, ATP: anterior temporal pole, GOS: superior occipital gyrus, GTI: inferior temporal gyrus, LG: lingual gyrus, MPFC: medial prefrontal cortex, OFC: orbitofrontal cortex.

FA+ group. Significant loci of activation were noted in the midbrain, bilaterally, right pons, right ATP (BA 21), right middle occipital gyrus (GOM, BA 19), and left LG (BA 19) (Table 3 and Figure 2).

Figure 2

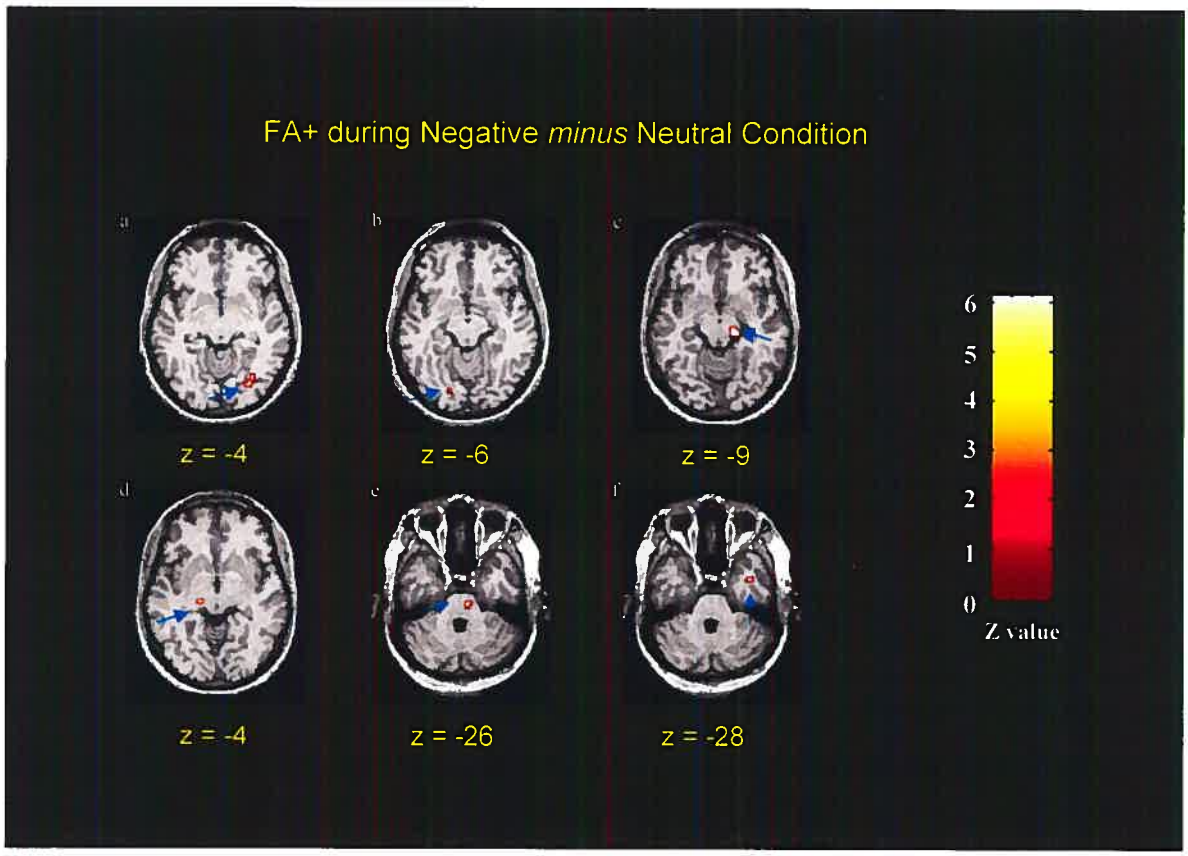


Figure 2. Statistical activation maps in the FA+ group for the Negative minus Neutral contrast: (a) right GOM (BA 19; z= 5.84, p≤0.001 corrected), (b) left LG (BA 19; z= 5.21, p≤0.005 corrected), (c) right midbrain (z=4.03, p≤0.003 corrected), (d) left midbrain (z=3.67, p≤0.01 corrected), (e) right pons (z=3.61, p≤0.03 corrected), and (f) right ATP (BA 21; z=3.22, p≤0.03 corrected). ATP: anterior temporal pole, GOM: middle occipital gyrus, LG: lingual gyrus.

Table 3. Regional brain activity in FA+ subjects (Negative minus Neutral)

Brain region	Brodmann Area	Talairach Coordinates (mm) x	y	z	Number of voxels	Z Statistic	Corrected p value
R GOM	19	45	-73	-4	16	5.84	0.001
L LG	19	-18	-82	-6	10	5.21	0.005
Right midbrain		18	-21	-9	33	4.03	0.003
Left midbrain		-18	-24	-4	10	3.67	0.01
Right pons		12	-33	-26	19	3.61	0.03
R ATP	21	42	-4	-28	12	3.22	0.03

Table 3. As in Table 2. ATP: anterior temporal pole, GOM: middle occipital gyrus, LG: lingual gyrus. L, left; R, right.

FA- group minus FA+ group. Significant loci of activation were detected in the left ACC (BA 32), right OFC (BA 47), left ATP (BA 21), left MPFC (BA 10), and left FG (BA 36) (Table 4 and Figure 3).

FA+ group minus FA- group. A significant locus of activation was detected in the left LG (BA 19) (Table 4 and Figure 3).

Table 4. FA- group minus FA+ group and FA+ group minus FA- group (Negative minus Neutral)

Brain region	Brodmann area	Talairach Coordinates (mm) x	y	z	Number of voxels	Z Statistic	Corrected p value
	FA- minus FA+						
L FG	36	-32	-7	-22	95	4.63	0.007
L ACC	32	-3	16	38	68	4.62	0.02
R OFC	47	45	23	-6	26	4.34	0.05
L ATP	21	-53	-6	-12	17	4.18	0.01
L MPFC	10	-26	55	1	12	3.94	0.01
Schizophrenia patients FA+ *minus* FA-, contrast = negative *minus* neutral							
L LG	19	-12	-73	-6	19	2.92	0.009

Table 4. As in Table 2. ACC: anterior cingulate cortex, ATP: anterior temporal pole, FG: fusiform gyrus, LG: lingual gyrus, OFC: orbitofrontal cortex. L, left; R, right.

Figure 3

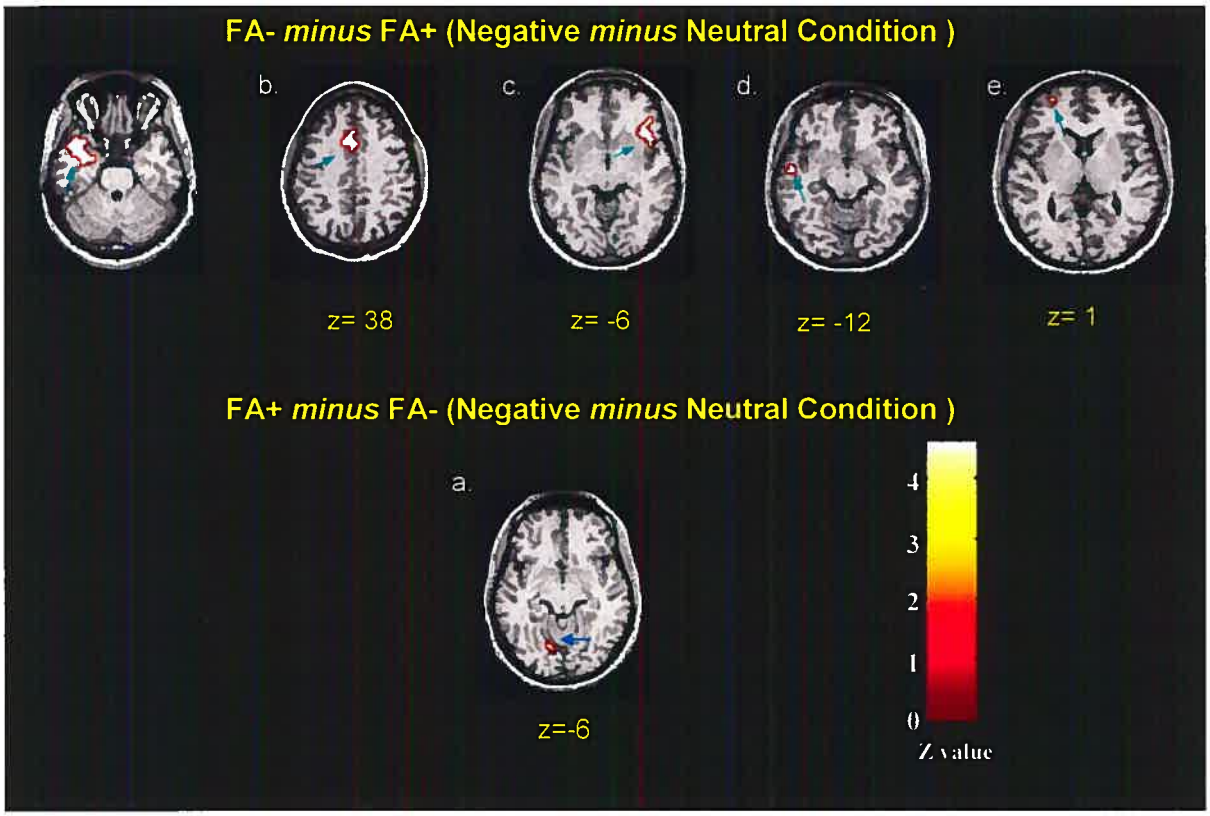


Figure 3. Statistical activation maps produced by the FA- group minus FA+ group contrast and the FA+ group minus FA- group contrast. FA- group minus FA+ group: (a) left FG(BA 36) (coordinates of maximum = (36, -32, -7); z= 4.63; p≤0.007, corrected; 95 voxels)), (b) left ACC (BA 32) (coordinates of maximum = (-3, 16, 38); z= 4.62; p≤0.002, corrected; 68 voxels); (c) the right OFC (BA 47) (coordinates of maximum = (45, 23, -6); z= 4.34; p≤0.005, corrected; 26 voxels); (d) the left ATP (BA 21) (coordinates of maximum = (-53, -6, -12); z= 4.18; p≤0.01, corrected; 17 voxels), and (e) the left MPFC (BA 10)

(coordinates of maximum = (-26, 55, 1); z= 3.94; p≤0.01, corrected; 12 voxels). FA+ group minus FA- group: (a) left LG (BA 19) (coordinates of maximum = (-12, -73, -6); z= 2.92; p≤0.009, corrected; 19 voxels). ACC: anterior cingulate cortex, ATP: anterior temporal pole, FG: fusiform gyrus, LG: lingual gyrus, MPFC: medial prefrontal cortex, OFC: orbitofrontal cortex.

3.3. fMRI Data: A Posteriori Correlational Analyses

Using the effect size - which represents the percent signal change of the BOLD response - at the regional maxima uncovered in the between-group comparisons, we analyzed whether the BOLD signal changes were correlated with the self-report rating scores using the simple regression function in SPM99. These analyses revealed, in the FA- group, the existence of a positive correlation between scores associated to viewing the negative pictures and magnitude of activation in the left ACC (BA 32; coordinates of maximum = (-6, 30, 35); z= 3.81; p≤0.001, uncorrected; 21 voxels).

4. Discussion

The present study was undertaken to compare regional brain activity in schizophrenia with (FA+) and without (FA-) flat affect during the viewing of emotionally negative pictures. In keeping with our hypotheses, experientially the viewing of the negative pictures induced a greater negative emotional state in the FA- group compared to the FA+ group. Neurally, relative to FA+ subjects, FA- subjects showed significantly greater BOLD signal increases in limbic/paralimbic brain regions during the viewing of the negative pictures.

The loci of activation noted, in both groups of subjects, in the various subdivisions of the visual cortex are consistent with the role of this cortical region in the early visual processing of emotional stimuli (Kee et al., 1998; Lang et al., 1998; Stark et al., 2004). Adolphs (2002) proposed that presentation of an affectively laden stimulus triggers an initial feed-forward information processing along occipital and temporal neocortices which leads to a coarse categorization of affect within the first 100 ms. Likewise, Streit and colleagues (1999) demonstrated that in healthy males the neural processes related to the evaluation of facial expressions of emotions start at about 180 ms after stimulus onset in occipitotemporal brain regions spreading rapidly along the ventral visual pathway and limbic structures to the inferior frontal areas. Of particular relevance to our study, Bradley and colleagues (2003) found, using fMRI, that functional activation in the occipital cortex was more extensive when normal participants view pictures strongly related to primary

motive states (i.e., victims of violent death, viewer-directed threat, and erotica). This functional activity was greater than that observed for less intense emotional (i.e., happy families or angry faces) or neutral images (i.e., household objects, neutral faces). Both the extent and strength of functional activity were related to the judged affective arousal of the different picture contents.

In the macaque, the extrastriate cortical visual areas project to the ipsilateral dorsolateral region of the pontine nuclei (Glickstein et al., 1990). In squirrel monkeys (Tigges et al., 1982), the extrastriate visual cortex sends projections to the pontine reticular formation and the midbrain reticular formation. Some evidence suggests that the midbrain and pons are involved in the mediation of autonomic responses such as skin conductance responses (Sequeira et al., 1995) and body temperature changes (Nagashima et al., 2000). The midbrain has been found activated in several functional neuroimaging studies of diverse emotional states (e.g., disgust, sadness, anger, fear, anxiety) (Damasio et al., 2000; Fredrikson et al., 1995; Lane et al., 1997a; Lévesque et al., 2003; Rauch et al., 1997). Given that autonomic responses often accompany the autonomic experience of primary emotions (Damasio et al., 2000), the bilateral midbrain activation noted here may be related to the autonomic responses associated with the perceptual processing of the negative pictures.

The ventrolateral part of the OFC (BA 47) has been found activated during external and/or internal induction of negative emotional states (e.g., sadness, anxiety, anger) (Beauregard et al., 1998; Damasio et al., 2000; Dougherty et al., 1999; Pardo et al., 1993; Fredrikson et al., 1995; George et al., 1995; Kimbrell et al., 1999; Lévesque et al., 2003; Pelletier et al., 2003). In view of the sensory inputs (olfactory, gustatory, visceral afferent, somatic sensory, and visual) as well as the limbic inputs that this cortical region receives from the amygdala, entorhinal and perirhinal cortex, and subiculum (Price, 1999), it appears conceivable that the activation of BA 47 in FA- subjects during the viewing of the negative pictures was related to the integration of viscerosensory information with information signaling changes in the subjects' emotional state.

The positive correlation found in FA- subjects between average ratings of negative emotion and BOLD signal increases in the rostral portion of the ACC is in line with the positive correlation previously reported in healthy subjects between the magnitude of sad feelings (externally induced by sad film excerpts) and that of BOLD signal increases in the same part of the ACC (Lévesque et al., 2003). This finding supports the view that the rostral subdivision of the ACC plays a pivotal role in the interoceptive and exteroceptive detection of emotional signals (Lane et al., 1997b).

The MPFC has been reported to be activated in several previous functional neuroimaging studies of negative emotional states (e.g., sadness, disgust) (Beauregard et al., 1998; Damasio et al., 2000; George et al., 1995; Lane et al., 1997a; Reiman et al., 1997). This prefrontal cortical region receives sensory information from the body and the external environment via the orbitofrontal cortex and is heavily interconnected with limbic structures, such as the amygdala, hypothalamus, midbrain periaqueductal gray region, and brainstem autonomic nuclei (Barbas, 1993; Carmichael and Price, 1995). It is noteworthy that a region of the MPFC close to that identified in this study has previously been postulated to be implicated in metacognitive representation of one's own emotional state (Lane. 2000; Reiman et al., 1997). In keeping with this, studies of individuals with damage to the MPFC suggest that this cortical area is involved in the conscious monitoring of the individual's emotional state (Damasio, 1995). In this context, it thus seems plausible that the MPFC activation noted here in FA- subjects related to reflective conscious awareness of the emotional state induced by viewing the negative pictures.

Given the rich interconnection of the insula with regions involved in autonomic regulation (Cechetto, 1994), we posit that the insular activation seen in FA- subjects during the viewing of the negative pictures may be a neural correlate of the autonomic changes associated with the subjective experience of a negative emotion. With respect to the ATP,

activity of this cortical region have been reported during a variety of negative emotional states (e.g., sadness, anger, and anxiety) (Chua et al., 1999; Damasio et al 2000; Dougherty et al., 1999; Kimbrell et al., 1999; Lane et al., 1997a; Lévesque et al 2003; Reiman et al., 1989). This paralimbic region receives inputs from unimodal and heteromodal sensory regions, as well as limbic inputs. In keeping with the conclusions derived from various lines of evidence regarding the anterior temporal pole (Mesulam, 1985), we propose that anterior temporopolar seen in the FA- group was associated with imparting affective tone to the subjects' experience.

The amygdala activation noted in FA- subjects is consistent with the results obtained in previous PET (Schneider et al., 1995; Lane et al., 1997a; Reiman et al., 1997; Blair et al., 1999) and fMRI (Lévesque et al., 2003; Schneider et al., 1997; Whalen et al., 1998) studies of negative emotions. The results of these functional neuroimaging studies combined to various evidence from experimental lesion studies in animals and clinical neuropsychology in humans strongly suggest that the amygdala is involved in the evaluation of the emotional significance of stimuli detected in the external environment (for a review, see Lane, 2000). In the present context, it seems likely that the amygdala activation measured in the FA- group during the viewing of the negative pictures was related to the appraisal process of these stimuli.

It has been postulated (Mayer et al., 1985) that flat affect in schizophrenia reflects a dysfunction in the right hemisphere. About hemispheric dominance for emotional processes, Davidson (1984) suggested that the prefrontal regions of the left and right hemispheres are specialized for approach (positive emotion) and withdrawal (negative emotion) processes, respectively. The results of the present fMRI study firmly stand against this view since they suggest that the diverse emotion processes recruited, during the viewing of emotionally negative pictures, are neurally instantiated by cerebral structures located not only in the right hemisphere but in the left hemisphere as well. In line with our results, Wager et al., (2003) recently performed a quantitative meta-analysis on 65 functional neuroimaging studies of emotion. They found no support for the hypothesis of overall right-lateralization of emotional function, and very limited support for valence-specific lateralization of emotional activity in the prefrontal cortex. This meta-analysis clearly demonstrated that lateralization of emotional activity is much more complex than predicted by previous theories about the neural bases of emotion.

A malfunction of the amygdala may be responsible for the reduced emotional expressiveness seen in some schizophrenias in response to emotionally-laden visual stimuli (Berenbaum and Oltmanns, 1992), and the difficulty of schizophrenia subjects with flat affect to identify the emotional valence of visual images (Gur et al., 2002; Paradiso et al.,

2003). The diminished emotional response found here in the FA+ subjects may also be related to such a malfunction. It is possible that this malfunction rendered the amygdala unable to correctly evaluate the emotional meaning of the pictures presented. Perhaps this disturbance prevented effective connectivity linking the amygdala to the brain regions implicated in the physiological dimension of emotion, such as the midbrain, the insula, and the ventrolateral portion of the OFC (BA 47). Likewise, from an experiential perspective, maybe this defect disturbed effective connectivity in the neural networks connecting the amygdala to the ATP, ACC, and MPFC.

It has also been proposed that flatness of affect in schizophrenia results from a dysfunction of the MPFC and ACC (Weinberger, 1987; Mega et al., 2001; Gur et al., 2002). In line with theses hypotheses, the results of the quantitative comparison between the FA+ and FA- groups provide support to the view that flatness of affect in schizophrenia is related to an abnormal functioning of several limbic/paralimbic brain regions normally implicated in various dimensions of emotion. Since the midbrain was activated in both groups during the viewing of the negative pictures, it is likely that the perceptual processing of these stimuli also led to an autonomic response in the FA+ subjects. Perhaps a disturbance of effective connectivity in the neural networks linking the midbrain and the medial prefrontal system (which encompasses the OFC and ACC) (Ongur et al., 1998) –

which is involved in self-awareness of emotion (Damasio, 1995; Reiman et al 1997; Lane, 2000) - was responsible for the abnormal functioning of the MPFC (BA 10) and ACC (BA 32), and the quasi absence of emotional reaction in FA+ subjects.

Lastly, we would like to acknowledge some of the limitations of this study. First, the sample size of our groups was relatively small. Second, no objective measures were performed to characterize the subjects' emotional state. Instead, self-report ratings were used. Self-report data are extremely susceptible to bias. Hence, a more objective measure would have definitely bolstered the results of this study. Third, the AB block design without permutation of the conditions restricts the interpretation of the present findings. Possibly, the expectation of the next block could influence the brain activation pattern of the present one. Fourth, no effective connectivity analyses were conducted between the amygdala or midbrain and other limbic/paralimbic brain regions. Given these limitations, our results should be considered as preliminary and awaiting independent replication.

Acknowledgements: This work was supported by the Fonds de la recherche en santé du Québec (FRSQ) to E.S. and by a doctoral studentship from AstraZeneca pharmaceuticals to the first author. We thank Dr. Pierre Lalonde and all the subjects who participated in the study, and the staff of the Département de radiologie, Centre Hospitalier de l'Université de Montréal (CHUM), Hôpital Notre-Dame, for their helpful technical assistance.

References

[1] Abrams, R., Taylor, M.A., 1978. A rating scale for emotional blunting. American Journal of Psychiatry 135, 226-229.

[2] Addington, D., Addington, J., Schissel, B., 1990. A depression rating scale for Schizophrenias. Schizophrenia Research 3(4), 247-251.

[3] Adolphs, R., 2002. Neural systems for recognizing emotion. Current Opinion in Neurobiology 12, 169-177.

[4] Alpert, M., Rosenberg, S., Pouget, E., Shaw, R., 2000. Prosody and lexical accuracy in flat affect schizophrenia. Psychiatry Research 97, 107-118.

[5] Alpert, M., Shaw, R.J., Pouget, E.R., Lim, K.O., 2002. A comparison of clinical ratings with vocal acoustic measures of flat affect and alogia. Psychiatry Research 36(5), 347-53.

[6] American Psychiatric Association. 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Press.

[7] Arieti, S., 1955. Interpretation of schizophrenia. Robert Brunner. New York, NY.

[8] Barbas, H., 1993. Organization of cortical afferent input to the orbitofrontal area in the rhesus monkey. Neuroscience 56, 841-864.

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

[10] Beauregard, M., LÈvesque, J., Paquette, V., 2004. Neural Basis of Conscious and Voluntary Self- Regulation of Emotion. In: Consciousness, Emotional Self-Regulation and the Brain (M. Beauregard, Ed.). John Benjamins Publishing.

[11] Berenbaum, H., Oltmanns, T.F., 1992. Emotional experience and expression in schizophrenia and depression. Journal of Abnormal Psychology 101, 37-44.

[12] Blair, R.J., Morris, J.S., Frith, C.D., Perrett, D.I., Dolan, R.J., 1999. Dissociable neural responses to facial expressions of sadness and anger. Brain 122, 883-93.

[13] Bleuler, E., 1950. Dementia Praecox or the group of schizophrenias (J. Zinkin, Trans.). New York: International Universities Press, (Original work published 1911).

[14] Bradley, M.M., Sabatinelli, D., Lang, P.J., Fitzsimmons, J.R., King, W., Desai, P., 2003. Activation of the visual cortex in motivated attention. Behavioral Neuroscience 117(2), 369-80.

[15] Breier, A., Schreiber, J.L., Dyer, J., Pickar, D., 1991. National Institute of Mental Health longitudinal study of chronic schizophrenia: Prognosis and predictors of outcome. Archives of General Psychiatry 48, 239-246.

[16] Bryson, G., Bell, M., Kaplan, E., Greig, T., Lysaker, P., 1998. Affect recognition in deficit syndrome schizophrenia. Psychiatry Research 77, 113-120.

[17] Carmichael, S.T., Price, J.L., 1995. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. Journal of Comparative Neurology 25, 615-641.

[18] Cechetto, D.F., 1994. Identification of a cortical site for stress-induced cardiovascular dysfunction. Integrative Physiology and Behavioral Sciences 29, 362-73.

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

[20] Cordes, D., Turski, P.A., Sorenson, J.A., 2000. Compensation of susceptibility-induced signal loss in echo-planar imaging for functional applications. Magnetic Resonance Imaging 18, 1055-1068.

[21] Crespo-Facorro, B., Paradiso, S., Andreasen, N.C., O'Leary, D.S., Watkins, G.L., Ponto, L.L., Hichwa, R.D., 2001. Neural mechanisms of anhedonia in schizophrenia: a PET study of response to unpleasant and pleasant odors. The Journal of the Medical Association 286(4), 427-35.

[22] Critchley, H.D., Mathias, C.J., Dolan, R.J., 2001. Neuroanatomical basis for first- and second-order representations of bodily states. Nature Neuroscience 4, 207-12.

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

[24] Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L., Parvizi, J., Hichwa, R.D., 2000. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nature Neuroscience 3(10), 1049-1056.

[25] Davidson, R.J., 1984. Affect, cognition and hemispheric specialization. In C.E. Izard, J. Kagan, & R. Zajonc (Eds.), Emotion, cognition and behaviour. New York: Cambridge University Press.

[26] Dolan, R., 1999. On the neurology of morals. Nature Neuroscience 2(11), 927-9.

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

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

[29] Friston, K.J., Frackowiak, R.S., 1997. Images of the future: a philosophical coda. In human brain function (R.S.J. Frackowiak, R.J Friston., et al. Eds.) San Diego, CA: Academic Press, p 487-517.

[30] George, M.S., Ketter, T.A., Parekh, P.I., Horwitz, B., Herscovitch, P., Post, R.M., 1995. Brain activity during transient sadness and happiness in healthy women. American Journal of Psychiatry 152, 341-51.

[31] Glickstein, M., May, J., Mercier, B., 1990. Visual corticopontine and tectopontine projections in the macaque. Archives of Italian Biology 128(2-4), 273-93.

[32] Gur, R.E., McGrath, C., Chan, R.M., Schroeder, L., Turner, T., Turetsky, B.I., Kohler, C., Alsop, D., Maldjian, J., Ragland, J.D., Gur, R.C., 2002. An fMRI study of facial emotion processing in patients with schizophrenia. American Journal of Psychiatry 159, 1992-1999.

[33] Iwase, M., Yamashita, K., Takahashi, K., Kajimoto, O., Shimizu A., Nishikawa, T., Shinosaki, K., Sugita, Y., Takeda, M., 1999. Diminished facial expression despite the existence of pleasant emotional experience in schizophrenia. Methods and Findings in Experimental and Clinical Pharmacology 21(3), 189-94.

[34] Kause, R., Steimer, E., Sanger-Alt, C., Wagner, G., 1989. Facial expression of schizophrenia patients and their interaction partners. Psychiatry 52, 1-12.

[35] Kay, S.R., Opler, L.A., Fiszbein, A., 1988. Manuel de cotation de la PANSS. Traduction française. Lépine JP.

[36] Kee, K.S., Kern, R.S., Green, M.F., 1998. Perception of emotion and neurocognitive functioning in schizophrenia: whatís the link? Psychiatry Research 81:57-65.

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

[38] Kohler, C., Bilker, W., Hagendoorn, M., Gur, R.E., Gur, R.C., 2000. Emotion recognition deficit in schizophrenia with symptomatology and cognition. Biological Psychiatry 48, 127-136.

[39] Kraepelin, E., 1919. Dementia praecox and paraphrenia (R.M. Barclay, Trans). Edinburgh: Livingstone. Verbal, vocal, and visible factors in judgements of anotherís affect. Journal of Personality and Social Psychology, 40, 312-320.

[40] Kring, A.M., Kerr, S.L., Earnst, K.S., 1999. Schizophrenia patients show facial reactions to emotional facial expressions. Psychophysiology 36(2), 186-92.

[41] Lane, R.D., Reiman, E.M., Ahern, G.L., Schwartz, G.E., Davidson, R.J., 1997a. Neuroanatomical correlates of happiness, sadness, and disgust. American Journal of Psychiatry 154, 926-933.

[42] Lane, R.D., Fink, G.R., Chau, P.M.L., Dolan, R.J., 1997b. Neural activation during selective attention to subjective emotional responses. NeuroReport 8, 3969-3972.

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

[44] Lang, P.J., ÷hman, A., Vaitl, D., 1988. The International Affective Picture System (photographic slides). Gainesville: Center for Research in Psychophysiology, University of Florida.

[45] Lang, P.J., Bradley, M.M., Fitzsimmons, J.R., Cuthbert, B.N., Scott, J.D., Moulder, B., Nangia. V., 1998. Emotional arousal and activation of the visual cortex: an fMRI analysis. Psychophysiology 35(2), 199-210.

[46] Lévesque, J., Eugene, F., Joanette, Y., Paquette, V., Mensour, B., Beaudoin, G., Leroux, J.M., Bourgouin, P., Beauregard, M., 2003. Neural circuitry underlying voluntary suppression of sadness. Biological Psychiatry 53, 502-510.

[47] Mattes, R.M., Schneider, F., Heimann, H., Birbaumer, N., 1995. Reduced emotional response of schizophrenia patients in remission during social interaction. Schizophrenia Research. 17, 249-55.

[48] Mayer, M., Alpert, M., Stastny, P., Perlick, D., Empfield, M., 1985. Multiple contributions to clinical presentation of flat affect in schizophrenia. Schizophrenia Bulletin 11, 420-426.

[49] Nagashima, K., Nakai, S., Tanaka, M., Kanosue, K., 2000. Neuronal circuitries involved in thermoregulation. Autonomic Neuroscience 85(1-3), 18-25.

[50] Mega, M.S., Cummings, J.L., 2001. The frontal lobes and neuropsychiatric illness. Edited by Salloway S., Malloy P., and Duffy J., American Psychiatric Publishing, inc. Washington, DC. London, England. 1st. Edition p 15-32.

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

[52] Ongur, D., An, X., Price, J.L., 1998. Prefrontal cortical projections to the hypothalamus in macaque monkeys. Journal of Comparative Neurology 401, 480-505.

[53] Pao, P.N., 1979. Schizophrenia Disorder: Theory and treatment from a psychodynamic point of view. New York, NY: International Universities Press.

[54] Paradiso, S., Andreasen, N.C., Crespo-Facorro, B., O'Leary, D.S., Watkins, G.L., Boles-Ponto, L.L., Hichwa, R.D., 2003. Emotions in unmedicated patients with schizophrenia during evaluation with positron emission tomography. American Journal of Psychiatry 160(10), 1775-83.

[55] Pardo, J.V., Pardo, P.J., Raichle, M.E., 1993. Neural correlates of self-induced dysphoria. American Journal of Psychiatry 150, 713-9.

[56] Pelletier, M., Bouthillier, A., Carrier, S., Breault, C., LÈvesque, J., Paquette, V., Mensour, B., Leroux, J.M., Beaudoin, G., Bourgouin, P., Beauregard, M., 2003. Separate neural circuits for primary emotions? Brain activity during self-induced sadness and happiness in professional actors. NeuroReport 14, 1111-1116.

[57] Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I., 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 16, 331-348.

[58] Pinel, P., 1801. A treatise on insanity. Translated by David DD. New York, Hafner Publishing Co. 1962, pp 165-166.

[59] Pogue-Geile, M.F., Harrow, M., (1985). Negative symptoms in schizophrenia: Their longitudinal course and prognostic importance. Schizophrenia Bulletin, 11, 427-439.

[60] Potkin, S.G., Alva, G., Fleming, K., Anand, R., Keator, D., Carreon, D., Doo, M., Jin, Y., Wu, J.C., Fallon, J.H., 2002. A PET study of the pathophysiology of negative symptoms in schizophrenia. Positron emission tomography. Amercan Journal of Psychiatry 159(2), 227-37.

[61] Price, J.L., 1999. Prefrontal cortical networks related to visceral function and mood. Annals of the New York Academy of Sciences 877, 383-396.

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

[63] Reiman, E.M., Fusselman, M.J., Fox, P.T., Raichle, M.E., 1989. Neuroanatomical correlates of anticipatory anxiety. Science 243, 1071-4.

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

[65] Schneider, F., Weiss, U., Kessler, C., Salloum, J.B., Posse, S., Grodd, W., Muller-Gartner, H.W., 1998. Differential amygdala activation in schizophrenia during sadness. Schizophrenia Research 34(3), 133-42.

[66] Sequeira, H., FA-M'Hamed, S., Roy, J.C., 1995. Fronto-parietal control of electrodermal activity in the cat. Journal of Autonomic Nervous System 53(2-3), 103-14.

[67] Sison, C.E., Alpert, M., Fudge, R., Stern, R.M., 1996. Constricted expressiveness and psychophysiological reactivity in schizophrenia. Journal of Nervous and Mental Diseases 184(10), 589-97.

[68] Song, A.W., 2001. Single-shot EPI with signal recovery from the susceptibility-induced losses. Magnetic Resonance Medicine 46, 407-411.

[69] Stark, R., Schienle, A., Walter, B., Kirsch, P., Blecker, C., Ott, U., Schafer, A., Sammer, G., Zimmermann, M., Vaitl, D., 2004. Hemodynamic effects of negative emotional pictures - a test-retest analysis. Neuropsychobiology 50(1), 108-18.

[70] Streit, M., Ioannides, A.A., Liu, L., Wolwer, W., Dammers, J., Gross, J., Gaebel, W., Muller-Gartner, H.W., 1999. Neurophysiological correlates of the recognition of facial expressions of emotion as revealed by magnetoencephalography. Brain Research and Cognitive Brain Research 7(4),481-91

[71] Sweet, L., Primeau, M., Fichtner, C., Lutz, G., 1998. Dissociation of affect recognition and mood state from blunting in patients with schizophrenia. Psychiatry Research 81, 301-308.

[72] Takahashi, H., Koeda, M., Oda, K., Matsuda, T., Matsushima, E., Matsuura, M., Asai, K., Okubo, Y., 2004. An fMRI study of differential neural response to affective pictures in schizophrenia. Neuroimage 22(3), 1247-54.

[73] Talairach, J., Tournoux, P., 1988. Co-planar stereotaxic atlas of the human brain, Stuttgart: Thieme Medical.

[74] Tigges, J., Tigges, M., Cross, N.A., McBride, R.L., Letbetter, W.D., Anschel, S., 1982. Subcortical structures projecting to visual cortical areas in squirrel monkey. Journal of Comparative Neurology 209(1), 29-40.

[75] Volz, M., Hamm, A.O., Kirsch, P., Rey, E.R., 2003. Temporal course of emotional startle modulation in schizophrenia patients. International Journal of Psychophysiology 49(2), 123-37.

[76] Wager, T.D., Phan, K.L., Liberzon, I., Taylor, S.F., 2003. Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. Neuroimage 19, 513-31.

[77] Weinberger, D.R., 1987. Implications of normal brain development for the pathogenesis of schizophrenia. Archives of General Psychiatry 44, 660-669.

[78] Whalen, P.J., Rauch, S.L., Etcoff, N.L., McInerney, S.C., Lee, M.B., Jenike, M.A., 1998. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. Journal of Neuroscience 18, 411-8.

[79] Woods, S.W., 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. Journal of Clinical Psychiatry 64(6), 663-7.

Differential haemodynamic brain activity in schizophrenia patients with blunted affect during quetiapine treatment

Cherine Fahim M.Sc[1,3], Emmanuel Stip M.D. M.Sc[2,3,5], Adham Mancini-Marïe M.D[2,3], Boualem Mensour Ph.D[5], and Mario Beauregard Ph.D[1, 4, 6].

1- Department of neurological sciences, faculty of medicine, University of Montreal

2- .Department of psychiatry, faculty of medicine, University of Montreal

3- Centre de Recherche Fernand-Séguin, Hôpital Louis-Hippolyte Lafontaine.

4- Centre de Recherche, Institut universitaire de gériatrie de Montréal (CRIUGM).

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

6- Département de radiologie, Faculté de médecine, Université de Montréal.

Correspondence should be addressed to: Emmanuel Stip, Centre de Recherche Fernand-Seguin, 7331 rue Hochelaga, Montréal (Québec) Canada, H1N 3V2. Tel (514) 251-4015 # 3557; Fax (514) 251-2617; [redacted]

Acknowledgements: This work was supported by AstraZeneca Pharmaceuticals LP and the Fond de la recherche en santé du Québec (FRSQ). We thank all the subjects who participated in the study, and the staff of the Département de radiologie, Centre Hospitalier de l'Université de Montréal (CHUM), Hôpital Notre-Dame, for their skilful technical assistance.

Abstract

Blood-oxygenation-level-dependent (BOLD) brain changes underlying response to quetiapine were examined using passive viewing of emotionally aversive and neutral stimuli. Twelve DSM-IV schizophrenia patients with flat affect/emotional withdrawal (FA+) (positive and negative symptoms scale + rating scale for emotional blunting) were scanned before and after 5.5 months of quetiapine treatment. Whole-brain, voxel-based methods were used to assess response-specific quetiapine effects. A post-hoc comparison to an independent group of 11 schizophrenia patients without flat affect/social withdrawal (FA-) was also performed to interpret the specificity of identified quetiapine effects. A 5.5-month treatment with quetiapine resulted in significant clinical improvement in the 12 study completers (mean ±SD post-treatment PANSS flat affect score of 5.50 ±0.76 at baseline to 2.08 ±1.00 at end point ($t=7.78$, $df=11$, $p<0.0001$). Treatment response was associated with significant BOLD changes both in sub-cortical an cortical structures: increases in prefrontal cortex activation right dorsolateral prefrontal (DLPFC, BA 46) and the right anterior cingulate cortex (ACC, BA 32); left putamen, right anterior temporal pole (ATP) and right amygdala. Conversely, before quetiapine, the same subjects activated only sub-cortical structures: the midbrain bilaterally and the right pons. The post-hoc conjunctional analyses demonstrated that FA- subjects activated the left ACC, left insula, left ATP (BA 21), left ATP (BA 38), left amygdala and right medial prefrontal cortex. Quetiapine seems to affect clinical recovery by modulating the functioning of specific sites from subcortical to cortical regions (i.e., modulating the mesocortical pathway). Unique BOLD changes in the putamen and DLPFC with quetiapine, in the FA+ post-quetiapine, relative to other drugs (used by FA-) may reflect modality-specific effects with implications for understanding mechanisms underlying different treatment mechanisms.

Key words: Schizophrenia, negative symptoms, flat affect, functional magnetic resonance imaging, quetiapine, atypical antipsychotics.

Introduction

Flat affect/emotional withdrawal deficit in schizophrenia is predictive of a number of outcome indices, and pose a significant obstacle to any attempts at social rehabilitation (Kirkpatrick and Buchanan, 1990; Breier et al. 1991; Keltner and Kring, 1998). It also has been shown to be a relatively enduring symptom that generally responds poorly to treatment (Pogue-Geile and Harrow, 1985). This raises the possibility that treatments producing improvements in flat affect might, in turn, prove to have synergistic effects with psychosocial interventions. On a related note, treatment with atypical antipsychotic medications has been reported to improve negative symptoms (Meltzer, 1999; Meltzer et al., 1999). However, most studies have not examined specific negative symptoms (i.e., flat affect) and have not investigated the direct association between changes in a specific negative symptom and brain functioning.

The critical question, in this paper, is whether quetiapine (an AstraZeneca atypical antipsychotic) would have a treatment specific effect on emotion modulation, by modulating the sub-cortical/cortical pathway, in schizophrenia patients with flat affect (FA+) and emotional withdrawal symptoms. As a first step in addressing this issue, this study examines changes in blood oxygenation level dependent (BOLD) activity associated with the passive viewing of aversive pictures. Functional magnetic resonance imaging (fMRI) BOLD response were contrasted post-hoc with those of a previous study done by

our group on schizophrenia patients without flat affect/emotional withdrawal symptoms (FA-) and schizophrenia patients FA+(submitted). Noteworthy, we did not find a significant difference between FA- patients and normal controls in emotion processing (Fahim et al., 2003). Therefore, we measured neural responses in FA+ to aversive (sadness, fear, disgust) emotions compared with neutral expressions. These emotional expressions represent, respectively, displays of social approval, internal distress, and external threat. We did not specifically wish to determine the effect of emotional category or intensity per se on patterns of subcortical and cortical response to these stimuli, since this was beyond the focus of our study.

Studies employing a variety of techniques have highlighted the importance of specific subcortical regions in the response to emotionally salient material (Calder et al., 2001; Davis and Whalen, 2001), namely, the amygdala, ventral striatum (including caudate nucleus, ventral putamen, and globus pallidus), midbrain and pons (Pardo et al., 1993; George et al., 1995; Lane et al., 1997a; Damasio et al., 2000; Beauregard et al., 2001; Levesque et al., 2003). These regions may be involved both in the identification and autonomic generation of emotional states (Phillips et al 2003a). There is also increasing evidence for the role of different regions of ventral and dorsal prefrontal cortex in the modulation, experience an expression of emotional states in response to emotionally salient material (e.g., Beauregard et al., 2001; Levesque et al., 2003). In the current study, these

subcortical, ventral, and dorsal prefrontal regions referred to subsequently as "subcortical and cortical structures", were therefore included as regions of interest (ROIs), and between-group differences in BOLD response within activated clusters located within these regions were examined. Furthermore, the extent to which these findings represent symptom-related activity in schizophrenia patients and the relative magnitude of subcortical and cortical structures' responses to quetiapine are discussed.

Based on the notions that (i) stimuli with strong affective content modulates neural information processing both at the cortical and subcortical levels (Ekman et al., 1994; Kosslyn et al., 1995), (ii) quetiapine modulates the mesocortical pathway, which projects from the midbrain and sends its axons to the limbic cortex (Stahl, 2002), (iii) this pathway is involved in emotion recognition, experience and expression (Lane et al., 1997a; Damasio et al., 2000) we predicted that:

[1] Pre-quetiapine: schizophrenia patients with flat affect would demonstrate an enhanced response only in subcortical regions.

[2] Post-quetiapine: schizophrenia patients with flat affect would demonstrate significant activity both within cortical and subcortical regions.

[3] When using a conjunctional analysis (post-hoc) schizophrenia patients with flat affect post-quetiapine would not significantly differ from schizophrenia patients without flat affect: both groups would reveal subcortical and cortical activation.

Materials and Methods

Subjects

Twelve FA+ subjects (3 women/9 men) participated in the study. The Mean age was 27.6 ± 8.9 years (range: 20-46) and the Mean level of education 10.4 ± 4.0. The average age of onset of schizophrenia was 22.3 ± 4.9. All subjects gave written informed consent after a detailed explanation, and the study was approved by local scientific and ethics committees (Hôpital Louis-Hippolyte Lafontaine and Centre hospitalier de l'Université de Montréal, Hôpital Notre-Dame).

Drug Administration

The starting dose of quetiapine was 25 mg administered once daily at bedtime. The dose was increased in 50 mg increments every two days up to 200 mg every night during the first week. If symptoms persisted after the first month the dosage was increased to a maximum of 700 mg/day based on clinical response and tolerability. Concomitant antipsychotic medications were not permitted. The Mean dose was 529 ± 138.9 mg.

Psychiatric Assessments

Subjects were investigated using the patient version of the Structured Clinical Interview for DSM-IV (SCID) (1994), the Positive and Negative Syndrom Scale (PANSS) (Kay et al 1986), and the Rating Scale for Emotional Blunting (RSEB) (Abrams and Taylor 1978) (Table 1). Criteria for entry into the study were a diagnosis of schizophrenia (based on the DSM-IV), no concomitant axis I or axis II disorder, and no medical or neurological disease.

FA- subjects had a score higher than 17 and FA+ subjects had a score lower than 10 on the RSEB.

In addition, patients were assessed for depressive symptoms (CDS: Calgary Depression Scale for Schizophrenia) (Addington et al., 1993), to investigate whether the flat affect symptom improvement was influenced by or due to a change in depressive symptoms. Before treatment with quetiapine, patients were on the following antipsychotic medications: haloperidol (N=2; mean dosage: 10 ± 0.0 mg); risperidone (N=9; 3.3 ± 1.4 mg); olanzapine (N=6; 21.2 ± 6.29 mg). Two patients took two antipsychotic medications, and one took three.

Behavioral Procedure

All subjects had two fMRI scans (before and after quetiapine treatment). The median delay between the first and second scans was 5.5-month (mean 5.92 ± 3.14). BOLD signal changes were measured during two experimental conditions, i.e., an *Aversive Emotional condition* and a *Neutral Emotional condition*. During the *Aversive Emotional condition*, a series of 44 emotionally-laden aversive pictures (e.g., plane crash, snake, spider, shark, angry face, sad face, mutilation, accident, burn victim, dead body, dying man, aimed gun, electric chair, etc.) were presented to the subjects whereas in the *Neutral Emotional condition*, subjects saw a series of 44 emotionally neutral pictures (e.g., tourist, rocks, boat, leaves, outlet, towel, spoon, mug, basket, fan, iron, shoes, fork, umbrella, lamp, plate, chair,

etc.). The pictures were selected from the International Affective Picture System (IAPS, Lang et al 1988). They were matched as much as possible in terms of visual complexity. Pre-quetiapine: the mean *valence* (ranging from pleasant=8 to unpleasant=1) was 2.66 ± 1.58 for the aversive pictures and 5.74 ± 1.47 for the neutral pictures; the mean *arousal* (ranging from calm=1 to excited=8) was 6.11 ± 2.14 for the aversive pictures and 2.97 ± 2.08 for the neutral pictures. Post-quetiapine: the mean *valence* was 2.48 ± 1.48 for the aversive pictures and 5.23 ± 1.23 for the neutral pictures; the mean *arousal* level was 6.17 ± 2.17 for the aversive pictures and 2.81 ± 1.94 for the neutral pictures. Without the arousal component, affective events are less intense (Lang et al 1988). There was no significant difference with respect to the mean valence ($F=2.14$, $t=1.32$, $df=86$, $p=0.2$) and mean arousal ($F=0.59$, $t=1.83$, $df=86$, $p=0.85$) of the pictures before vs. after quetiapine treatment. During the functional scan, four blocks of negative pictures and four blocks of neutral pictures were presented to the subjects. The blocks were presented in an alternating manner (one block negative, then one block neutral, then one block negative, then one block neutral, etc.). Each picture was presented for a period of 2.88 s, and each block – which lasted 31.68 sec - comprised 11 pictures. Blocks were separated by resting periods of 14.4 sec, during which subjects viewed a blank cyan screen. Subjects were instructed to look carefully at each of the 88 pictures presented to them during the functional scan. To assess the subjective responses of the subjects to the stimuli, immediately at the end of the run, subjects were asked to rate verbally on a subjective rating scale ranging from 0

(absence of any emotional reaction) to 8 (strongest emotional reaction ever felt in one's lifetime), the intensity of emotion felt during the viewing of negative IAPS pictures.

Image Acquisition and Analysis

Echoplanar images (EPI) were acquired on a 1.5 Tesla system (Magnetom Vision, Siemens Electric, Erlangen, Germany). Twenty-eight slices (5 mm thick) were acquired every 2.65s in an inclined axial plane, aligned with the AC-PC axis. These T2* weighted functional images were acquired using an EPI pulse sequence (TE = 44 ms, Flip = 90°, FOV = 215 mm, Matrix = 64 x 64, Voxel size = 3.36 mm X 3.36 mm X 5 mm). Following functional scanning, high-resolution data were acquired via a Tl-weighted three-dimensional volume acquisition obtained using a gradient echo pulse sequence (TE = 44 ms, Flip = 12° FOV = 250 mm, Matrix = 256 x 256, Voxel size = 0.94 mm^3).

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

implemented for every subject. The images for all subjects were then spatially normalized into an MRI stereotactic space (Talairach and Tournoux 1988) using this masked mean image. Images then were convolved in space with a three-dimensional isotropic gaussian kernel (12 mm FWHM) to improve the signal-to-noise ratio and to accommodate for residual variations in functional neuroanatomy that usually persist between subjects after spatial normalization.

For the statistical analysis, the time series of the images were convolved with the delayed box-car function, which approximates the activation patterns. Effects at each and every voxel were estimated using the general linear model. Voxel values for the contrasts of interest yielded a statistical parametric map of the t statistic (SPM *t*), subsequently transformed to the unit normal distribution, (SPM Z).

A "fixed-effects model" was implemented to contrast the brain activity associated with the viewing of the aversive pictures and that associated with the viewing of the emotionally neutral pictures (Aversive minus Neutral). This "fixed-effects model" produced individual contrast images, which were used as raw data for the implementation of a "random-effects model", which takes into account intersubject variance and permits population-level inferences (Friston and Frackowiack 1997). Within such "random-effects model", and using these individual contrast images, a one sample t-test then a two-sample t-test were carried out, voxel-by-voxel, to directly compare the mean BOLD response

between the two groups of subjects (aversive *minus* neutral for the same group then FA+ group minus FA- group and FA- group minus FA+ group, respectively) with regard to the Aversive minus Neutral contrast. Such random-effects model was used in this study, because this model takes inter-subject variability into account, thus it can be used with large samples of subjects to make inferences at the population level. A sample size of 8 to 16 subjects is usually considered sufficient for random-effects analyses to be used (Friston et al., 1999). Using this model, if inter-subject variability is important for a given locus of activation (relative to average activation), this activation will be considered insignificant. This would not be the case with fixed-effects analyses, in which inter-subject variability is not considered (Friston et al., 1999).

An à priori search strategy was used, and a small volume correction was performed in the brain regions of interest (ROI) defined à priori. The search volume corresponding to the ROIs was defined à priori, using small volume correction (SVC) and box volume function in SPM99, and based on the neuroanatomic boundaries of these regions noted in the MR reference image (Montreal Neurological Institute (MNI) template) and the Talairach and Tournoux (1988) atlas. For this à priori search, a probability threshold for multiple comparison of a corrected $P<0.05$ was used. Only clusters showing a spatial extent of at least five contiguous voxels were kept for image analysis. The à priori search strategy encompassed the orbitofrontal cortex (OFC Brodmann's areas (BA) 11; box-center situated at 30,28,-16 mm bilaterally; box-volume= 44,25,16), the anterior cingulate cortex (ACC

BA 32; box-center situated at 4.5, 22.5, 29 mm bilaterally; box-volume= 13, 40, 53), the medial prefrontal cortex (MPFC BA 10; box-center situated at 2.5, 50, 22 mm bilaterally; box-volume= 5, 10, 32), the anterior temporal pole (ATP BA 21; box-center situated at 56, -23.5, -2 mm bilaterally; box-volume= 8, 10, 19), the anterior temporal pole (ATP BA 38; box-center situated at 40, 10, -22 mm bilaterally; box-volume= 20, 12, 34), the insula (box-center situated at 39, -2, -6 mm bilaterally; box-volume= 4, 32, 2), the amygdala (box-center situated at 21, -2, -14 mm bilaterally; box-volume= 8, 10, 11) and the midbrain (box-center situated at 6.5, 8, -6.5 mm bilaterally; box-volume= 10, 25, 12). These brain regions have been found activated on a more or less consistent basis in previous functional neuroimaging studies of aversive emotional states (for a complete review please refer to Phan et al., 2002; Eugene et al., 2003).

To assist in interpreting any identified BOLD changes after quetiapine treatment, several additional post-hoc analyses were performed to investigate the potential effect of quetiapine on emotion modulation. BOLD changes with response to the 5.5 months treatment with quetiapine were statistically contrasted to those seen in a previously acquired data set of comparably recruited schizophrenia patients without flat affect/emotional withdrawal symptoms (FA-) (n = 11; mean ± SD age, 25.7 ±4.4, range 21-37 years, mean schizophrenia age of onset 21.3 ±2.7, mean years of education 10.4 ±2.6) who had been similarly scanned: same fMRI machine, same block design, same run, same pictures. In the absence of a controlled randomized trial, this set of post hoc analyses

provided a critical perspective for interpreting the main quetiapine response findings. A fixed-effects model was implemented to do the conjunctional analysis. The contrasts (aversive *minus* negative) for 23 subjects (FA+ post quetiapine n=12 *plus* the FA- n=11, total n=23) were selected to yield the total conjunctional analysis using the SPM99 "define new contrast" in the SPM contrast manager window.

Results

Psychiatric assessment data

A 5.5-month treatment with quetiapine resulted in significant clinical improvement in the 12 study completers (mean ±SD post-treatment PANSS flat affect score of 5.50 ±0.76 at baseline to 2.08 ±1.00 at end point ($t=7.78$, $df=11$, $p<0.0001$). Interestingly, the difference in the CDS was insignificant $p<0.23$.

Table 1. Results of psychiatric assessment tests in schizophrenia patients with flat affect pre and post-quetiapine.

	Mean score and SD FA+ *pre* N=12	Mean score and SD FA+ *post* N=12	p value
RSEB	19.86 ±1.70	4.08 ±1.40	0.0001*
PANSS: Flat affect	5.50 ±0.76	2.08 ±1.00	0.0001*
PANSS: Emotional withdrawal	5.00 ±1.04	2.08 ±0.90	0.0001*
PANSS: positive symptoms	21.43 ±6.87	16.08 ±6.88	0.13
PANSS: negative symptoms	31.29 ±5.09	17.50 ±4.81	0.0001*
PANSS: *total*	102.43 ±13.81	68.50 ±17.57	0.0001*
CDS	6.27 ±4.71	4.00 ±4.17	0.23

Table 2. Results of psychiatric assessment tests

	Mean score and SD FA+	Mean score and SD FA-	p value
RSEB	19.86 ±1.70	6.00 ±1.41	0.0001
PANSS: Flat affect	5.50 ±0.76	1.45 ±0.82	0.0001
PANSS: Emotional withdrawal	5.00 ±1.04	1.73 ±0.90	0.0001
PANSS: positive symptoms	3.09 ±1.38	3.23 ±1.31	0.56
PANSS: negative symptoms	4.48 ±1.04	2.05 ±0.95	0.02

PANSS:general psychopathology	3.06 ±1.24	2.53 ±1.08	0.33
PANSS: total	3.40 ±1.23	2.59 ±1.10	0.31
CDS	6.7 ±4.53	4.1 ±3.71	0.12

Table 2. CDS: Calgary Depression Rating Scale; PANSS: Positive and Negative Symptoms Scale; RSEB: Rating Scale for Emotional Blunting.

Table 3. Results of psychiatric assessment tests in schizophrenia patients with flat affect post-quetiapine and schizophrenia patients without flat affect.

	Mean score and SD FA+ *post* N=12	Mean score and SD FA- N=11	p value
PANSS: Flat affect	2.08 ±1.00	1.45 ±0.82	0.12
PANSS: Emotional withdrawal	2.08 ±0.90	1.73 ±0.90	0.35
PANSS: positive symptoms	16.08 ±6.88	22.64 ±5.50	0.19
PANSS: negative symptoms	17.50 ±4.81	14.36 ±4.25	0.22
PANSS: *total*	68.50 ±17.57	77.55 ±14.92	0.34
CDS	4.00 ±4.17	4.1 ±3.71	1.00

Self-report data

Experientially, pre-quetiapine, viewing of the aversive pictures did not induce a aversive emotional state (1.79 ±2.00). Conversely, post-quetiapine viewing of the aversive pictures induced a aversive emotional state whose intensity was significantly greater than pre-treatment (6.67 ±0.78) (F=4.15, t=-7.91, df=22, p=0.0001) on a scale varying from 0-no emotion felt to 8-highest emotion felt in one's life. In fact, patients demonstrated considerable insight into their feelings. This is in accordance with their insignificant difference on the sub-symptom, lack of judgement and insight, on the PANSS score (FA+ before 3.10 ±0.99; FA+ after 2.50 ±1.24; p=0.23).

fMRI Data: Subtraction Approach

Pre-quetiapine. Significant locus of activation was noted in subcortical structures: in the midbrain bilaterally and right pons when the brain activity associated with the viewing of the emotionally neutral pictures was subtracted from that associated with the viewing of the emotionally aversive pictures (Aversive minus Neutral contrast) (Table 3 and Figure 1).

fMRI Data: Subtraction Approach

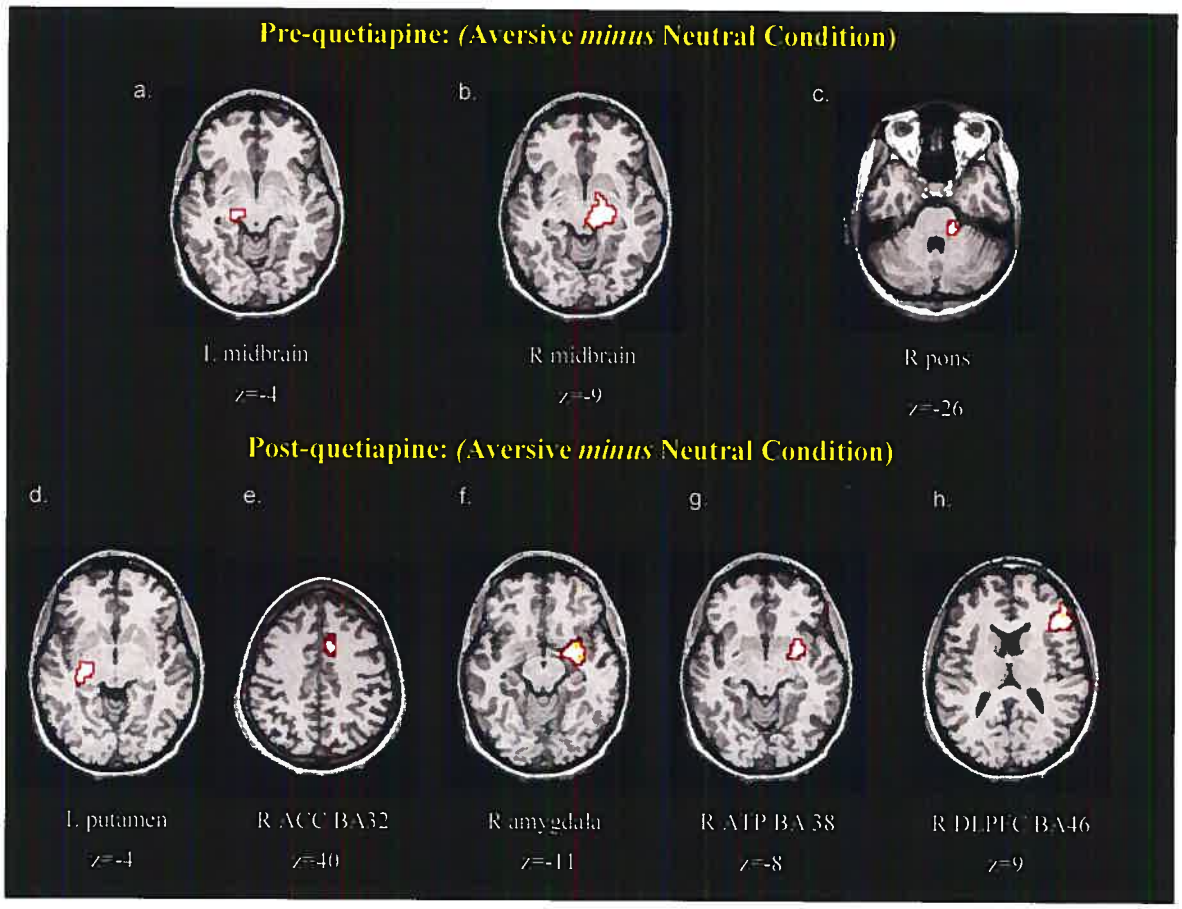
Pre-quetiapine. Significant locus of activation was noted in subcortical structures: in the midbrain bilaterally and right pons when the brain activity associated with the viewing of the emotionally neutral pictures was subtracted from that associated with the viewing of the emotionally aversive pictures (Aversive minus Neutral contrast) (Table 3 and Figure 1).

Table 4. Regional brain activity in FA+ schizophrenia patients:

Schizophrenia patients FA+ pre quetiapine, contrast = aversive *minus* neutral

Brain region	Brodmann's area	Coordinates			Voxels	z score	Corrected p value
		X	y	z			
Right midbrain		18	-21	-9	33	4.03	0.003
Left midbrain		-18	-24	-4	10	3.67	0.01
Right pons		12	-33	-26	19	3.61	0.03

Figure 1



Post-quetiapine. The Aversive minus Neutral contrast revealed significant loci of activation both cortical and subcortical: in the left putamen, right dorsolateral prefrontal cortex (DLPFC BA 47), right anterior temporal pole (ATP, BA 38), right amygdala, and in the right anterior cingulate cortex (ACC, BA 32). (Table 4 and Figure 1).

Table 5. Regional brain activity in FA+ schizophrenia patients:

Schizophrenia patients FA+ post quetiapine, contrast = aversive *minus* neutral

Brain region	Brodmann's area	Coordinates x	y	z	Voxels	z score	Corrected p value
Left putamen		-27	-17	-4	22	4.30	0.004
Right DLPFC	46	47	29	9	65	4.19	0.01
Right ATP	38	29	-3	-8	33	3.48	0.03
R amygdala		25	-1	-11	20	2.95	0.05
Right ACC	32	8	14	40	11	2.89	0.04

Schizophrenia patients without flat affect. Significant loci of activation were noted in the left ACC (BA 32), left insula, left ATP (BA 21), left ATP (BA 38), left amygdala, right medial prefrontal cortex (Table 5).

Table 6. Regional brain activity in FA- schizophrenia patients:

Schizophrenia patients FA-, contrast = aversive *minus* neutral

Brain region	**Brodmann's area**	**Coordinates**			**Voxels**	**z score**	**Corrected p value**
		x	**y**	**z**			
LACC	32	-8	16	37	22	4.13	0.01
L insula		-36	8	-13	12	4.11	0.01
LATP	21	-45	8	-23	13	4.04	0.01
LATP	38	-48	10	-26	13	3.77	0.05
L amygdala		-25	-7	-11	9	3.72	0.003
RMPFC	10	3	56	19	7	3.57	0.01

Conjunctional analysis (FA+ post-quetiapine n=12 *plus* FA- n=11, total n=23). The Aversive minus Neutral contrast showed significant loci of activation in both cortical and subcortical: in the right middle prefrontal cortex (RMPFC, BA 10), right fusiform cortex (BA 37), right thalamus, right middle prefrontal cortex (RMPFC, BA 9), right putamen, right midbrain and left amygdala. (Table 6).

Table 7. Regional brain activity in FA+ *plus* FA- post-quetiapine schizophrenia patients (Fixed-effects conjunctional analysis): *contrast = aversive minus neutral*

Brain region	Brodmann's area	Coordinates x	y	z	Voxels	z score	Corrected p value
RMPFC	10	35	23	4	19	6.39	0.0001
R fusiform	37	38	-49	-7	100	6.07	0.0001
R thalamus		20	-29	-1	135	6.05	0.0001
RMPFC	9	38	9	24	30	5.56	0.001
R Putamen		29	-17	-1	48	5.31	0.002
R midbrain		2	-33	-28	14	4.97	0.01
L amygdala		-20	-6	-12	5	3.61	0.005

fMRI Data: A Posteriori Correlation Analyses

Correlational analyses were conducted a posteriori between self-report ratings and BOLD signal increases found in the ROIs. These analyses revealed the existence of a positive correlation in the right putamen (coordinates of maximum = (19, 6, 10); z= 2.94; $p \leq 0.002$, uncorrected; 12 voxels); right ATP (BA 38; coordinates of maximum = (33, 2, -23); z= 2.68; $p \leq 0.004$, uncorrected; 23 voxels) and the right medial prefrontal cortex (MPFC BA 9; coordinates of maximum = (6, 56, 27); z= 2.52; $p \leq 0.006$, uncorrected; 45 voxels). This

simple regression analysis was done using the basic models-simple regression correlation analysis function in SPM 99 allowing us to correlate the subjective rating scale score (of the patients' experience of emotion felt during the scan), with the aversive-minus neutral condition using the one-sample t-test after quetiapine.

Discussion

While far from being conclusive, findings from the present exploratory study suggest that a daily mean dose of 529 ±138.9 mg quetiapine potentially has a positive effect in treating flat affect symptoms in schizophrenia patients. On one hand, post quetiapine subjects rated the pictures as more emotional. On the other hand, quetiapine modulated the subcortical/cortical pathway.

The neurobiological correlates of emotion processing: from subcortical to cortical

A distinctive and important feature of the emotional behavior of humans is the diversity and complexity of emotional strategies. That is, in contrast to lower mammals, changes in our emotional state are not only triggered by the situation through the autonomic nervous system (subcortical structures), but also further analyzed (cortical structures). Clearly, the evolutionary process of the cerebral cortex development resulted in a corticalisation of emotional as well as higher social functions, which further analyses and decides upon the reaction to the emotional situation. Thus, setting the mood and modulating emotion based on past or anticipated future consequences of behavior.

Sorting these principles out is important because of the potentially beneficial effects of quetiapine in improving flat affect symptoms through its modulation of the subcortical/cortical structures involved in emotion processing. Before quetiapine treatment, the passive viewing of the aversive pictures revealed significant loci of activation in the midbrain bilaterally and the pons. Some evidence suggests that these cerebral structures are involved in the mediation of autonomic responses such as skin conductance responses (Sequeira and Roy, 1993) and body temperature changes (Nagashima et al., 2000). Given that autonomic responses often accompany the autonomic experience of primary emotions (Damasio et al., 2000), the bilateral midbrain activation noted here may be related to the autonomic responses associated with subjects' perception of IAPS images. However, this autonomic state was "*lost in translation*" from the midbrain to the prefrontal cortex. We interpret these findings as suggesting, at the biological level, an underactivation of weakly connected networks in FA+ schizophrenia patients from the midbrain to the prefrontal cortex. These findings also suggest that a key element of any network is its ability to maintain stability and control excitation. An emotional situation produces various levels of excitatory buildup. Hence, it could be argued that FA+ schizophrenia patients may produce a dysregulation of this network because of failure of excitation from the midbrain to the prefrontal cortex.

Post-quetiapine, significant loci of activation were revealed in both subcortical and cortical structures. The amygdala is involved in the evaluation of the emotional significance of stimuli detected in the external environment (for a review, see Lane and Nadel 2000). In the present context, it seems plausible that the amygdala activation measured during the viewing of the aversive pictures was related to the appraisal process of these stimuli. With respect to the activation observed in the anterior temporopolar cortex, activity of this cortical region has been reported during a variety of aversive emotional states (e.g., sadness, anger, and anxiety) (Chua et al.,1999; Damasio et al 2000; Dougherty et al., 1999; Kimbrell et al., 1999; Lane et al., 1997a; Lévesque et al 2003; Reiman et al., 1989). This paralimbic region receives inputs from unimodal and heteromodal sensory regions, as well as limbic inputs. In keeping with the conclusions derived from various lines of evidence regarding the anterior temporal pole (Mesulam 1985), we propose that anterior temporopolar seen here was associated with imparting affective tone to the subjects' experience. The anterior cingulate cortex plays a pivotal role in the interoceptive and exteroceptive detection of emotional signals (Lane et al 1997b). Activation of the DLPFC is of particular interest. This area is involved in looking up information in memory (perhaps as associations and emotion recognition of the visible pictures) (Kosslyn et al., 1995). The unique changes in the putamen activity with treatment response are noteworthy, as they support a critical role for emotion modulation with quetiapine response compared with the FA- group. Although both groups demonstrated similar loci of activation, only FA+ subjects post quetiapine were associated with putamen activation. Furthermore, this region

correlated with the subjective rating score of emotions felt during the scan, post-quetiapine. Activation of the putamen previously has been associated with emotional processing tasks in normal control participants, including the active rethinking and reappraisal of emotional feelings (Pardo et al., 1993; George et al., 1995; Lane et al., 1997a; Damasio et al., 2000).

The positive correlation found between average ratings of aversive emotion and BOLD signal increases in the MPFC is in line with the positive correlation noted previously (Lévesque et al 2003) between the magnitude of sad feelings and BOLD signal increases in the same part of the MPFC. This prefrontal cortical region receives sensory information from the body and the external environment via the orbitofrontal cortex and is heavily interconnected with limbic structures, such as the amygdala, hypothalamus, midbrain periaqueductal gray region, and brainstem autonomic nuclei (Barbas 1993; Carmichael and Price 1995). It is noteworthy that a region of the medial prefrontal cortex close to that identified in this study has been implicated in metacognitive representation of one's own emotional state (Lane 2000; Reiman et al 1997). In keeping with this, studies of individuals with damage to the medial prefrontal cortex suggest that this cortical area is involved in the conscious monitoring of the individual's emotional state (Damasio 1995). In this context, it thus seems plausible that the medial prefrontal noted here is related to reflective conscious awareness of the emotional state induced by viewing the aversive pictures. Overall, on one hand, sub-cortical structures could be responsible for registering bodily responses to aversive stimuli. On the other hand, cortical structures may be involved

in the modulation, experience and expression of these emotions. the question now poses itself: what happened during this 5.5 months period between the two scans that modulated the neural processing of emotional information from the sub-cortical to cortical structures?

Possible mechanism of action of quetiapine in improving flat affect: the mesocortical pathway

The preceding section highlighted the role that quetiapine may play in improving flat affect symptoms by modulating different brain regions involved in emotion processing. Going one step further, in this section we will discuss quetiapine proposed mechanism of action. On theoretical grounds, typical dopamine D2 antagonists generally have no beneficial effect on schizophrenia negative symptoms and may even be detrimental to some of the cognitive, social and affective functions (Sharma, 1999). In contrast, accumulating data suggest that second generation antipsychotic agents (atypical) ameliorates some cognitive and negative deficits in schizophrenia patients (see Meltzer and McGurk, 1999 for review). Yet, relatively little is known about the mechanisms that mediate a specific negative symptom-enhancing effect of atypical antipsychotics, as is the case of flat affect in this study. In this vein, it was suggested that a preponderance of the serotonin (5-HT)-2A antagonism over D2 blockade exerted by atypical antipsychotics may enhance dopaminergic output in the prefrontal cortex and may thus account, at least in part, for their beneficial cognitive effects in schizophrenia (Ruiu et al., 2000; Ichikawa and Meltzer, 1999; Williams et al., 2002). In an elegant description of how 5-HT2A antagonism could

enhance prefrontal dopamine output, Van Oekelen and colleagues (2003) stated that the piriform cortex has a population of GABA-ergic interneurons that are excited by activation of 5-HT2A receptors (Marek and Aghajanian, 1992; Morilak and Ciaranello, 1993; Morilak et al., 1993). Consequently, 5-HT2A receptor antagonists, i.e, antipsychotics with this property prevent the stimulation by 5-HT of cortical GABA-ergic interneurons. The reduction in cortical GABA-release attenuates the inhibitory effect of GABA-ergic interneurons on glutamergic neurons (Bergson et al., 1995; Carlsson et al., 1997). The increased activity of cortical glutamatergic neurons enhances the glutamate release from cortical afferents to the ventral tegmental area (VTA), resulting in an increase in dopaminergic neuronal firing (Bergson et al., 1995; Carlsson et al., 1997; Pehek et al.,1996; Svensson et al., 1993). The increased activation of dopaminergic neurons projecting to the frontal cortex increases the cortical dopamine release, leading to stimulation of cortical dopamine1 (D1) receptors (Bergson et al., 1995; Williams and Goldman-Rakic, 1995). This finding is very intriguing, and it may explain the mechanism of action of quetiapine in reducing flat affect symptom. Hence, we suggest that the higher ratio of serotonin (5-HT2A) receptor to dopamine (D2) receptor antagonism may have played a role. A higher ratio of 5-HT2A to D2 receptor binding may be associated with improving negative symptoms and reduced frequency of extrapyramidal symptoms (Meltzer et al., 1989; Ichikawa et al., 1999). A recent preclinical study suggests that atypical antipsychotics may dampen neurotransmitter function in the mesolimbic/mesocortical tract and may facilitate neurotransmission of various transmitters (dopamine, serotonin) in anterior

limbic/prefrontal cortical regions (Meltzer, 2004). Of particular relevance to our study, the mesocortical dopamine pathway projects to areas of the cerebral cortex, such as the DLPFC, and the limbic cortex (Pehek et al., 2001).

Relatedly, quetiapine is an effective 5-HT2A and D2 receptor antagonist (Gefvert et al., 1998) and has been reported to be a 5-HT1A receptor partial agonist, increasing DA and ACh release in the prefrontal cortex (see review in Sharma, 2001). It is noteworthy that quetiapine 5-HT2A antagonism not only reverses D2 antagonism but causes a net increase in dopamine activity in the mesocortical dopamine pathway (Gobert and Miller, 1996; Pehek et al., 2001). This pathway has long been considered critical in the processing of complex emotional behaviors (James, 1884; Papez, 1927; MacLean, 1949; Rolls, 1990; Damasio, 1996). Comparative anatomical studies provide material support for this hypothesis. Reciprocal pathways linking limbic structures (anterior cingulate, amygdala) with widely distributed brainstem, striatal (putamen), and neocortical sites are now well defined (Carmichael and Price, 1995), and clear associations with specific emotional behaviors have been demonstrated (for a complete review refer to Phan et al., 2002). By extrapolation, these regions are also assumed to be the neural substrates responsible for the systematic integration of exteroceptive and interoceptive inputs required for the combined sensory, cognitive, and autonomic processing at the core of normal and abnormal human emotional experience. Based on these findings, we propose that quetiapine exerted a combined bottom-up and top-down mechanisms in ameliorating flat affect symptoms in our

population by *"normalizing"* the function of the mesocortical dopamine pathway. The prefrontal cortex and anterior limbic regions are of special interest because of their involvement in emotion regulation and expression. Before quetiapine treatment schizophrenia patients FA+ activated the midbrain and pons, without showing any significant activation in the mesocortical pathway involved in emotion processing. However, during quetiapine treatment, the second scan revealed (i) significant activation of this pathway (Table 3-Figure 1 and 2), (ii) improvement in flat affect/emotional withdrawal symptoms (Table 1), (iii) subjects rated the pictures as emotional.

The tolerability of quetiapine was excellent. In several cases, parents confirmed the patient's report of improved symptoms. Patient tolerability was further reflected, at least in part, by the high retention rate in this trial. Furthermore, the improvement in core flat affect re-experiencing symptoms is especially noteworthy because these particular symptoms are often the most refractory to treatment. Overall a positive response to quetiapine is notable as this was a chronic and relatively treatment resistant clinical population.

Conclusion and Limitations

Overall a positive response to quetiapine is notable as this was a chronic and relatively treatment resistant clinical population. Despite the absence of a prospective, randomized study design, we have attempted, using the post-hoc conjunctional BA- comparison to provide some clues for further brain activation in response to emotional stimuli. The 2

groups were studied as independent cohorts, yet they met identical inclusion criteria, and were recruited through the same media outlets (Louis H-Lafontaine Hospital). Most notably, the conjunctional analyses demonstrated a complex set of a similar pattern, of brain activation, between BA+ (post-quetiapine) and BA-. Most significant, in contrast to the BA- increases in putamen activation was only noted in the BA+ group during quetiapine treatment. This could be associated with the known quetiapine profile in demonstrating fewer extrapyramidal side-effects and reversing D2 blockers in the striatum (Review in Sharma, 2001). The results of this study need to be considered in the context of several potential limitations: the relatively small sample size, non-blind and open label design, thus the fMRI alterations could be due to time. It is therefore difficult to ascertain whether the differential brain activation was only due to quetiapine treatment or to the time difference between the two scans. Further studies, using randomized, controlled and double-blind methodology are needed to further investigate the potential effect of quetiapine in treating blunted affect symptoms in schizophrenia.

References

1) Barbas H. Organization of cortical afferent input to the orbitofrontal area in the rhesus monkey. Neuroscience 1993;56:841-64.

2) Bergson C, Mrztjak L, Smiley JF. Regional, cellular and subcellular variations in the distribution of D1 and D5 dopamine receptors in the primate brain. J Neurosci 1995;12:7821-36.

3) Calder AJ, Lawrence AD, Young AW. Neuropsychology of fear and loathing. Nat Rev Neurosci 2001;2:352–63.

4) Caligiuri MP, Brown GG, Meloy MJ. An fMRI study of affective state and medication on cortical and subcortical brain regions during motor performance in bipolar disorder. Psychiatry Res 2003;123:171-182.

5) Carlsson A, Hansson LO, Waters N. Neurotransmitter aberrations in schizophrenia: new perspectives and therapeutic implications. Life Sciences 1997;61:75–94.

6) Carmichael ST, Price JL. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. J Comp Neurol 1995;25:615-641.

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

8) Ekman P, Davidson RJ. The nature of emotion: Fundamental questions. Cambridge: MIT Press, 1994.

9) Eugene F, Levesque J, Mensour B, Leroux JM, Beaudoin G, Bourgouin P, Beauregard M. The impact of individual differences on the neural circuitry underlying sadness. Neuroimage. 2003;19(2 Pt 1):354-64.

10) Fahim C, Stip E, Leroux JM, Boualem M, Beaudoin G. Cerebral mechanisms involved in implicit emotional processing in schizophrenia patients without flat affect and normal controls: a functional magnetic resonance imaging approach. Brain Cogn 2003;51:193-195.

11) Damasio AR. On some functions of the human prefrontal cortex. Ann N Y Acad Sci 1995;769:241-251.

12) Damasio AR. The somatic marker hypothesis and the possible functions of the prefrontal cortex. Philos Trans R Soc Lond B Biol Sci 1996;351:1413–1420.

13) Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto L, Parvizi J. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nat Neurosci 2000;3(10):1049-1056.

14) Dougherty DD, Shin LM, Alpert NM, Pitman RK, Orr SP, Lasko M. Anger in healthy men: a PET study using script-driven imagery. Biol Psychiatry 1999;46:466-72.

15) Gefvert O, Bergstrom M, Langstrom B, Lundberg T, Lindstrom L, Yates R. Time course of central nervous dopamine-D2 and 5-HT2 receptor blockade and plasma drug concentrations after discontinuation of quetiapine (Seroquel) in patients with schizophrenia. Psychopharmacology (Berl). 1998;135(2):119-26.

16) George MS, Ketter TA, Parekh PI, Horwitz B, Herscovitch P, Post RM. Brain activity during transient sadness and happiness in healthy women. Am J Psychiatry 1995;152:341–351.

17) Gobert A, Millan MJ. Serotonin (5-HT)2A receptor activation enhances dialysate levels of dopamine and noradrenaline, but not 5-HT, in the frontal cortex of freely-moving rats. Neuropharmacol 1999;38:315–317.

18) Keltner D, Kring AM. Emotion, social function, and psychopathology. Rev Gen Psychol 1998;2:320–342.

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

20) Kirkpatrick B, Buchanan RW. The neural basis of the deficit syndrome of schizophrenia. J Nerv Ment Dis. 1990;178(9):545-55.

21) Kosslyn SM, Koanig O. Wet mind: The new cognitive neuroscience. New York: Free Press, 1995.

22) Kring AM, Neale JM. Do schizophrenic patients show a disjunctive relationship among expressive, experiential, and psychophysiological components of emotion?. J. Abnorm. Psychology 1996;105:249–257.

23) Ichikawa J, Meltzer HY. Relationship between dopaminergic and serotonergic neuronal activity in the frontal cortex and the action of typical and atypical antipsychotic drugs. Eur Arch Psychiatry Clin Neurosci. 1999;249 Suppl 4:90-8.

24) James W: What is an emotion? Mind 1884; 9:188–205.

25) Lane RD, Reiman EM, Ahern GL, Schwartz GE, Davidson RJ. Neuroanatomical correlates of happiness, sadness, and disgust. Am J Psychiatry 1997a;154:926-933.

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

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

28) Lévesque J, Eugene F, Joanette Y, Paquette V, Mensour B, Beaudoin G. Neural circuitry underlying voluntary suppression of sadness. Biol Psychiatry 2003;53:502-510.

29) MacLean PD, Psychosomatic disease and the visceral brain: recent developments bearing on the Papex theory of emotion. Psychosom Med 1949;11:338–353.

30) Meltzer HY. Treatment of schizophrenia and spectrum disorders: pharmacotherapy, psychosocial treatments, and neurotransmitter interactions. Biol Psychiatry 1999;46(10):1321-7.

31) Meltzer HY, Park S, Kessler R. Cognition, schizophrenia, and the atypical antipsychotic drugs. Proc Natl Acad Sci U S A. 1999;96(24):13591-3.

32) Meltzer HY. What's atypical about atypical antipsychotic drugs? Curr Opin Pharmacol. 2004 Feb;4(1):53-7.

33) Pardo JV, Raichle ME. Neural correlates of self-induced dysphoria. Am J Psychiatry 1993;150:713–719.

34) Papez JW. A proposed mechanism of emotion. Arch Neurol Psychiatry 1927; 38:725–743.

35) Phillips ML, Drevets WC, Rauch SL, Lane RD. The neurobiology of emotion perception I: The neural basis of normal emotion perception. Biol Psychiatry 2003;54:504–514.

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

37) Ruiu S, Marchese G, Saba PL, Gessa GL, Pani L. The 5-HT2 antagonist ritanserin blocks dopamine re-uptake in the rat frontal cortex. Mol Psychiatry 2000;5(6):673-7.

38) Marek GJ, Aghajanian GK. Excitation of interneurons in piriform cortex by 5-hydroxytryptamine: blockade by MDL 100,907, a highly selective 5-HT2A receptor antagonist. J Pharmacol Exp Ther 1992;260(1):146–159.

39) Meltzer HY, McGurk SR. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. Schizophr Bull 1999;25(2):233-55.

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

41) Morilak DA, Ciaranello RD. 5-HT2 receptor immunoreactivity on cholinergic neurons of the pontomesencephalic tegmentum shown by double immunofluorescence. Brain Res 1993;627(1):49–54.

42) Morilak DA, Garlow SJ, Ciaranello RD. Immunocytochemical localization and description of neurons expressing serotonin2 receptors in the rat brain. Neuroscience 1993;54:701–717.

43) Nagashima K, Nakai S, Tanaka M, Kanosue K, Neuronal circuitries involved in thermoregulation. Auton Neurosci 2000;85:18–25.

44) Pehek EA. Local infusion of the seotonin antagonist ritanserin or ICS205930 increases in vivo dopamine release in the rat medial frontal cortex. Synapse 1996;24:12–19.

45) Pehek EA, McFarlane HG, Maguschak K, Price B, Pluto CP. M100,907, a selective 5-HT(2A) antagonist, attenuates dopamine release in the rat medial prefrontal cortex. Brain Res. 2001 Jan 5;888(1):51-59.

46) Rolls ET. A theory of emotion, and its application to understanding the neural basis of emotion. Cognition & Emotion 1990;4:161–190.

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

48) Sharma T. Cognitive effects of conventional and atypical antipsychotics in schizophrenia. Br J Psychiatry Suppl. 1999;(38):44-51.

49) Sharma T. Quetiapine--efficacy in different domains. Eur Neuropsychopharmacol. 2001 Oct;11 Suppl 4:S385-90.

50) Stahl SM, Essential psychopharmacology of antipsychotics and mood stabilizers. Second edition. Cambridge University Press 2002 pp11-75

51) Svensson TH, Norkinos GG, Anderson JL, Modulation of dopaminergic neurotransmission by 5-HT2 antagonism. In: P.M. Vanhoutte, P.R. Saxena, R. Paoletti

and N. Brunello, Editors, Serotonin, from biology to pharmacology and therapeutics, Kluwer, Dordrecht, The Netherlands 1993; pp. 263–270.

52) Van Oekelen D, Luyten WH, Leysen JE. 5-HT2A and 5-HT2C receptors and their atypical regulation properties. Life Sci 2003;72(22):2429-49.

53) Williams GV, Rao SG, Goldman-Rakic PS. The physiological role of 5-HT2A receptors in working memory. J Neurosci 2002;22(7):2843-54.

Discussion

It should be noted that we do not suggest any categorical subtypes of schizophrenia patients based on the with flat affect/without flat affect symptomatology. However, our findings, demonstrating differential haemodynamic flow between schizophrenia patients with and without flat affect, mean that the quest for the symptom-specific-neuropathology of schizophrenia could help explain the multiplicity of neuro-circuit dysfunction in this heterogeneous disorder. Furthermore, we suggest that a daily mean dose of 529±138.9 mg quetiapine could have a role in improving flat affect/emotional withdrawal symptoms in schizophrenia patients.

1. Neuroimaging emotional experience and potential treatment in schizophrenia: What we have found.

We interpret our findings (based on the three articles) as suggesting, at the biological level, an underactivation of weakly connected networks in FA+ schizophrenia patients from the midbrain to the prefrontal cortex, through the amygdala. This could establish an important link between experimental findings and the clinical phenomenology of schizophrenia. However, FA- displayed similar activation of the key brain regions involved in emotion processing, which coincides with their experiential response. I will now discuss the role each brain region played in emotion processing starting with emotion perception in the visual cortex to emotion modulation in the prefrontal cortex.

1.1. The visual cortex

The perception of a stimulus, through the visual cortex, can result in an emotional response (Adolphs, 2002). However, modulation of perception by emotion has been more difficult to demonstrate, because of the multiplicity of neuronal circuits involved. Of particular relevance to this thesis, Taylor et al., (2005) reported, using PET, that schizophrenia patients showed reduced modulation of visual cortex by salient stimuli. Their results showed that patients with schizophrenia exhibit impaired neural responses to emotionally salient stimuli in the ventral striatum and amygdala, supporting a role for these structures in the pathophysiology of the illness. Moreover, reduced modulation of visual cortex by emotionally salient stimuli also suggests a failure to organize cerebral activity at a global level.

1.2. Midbrain

William James (1884) proposed that stimuli that provoke emotion induce changes in the viscera and that the self-perception of these visceral changes is what produces emotional experience. However, before producing this experience, one should choose the appropriate emotional strategy. Several recent studies have provided evidence that the midbrain has been identified as a region containing distinct neural substrates, which triggers an emotional strategy, i.e., active versus passive/avoidant (Behbehani, 1995;

Bandler et al., 2000). For example, if confronted with faces expressing negative emotions (fear, despair, anger, disgust, sadness) it is often appropriate to intervene or escape (i.e., choose an active or avoidant strategy).

In a recent study in the macaque, the authors (Bandler et al., 2000), examined the connections of the orbital-mesial prefrontal cortex with the brainstem (midbrain). A series of retrograde and anterograde tracing experiments revealed that projections to and from the brainstem arose predominantly from the mesial prefrontal cortex (Brodmann's area 9/10), orbital and anterior cingulate cortices. Hence, they are interconnected reciprocally. In other words, the midbrain has long been recognized as a structure that integrates somatic, autonomic, and sensory components of emotional behavior (for a historical review see Bandler, 1988). Specifically, in a recent study, Damasio and colleagues (2000) demonstrated that neural activation was observed in the prefrontal cortex, anterior cingulate gyrus and brainstem for sadness and anger, the midbrain was active in anger and fear, and both sides of the midline cerebellum were significantly activated for sadness, anger and fear.

The brainstem is the source of several ascending neural pathways, each of which originates in distinct sets of nuclei. These pathways, which reach widespread regions of the cortex, affect the operations of the cerebral cortex both by modulating aspects of its overall activity and by conveying to specific regions the contents with which a subjective sense can

be created (Bandler and Shipley, 1994). This may account, at least in part, for the differences in our FA- group results compared with FA+ (i.e., the differences in the selection of emotional coping strategies). The FA+ group would 'prefer' an avoidant emotional strategy, hence, no transmission of information to the prefrontal cortex. In contrast, the FA- group would 'choose' the active emotional coping strategy and would transmit the information to the prefrontal cortex. This view is consistent with other experimental findings, most notably those who have demonstrated that the midbrain has is a region containing distinct neural substrates which triggers an emotional strategy, i.e., active versus passive/avoidant (Behbehani, 1995, Bandler et al., 2000). Of particular note, several research groups (Carrive et al., 1997; Dielenberg et al., 2001; Comoli et al., 2003) have reported that the midbrain may be a component of a circuit that triggers emotional coping in response to psychological (i.e. cortical) stress. Consistent with this suggestion is a recent report stating that for the rat, the presence of (but not contact with) a natural predator (i.e. a cat), which triggers stress, evokes very strong Fos expression (the expression of immediate-early genes as markers of neuronal activation) within the midbrain (Canteras and Goto, 1999). Along these lines, the midbrain was found to evoke passive/avoidant emotional coping strategies (quiescence, immobility, hyporeactivity) that were characterized by disengagement or withdrawal from the external environment and sympathoinhibition (hypotension, bradycardia) (Bernard and Bandler, 1998; Bandler et al., 2000). Of relevance to the previous findings, feedback from bodily responses to an emotionally salient stimulus is of primordial importance in determining the nature and

extent of emotional feeling (James, 1884; Cannon, 1929). Furthermore, brainstem regions share a major feature in that they are all indirect recipients of signals from the external milieu and generate regulatory signals necessary to maintain homeostasis (Damasio et al., 2000; Davidson and Irwin, 1999). Hence, brainstem processing of emotions is perhaps not directly accessible to consciousness. This suggests that this kind of activation in the FA+ group may be related to a particular physiological program that prevents them from feeling emotions. In support of this interpretation, is the important functions that are classically associated with the brainstem (defensive reactions in response to threatening or nociceptive stimuli) trigger distinct co-ordinated patterns of skeletal, autonomic and antinociceptive adjustments by selectively targeting specific midbrain circuits. The intriguing function attributed to the brainstem, i.e., emotional processing, becomes less intriguing when it is seen in the perspective of homeostasis, the ultimate physiological role of the human body and mind. From a psychodynamical view, we are proposing a repression mechanism used by the FA+ group to suppress emotions. The question 'why' are they using such a mechanism needs further investigation (see section 2 in the discussion).

1.3. The Insula

The insular cortex is a highly developed mesocortical structure that is a major component of the limbic system (Mesulam and Mufson, 1982). By virtue of its connections with cortical and subcortical regions, it constitutes a sensory integration region and plays an important role in human emotion (for a review, see Augustine, 1996). In this review, the

author has reported that connections have been described between the insula and the orbital cortex and the frontal operculum. Specifically, it has an abundance of local intrainsular connections and projections to subdivisions of the cingulate gyrus. The insula has connections with the lateral, lateral basal, central, cortical and medial amygdaloid nuclei. Furthermore, confirmation has been given to the insula as a visceral sensory area, hence, is engaged in tasks that depend on interactions between the extrapersonal world (e.g., emotional stimuli) and the internal milieu (Mesulam and Mufson, 1982). Interestingly, difficulties in distinguishing between representations of internal versus external perceptions, or actions, have been linked to psychotic symptoms in schizophrenia (Frith and Dolan, 1997). Of particular relevance to our study, the paralimbic insular cortex is involved in the expression of autonomic patterns in response to affective stimuli, and in the integration of sensory events with appropriate emotional responses (Mesulam and Mufson, 1982). Indeed, functional imaging studies have shown that the insular cortex is engaged in emotional responses to sensory stimuli (Reiman et al., 1997). Thereupon, we suggest that abnormalities in the insular cortex might underly the abnormal peripheral and behavioral responses to emotional stimuli that have been described in schizophrenia FA+. We therefore propose that abnormalities in the insular cortex and its connections with pivotal other limbic regions may have played a role leading to the failure in the normal emotional process that permits patients to adapt between internally (autonomic and visceral information) and externally generated sensory events (emotional stimuli depicted by the IAPS pictures) in schizophrenia FA+. This inadaptation may lead, at least in part, to "non-

emotional response" or flat affect seen in FA+. This hypothesis is consistent with the notion that the insulo-orbito-temporal component of the paralimbic brain is considered an integrated unit of cerebral organization involved in emotion (Mesulam and Mufson, 1982).

1.4. The amygdala

The descending sympathetic neurons receive projections from the hypothalamus, and the hypothalamus receives projections from the amygdala. Worth mentioning, in regard to the feedback theory of visceral information to the brain, the major nerve that carries visceral afferent information back to the brain is the vagus. These vagal afferents terminate in the midbrain, which then projects to the central nucleus of the amygdala, which projects to the rest of the amygdala and insula. The amygdala and insula then project to several neocortical areas including the temporal, parietal and frontal lobes inputs (reviewed in Heilman and Gilmore, 1998). Hence, in this manner the amygdala may directly influence the experience of emotion, especially considering the fact that it also receives neocortical input. However, we should bare in mind that the amygdala is not acting in a vaccum. Stimulation of other areas, including the insula and orbitofrontal cortex, can also induce autonomic and visceral changes, and these structures also receive input from the neocortex, hence influencing emotional experience.

Patients presenting enduring poverty of speech, flat affect, diminished social drive, and diminished sense of purpose have been noted to have lesions of the amygdala (Scoville

et al., 1953; Jacobson, 1986). Further evidence on the role of the amygdala in flat affect comes from neuroethological studies. Bilateral lesions of the amygdala cause mammals to present flat affect symptoms with a clear lack of social drive and poverty of vocalizations (which resembles poverty of speech) (Kling, 1972; Ploog, 1981). Thus, the features of amygdalar lesions suggest that diminished social drive, flat affect, and poverty of speech may have a common neural basis, and that this constellation of attributes may represent appropriate aspects of the definition of a negative symptom subtype (Carpenter et al., 1991). Interestingly, Ferrier and colleagues (1983a) found that Type II patients, which predominantly have flat affect and poverty of speech (according to Crow, 1985), had less cholecystokinin immunoreactivity in the amygdala and hippocampus than did control, whereas Type I (without flat affect) patients did not differ from controls. These researchers concluded that the selectivity of these changes to limbic lobe may reflect the presence of a degenerative process in that area. Furthermore, Ferrier et al., noted that the association of changes in hippocampus and amygdala with negative symptoms of schizophrenia suggests a separate mechanism underlying these symptoms.

In summary, the amygdala may generate depressed responses to its inputs (visual cortex and/or midbrain), for any of several possible reasons (discussed in section 2 of this discussion). Such a local imbalance in the model circuit of Figure 1 (page 158) could generate many negative symptoms that are characteristic of schizophrenia. We suggest that the most immediate effect of such a depressed response in emotion-representing areas is

flat affect. This defect, in turn, may cause an inability to represent others' beliefs and intentions, in the sense that all mental states that depend on interpreting one's own emotional state, or the emotional states of others, will be diminished. Most importantly, the emotional experience itself will be lost because emotionally charged sensory inputs, such as the emotional IAPS pictures presented to the patients in our study, activated the appropriate parts of the visual cortex and midbrain but did not elicit an appropriate emotional response in the amygdala and related emotion-representing circuits. As a result, the prefrontal cortex will not be adequately activated, and a hypofrontal condition will emerge (Weinberger 1988). Given a hypofrontal response, top-down signals from the prefrontal cortex to the sensory cortices will also be reduced or eliminated. As a result, the sensory representations will not be able to use these top-down signals to organize information-processing according to its emotional meaning. Consequently, emotional experience is lost.

1.5. The Prefrontal cortex

Data reporting hypofrontality in schizophrenia date back to the elegant studies of Ingvar and Franzen (1974). Using the intracarotid xenon technique, the authors showed that while nonschizophrenia subjects had the highest levels of blood flow to anterior cortical areas (which they termed hyperfrontality), schizophrenia patients showed relatively decreased frontal function. The interesting result from this study was that there was a correlation between the degree of hypofrontality and negative symptoms. This finding has been confirmed by Volkow and colleagues (1987), who reported that patients with more

negative symptoms showed more severe hypofrontality (i.e., lower frontal cerebral glucose metabolism as measured with positron emission tomography) than did patients with fewer negative symptoms. Further evidence of frontal cortex malfunction in schizophrenia patients with major negative symptoms has come from Owen and colleagues (1987). They found an association between the clinical characteristics of flat affect patients clinical characteristics and a decrease in monoamine oxidase-B concentrations in frontal and temporal, as well as amygdala, in comparison to patients without flat affect.

Our findings show that activity in the prefrontal cortex (BA 10; 47 and BA 32) is modulated by emotional valence in the FA-. This is in line with results of some previous neuroimaging studies (Gur et al., 2002; Davidson and Irwin, 1999; Bechara et al., 1994; Lévesque et al., 2003). Further evidence of the role of the mesial prefrontal (MPFC), orbitofrontal (OFC), and anterior cingulate cortices (ACC) in voluntary emotional self-regulation (Lévesque et al., 2003; Beauregard et al., 2001), social learning and in the internal representation of emotional experience (Arbib et al., 2000) was previously demonstrated (Phan et al., 2002). Of particular note, it is well established that damage within the OMACC (orbitofrontal, mesial and anterior cingulate cortices) dramatically alters the capacity of higher mammals to cope emotionally (Nauta, 1971; Moll et al., 2002) and socially (Bechara et al., 1994; Anderson et al., 1999) with different situations. According to Phillips (2003), the information is conveyed to the prefrontal cortex for the regulation of emotional experiences and behavior. This theory is in accordance with our

coefficient correlation analysis of r=0.71 between the midbrain and mesial prefrontal cortex (analysis done using SPM99 and the matlab functions). On a related note, in a recent article by Beauregard et al., (2001), the authors showed that the prefrontal cortex plays a role in conscious and voluntary emotional self-regulation, where the information is accessible to consciousness, thus providing an integrated perception of emotions. In sum, and of relevance to our study, the amygdala and prefrontal cortex are considered to be key nodes of the neural circuit of emotional processing, the former a main signal generator and the latter a modulator (Davidson, 1999).

Overall, the cortical and subcortical areas we have discussed have rich interconnections. None acts in a vacuum. Therefore, the functional anatomic modules that mediate emotional experience are richlly interconnected and form a modular network. Emotional experience depends on the patterns of neural activation of this modular network, which we have seen is abnormal in FA+ and seems to be similar to normal in FA-.

2. Clinical and Biological Implications

The conceptualization of the importance of understanding flat affect neurophysiology has several implications. First, it is crucial to progress in etiologic and therapeutic research. The clearest preonset signal of deterioration in schizophrenia is the appearance of "prodromal" symptoms. According to Hafner and colleagues (1999), the first symptoms are gradually developing nonspecific negative symptoms starting 3 to 5 years before onset,

followed by positive symptoms around 1 year before onset of the disease. Here comes the importance of investigating flat affect. Second, understanding the neuropathology of flat affect is of paramount importance, both to clinicians responsible for the care and treatment of schizophrenia patients and to researchers who attempt to delineate the underpinnings of schizophrenia neuropathology. The with flat affect/without flat affect distinction is particularly crucial for studying emotional responding in schizophrenia. Previous studies of emotional responding have likely included both with flat affect and without flat affect, who may have different patterns of emotional responding. Third, whether the social deficits are the consequence of flat affect or vice versa have not yet been investigated in schizophrenia patients. Thus, elucidation of the inconsistency (between the findings of different studies), constitute a critical step toward understanding the neural mechanisms responsible for these cognitive processes. Especially, since emotional activity is at the heart of every interpersonal interaction and is therefore of central importance for all therapies and rehabilitation strategies. Of particular note, although schizophrenia is often characterized as a heterogeneous disorder, efforts to validate stable and meaningful subtypes have met limited success. Thus, the issue of whether schizophrenia reflects a continuum of severity or a number of discrete subtypes remains controversial. Recent studies (Liddle, 1987; Tsuang et al., 1990; Andreasen and Carpenter, 1993) reached the conclusion that schizophrenia probably includes different diseases or reflects several dimensions of psychopathology, each underlain by its own pathophysiology. From a genetic point of view, this etiologic heterogeneity is one of the most likely explanations for the slow

progress in the identification of susceptibility genes and consistent biological markers for schizophrenia. There are likely multiple susceptibility genes. At least seven genes have been proposed to be associated with schizophrenia (Harrison and Owen, 2003). Distinguishing schizophrenia patients according to symptom presence or severity may be one strategy for identifying such subtypes. Indeed, that there may be more than one pathologic process in schizophrenia, each with its independent antecedents and consequences, has been proposed (Crow, 1980b, Strauss et al., 1973).

Overall, investigating flat affect has implications for early detection, preventive intervention, and future research. The aims of early detection are to identify subjects at high risk of emotion abnormalities (e.g., flat affect). Hence, we need to focus preonset early detection efforts not just on those who are prodromally symptomatic (with positive symptoms) but also on premorbid individuals who are at high risk for negative symptoms. Early interventions that reduce duration of untreated psychosis will improve lifetime prognosis, and intervention in the prodrome will delay or prevent onset.

3. Discussing Methodological Issues

3.1. Why choosing the Rating Scale for Emotional Blunting (RSEB) and the Calgary Depression Scale (CDS)?

The RSEB is the only scale specifically measuring flat affect symptoms in schizophrenia. It was developed by reviewing the literature from Pinel's era (1801) to 1978 to determine clinical descriptions of emotional blunting. This construct is all that the scale measures. Predictive validity, in this scale, was assessed by comparing total scores with response to treatment; subjects with higher blunting scores showed a poorer response to treatment (Abrams & Taylor, 1978). The RSEB includes four "indifference" items, three of which are based on the patients's self-report (lack of affection for family, unconcern for own present situation, and unconcern for own future) and one of which is based on observation (indifference to surroundings). Most importantly, it contains items describing flat affect: absent, shallow, incongruous mood; constricted affect; unvarying affect (lacks modulation, lacks warmth and empathy); the patient is seclusive/withdrawn, and avoids social contact. It must be emphasized that none of the prevailing concepts of negative symptoms has been proven to have construct validity. We have attempted, as much as possible, to approach flat affect construct validity by implementing the RSEB.

The distinction that Carpenter et al., (1985) made between primary and secondary negative symptoms is pertinent. The authors stated that some negative symptoms are secondary to positive symptoms or other consequences of the disease. For example social

withdrawal could be a response to delusions or hallucinations. Such symptoms should be distinguished from primary negative symptoms that are enduring and resistant to treatment. In this vein, in a survey of 500 chronic institutionalized patients, Johnstone anf Owens (1980), demonstrated that negative symptoms may be unrelated to the presence of positive symptoms. In this vein, we have attempted, as much as possible, to distinguish flat affect symptoms from depression. To that end we have used the Calgary Depression Scale (CDS). Furthermore, we have investigated the depression symptom on the PANSS and found no significant difference between the two groups ($F=0.43$, $t=-0.71$, $df=23$, $p=0.5$). Our findings show no significant difference between the two groups with respect to depression symptoms, which suggest that flat affect symptoms are not secondary to depression in the FA+. Interestingly, a schizophrenia patient with the deficit syndrome (mostly presenting flat affect) and a schizophrenia patient who is depressed may have highly similar presentations in terms of diminished emotional experience. However, such patients show highly different treatment responses. For example, the emotional deficits of the depressed schizophrenia patient would decrease in response to treatment with a selective serotonin reuptake inhibitor (SSRI), while that of the deficit patient would remain unchanged (Limpert and Amador, 2001).

3.2. Why Choosing IAPS?

Our work supports cognitive theorists, who have been primarily concerned with emotional experience. For example, the James-Lange (1884) theory of emotional consciousness contends that perceptions (visual cortex) of an event produce specific visceral (midbrain, insula, amygdala and orbitofrontal cortex) patterns of arousal that result in an emotional experience and modulation (prefrontal cortex) when perceived by the individual. Furthermore, we should note that the experimental study of affect requires quantitative stimulus tools to evoke affective states reliably in a laboratory setting, which is quite a difficult task requiring validity and reliability. Toward that end, we have used the International Affective Picture system (IAPS, Lang et al., 1997), a standardized and well-characterized collection of visual images designed to evoke either neutral, positive, or negative emotional states. We used evocative pictures of negative/aversive and neutral scenes with minimal cognitive demands so as to examine the automatic emotional response that requires no elaborate rating or categorization of stimuli for the subjects. Facial expressions do not necessarily elicit strong emotions, and cognitive demands such as discriminating analogous facial expressions might affect brain activations (Critchley et al., 2000). Findings (for example, Davis et al., 1995) show that mean dimensional self reports of affective responses were highly replicable across cohorts. Mean categorical response profiles for individual slides were also similar across different cohorts and for different experimental conditions. Valence calculated from weighted categorical self report scores was highly correlated with the self reported valence ($r = +0.98$), demonstrating a simple,

linear relationship between dimensional and categorical (differential) measures of affect. Categorical response strength was synergically patterned, i.e. invariably correlated positively for affect of the same dimensional valence and generally correlated negatively for affect of opposite valence. Facial electromyograms associated with affective responses to slides were correlated with valence.

3.3. Why choosing a passive-viewing method?

We deliberately chose a passive viewing method and avoided the use of a cognitive task in conjunction with the presentation of the stimuli because of the known interactions between cognition and emotion (Simpson et al., 2000). Functional imaging studies have corroborated the notion that the amygdala activation appears to depend on relatively passive or implicit processing emotion, whereas requiring subjects to label the emotion can instead result in deactivation (Hariri et al., 2000) and concomitant suppression of emotional psychophysiological responses (Kapler et al., 2001). The reduction of amygdala responses to emotional expressions, when the demand for explicit emotion recognition is increased, is a common observation across studies (Critchley et al., 2000) and may be mediated by the amygdala's inhibition by frontal cortex. Furthermore, we presented stimuli for a relatively short period (2.88 s) with no gap between in the images (in each block of the four negative blocks). We hypothesize that the lack of a specific cognitive instruction together with the brief presentation time profoundly influenced the activity in the midbrain and prefrontal cortex. Poppel (1997) showed that it takes only 3 s to perceive a complex visual scene.

When images are shown for a longer period, cognitive mechanisms that try to come to an alternative interpretation of the stimulus are elicited. Of particular relevance to our study, passive emotional tasks with minimal cognitive demands activate the amygdala and other subcortical regions more often than emotional tasks with greater cognitive demands (Phan et al., 2002). Thus, we successfully observed robust activation in widespread cortical and subcortical regions as reported in previous studies (Lane et al., 1997a and Lane et al., 1997b).

3.4. Why choosing quetiapine?

Due to the differences among antipsychotics available today, optimizing treatment for individual patients requires choosing the most appropriate drug and, if necessary, switching to a different drug if the first proves unsatisfactory. The treating physician must carefully match the diverse needs of schizophrenia patients with the varied characteristics of the second-generation antipsychotics. In this vein, negative symptoms, specifically blunted affect, can be a part of the pathology of the disease (primary), or it can be secondary to other symptom groups (e.g. positive, depressive, or EPS) of antipsychotic drugs. We believe that a good approach for detecting whether antipsychotics have an improving effect on primary negative symptoms is to conduct studies among patients who are clinically stable, with a high level of negative symptoms using an atypical with low EPS, because of the known interaction with EPS and blunted affect.

To that end we have chosen quetiapine. In an open-label extension phase of three double-blind randomized trials, quetiapine effectively controled schzophrenia symptoms for up to 3 years (Buckley et al., 2004). Moreover, quetiapine has a low risk of EPS and appears to be the only atypical antipsychotic without a dose-related increase in EPS (Gerlach, 2002). It should be noted that the absence of EPS is of particular relevance to our study, because we wanted to control that the EPS symptoms are not the cause of blunted affect. Furthermore, the twelve study participants have already benn treated with other typical and atypical antipsychotics. However, they were not prescribed quetiapine before. Indeed, quetiapine has been shown to be clinically effective in patients with only partial response to other antipsychotic treatments (Emsley et al., 2000). Noteworthy, quetiapine's relatively benign tolerability profile distinguishes it from other commonly used atypical agents, with respect to bodyweight, EPS and plasma prolactin levels (Buckley et al., 2004). Particulary, quetiapine, like clozapine, show much lower D2 receptor occupancy in vivo than other antipsychotics (Kapur et al., 2000). In this study, using PET, the authors showed that 12 hours after intake of the last dose, D2 receptor occupancy droped from 58%-64% (high blockade) to 30%-40% (low blockade). This low D2 occupancy probably reflects a more rapid dissociation from the receptors than with other antipsychotics, which could account for quetiapine's low EPS.

4. Limitations

The results of this thesis need to be considered in the context of several potential limitations. First, while fMRI use is widespread, there is insufficient knowledge of the physiological basis of the fMRI signal to interpret the data confidently with respect to neural activity (Arbib et al. 2000). Logothetis and colleagues (2001) conducted the first simultaneous intracortical recordings of neural signals and blood oxygenation level dependent (BOLD) responses. The authors simultaneously scanned and recorded from cortex in anesthetized monkeys, using fMRI and electrophysiological recording. The monkeys viewed moving checkerboard patterns while electrodes placed in primary visual cortex measured single- and multi unit neural spiking activity, as well as local field potentials (LFPs), which reflect the dendro-somatic inputs of the neural population. Simultaneous fMRI scanning was used to define a region of interest near the electrode tip that showed a significant BOLD response to the stimulus. They found that the BOLD response was significantly correlated with the LFPs, which were stronger and more sustained than the single- and multi unit neural spiking activity. These results indicate that the BOLD signal does indeed reflect an increase in neural activity.

Second, it should be noted that our task could be regarded as an emotion-induction task. However, the finding needs to be interpreted cautiously because, strictly speaking, our task was testing the access to autonoetic perception of elicited emotions. It might be possible that the ability of schizophrenic patients to access their emotions (categorization of

feeling) was different from that of normal controls. Our behavioral results might not necessarily reflect gut-level elicited emotion that drives emotional behavior. Autonomic data such as skin conductance responses would help to measure gut-level emotional response.

Third limitation is the use of a relatively small sample size, non-blind and open label design of the quetiapine experiment. It is therefore difficult to ascertain whether the differential brain activation was only due to quetiapine treatment or to the time difference between the two scans. Further studies, using randomized, controlled and double-blind methodology are needed to further investigate the potential effect of quetiapine in treating flat affect/emotional withdrawal symptoms in schizophrenia.

5. Conclusion

In conclusion, these findings point to the existence of differential neurophysiological mechanisms in emotion processing between FA- and FA+, and a recognition of the special roles played by different subcortical and cortical brain regions in co-ordinating distinct strategies for processing emotions and hence, coping with different types of negative reactions, stress, and threat. In summary, there is a differential haemodynamic flow in key brain regions involved in emotion processing between schizophrenia patients FA+ and FA-, which supports the heterogeneity model in schizophrenia. This is not to say, of course, that it can accommodate the full diversity of

schizophrenia, nor that it provides the same information as from biological and course-related measures and as from other phenomenological variables. Rather, as we have proposed, better understanding of schizophrenia may require explanation of its various guises and components. Most importantly, reporting quetiapine as a potential treatment for flat affect symptoms in schizophrenia FA+ is of primordial importance due to fact that these symptoms are the most debilitating, respond poorly to treatment and is considered one of the most enduring symptoms. However, due to the small sample and methodological concerns over the reliability of the functional magnetic resonance imaging findings, these results await further exploration and replication. We hope that we were able to provide more focus on the dichotomy, present in the literature, concerning emotional deficits in schizophrenia. Accordingly, arguments could be made that the continued search for specific neural circuit abnormalities in schizophrenia should put aside the search for a "unitary" neural circuit, and start searching for symptoms specific neural circuits, because no single unitary model will likely justify the widespread functional and structural deficits of schizophrenia. In this context, each symptom will have its own specific associated neural circuit.

Bibliographie

Abrams, R. & Taylor, M.A. (1978). A rating scale for emotional blunting. *American Journal of psychiatry*, 135, 226-29.

Ainsworth, M., Blehar, M., Waters, E. & Wall, S. (1978). Patterns of attachment: A psychological study of the strange situation. Hillsdale, NJ: Erlbaum.

Alpert, M., Rosenberg, S., Pouget, E. & Shaw, R. (2000). Prosody and lexical accuracy in flat affect schizophrenia. *Psychiatry Research*, 97, 107-118.

Alpert, M., Shaw, R.J., Pouget, E.R. & Lim, K.O. (2002). A comparison of clinical ratings with vocal acoustic measures of flat affect and alogia. *Psychiatry Research*, 36(5), 347-353.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Press.

Anderson, S., Bechara, A., Damasio, H., Tranel, D. & Damasio, A. (1999). Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nature Neuroscience*, 2(11), 1032-37.

Andreasen, N.C. & Olsen, S. (1982). Negative v positive schizophrenia. Definition and validation. *Archives of General Psychiatry*, 39(7), 789-94.

Andreasen, N.C. & Carpenter, W.T. (1993). Diagnosis and classification of schizophrenia. *Schizophrenia Bulletin*, 19(2), 199-214.

Andreasen, N.C., O'Leary, D.S., Flaum, M., Nopoulos, P., Watkins, G.L., Boles Ponto, L.L. & Hichwa, R.D. (1997). Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naive patients. *Lancet*, 349(9067), 1730-4.

Andreasen, N.C., Paradiso, S. & O'Leary, D.S. (1998). "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophrenia Bulletin*, 24(2), 203-18.

Arbib, M.A., Billard, A., Iacoboni, M. & Oztop, E. (2000). Synthetic brain imaging: grasping, mirror neurons and imitation. *Neural Networks*, 13(8-9), 975-97.

Archer, J., Hay, D.C. & Young, A.W. (1992). Face processing in psychiatric conditions. *British Journal of Clinical Psychology*, 31, 45-61.

Arieti S. (1955). Interpretation of schizophrenia. New York, NY: Robert Brunner.

Arvanitis, L.A., Miller, B.G. (1997). Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. *Biological Psychiatry*, 42(4), 233-246.

Augustine, J.R., (1996). Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Research Reviews*, 22, 229-244.

Bandler, R. & Shipley, M. (1994). Columnar organization in the midbrain periaqueductal gray-modules for emotional expression? *Trends in Neurosciences,* 17, 379-89.

Bandler, R., Keay, K.A., Floyd, N. & Price, J. (2000). Central circuits mediating patterned autonomic activity during active vs passive emotional coping. *Brain Research Bulletin,* 53(1), 95-104.

Bandler R. (1988). Brain mechanisms of aggression as revealed by electrical and chemical stimultion: suggestion of a central role for the midbrain periaqueductal grey matter region. In A. Epstein and A. Morrison (eds): Progress in psychobiology and Physiological Psychology, Vol 13. New York: Academic Press; pp. 67-153.

Beauregard, M., Levesque, J. & Bourgouin, P. (2001). Neural correlates of conscious self-regulation of emotion. *Journal of Neuroscience,* 21(18), RC165.

Bechara, A., Damasio, A., Damasio, H. & Anderson, S.W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition,* 50, 7-15.

Bechara, A., Damasio, H., Tranel, D. & Damasio, A.R. (1997). Deciding advantageously before knowing the advantageous strategy. *Science,* 275, 1293-95.

Behbehani, M.M. (1995). Functional-characteristics of the midbrain periaqueductal gray. *Progress in Neurobiology,* 46, 575-605.

Berenbaum, H. & Oltmanns, T.F. (1992). Emotional experience and expression in schizophrenia and depression. *Journal of Abnormal Psychology*, 101, 37-44.

Bernard, J.F. & Bandler, R., (1998). Parallel circuits for emotional coping behaviour: New pieces in the puzzle. *Journal of Comparative Neurology,* 401, 429-36.

Berrios, G.E. (1985). Positive and negative symptoms and Jackson. A conceptual history. *Archives of General Psychiatry*, 42(1), 95-7.

Blanchard, J.J., Mueser, K.T. & Bellack, A.S. (1998). Anhedonia, positive and negative affect, and social functioning in schizophrenia. *Schizophrenia Bulletin,* 24(3), 413-24.

Bleuler, E. (1950). Dementia Praecox or the group of schizophrenias (J. Zinkin, Trans.). New York: International Universities Press; 1950 (Original work published 1911).

Borod, J.C., Welkowitz, J., Alpert, M., Brozgold, A.Z., Martin, C., Peselow, E. & Diller, L. (1990). Parameters of emotional processing in neuropsychiatric disorders: conceptual issues and a battery of tests. *Journal of Community Disorders*, 23, 247-271.

Bowlby, J. (1973). Attachment and loss: Vol.2. Separation. New York: Basic Books.

Breier, A., Schreiber, J.L., Dyer, J. & Pickar, D. (1991). National Institute of Mental Health longitudinal study of chronic schizophrenia: Prognosis and predictors of outcome. *Archives of General Psychiatry,* 48, 239-46.

Bretherton, I. (1992). The origins of attachment theory: John Bowlby and Mary Ainsworth. *Developmental Psychology*, 28, 759-75.

Bryson, G., Bell, M., Kaplan, E., Greig, T. & Lysaker, P. (1998). Affect recognition in deficit syndrome schizophrenia. *Psychiatry Research,* 77, 113-20.

Buchanan, R.W., Breier, A., Kirkpatrick, B., Ball, P. & Carpenter, W.T. Jr. (1998). Positive and negative symptom response to clozapine in schizophrenic patients with and without the deficit syndrome. *American Journal of Psychiatry,* 155, 751-760.

Buchsbaum, M.S., (1990). The frontal lobes, basal ganglia, and temporal lobes as sites for schizophrenia. *Schizophrenia Bulletin,* 16, 379-89.

Buckley, P.F. (2004). Maintenance treatment for schizophrenia with quetiapine. Human Psychopharmacology, 19, 121-24

Cannon, W.B. (1929). Bodily changes in pain, hunger, fear and rage, vol 2. New York: Appleton.

Canteras, N. & Goto, M. (1999). Fos-like immunoreactivity in the periaqueductal gray of rats exposed to a natural predator. *NeuroReport,* 10, 413-18.

Carpenter, W.T. Jr., Heinrichs, D.W. & Wagman, A.M. (1988). Deficit and nondeficit forms of schizophrenia: the concept. *American Journal of Psychiatry,* 145(5), 578-83.

Carpenter, W.T., Buchanan, R.W. & Kirkpatrick, B. (1991). The concept of the negative symptoms of schizophrenia In Negative Schizophrenia Symptoms: Pathophysiology and Clinical Implications. Edited by Greden J and Tandon R. American Psychiatric Press. Washington, DC.

Carrive, P., Leung, P., Harris, J. & Paxinos, G. (1997). Conditioned fear to context is associated with increased Fos expression in the caudal ventrolateral region of the midbrain periaqueductal gray. *Neuroscience,* 78(1), 165-77.

Cohen, A.S. & Docherty, N.M. (2004). Affective reactivity of speech and emotional experience in patients with schizophrenia. *Schizophrenia Research,* 69(1), 7-14.

Comoli, E., Ribeiro-Barbosa, E.R. & Canteras, N.S. (2003). Predatory hunting and exposure to a live predator induce opposite patterns of Fos immunoreactivity in the PAG. *Behavioral Brain Reserach,* 138(1), 17-28.

Creasey, G., Ottlinger, K., Devico, K., Murray, T., Harvey, A. & Hesson-McInnis, M. (1997). Children's affective responses, cognitive appraisals, and coping strategies in response to the negative affect of parents and peers. *Journal of Experimental Child Psychology,* 67(1), 39-56.

Crespo-Facorro, B., Paradiso, S., Andreasen, N.C., O'Leary, D.S., Watkins, G.L., Ponto, L.L. & Hichwa, R.D. (2001). Neural mechanisms of anhedonia in schizophrenia: a PET study of response to unpleasant and pleasant odors. *Journal of the American Medical Association,* 286(4), 427-35.

Critchley, H., Daly, E., Phillips, M., Brammer, M., Bullmore, E., Williams, S., Van Amelsvoort, T., Robertson, D., David, A. & Murphy, D. (2000). Explicit and implicit neural mechanisms for processing of social information from facial expressions: a functional magnetic imaging study. *Human Brain Mapping,* 9, 93-105

Crow, T.J. (1980a). Molecular pathology of schizophrenia: more than one disease process? *British Medical Journal,* 280(6207), 66-8.

Crow, T.J. (1987). Integrated viral genes as potential pathogens in the functional psychoses. *Journal of Psychiatric Research,* 21, 479-85.

Crow, T.J. (1985). The two-syndrome concept: origins and current status. *Schizophrenia Bulletin,* 11, 471-486.

Cutting, J. (1981). Judgement of emotional expression in schizophrenics. *British Journal of psychiatry,*139, 1-6.

Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L.L., Parvizi, J. & Hichwa, R.D. (2000). Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature Neuroscience,* 3(10), 1049-56.

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

Davis, W.J., Rahman, M.A., Smith, L.J., Burns, A., Senecal, L., McArthur, D., Halpern, J.A., Perlmutter, A., Sickels, W. & Wagner, W. (1995). Properties of human affect induced by static color slides (IAPS): dimensional, categorical and electromyographic analysis. *Biological Psychology,* 41(3), 229-53.

Dielenberg, R.A., Hunt, G.E. & McGregor, I.S. (2001). "When a rat smells a cat": the distribution of Fos immunoreactivity in rat brain following exposure to a predatory odor. *Neuroscience,* 104(4), 1085-97.

Dolan, R. (1999). On the neurology of morals. *Nature Neuroscience,* 2(11), 927-9.

Done, D., Crow, T.J., Johnstone, E.C. & Sacker, A. (1994). Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. *British Medical Journal,* 309, 699-703.

Earnst, K.S. & Kring, A.M., (1999). Emotional responding in deficit and non-deficit schizophrenia. *Psychiatry Research,* 88(3), 191-207.

Edwards, J., Jackson, H.J. & Pattison, P.E. (2002). Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review. *Clinical Psychology Reviews,* 22(6), 789-832.

Eisenberg, N., Fabes, R.A., Schaller, M., Carlo, G. & Miller, P.A. (1991). The relations of parental characteristics and practices to children's vicarious emotional responding. *Child Development,* 62(6), 1393-408.

Ellenbroek, B.A., Lubbers, L.J., Cools, A.R. (1996). Activity of "Seroquel" (ICI 204-636) in animal models for atypical properties of antipsychotics: a comparison with clozapine. *Neuropsychopharmacology*, 15, 406-416.

Emsley, R.A., Raniwalla, J., Bailey, P.J. (2000). For the PRIZE Study Group. A comparison of the effects of quetiapine ("Seroquel") and haloperidol in schizophrenic

patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. International Clinical Psychopharmacology, 15, 121-31.

Fahim, C., Stip, E., Leroux, J-M., Boualem, M. & Beaudoin, G. (2003). Cerebral mechanisms involved in implicit emotional processing in schizophrenia patients without blunted affect and normal controls: a functional magnetic resonance imaging approach. *Brain and Cognition,* 51, 193-95.

Farmer, A.E., McGuffin, P. & Spitznagel, E.L. (1983). Heterogeneity in schizophrenia: a cluster-analytic approach. *Psychiatry research,* 8, 1-12.

Feinberg, T.E., Rifkin, A., Schaffer, C. & Walker, E. (1986). Facial discrimination and emotional recognition in schizophrenia and affective disorders. *Archives of General Psychiatry,* 43, 276-9.

Ferrier, I.N., Roberts, G.W., Crow, T.J., Johnstone, E.C., Owens, D.G., Lee, Y.C., O'Shaughnessy, D., Adrian, T.E., Polak, J.M. & Bloom, S.R. (1983). Reduced cholecystokinin-like and somatostatin-like immunoreactivity in limbic lobe is associated with negative symptoms in schizophrenia. *Life Sciences,* 33(5), 475-82.

Frith, C.D. & Dolan, R.J. (1997). Brain mechanisms associated with top-down processes in perception. *Philosophical Transactions of The Royal Society B: Biological Sciences,* 352, 1221-1230.

Gerlach, J. (2002) Improving outcome in schizophrenia: the potential importance of EPS and neuroleptic dysphoria. Annals of Clinical Psychiatry, 14, 47-57.

Gessler, S., Cutting, J., Frith, C.D. & Weinman, J. (1998). Schizophrenic inability to judge facial emotion: a controlled study. *British Journal of Clinical Psychology,* 28, 19-29.

Green, M.F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *American Journal of Psychiatry,* 153(3), 321-30.

Grimes, K. & Walker, E.F. (1994). Childhood emotional expressions, educational attainment, and age at onset of illness in schizophrenia. *Journal of Abnormal Psychology,* 103(4), 784-90.

Goldstein, M.J. (1970). Premorbid adjustment, paranoid status, and patterns of response to phenothiazine in acute schizophrenics. *Schizophrenia Bulletin,* 3, 24-37.

Goldstein, J.M., Litwin, L.C., Sutton, E.B. (1993). Seroquel: electrophysiological profile of a potential atypical antipsychotic. *Psychopharmacology (Berl)*, 112, 293-298.

Gur, R.E., McGrath, C., Chan, R.M., Schroeder, L., Turner, T., Turetsky, B.I., Kohler, C., Alsop, D., Maldjian, J., Ragland, J.D. & Gur, R.C. (2002). An fMRI study of facial emotion processing in patients with schizophrenia. *American Journal of psychiatry,* 159, 1992-99.

Habel, U., Gur, R.C., Mandal, M.K., Salloum, J.B., Gur, R.E. & Schneider, F. (2000). Emotional processing in schizophrenia across cultures: standarized measures of discrimination and experience. *Schizophrenia Research,* 42, 57-66.

Hafner, H., Loffler, W., Maurer, K., Hambrecht, M. & an der Heiden, W. (1999). Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. *Acta Psychiatrica Scandinavica,* 100(2), 105-18.

Hans, S.L., Auerbach, J.G., Asarnow, J.R., Styr, B. & Marcus, J. (2000). Social adjustment of adolescents at risk for schizophrenia: the Jerusalem Infant Development Study. *Journal of the American Academy of Child and Adolescent Psychiatry,* 39(11), 1406-14.

Hafner, H., Loffler, W., Maurer, K., Hambrecht, M. & an der Heiden, W. (1999). Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. *Acta Psychiatrica Scandinavica,* 100, 105-18.

Hariri, A.R., Bookheimer, S.Y. & Mazziotta, J.C. (2000). Modulating emotional responses: effects of a neocortical network on the limbic system. *Neuroreport,* 11, 43-48.

Harrison, P.J. & Owen, M.J. (2003). Genes for schizophrenia: recent findings and their pathophysiological implications. *Lancet,* 361, 417-19.

Harrison, P.J. & Weinberger, D.R. (2005). Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Molecular Psychiatry,* 10(1), 40-68.

Harvey, A.G. & Bryant, R.A. (1998). The effect of attempted thought suppression in acute stress disorder. *Behaviour Research and Therapy,* 36(6), 583-90.

Haskins, B., Shutty, M.S. Jr. & Kellogg, E. (1995). Affect processing in chronically psychotic patients: development of a reliable assessment tool. *Schizophrenia Research,* 15, 291-297.

Heilman, K.M. & Gilmore, R.L. (1998). Cortical influences in emotion. *Journal of Clinical Neurophysiology,* 15(5), 409-23.

Heimberg, C., Gur, R.E., Erwin, R.J., Shtasel, D.L. & Gur, R.C. (1992). Facial emotion discrimination: III. Behavioral findings in schizophrenia. *Psychiatry Research,* 42, 253-65.

Ho, B.C., Andreasen, N.C. & Flaum, M. (1997). Dependence on public financial support early in the course of schizophrenia. *Psychiatric Services,* 48, 948-950.

Hong, L.E., Tagamets, M., Avila, M., Wonodi, I., Holcomb, H., Thaker, G.K. (2005). Specific motion processing pathway deficit during eye tracking in schizophrenia: a performance-matched functional magnetic resonance imaging study. *Biological Psychiatry*, 57(7), 726-32.

Ioannides, A.A., Poghosyan, V., Dammers, J. & Streit, M. (2004). Real-time neural activity and connectivity in healthy individuals and schizophrenia patients. *Neuroimage,* 23(2), 473-82.

Ingraham, L.J., Kugelmass, S., Frenkel, M.N. & Mirsky, A.F. (1995). Twenty-five-year follow-up of the Israeli High Risk Study: current and lifetime psychopathology. *Schizophrenia Bulletin,* 21, 183-92.

Ingvar, D.H. & Franzen, G. (1974). Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. *Acta Psychiatrica Scandinavica,* 50, 425-462.

Iwase, M., Yamashita, K., Takahashi, K., Kajimoto, O., Shimizu, A., Nishikawa, T., Shinosaki, K., Sugita, Y. & Takeda, M. (1999). Diminished facial expression despite the existence of pleasant emotional experience in schizophrenia. *Methods and Findings in Experimental and Clinical Pharmacology,* 21(3), 189-94.

Jacobson, R. (1986). Disorders of facial recognition, social behaviour and affect after combined bilateral amygdalotomy and subcaudate tractotomy: a clinical and experimental study. *Psychological Medicine,* 16, 439-450.

Jackson, J.H. (1875). On temporary mental disorders after epileptic paroxysms. *West Riding Lunatic Asylum Medical Report,* 5, 105-129.

Jackson, J.H. (1889). On postepileptic states: a contribution to the comparative study of insanities. *Journal of Mental Science,* 34, 490-500.

James, W. (1884). What is an emotion? *Mind* 9, 188-205.

Johnstone, E.C. & Owens, D.G. (1980). The disabilities of chronic schizophrenia. *British Journal of Psychiatry,* 137, 495-6.

Johnston, P.J., Katsikitis, M. & Carr, V.J. (2001). A generalised deficit can account for problems in facial emotion recognition in schizophrenia. *Biological Psychology,* 58(3), 203-27.

Jones, E.G. (1995). Cortical development and neuropathology in schizophrenia. *Ciba Foundation Symposium,* 193, 277-95.

Jones, E.G. (1997). Cortical development and thalamic pathology in schizophrenia. *Schizophrenia Bulletin,* 23(3), 483-501.

Kapler, E.S., Hariri, A.R. & Mattay, V.S. (2001). Correlated attenuation of amygdala and autonomic responses: a simultaneous fMRI and SCR study. *Society for Neuroscience Abstracts,* 645, 3.

Kapur, S., Remington, G. Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient (2001). *Biological Psychiatry,* 50(11), 873-83.

Kapur, S., Seeman, P. (2002). Atypical antipsychotics, cortical D(2) receptors and sensitivity to endogenous dopamine. *British Journal of Psychiatry*, 180, 465-6.

Kapur, S., Zipursky, R., Jones, C., Shammi, C.S., Remington, G., Seeman, P. (2000). A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. *Archives of General Psychiatry*, 57(6), 553-9.

Kling, A. (1972). Effects of amygdalectomy on social-affective behavior in non-human primates, in The Neurobiology of the Amygdala. Edited by Eleftheriou BE. New York, Plenum, pp 511-536.

Kirkpatrick, B., Buchanan, R., Ross, D.E. & Carpenter, W.T. (2001). A seperate disease within the syndrome of schizophrenia. *Archives of General Psychiatry,* 58, 165-171.

Kohler, C., Bilker, W., Hagendoorn, M., Gur, R. & Gur, R. (2000). Emotion recognition deficit in schizophrenia with symptomatology and cognition. *Biological Psychiatry,* 48, 127-36.

Kosaka, H., Omori, M., Murata, T., Iidaka, T., Yamada, H., Okada, T., Takahashi, T., Sadato, N., Itoh, H., Yonekura, Y. & Wada, Y. (2002). Differential amygdala response during facial recognition in patients with schizophrenia: an fMRI study. *Schizophrenia Research,* 57(1), 87-95.

Krause, E.D., Mendelson, T. & Lynch, T.R. (2003). Childhood emotional invalidation and adult psychological distress: the mediating role of emotional inhibition. *Child Abuse and Neglect,* 27(2), 199-213.

Kring, A.M., Kerr, S.L. & Earnst, K.S. (1999). Schizophrenic patients show facial reactions to emotional facial expressions. *Psychophysiology,* 36(2), 186-92.

Lee, K.H., Farrow, T.F., Spence, S.A. & Woodruff, P.W. (2004). Social cognition, brain networks and schizophrenia. *Psychological Medicine,* 34(3), 391-400.

Kline, J.S., Smith, J.E. & Ellis, H.C. (1992). Paranoid and nonparanoid schizophrenic processing of facially displayed affect. *Journal of psychiatric Research,* 26, 169-82.

Levesque, J., Eugene, F., Joanette, Y., Paquette, V., Mensour, B., Beaudoin, G., Leroux, J-M., Bourgouin, P. & Beauregard, M. (2003). Neural circuitry underlying voluntary suppression of sadness. *Biological Psychiatry,* 53, 502-10.

Lewis, S.F. & Garver, D.L. (1995). Treatment and diagnostic subtype in facial affect recognition in schizophrenia. *Journal of psychiatric Research,* 29(1), 5-11.

Lewis, D.A. & Lieberman, J.A. (2000). Catching up on schizophrenia: natural history and neurobiology. *Neuron,* 28(2), 325-34.

Liddle, P.F. (1987). The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. *British Journal of psychiatry,* 151, 145-51.

Limpert, C. & Amador, X. (2001). Negative symptoms and the experience of emotion. In Negative symptom and cognitive deficit treatment response in schizophrenia. Edited by Richard S.E. Keefe and Joseph P. McEvoy. 1st edition. American Psychiatric Press. Washington DC.

Lublin, H., Eberhard, J., Levander, S. (2005). Current therapy issues and unmet clinical needs in the treatment of schizophrenia: a review of the new generation antipsychotics. *Internatioinal Clinical Psychopharmacology*, 20(4), 183-198.

Mattes, R.M., Schneider, F., Heimann, H. & Birbaumer, N. (1995). Reduced emotional response of schizophrenic patients in remission during social interaction. *Schizophrenia Research,* 17(3), 249-55.

Mayer, M., Alpert, M., Stastny, P., Perlick, D. & Empfield, M. (1985). Multiple contributions to clinical presentation of blunted affect in schizophrenia. *Schizophrenia Bulletin,* 11, 420-6.

McGlashan, T.H. & Fenton, W.S. (1992). The positive-negative distinction in schizophrenia: review of natural history validators. *Archives of General Psychiatry,* 49, 63-72.

McGlashan, T.H. & Hoffman, R.E. (2000). Schizophrenia as a disorder of developmentally reduced synaptic connectivity. *Archives of General Psychiatry,* 57(7), 637-48.

Mega, M.S. & Cummings, J.L. (2001). The frontal lobes and neuropsychiatric illness. In: Salloway S, Malloy P, and Duffy J, editors. American Psychiatric Publishing, inc. Washington, DC. London, England. 1st. Edition.

Meltzer, H.Y. & Gudelsky, G.A. (1992). Dopaminergic and serotonergic effects of clozapine: implications for a unique clinical profile. *Arzneimittelforschung* 42, 268–272

Mesulam, M.M. & Mufson, E.J., (1982). Insula of the old world monkey. I: Architectonics in the insulo-orbito-temporal component of the paralimbic brain. *Journal of Comparative Neurology,* 212, 1–22.

Mirsky, A.F., Kugelmass, S., Ingraham, L.J., Frenkel, E. & Nathan, M. (1995). Overview and summary: twenty-five-year follow-up of high-risk children. *Schizophrenia Bulletin,* 21, 227-39.

Mirsky, A.F., Kugelmass, S., Ingraham, L.J., Frenkel, E. & Nathan, M. (1995). Overview and summary: twenty-five-year followup of high-risk children. *Schizophrenia Bulletin,* 21(2), 227-39.

Moll, J., de Oliveira-Souza, R., Eslinger, P.J., Bramati, I.E., Mourao-Miranda, J., Andreiuolo, P.A. & Pessoa, L. (2002). The neural correlates of moral sensitivity: a functional magnetic resonance imaging investigation of basic and moral emotions. *Journal of Neuroscience,* 22(7), 2730-36.

Morrison, R.L., Bellack, A.S. & Mueser, K.T. (1988). Deficits in facial-affect recognition and schizophrenia. *Schizophrenia Bulletin,* 14, 67-83.

Murphy, K.J. & Regan, C.M. (1998). Contributions of cell adhesion molecules to altered synaptic weightings during memory consolidation. *Neurobiology of Learning and Memory,* 70, 73-81.

Murray, C.J.L. & Lopez, A.D. (1996). The global burden of disease and injury series: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. vol 1. Cambridge, MA: Harvard University Press.

Nauta, W.J.H. (1971). The problem of the frontal lobes: a reinterpretation. *Journal of Psychiatric Research,* 8, 167-87.

Pao, P.N. (1979). Schizophrenic Disorder: Theory and treatment from a psychodynamic point of view. New York, NY: International Universities Press.

Paradiso, S., Andreasen, N.C., Crespo-Facorro, B., O'Leary, D.S., Watkins, G.L., Boles Ponto, L.L. & Hichwa, R.D. (2003). Emotions in unmedicated patients with

schizophrenia during evaluation with positron emission tomography. *American Journal of Psychiatry,* 160(10), 1775-83.

Phan, K.L., Wager, T., Taylor, S.F. & Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage,* 16, 331-48.

Phillips, M.L. (2003). Understanding the neurobiology of emotion perception: implications for psychiatry. *British Journal of Psychiatry,* 182, 190-2.

Ploog, D. (1981). Neurobiology of primate audio-vocal behavior. *Brain Research Reviews,* 3, 35-61.

Poppel, E. (1997). A hierarchical model of temporal perception. *Trends in Cognitive Sciences,* 1, 56-61.

Price, J.L., Carmichael, S.T. & Drevets, W.C. (1996). Networks related to the orbital and medial prefrontal cortex: A substrate for emotional behavior? *Progress in Brain Research,* 106, 523-36.

Purdon, C. (1999). Thought suppression and psychopathology. *Behaviour Research and Therapy,* 1999;37(11), 1029-54.

Pogue-Geile, M.F. & Harrow, M. (1985). Negative symptoms in schizophrenia: Their longitudinal course and prognostic importance. *Schizophrenia Bulletin,* 11, 427-39.

Olin, S.S. & Mednick, S.A. (1996). Risk factors of psychosis: identifying vulnerable populations premorbidity. *Schizophrenia Bulletin,* 22, 223-40.

Owen, F., Crow, T.J., Frith, C.D., Johnson, J.A., Johnstone, E.C., Lofthouse, R., Owens, D.G. & Poulter, M. (1987). Selective decreases in MAO-B activity in post-mortem brains from schizophrenic patients with type II syndrome. *British Journal of Psychiatry,* 151, 514-9.

Roff, J.D. & Knight, R. (1978). Young adult schizophrenics: prediction of outcome and antecedent childhood factors. *Journal of Consultation and Clinical Psychology,* 46, 947-52.

Ross, R.G., Olincy, A., Mikulich, S.K., Radant, A.D., Harris J.G., Waldo, M. (2002). Admixture analysis of smooth pursuit eye movements in probands with schizophrenia

and their relatives suggests gain and leading saccades are potential endophenotypes, *Psychophysiology*, 39, 809-819.

Samson, J.A., Gurrera, R.J., Nisenson, L. & Schildkraut, J.J. (1995). Platelet monoamine oxidase activity and deficit syndrome schizophrenia. *Psychiatry Research,* 56(1), 25-31.

Schneider, F., Weiss, U., Kessler, C., Salloum, J.B., Posse, S., Grodd, W. & Muller-Gartner, H.W. (1998). Differential amygdala activation in schizophrenia during sadness. *Schizophrenia Research,* 34(3), 133-42.

Schuldberg, D., Quinlan, D.M. & Glazer, W. (1999). Positive and negative symptoms and adjustment in severely mentally ill outpatients. *Psychiatry Research,* 85, 177-88.

Scoville, W.B., Dunsmore, R.H., Liberson & W.T. (1953). Observations on medical temporal lobotomy and uncotomy in the treatment of psychotic states. *Proceedings of the Association of Research on Nervous and Mental Diseases,* 31, 347-369.

Seeman P, Lee T, Chau-Wong M (1976). Antipsychotic drug and neuroleptic/dopamine receptors. *Nature*, 261, 717-719.

Seeman P, Corbett R, Van Tol HH. (1997). Atypical neuroleptics have low affinity for dopamine D2 receptors or are selective for D4 receptors. *Neuropsychopharmacology*,16, 93-110; discussion 111-135.

Seeman P. (2002). Atypical antipsychotics: mechanism of action. *Canadian Journal of Psychiatry*, 47(1), 27-38.

Selemon, L.D. & Rajkowska, G. (2003). Cellular pathology in the dorsolateral prefrontal cortex distinguishes schizophrenia from bipolar disorder. *Current Molecular Medicine,* 3(5), 427-36.

Selemon, L.D. & Goldman-Rakic, P.S. (1999). The reduced neuropil hypothesis: a circuit based model of schizophrenia. *Biological Psychiatry,* 45(1), 17-25.

Seidman, L.J. (1983). Schizophrenia and brain dysfunction: an integration of recent neurodiagnostic findings. *Psychological Bulletin,* 94, 195-238.

Simpson, J.R., Ongur, D. & Akbudak, E. The emotional modulation of cognitive processing: an fMRI study. Journal of *Cognitive Neuroscience,* 12(Suppl.2), 157-170.

Sison, C.E., Alpert, M., Fudge, R & Stern, R.M. (1996). Constricted expressiveness and psychophysiological reactivity in schizophrenia. *Journal of Nervous and Mental Disorders,* 184(10), 589-97.

Strauss, M.E. (1973). Behavioral differences between acute and chronic schizophrenics. Course of psychosis, effects of institutionalization, or sampling bias? *Psychological Bulletin,* 79, 271-9.

Sugahara, M. & Shiraishi, H. (1999). Dopamine D1 and D2 receptor agents and their interaction influence the synaptic density of the rat prefrontal cortex. *Neuroscience Letters,* 259(3), 141-4.

Sweet, L., Primeau, M., Fichtner, C. & Lutz, G. (1998). Dissociation of affect recognition and mood state from blunting in patients with schizophrenia. *Psychiatry Research,* 81, 301-8.

Tamminga, C.A., Buchanan, R.W. & Gold, J.M. (1998). The role of negative symptoms and cognitive dysfunction in schizophrenia outcome. *International Clinical Psychopharmacology,* 13(suppl 3), S21-S26.

Tandon, R. (2004). Quetiapine has a direct effect on the negative symptoms of schizophrenia. *Human Psychopharmacology*, 19(8), 559-63.

Tauscher-Wisniewski S, Kapur S, Tauscher J, Jones C, Daskalakis ZJ, Papatheodorou G, Epstein I, Christensen BK, Zipursky RB (2002). Quetiapine: an effective antipsychotic in first-episode schizophrenia despite only transiently high dopamine-2 receptor blockade. *Journal of Clinical Psychiatry*, 63(11), 992-7.

Taylor, S.F., Phan, K.L., Britton, J.C., Liberzon, I. (2005). Neural response to emotional salience in schizophrenia. *Neuropsychopharmacology,* 30(5), 984-95.

Tsuang, M.T., Lyons, M.L. & Faraone, S.V. (1990). Heterogeneity of schizophrenia: Conceptual models and analytic strategies. *British Journal of Psychiatry,* 156, 17-26.

Volkow, N.D., Wolf, A.P., Van Gelder, P., Brodie, J.D., Overall, J.E., Cancro, R. & Gomez-Mont, F. (1987). Phenomenological correlates of metabolic activity in 18 patients with chronic schizophrenia. *American Journal of Psychiatry,* 144(2), 151-8.

Vuilleumier, P., Richardson, M.P., Armony, J.L., Driver, J. & Dolan, R.J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nature Neuroscience,* 7(11), 1271-8.

Watt, N.F. (1978). Patterns of childhood social development in adult schizophrenics. *Archives of General Psychiatry,* 35, 160-5.

Weddell, R.A., Miller, J.D. & Trevarthen, C. (1990). Voluntary emotional facial expression in patients with focal cerebral lesions. *Neuropsychologia,* 28, 49-60.

Weinberger, D.R. & Wyatt, R.J. (1982). Brain morphology in schizophrenia: In vivo studies. In: Henn F, Nasrallah H, editors. Schizophrenia as a Brain Disease. Oxford: Oxford Univ Press, pp 148-175.

Weinberger, D.F. (1988). Schizophrenia and the frontal lobe. *Trends in Neurosciences,* 11, 367-370.

Weinberger, D.R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry,* 44, 660-9.

Weinberger, D.R. (1995). From neuropathology to neurodevelopment. *Lancet,* 346(8974), 552-7.

Whittaker, J.F., Connell, J. & Deakin, J.F.W. (1994). Receptive and expressive social communication in schizophrenia. *Psychopathology,* 27, 262-7.

Whitty, P., Clarke, M., Browne, S., McTigue, O., Kamali, M., Feeney, L., Lane, A., Kinsella, A., Waddington, J.L., Larkin, C. & O'Callaghan, E. (2003). Prospective evaluation of neurological soft signs in first-episode schizophrenia in relation to psychopathology: state versus trait phenomena. *Psychological Medicine,* 33(8), 1479-84.

World Health Organization. International classification of diseases, 10th edn. Geneva: WHO, 1994.

Wu, J.C., Amen, D. & Bracha, H.S. (2000). Neuroimaging in clinical practice, in Kaplan and Sadock's Comprehensive Textbook of Psychiatry, 7th ed. Edited by Sadock BJ, Sadock VA. New York, Williams & Wilkins, pp 373-385.