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Abnormal Brain Connectivity in Schizophrenia:

Investigations into Episodic Memory Networks

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Abstract

Abnormal connectivity between the prefrontal cortex (PFC) and other brain regions has been demonstrated in subjects with schizophrenia. We tested if abnormal connectivity, particularly between PFC and the medial temporal lobes (MTL), underlies the reduced brain activity and level of accuracy observed in schizophrenia subjects during episodic memory tests. We used fMRI to examine activation in fifteen chronic, medicated schizophrenia subjects and eighteen control subjects in two different recognition memory tests. The item recognition memory test required subjects to make old/new judgments, and the associative recognition memory test required them to make intact/rearranged judgments. We examined brain connectivity separately, with a structural equation modeling, based on anatomical links found in the literature. During associative recognition memory, subjects with schizophrenia failed to demonstrate the significant connectivity bilaterally between different areas of PFC and posterior MTL/fusiform regions that was observed in control subjects. However, during recognition memory of individual items, subjects with schizophrenia demonstrated significant connectivity between the anterior part of the MTL and medial PFC similar to control subjects. These findings provide evidence of a lack of proper integration between PFC and fusiform/MTL areas underlying episodic memory deficits of visual objects in schizophrenia, particularly during associative recognition memory.

Résumé

Certains expliquent les déficits cognitifs et symptômes qu'on retrouve chez les personnes schizophrènes par une réduction de connectivité entre les réseaux neuronaux. Nous avons testé cette hypothèse à l'aide de l'imagerie fonctionnelle, par l'intermédiaire d'une tâche mnésique qui dissocie la reconnaissance d'items individuels de la reconnaissance associative. Nous avons comparé la connectivité de personnes schizophrènes à celle de sujets sains entre différentes régions, temporales et préfrontales entre autres. Nous notons, pour la mémoire d'associations, l'absence chez les personnes schizophrènes de deux connectivités significatives chez les personnes saines, l'une entre le fusiforme et le cortex ventrolatéral et l'autre entre les cortex parahippocampique et dorsolatéral. Par contre, les deux groupes ont déployé suffisamment de connectivité lors de la mémoire d'items pour que soit significative la corrélation entre les cortex périrhinal et orbitofrontal. Le tout suggère que la déconnectivité pourrait expliquer le déficit associé à la reconnaissance d'associations chez les personnes schizophrènes.

Acknowledgments

In the theoretical context, I reproduce, with a few changes, a meta-analysis that has been previously published. While I was the first author of this meta-analysis, it received many insightful contributions from the following co-authors: Amélie M. Achim, Alonso Montoya, Samarthji Lal, and my supervisor, Martin Lepage. The description of the fMRI experiment reproduces a few part of a submitted paper to which I was a co-author. Throughout my master, I received the financial support from the Québec government (FRSQ).

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Introduction

Schizophrenia is a very severe mental disorder. In addition to being distressing to the patient, the disorder is disruptive for the loved ones, and for the society. Schizophrenia is indeed among the top five causes of disability and of suicide for young adults in developed countries (Green, 2001). The lifetime prevalence of the disease is approximately 1/100 (Freedman, 2003). The onset of schizophrenia commonly occurs in the late teens or twenties, and leads to profound academic, occupational, and social impairments. This symptomatically complex disorder is characterized by "positive" symptoms such as hallucinations, delusions, and disorganized thought; and "negative" symptoms such as anhedonia, avolition, social withdrawal, and blunted affect. While depression is often considered as a non-specific accompaniment of schizophrenia, a larger number of schizophrenia subjects experience it before or after the onset of psychosis, up to 70%, according to some studies (Cutting, 2000).

In recent years, through clinical neuropsychological assessment and experimental cognitive tests, researchers have shown that schizophrenia subjects are affected by deficits in a large number of cognitive functions, encompassing among others attention, executive functions, language, visuo-spatial abilities, working memory, and episodic memory. An important program of research has thus been to explain how these deficits arise from the brain defects associated with schizophrenia.

It is with this perspective in mind that our laboratory, led by Martin Lepage, started recently to examine, with the help of functional Magnetic Resonance Imaging

(fMRI), the neural activity of schizophrenia subjects in a memory task. The specific aim of my project is to assess whether we can understand memory problems in schizophrenia in terms of faulty connectivity between specific brain regions.

The following thesis contains three sections. First, I review the evidence pertaining to anatomical studies and connectivity analyses of functional neuroimaging data which provide strong evidence for a faulty connection between brain regions as the main pathophysiological manifestation of schizophrenia. In the second section, I present a recently published meta-analysis that identified cognitive and clinical variables that have a significant moderating effect on performance of schizophrenia subjects in episodic memory tests. In the third section, I present the connectivity analysis that we have conducted on a group of control and schizophrenia subjects in a recognition memory task. In this analysis, we show among other results that schizophrenia subjects present significant lack of connectivity between different regions, including prefrontal and temporal cortex, in the network associated to the pair memory recognition.

Theoretical context

The modern conceptual framework of schizophrenia can be traced back to the work of Emil Kraepelin, when he developed the concept of dementia praecox as a distinct disease characterized by a pattern of symptoms including psychosis and sub-acute functioning of mental capacity (Callicott et al., 2000) . Already at that time, Kraepelin postulated that brain insults were at the core of the development of the disease: "*Partial damage to, or destruction of, cells of the cerebral cortex must probably occur, which may be compensated for in some cases, but which mostly brings in its wake a singular, permanent impairment of the inner life (page 154)*" (as reported by (McCarley, Shenton, O'Donnell, & Nestor, 1993). Post-mortem studies as well as studies employing newer technologies such as neuroimaging have provided substantial evidence that schizophrenia is indeed affected by cortical, subcortical, and cerebellar damage.

Anatomical data on schizophrenia

Neuropathology at the cellular level

One strategy in the search of brain defects in schizophrenia has been to look for aberrant local or clustered neurons in several parts of the brain of schizophrenia subjects. Researchers have indeed observed several qualitative and quantitative changes. The most reliable observations include: 1) reduced cell bodies of pyramidal neurons of the hippocampus, particularly in the subiculum, CA1 layer (Arnold et al., 1995); 2) reduced neuron size in the lamina II of the entorhinal cortex (Kovalenko et

al., 2003); 3) changes in neuronal density observed in prefrontal and hippocampus, but not found in occipital cortex (Conrad, Abebe, Austin, Forsythe, & Scheibel, 1991; Harrison, 1999; Rajkowska, Selemon, & Goldman-Rakic, 1998); 4) reduced density of some interneurons and their synapses in the neocortex, particularly in the frontal and temporal lobes (Harrison & Weinberger, 2005); 5) and, fewer neurons in the thalamus (Highley, Walker, Crow, Esiri, & Harrison, 2003).

While these observations are clearly signaling for abnormal cortical structure, none indicates a state of insult in any region as profound as those observed for example in Alzheimer's Disease. Furthermore, at the cellular level, researchers do not observe pathologically significant neurogliosis (Arnold et al., 1998; Benes, McSparren, Bird, SanGiovanni, & Vincent, 1991). Other sources of data provided support to a developmental origin of the pathophysiology. One of the most important discoveries along this line was the observation of abnormal cortical subplate developments in schizophrenia (E. G. Jones, 1995). The cortical subplate is a transitional structure playing a key role in the formation of connections in the cerebral cortex (Kandel, Schwartz, & Jessell, 2002). In schizophrenia subjects, the number of these neurons in the superficial white matter of both prefrontal and temporal lobe cortices is significantly reduced, but is greater in deeper white matter, which is probably the result of abnormal migration (Akbarian et al., 1996; Akbarian et al., 1993; Arnold, Hyman, Van Hoesen, & Damasio, 1991). Because the cortical subplate gives rise to the white matter necessary for local connectivity, this defect could lead to defective local connectivity, particularly in frontal and temporal lobes (Harrison, 1999; T. C. Jones & Jacoby, 2001). These, and other evidence, led investigators to

formulate the view that schizophrenia was fundamentally a neurodevelopmental disorder (Harrison & Weinberger, 2005; Raedler, Knable, & Weinberger, 1998). This model holds that genes and environmental insults exert a role early in the development of a vulnerable person which affects the normal development of the brain up until the adulthood, when the psychotic and negative symptoms appear more critical. A spectrum of animal models suggests indeed that damage to the hippocampus early in the development of neonatally rats increases substantially the risk of aberrant development of the prefrontal cortex during adolescence (Harrison & Lewis, 2003; Harrison & Weinberger, 2005), decreases the expression of mRNAs for dopamine transporter in adult rats , and augments the apparition in adult rats of behaviour that mimic some of the symptoms observed in schizophrenia (Lipska, Lerman, Khaing, & Weinberger, 2003; Weinberger & Marenco, 2003).

From this very short review of neuropathology in schizophrenia, we can safely draw two conclusions. First, the neuropathology in schizophrenia seems to stem from defective developmental alterations in various parameters of the microcircuitry of the brain that could potentially result in reduced communication between the different regions of the brain (Harrison & Weinberger, 2005). This statement does not deny that a neurodegenerative process like apoptosis – a highly regulated form of cell death -- might contribute to the pathophysiology of schizophrenia following the onset of psychosis (Jarskog, Glantz, Gilmore, & Lieberman, 2005), as some interaction between a developmental altered microcuirtry and cellular death might be possible. Second, many of these alterations observed at the cellular level imply regions involved in memory, including the hippocampus, enthorhinal cortex, thalamus, and

frontal lobes. As we will see, these regions are part of a network that is of crucial importance to episodic memory.

Volumetric studies

This second conclusion is indeed highly convergent with evidence found from cerebral volumetric studies. These studies suggest that brain volume reductions are a vulnerability factor of schizophrenia. Volume reductions in several cortical regions, preferentially in prefrontal, temporal, limbic, as well as in the thalamic nuclei (N. C. Andreasen et al., 1994; Arnold, 1999; R. E. Gur, Cowell et al., 2000; R. E. Gur et al., 1998; R. E. Gur, Turetsky et al., 2000; Harrison, 1999; Heckers, 1997; Pantelis et al., 2003; B. Turetsky et al., 1995; B. I. Turetsky, Moberg, Roalf, Arnold, & Gur, 2003; Velakoulis et al., 2002). In one critical review of 118 studies (McCarley et al., 1999), the investigators noted that the temporal lobe suffers the most important brain volume reductions relative to other brain regions. Moreover, in two meta-analyses of MRI hippocampal volumetric studies (Nelson, Saykin, Flashman, & Riordan, 1998; Wright et al., 2000), researchers found evidence across studies of a consistent bilateral hippocampal volume reduction of approximately 5%. Meta-analyses of frontal lobe volumes also reported reductions associated with schizophrenia (Davidson & Heinrichs, 2003; Wright et al., 2000; Zakzanis & Heinrichs, 1999) of similar magnitude (effect sizes varying from 0.34 to 0.44, which correspond approximately to a reduction of 4%-6%). Of importance, it has been shown that frontal and temporal lobe volume reductions were present at the onset of the disease, ruling out possible drug effects on neural volume (R. E. Gur, Turetsky, Bilker, & Gur, 1999; Pantelis et al., 2003). Regression analyses examining the relationship between

left frontal lobe and left temporal lobe volumes reductions showed that these reductions were correlated in schizophrenia subjects (Bullmore et al., 1998).

In summary, while this short review of anatomical data is admittedly incomplete, it nonetheless shows the critical importance of the medial temporal lobe (MTL) in the manifestation of the psychopathology of schizophrenia. Early manifestation of aberrant development of this region affects the dopamine circuitry as well as the development of the cortex occurring later in persons vulnerable to schizophrenia. It also appears to lead to reduced gray matter in the MTL, although aberrant apoptosis following psychosis (and perhaps medication) appears to participate in this process (Cahn, Hulshoff Pol, Bongers et al., 2002; Cahn, Hulshoff Pol, Lems et al., 2002; Jarskog et al., 2005; Jarskog, Selinger, Lieberman, & Gilmore, 2004). It is likely that these abnormal processes predispose schizophrenia subjects to aberrant long-term changes in connection strength between the MTL and the rest of the brain, affecting modulatory neurotransmitter systems, particularly between the MTL and the prefrontal cortex (Friston, 1998). Similarly, one could expect that MTL pathology is likely associated with the neuropsychological impairments of schizophrenia (Harrison, 2004).

Functional imaging: the method

One limitation of the studies examining anatomical and volumetric data is that they do not investigate the brain in action. The advent of functional neuroimaging has made available the investigation of brain activity as subjects are performing a task. Moreover, recent developments in statistical techniques make it possible to point out within a given network the faulty connectivity that contributes to a normal or

abnormal activity of the brain. Together, these techniques provide a way to empirically test *in vivo* the regions in the brain that do not show proper communication. In the next few paragraphs, I will provide a brief description of how these techniques work.

The potential of the functional imaging is to provide a means to investigate non-invasively the distributed cortical areas sustaining a cognitive task. Functional imaging relies on the correspondence between physical changes in the brain (e.g., blood flow) and mental functioning (e.g., reading and memorizing a word). Functional Magnetic Resonance Imaging (fMRI), one of the imaging techniques relies on two properties of the brain (Raichle, 1998). First, deoxygenated haemoglobin is more senstive to a magnetic field than oxygenated blood, giving rise to a slightly different magnetic resonance signals between the two. An MR scanner is used to detect this signal difference, and this provides the BOLD contrast. Second, hemodynamic activity is closely linked to neural activity. When neurons are active, they consume oxygen supplied by local capillaries. Approximately 4-6 seconds after a burst of neural activity, a hemodynamic response occurs and oxygen-rich blood.infuses this region of the brain. Thus, sudden changes of BOLD signal are interpreted as sudden changes of brain activity (Friston, Frith, Turner, & Frackowiak, 1995).

To detect such changes, one must include in any functional imaging paradigm measurements from at least two brain states. In order to identify the neural substrates of one cognitive process of interest (eg. novelty detection), one must contrast an

activation task (eg. presentation of novel items) that engages the process of interest with a baseline task that does not (eg. presentation of already seen items) (Price, 2000). The standard statistical tests used to find voxels in which the changes are significant represent are univariate, because one measures each voxel in the map somewhat independently from each other.

Because it focuses on the neural correlates of a fine-grained process, this standard technique is framed in a logic looking at the functional specialization of the brain. However, one can be interested in examining in functional integration, that is, the capacity of different functionally specialized systems to work together as a necessary condition for the optimal performance of the brain (Friston, Frith, Frackowiak, & Turner, 1995). Such analysis will require a different approach. Functional connectivity analysis is a broad term which refers to the different mathematical techniques which statistically assess the temporal coherence among the activity of different neurons (Horwitz, 2003). Functional connectivity is thus calculated from correlational measurements, which can be computed from trial-to-trial covariability, block-to-block covariability, or subject-to-subject covariability. This functional connectivity analysis, though they may rely on multiple univariate correlations or regressions, needs to integrate a multivariate analysis in order to identify the contribution of each node into a brain network. A strategy often selected by researchers is to take one voxel or one region of interest (ROI) and use it as a "seed" voxel/region to which ROI from all other regions of interest or in the whole brain will be regressed (Della-Maggiore et al., 2000)

Effective connectivity differs from functional connectivity in two ways. First, it incorporates an anatomical model in which regions of interest (nodes) are selected, either from a preliminary univariate analysis or *a priori*. Second, it requires a multivariate statistical technique, which makes it possible to identify connection strengths that best predict the observed variance-covariance structure of the data, with respect to the specified anatomical model. Structural equation modeling (also known as path analysis) is the statistical technique most appropriate when the model encompasses many brain regions. Each connection strength in this model thus reflects the influence one node has on the other (Friston, 1994). Faulty connectivity in one group of subjects can be expressed by reduced or inflated path coefficients compared to a control group, or yet by the uncovering of an entirely different network.

Connectivity in schizophrenia

Recently, several researchers have suggested that schizophrenia brought about a state of dysconnectivity in the brain, more precisely by a lack of proper connectivity (Friston, Herold, & Fletcher, 1995; McGuire & Frith, 1996; Weinberger, Aloia, Goldberg, & Berman, 1994; Weinberger, Berman, Suddath, & Torrey, 1992) or a "cognitive dysmetria"[1] (N. Andreasen, 2000; N. C. Andreasen et al., 1996). In concrete terms, this hypothesis suggests that, in schizophrenia subjects, brain areas communicate poorly between themselves. Poor communication implies that a change of the level of activity in one specific region fails to modulate sufficiently the activity

[1] The expression « cognitive dysmetria » (from the greek *metron*, meaning the proper measure), refers to the difficulty for the patients to coordinate the adequate mental activity necessary for doing a mental task. The defective neural substrates she proposes include the cerebellum and the thalamus, in addition to the prefrontal cortex. The key element remains nonetheless the fact that schizophrenia is associated with improper connectivity communication.

of the other parts of the brain to which it is normally connected. This lack of modulation, rather a lack of activation per se, appears critical for the occurrences of cognitive dysfunctions and psychotic symptoms in schizophrenia. People with schizophrenia who are prone to auditory hallucinations, for example, have demonstrated normal activation in left prefrontal cortex when engaged in speech generation. However, these activations did not seem to modulate appropriately the activity in temporal and cerebellar cortex, key regions for self-monitoring speech generation (Shergill et al., 2004; Shergill, Brammer, Williams, Murray, & McGuire, 2000). In fact, any cognitive task typically engages a large network of distinct functional regions. It is likely that a lack of communication between these regions might induce a failure to perform at optimal level.

The hypothesis that dysconnectivity might explain the cognitive dysfunctions observed in schizophrenia first stemmed from functional studies which showed co-occurrences (or lack thereof) of activated brain regions. In fact, such co-occurrences (or lack of co-occurrences) can only suggest, but do not test directly, the dysconnectivity hypothesis. In recent years, though, several studies have examined both functional and effective connectivity in schizophrenia. Most of the studies that have analyzed connectivity in schizophrenia have selected semantic memory or working memory as their challenging cognitive functions. These two functions were selected because the neural correlates of both are hypothesized to involve a network of different cortical regions, and because the prefrontal cortex is considered to be a key region in each of these networks. Semantic memory and working memory were

further selected because many investigators hypothesized that deficits in semantic and working memory associated with schizophrenia could result from ineffective frontotemporal and/or frontoparietal connectivity (Bullmore, Frangou, & Murray, 1997; Friston, 1998; McGuire & Frith, 1996).

Before summarizing these studies, it should be mentioned that, with the publication of the very first functional imaging study, which showed significantly reduced blood flow in the frontal regions of schizophrenia subjects relative to the mean blood flow of the brain of controls (Ingvar & Franzen, 1974), the so-called "hypofrontality" result had become a landmark in brain imaging research with schizophrenia. Many studies that utilized a variety of tasks known to activate the prefrontal cortex have since shown abnormal activation of this region in schizophrenia (N. C. Andreasen et al., 1996; N. C. Andreasen et al., 1992; Buchsbaum et al., 1992; Callicott et al., 2000; Callicott et al., 1998; Carter et al., 1998; Catafau et al., 1994; Manoach et al., 2000; Manoach et al., 1999; Spence, Hirsch, Brooks, & Grasby, 1998; Stevens, Goldman-Rakic, Gore, Fulbright, & Wexler, 1998; Volz et al., 1997; Weinberger, Berman, & Illowsky, 1988; Weinberger et al., 1992; Weinberger, Berman, & Zec, 1986). We can mention in passing that some researchers now question the straight-forward interpretation that schizophrenia subjects suffer from hypofrontality (Bertolino et al., 2000; Manoach, 2003, GUR RIP). Several problems indeed limit the interpretation given to the results of the pioneer studies in schizophrenia. First, many of these studies did not match the performance of subjects to the performance of controls. Hence, the difference of brain

activation could simply reflect impaired performance (N. C. Andreasen et al., 1996; R. C. Gur & Gur, 1995). A second problem relates to the unwarranted assumption that group differences of brain activation will remain stable along any level of cognitive difficulty. Several studies reported dynamic changes of activations along different level of difficulty (Callicott et al., 2003; Curtis et al., 1999; Manoach et al., 2000; Manoach et al., 1999; Stevens et al., 1998; B. I. Turetsky, Cannon, & Gur, 2000). One could interpret these data as showing that brains of schizophrenia subjects are capable of exhibiting activation of similar magnitude than controls, but not for the same level of performance. This interpretation would imply that differences of functional connectivity would depend on the level of difficulty of the task.

Frontotemporal dysconnectivity

A large part of the work on the dysconnectivity hypothesis in schizophrenia has focused to a large extent on the frontotemporal interaction model. This preference for the frontotemporal model is motivated by several theoretical reasons, most notably because some of the core symptoms of schizophrenia, including hallucinations and problems with thought content, were found to be present in animal studies and in other human neuropsychological case studies where a disruption of a neural frontotemporal integration was noted (Burns, 2002, Hoffman, 1998). Another reason is the presence of substantial deficits of schizophrenia subjects in verbal fluency (for a recent meta-analysis, see (Bokat & Goldberg, 2003)).

Tests measuring the integrity of semantic memory have been frequently selected to assess the integrity of frontotemporal connectivity in control subjects.

Semantic memory refers to the knowledge we have acquired and retained about the world, knowledge about facts, about objects, and about the meaning of words (Cabeza & Nyberg, 2000a). It is considered to form, along with episodic memory--the memory for personal experiences-- what is called declarative memory, a type of memory which can be consciously and intentionallaly recollected[2] (Cohen & Eichenbaum, 1993; Gabrieli, Brewer, Desmond, & Glover, 1997)

Semantic categorization and verbal fluency are hypothesized to challenge overlapping processes for semantic memory. Semantic categorization consists in deciding if a concept possesses or not a given property (e.g. is it living?). After reading a word, a subject must retrieve the associated concept in its semantic memory in order to perform the category task. During a verbal fluency task, too, targeted words are part of a pre-determined category (e.g. words that meet a phonemic or semantic criterion), but verbal fluency adds an element of self-initiation necessary for the retrieval of the targeted words. The tasks are therefore similar in that they both require subjects to access information stored in long-term memory. This process is at the heart of declarative memory, but contrary to episodic memory, the fixed criterion

[2] This definition, which is on its way to becoming classic, has in fact attracted its good share of controversies in recent years, the extent of which goes beyond the scope of our thesis. Suffice it to mention one obvious difficulty: it is not clear to what level of awareness an animal can bring declarative knowledge to mind. Tentative ways to lighten the definite criteria to declarative memory have been proposed, for example that declarative memory is the system storing information which, during retrieval, can be expressed behaviorally (by speech or actions) as the content of propositional attitudes (Carruthers, 1998). This definition however renders more explicit two incompatible views about declarative memory. At one end of the spectrum, theorists like Endel Tulving promote the view that the capacity to recollect (to re-experience) an event is a distinctive component of episodic memory, which makes it a "separate entity", functionally different (and suggestively anatomically different as well) from semantic memory (Tulving, 2002, p.12). The opinion at the other end of the spectrum is that episodic and semantic memories consist of one system and are distinguished only by cognitive features not essential to declarative memory (Craik, 2001). The remaining common ground is that procedural knowledge and priming do not participate in declarative memory, such that knowledge coming from these skills are, under any circumstances, available in a declarative format only through a "metaknowledge" system and not from direct conscious introspection (Kihlstrom, 1987).

to which the target is appraised does not refer to an episodic moment in the life of the subject, but on a semantic property shared (or not) by a target. The first study to examine directly the connectivity underlying semantic processing in schizophrenia used a structural equation modeling design (Jennings, McIntosh, Kapur, Zipursky, & Houle, 1998). In this study, investigators compared a control group to a medicamented schizophrenia group with a PANSS total score of symptom severity in the 50th percentile, using a semantic categorization (Is it living?) contrasted to a simple phonetic decision task (does the word has the letter A?) (Jennings et al., 1998). Functional neuroimaging studies have largely demonstrated that semantic processing engages a network that includes respectively the left lateral temporal, the anterior cingulate, and the inferior prefrontal cortices. (Price, 2000, Henry, 2004 #1737). These regions were highly activated in the control group, and these regions exhibited significant internal connectivity between themselves (Jennings et al., 1998). In addition to this network, control subjects demonstrated positive connectivity between left anterior prefrontal cortex (BA 10) and anterior cingulate, and negative connectivity from VLPFC (BA45) to left anterior prefrontal (BA 10). In contrast, schizophrenia subjects showed a different connectivity network. They exhibited relative intact connectivity stemming from lateral temporal and left anterior prefrontal cortex. However, the connectivity in the network consisting of the left VLPFC (BA 45), anterior cingulate (BA 32), and right anterior prefrontal (BA 10) was abnormal. In particular, the right anterior prefrontal showed the largest difference of connectity between the groups. In particular, the efferent connection from left VLPFC to right anterior prefrontal cortex appear largely negative in the schizophrenia group. The

anterior cingulate showed largely reduced efferent connectivity with all prefrontal cortex regions in the schizophrenia group. Of particular interest given the first hypothesis on functional connectivity in schizophrenia, while schizophrenia subjects exhibited strong activations in left VLPFC, the connectivity between BA 45 and the lateral temporal lobe (BA 22) was largely more negative compared to controls. This provided evidence that VLPFC did not modulate the activity of the temporal lobe in schizophrenia subjects to the level shown by the control group, signaling that individuals with schizophrenia are less capable than control subjects to adapt their response to cognitive demands (Jennings et al., 1998).

This result neatly fit the data with verbal fluency tasks, in which schizophrenia subjects failed to show the expected reductions of activity in the superior temporal cortex even though they were matched to controls behaviorally and showed no hypofrontality (C. D. Frith et al., 1995). A subsequent analysis of this study tested the hypothesis that this temporal lobe deactivation was precisely the result of faulty frontotemporal connectivity in this task too (Josin & Liddle, 2001). Investigators in this PET study employed three conditions: word repeating, class identification, and verbal fluency. The schizophrenia group consisted of patients with severe positive and negative symptoms (C. D. Frith et al., 1995). For the functional analysis, a seed region in the left inferior frontal region (voxel coordinates not provided) highly activated in the verbal fluency condition was selected, and its activity was regressed along all three conditions with the rest of the brain. Left inferior frontal lobe is usually minimally activated in word repeating but highly activated in verbal fluency. Conversely, left superior temporal gyrus (the Wernicke area) remains as much active

during word repeating than during word generation. Thus, negative correlations between these two regions were expected and observed in controls. However, in schizophrenia subjects, the connectivity between the seed region and voxels in inferior, middle, and superior temporal gyri were positive and significantly different than in controls (Josin & Liddle, 2001). The faulty connectivity with the seed region was not limited to temporal lobes, though: left inferior parietal obule, thalamus, left lingual gyrus, and anterior cingulate (ACC) all showed group differences of connectivity with the left inferior frontal seed region.

The importance of the ACC in the frontotemporal network thought to be disrupted in schizophrenia has been illustrated in a study that used a working memory paradigm. Working memory is a cognitive function that requires manipulation and temporary storage of information (Baddeley, 1998). The active network for working memory comprises different regions in the prefrontal cortex, parietal cortex, superior temporal gyrus, and anterior cingulate (Baddeley, 1998). The interaction of three of these regions was directly examined by Fletcher and colleagues (P. Fletcher, McKenna, Friston, Frith, & Dolan, 1999). These investigators tested if the interaction between prefrontal cortex and anterior cingular cortex could predict the activity in superior temporal lobe. In this study, investigators scanned subjects while they encoded and retrieved list of words of length varying from 1 to 12. This task challenges working memory, for the processes being studied during most of the scans are the loading of, access to, and rehearsal of information stored in working memory. Their results showed a positive interaction in the control group, but an absence of interaction in the schizophrenia group. This result means that the coupling of activity

between the prefrontal cortex and anterior cingulate cortex was a good predictor of the activity of the activity in the temporal in the healthy group, but not in schizophrenia subjects.

This observation of abnormal frontotemporal connectivity did not receive replication from all studies, though. One study, which also used a seed voxel connectivity paradigm, selected a ROI slightly more dorsal (left BA46) (Spence et al., 2000). This study differed from the previous on two important aspects: schizophrenia subjects were clinically stabilized and were currently experiencing few symptoms (less than 1.5 on any item of the Manchester Scale), and verbal fluency was directly compared to word repeating only. In this study, no difference of connectivity was observed between left dorsolateral prefrontal cortex (DLPFC) and the superior temporal gyrus, but patients showed a significant decrease in connectivity between left DLPFC and ACC as well as within the left prefrontal cortex (notably with regions corresponding to BA 10 and BA 45) (Spence et al., 2000) . Spence et al. suggested that the clinically stable condition of the schizophrenia subjects explained their failure to replicate the findings of faulty connectivity between DLPFC and the temporal lobe. The suggestion that the faulty connectivity between prefrontal and superior lateral cortices might be related to current symptoms of patients received further support from a more recent functional analysis showing that the lack of connectivity in schizophrenia between one seed in DLPFC and one seed in superior temporal gyrus, both active in a sentence completion task, was almost entirely driven by subjects experiencing hallucinations on the day of the experiment (37% of the sample) (Lawrie et al., 2002).

On the other hand, the findings in the functional analysis studies suggest that the ACC's functional integration with other prefrontal regions is abnormal even when schizophrenia subjects are clinically stable. ACC has extended anatomical connections with the many associative areas, most importantly DLPFC, and is implicated in attention and response selection (Spence et al., 2000). In a recent functional analysis, connectivity from the ACC with the rest of the brain was examined in relation to the performance of never-treated, first-episode schizophrenia subjects, in a verbal fluency task contrasted to silent reading, with a statistical technique that can test for psychophysiological interactions (Boksman et al., 2005). A right ACC ROI showing the most intense activity in the verbal fluency-baseline contrast was taken as a seed. The most significant differences between the schizophrenia subjects and the control groups included increased connectivity between this right ACC seed voxel and the right inferior temporal as well as left prefrontal gyri (BA47). Other selected seed voxels, including left DLPFC, right thalamus, and right prefrontal cortex, failed to demonstrate any significant difference of functional connectivity.

Frontoparietal connectivity

Frontoparietal dysconnectivity has also been proposed (Burns et al., 2003; Lewis, 2000) for explaining the low performance in WM tests by subjects. One common test used to manipulate working memory is one of the various version the *n*-back tasks (Braver et al., 1997). The n-back tasks require subjects to maintain and continuously update into working memory a different target (P. O. Harvey et al.,

2005). Load and mental manipulation within WM are set by a predetermined level of complexity. In the case of a 2-back task, subjects must update the target with the cue presented two stimuli back, and judge the similarity of the current cue with the correct target. In the case of the 0-back task, subjects are simply required to identify a single pre-specified letter. Meyer-Lindenberg and colleagues (A. Meyer-Lindenberg et al., 2001) compared, in a PET scan, the differences of activation between a 2-back and an 0-back tasks in a group of 13 controls and 13 schizophrenia subjects. In this study, control subjects produced significantly fewer errors than schizophrenia subjects. (Controls = 77%, Schizophrenia=53%, chance level was 25%). Control subjects also showed increased activations (at $p<0.001$) in inferior parietal lobe (IPL), bilaterally, and middle frontal lobe (mainly BA6/44). To analyze connectivity patterns within and between groups, the investigators used a canonical variates analysis, from which they extracted eigenvalues and brain scan loadings. This multivariate method yields a functional connectivity analysis, but has the merit of grouping together regions where the brain activations of the two groups differ the most. In the first significant pattern, schizophrenia subjects did not display the strong bilateral DLPFC-VLPFC-cingulate-parietal network observed in controls, and instead showed strong connectivity in an infero-temporal-cerebellum pathway (A. Meyer-Lindenberg et al., 2001). The authors interpreted this difference as a trait marker, but it could also reflect a performance-deficit trait, given that control subjects were significantly better in the performance as well. Kim et al. (Kim et al., 2003) also examined correlational connectivity in a PET scan during a somewhat easier n-back task; during the 2-back condition, subjects were required to continuously monitor a sequence of stimuli and to respond whenever

the third stimulus of a predetermined sequence of three stimuli appeared on the screen. Such task differs substantially from a classical n-back in that subjects are not required to continuously refresh their span of three stimuli in order to be able to respond. As a result, both schizophrenia and control groups performed almost perfectly. The pattern of activations identified in the standard univariate analysis engaged similar networks to those activated in traditional 2-back (Jacobsen et al., 2004; Kim et al., 2003). In this study, Spearman correlations between lateral prefrontal activation and activated regions of interest were computed in each group, and group differences were assessed by Wilcoxon rank sum test. The functional connectivity in control subjects between right DLPFC and both left and right parietal was significantly stronger than in schizophrenia.

Two studies of Schlosser and colleagues (Schlosser, Gesierich, Kaufmann, Vucurevic, Hunsche et al., 2003; Schlosser, Gesierich, Kaufmann, Vucurevic, & Stoeter, 2003) however provided diverging evidence to the results observed in the study of Meyer-Lindenberg et al and Kim et al.. Using the same task conditions (2-back vs 0-back), Schlosser and colleagues examined the effective connectivity between pathways with structural equation modeling. They also selected different groups of patients, namely an unmedicated group, a group with prescribed atypical antipsychotic medication, and a group with typical antipsychotic medication (all three groups performed significantly at a lower level on the task than healthy controls). Overall, the studies of Schlosser and colleagues did not replicate the observation that control subjects displayed stronger fronto-parietal connectivity while performing the task. The most robust results of their studies consisted of schizophrenia subjects

displaying reduced inter-hemispheric connectivity, reduced cerebellum-cortical connectivity, and increased thalamo-dorsolateral connectivity.

Conclusions on functional/effective connectivity in schizophrenia

While the results from this study are not easy to reconcile, we suggest that the following patterns emerge from our review:

1) Studies examining frontotemporal and frontoparietal connectivity generally supported the hypothesis that schizophrenia is characterized by a lack of connectivity in networks involving frontal cortex. However, at least one study failed to demonstrate this (Spence et al., 2000);

2) The clinical state (acute versus stabilized) and the severity of the symptoms of the schizophrenia subjects might alter the connectivity in different ways. For example, schizophrenia subjects experiencing acute symptoms often show hyperconnectivity, particularly between regions thought to be less critical for the task being tested]. However, the relationship between symptoms and connectivity appears even more critical within the frontotemporal network. The connectivity disruption in the frontotemporal network appears to be sensitive to the level of positive symptoms experienced by the schizophrenia subject. This suggests that the lack of connectivity between DLPFC and lateral temporal lobes might not offer a trait-marker of schizophrenia, but rather a symptom-marker of one or many positive symptoms. This observation is further supported by studies showing increased activity in superior temporal gyrus in people experiencing auditory hallucinations (Shergill, Bullmore, Simmons, Murray, & McGuire, 2000; Sommer, Aleman, & Kahn, 2003) . While interesting on its own, this conclusion constitutes a serious drawback to the idea that

frontotemporal dysconnectivity defines schizophrenia (Friston, 1998; McGuire & Frith, 1996), because both the biological underpinning of the frontotemporal lack of connectivity (ie. the numerous anatomical insults present in schizophrenia) as well as the outcome of the lack of frontotemporal connectivity (as observed in cognitive tasks) appear to be stable across the subject lifetime;

3) The ACC was a region frequently implicated in disrupted connectivity in schizophrenia. Overall, ACC appeared to interact disruptively in groups of schizophrenia subjects with different symptoms profile, in a large variety of taks, but only when subjects failed to perform perfectly (as opposed to Jennings et al. and to Kim et al.). It thus remains to be seen if the disrupted connectivity involving ACC corresponds to a trait-marker of schizophrenia or simply reflects the level of performance obtained by subjects. This latter interpretation relies on the fact that ACC is sometimes described as a region monitoring the level of prefrontal resources to the difficulty of the undergoing task.(P. O. Harvey et al., 2005). Medication might alter the connectivity as well. Dopamine antagonists reduce activity in ACC (Blasi et al., 2005; P. C. Fletcher, Frith, Grasby, Friston, & Dolan, 1996). It is thus possible that the increased connectivity of the different regions linked to ACC in never-treated patients becomes a decreased connectivity after patients are medicated;

4) An almost universal finding is the studies we have reviewed is a reduction of interhemispheric connectivity in schizophrenia subjects.. The lack of interhemispheric connectivity, if proven to affect all regions of the brain, might potentially have an important effect on performance, particularly for those which necessitates the involvement of both hemispheres.

5) Finally, investigators have used many different ways to assess either functional or effective connectivity in control and schizophrenia subjects, ways that are not equivalent to each other. The variety of results we have reviewed might possibly turn out to be the result of methodological differences.

Conclusion on anatomy and connectivity in schizophrenia

In the first section, we have concluded that the regions most implicated in group differences between schizophrenia and healthy subjects, from the perspective of neuroanatomy, were the prefrontal cortex and the MTL. Surprisingly, one aspect that our review on connectivity does not address is precisely the quality of the connectivity between prefrontal cortex and MTL. A very recent publication by Meyer-Lindenberg and colleagues remedies the situation. The investigators performed a new connectivity analysis of their paradigm, this time by taking hippocampus as a selected ROI. They specifically assessed the functional connectivity of this region with the rest of the brain in schizophrenia (A. S. Meyer-Lindenberg et al., 2005). They matched the performance of 22 schizophrenia subjects with the performance of control subjects in a task that contrasted a 2-back condition to a 0-back condition. In control subjects, the activation observed in hippocampus is negatively correlated to the activations observed in prefrontal and parietal regions during the 0-back condition, but these activations are decoupled during the 2-back. In schizophrenia subjects, the negative correlation between left hippocampus and DLPFC and inferior parietal lobe (BA 40) is still present during the 2-back condition. This result suggests that, in the schizophrenia group, the prefrontal and parietal

cortices did not modulate the activity in the hippocampus, signaling a lack of connectivity.

The authors acknowledged that the role of hippocampus in working memory is still unclear. Their tentative interpretation of the decoupling of activation between hippocampus and DLPFC, as observed in control subjects, is that the decoupling reflects the suppression of the hippocampus involvement in activity unrelated to the working memory task. According to this interpretation, the hippocampus appears negatively correlated to the rest of the brain during the 0-conditoin because it is doing something else. However, during the 2-condition, subject are fully engaged in the working memory tasks, and as a consequence, top-down processes refrain the hippocampus to do something else. Schizophrenia subjects, they claimed, are not capable of modulating the activity of the hippocampus by similar top-down processes.

The problem with this finding is precisely the lack of knowledge concerning the role of hippocampus during working memory. By their very nature, functional neuroimaging studies are correlational. Unless one provides a theoretical basis for the contribution of one region in a functional network, any interpretation for the role of this region lacks validity (Stuss & Anderson, 2004). The hippocampus, for example, has been shown to be active in neuroimaging studies of conditional eyeblink learning, a form of conditional learning where an air puff to the eyes occurs simultaneously to a painful stimulus. Yet, the hippocampus is not necessary at all for this learning, as hippocampal-lesioned animals still learn the conditioning perfectly (Woodruff-Pak & Stienmetz, 2000). Instead, it appears that hippocampal activity is necessary for long-trace procedure, that is, for conditional eyeblink learning in cases where the

conditional and unconditional stimuli are separated in time (Woodruff-Pak & Stienmetz, 2000). Hippocampal activity in conditional eyeblink learning thus appears incidental to the task under study (conditional learning), but necessary for another process, the associative learning over a time delay. The lack of understanding of hippocampus during working memory, combined to the fact that schizophrenia subjects with lesions to hippocampus often demonstrate normal working memory performance, leaves open the possibility that its activity in the pattern of results observed by Meyer-Lindenberg and colleagues are incidental to working memory and rather reflect activity for associative learning of the stimuli over time. We believe in fact that this lack of connectivity between hippocampus and prefrontal cortex is an important finding, but that it must be interpreted in the light of a demonstration of a strong episodic memory deficit in schizophrenia. In the next section, I will present part of a meta-analysis that we have conducted in order to grasp a better understanding of the episodic memory performance in schizophrenia. As we will see, certain aspects of episodic memory are indeed largely affected in schizophrenia, and suggest disrupted MTL-prefrontal cortex.

Recognition memory in schizophrenia

Theoretical context

We have already pointed out that episodic memory along with with semantic memory types of information that we have access consciously. Episodic memory differs from semantic memory on at least two cognitive aspects: it refers to personal events or experiences, and it indexes information with a temporal and contextual component (Tulving, 1983). Typically, episodic memory tests consist of an encoding phase, during which items to be memorized are presented to subjects. After a delay, in which consolidation of information is likely to occur, a retrieval phase follows. During this phase, the subject will deploy cognitive operations in order to retrieve the stored information. Different tests have been used, including free recall, cued-recall, and several tests of recognition memory. Free recall differs from recognition memory in that no cue is provided to the subject to guide them in the retrieval of the target items. In contrast, during recognition memory, the target items are presented in a list that also included new, never-presented items.

Several reasons explain why we preferred the recognition format to the free recall for our connectivity analysis. First, the recognition format is more amendable to fMRI studies than free recall since free recall necessitates a vocal response, which could cause more artifact movements than mouse clicking. Second, the recognition format appears to have several advantages, including better psychometrics when comparing recollective to familiarity processes (A.P. Yonelinas, 2002), and less vulnerability to lack of motivation. Finally, a third reason for selecting recognition memory is

theoretically motivated. The recognition memory format as tested in schizophrenia appears to have a high variability in performance across the reported studies in the scientific literature. We were thus motivated in performing a meta-analysis in order to uncover the cognitive and clinical moderator variables that account for this variability in schizophrenia.

One of the most robust findings of studies that have investigated cognitive functioning in schizophrenia is that episodic memory is significantly impaired (Aleman, Hijman, de Haan, & Kahn, 1999; Heinrichs & Zakzanis, 1998; A. J. Saykin et al., 1991). The magnitude of this impairment seems to depend, however, on the kind of memory test administered to the subjects. In a meta-analysis of 70 published studies reporting memory performance data in people with schizophrenia, Aleman and collaborators (Aleman et al., 1999) observed severe impairments on tests of delayed and immediate free recall (mean effect size (d) of 1.20 and 1.27 respectively), but only a moderate impairment of recognition memory relative to healthy comparison groups (d = 0.64). In the context of a general cognitive deficit and with other cognitive domains such as executive functions yielding much greater impairments, this latter finding seems to be of limited theoretical and/or clinical interests. Why should one explore recognition memory? The answer resides in the high variability in recognition memory performance across the reported studies. Whereas some studies report no significant differences between a schizophrenia group and a control group (Bauman & Murray, 1968; Beatty, Jocic, Monson, & Staton, 1993; Goldberg, Weinberger, Pliskin, Berman, & Podd, 1989; Koh, 1978;

Nathaniel-James, Brown, & Ron, 1996), other studies describe a recognition memory deficit so severe (Danion, Rizzo, & Bruant, 1999; Gold, Randolph, Carpenter, Goldberg, & Weinberger, 1992; Stirling, Hellewell, & Hewitt, 1997) that some researchers have suggested that there exists an amnesic syndrome in schizophrenia (McKenna et al., 1990). One source of variability might result from the fact that recognition tests have been used to measure what could be different memory processes, including item memory, source memory, and associative memory. In item recognition tests, subjects are required to discriminate between recently studied (old) and never presented before (new) items, whereas associative and source recognition tests require subjects to single out items based on their physical (e.g. size or color) or contextual features (e.g. place or time) at the time of encoding. Work in cognitive psychology suggests that item memory relies on two different decisional bases, one termed conscious recollection and the other familiarity detection, whereas associative recognition memory relies preferentially on conscious recollection (A.P. Yonelinas, 2002). Several studies (Danion et al., 1999; Huron et al., 1995; Keefe, Arnold, Bayen, McEvoy, & Wilson, 2002; Rizzo, Danion, van der Linden, & Grange, 1996; Schwartz, Deutsch, Cohen, Warden, & Deutsch, 1991; Weiss, Dodson, Goff, Schacter, & Heckers, 2002) have reported that schizophrenia subjects have significantly impaired performance on tests of associative recognition relative to a control group. The group differences observed in these studies are particularly interesting because both groups performed well on an item recognition test. This intact item recognition performance points to a relative sparing of familiarity in these patients, whereas their poor performance on associative tasks suggests that their

ability to consciously recollect information is significantly impaired. According to Danion and his collaborators (1999), this dissociation between item and associative recognition hints at a specific impairment in the ability to "bind the separate components of events into a coherent, relational memory representation." (p.643).

Another potential cognitive moderator is the material specificity (whether the item is a verbal or figural stimulus). Some studies of recognition memory have reported a preferential verbal memory deficit (Kareken, 1996; Keefe, Arnold, Bayen, & Harvey, 1999; A.J. Saykin et al., 1994), whereas others have reported a preferential figural (non-verbal) memory deficit (Aggleton & Shaw, 1996; Whittaker, Deakin, & Tomenson, 2001). The conflicting results are further complicated by several other reports that found no significant differences in cognitive performance for tasks using verbal and non-verbal stimuli, including two meta-analyses investigating recognition memory performance in schizophrenia (Aleman et al., 1999; Calev, Edelist, Kugelmass, & Lerer, 1991; Calev, Korin, Kugelmass, & Lerer, 1987; Clare, McKenna, Mortimer, & Baddeley, 1993; Heinrichs & Zakzanis, 1998; Tracy et al., 2001).

The format in which item recognition memory is tested may also account for the high variability in recognition memory performance in schizophrenia. Thus, whether a yes-no (also known as old-new) or a forced-choice (FC) test is used might moderate patients' performance differently than it does the performance of control subjects. In this regard, the yes-no test is believed to be more difficult than the forced-choice recognition test. This view is held in part because the yes-no test requires the subject to "develop and maintain an appropriate criterion for evaluating memory

characteristics" (Nolde, Johnson, & Raye, 1998), p.401. Another reason is that the yes-no test provides less information to the subject. This latter characteristic of the yes-no test makes it more difficult for the subject to rely on familiarity detection to discriminate old from new items, thus necessitating the retrieval and evaluation of additional episodic details (Nolde, Johnson, & Raye, 1998). Because these differences should enhance the memory performance of subjects who rely more on familiarity and priming as a basis for their recognition memory judgments, some researchers have hypothesized that patients with MTL damage might do relatively better on FC tests than on yes-no tests (Kroll, Yonelinas, Dobbins, & Frederick, 2002; A. P. Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998).

In addition to these cognitive variables, several clinical variables have been shown to account for a significant portion of the variability in memory performance in schizophrenia (Stip, 1996). Many reports indicate that the type of medication taken by patients is an important variable. In the absence of concomitant anticholinergic medication, traditional neuroleptics seem to have no detrimental effects on memory, and even some overall positive effects on memory have been reported (Blyler & Gold, 2000; Gilbertson & van Kammen, 1997). However, many reports indicate that anticholinergics interfere with memory performance (Fennig, Levine, Naisberg, & Elizur, 1987; Silver & Geraisy, 1995; Spohn & Strauss, 1989). Since not all individuals take anticholinergic medication, its effect on mean memory performance should depend on the proportions of people within the group that are taking the medication. The symptom profile of the patients also influences their performance on memory tests. Many studies, including the Aleman meta-analysis, have come to the

conclusion that negative symptoms are associated with lower memory performance (Gold et al., 1992; Palmer et al., 1997; Paulsen, 1995). On the other hand, the relationship between positive symptoms and impaired verbal memory is less clear, with some authors reporting significant associations (Mahurin, Velligan, & Miller, 1998; Norman et al., 1997) and others concluding that positive symptoms are associated with relatively spared memory functioning (Basso, Nasrallah, Olson, & Bornstein, 1998; Brazo et al., 2002). Controversies also abound regarding the effects of illness chronicity on memory deficits, with some studies finding a positive link between chronicity and memory impairment (Chan et al., 2000; McKenna et al., 1990). Other studies have shown that performance on recall and recognition memory tests is stable over time (Heaton et al., 2001; Hoff et al., 1999).

Clearly, several cognitive and clinical moderator variables have been associated with poor recognition memory performance in schizophrenia. To assess the magnitude of the impairment in recognition memory in schizophrenia and to identify cognitive (test-related) and clinical variables that modulate performance in the patient group, we performed a meta-analysis based on published studies. The three interrelated goals of this meta-analysis were: 1) to compute a robust estimate of recognition memory performance based on published studies; 2) to evaluate the moderating effect on performance of multiple cognitive and clinical variables; and 3) to use this dataset to test some of the hypotheses that have been put forth concerning recognition memory in schizophrenia (e.g. intact item recognition versus impaired associative recognition).

Meta-analysis

Methods

We have put into the appendix the detailed method of our meta-analysis. Briefly, we calculated an effect size for any measure of a recognition test of episodic memory which compared a schizophrenia group to a control group or to normative data. To distinguish episodic memory tests from working memory tests, the encoding phase that preceded recognition testing had to include at least ten items. Acceptable tests included paradigms of yes-no recognition, forced-choice recognition and several paradigms of associative recognition memory. When one study offered multiple measures, their effect sizes were averaged (after a Fisher transformation) into the general analysis, but were kept separated we compared one factor to another (eg. verbal vs figural). We accepted groups of subjects with diagnosed schizophrenia only (except for a few studies that included less than 20% of schizoaffective patients as well).

The contrasts performed in this meta-analysis are listed below, with the number of levels and the operational definition assigned to each level in this meta-analysis. For cognitive variables, the following variables were selected: a) Material specificity, which included two levels: verbal stimuli, for all tests using words as stimuli, and figural stimuli, for all tests not using words. Hence, tests that we grouped together under the term *figural* consisted of different stimuli, with some being more verbal than others. Furthermore, as previous studies suggested that there is a preferential impairment of face recognition in schizophrenia (Feinberg, Rifkin, Schaffer, & Walker, 1986; Whittaker et al., 2001), a contrast between face stimuli,

abstract designs and pictures of objects was also examined; b) Type of information retrieved, with two levels: item memory for all tests in which subjects must discriminate between target material and distracters, and associative memory for tests in which subjects must select the appropriate contextual information related to the item studied. Under this definition, associative tests included source (e.g. was item A presented in source 1 or source 2?) and pair tests (e.g. was item A associated with item B or item C?), as well as recency (e.g. did item A appear before/after item B?) and frequency judgment tests (e.g. did item A appear once/twice?). However, there are indications that recency and frequency tests are sensitive to functional deficits in planned processing rather than to deficits in the storage of associations (Mayes et al., 2001). Consequently, we were also interested in the contrasts between the different associative memory tests; c) The recognition format, with two levels: yes-no, for all tests with sequential displayed stimuli, and forced-choice for all tests assessing subjects by displaying the old stimulus among the foils; we also look at the type of measure (hit, d' or FA);

As for clinical variables, we evaluated the contrast between levels of: a) Mean scores on the Scale for the Assessment of Negative Symptoms (SANS) (N. C. Andreasen, 1984a), on the Scale for the Assessment of Positive Symptoms (SAPS) (N. C. Andreasen, 1984b), and on the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987); b) Severity of psychopathology based on the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1980); c) Patient status (outpatients vs. inpatients); d) Chronicity, or the duration of illness (number of months since diagnosis); e) Antipsychotic medication, including the mean dose of

typical neuroleptics per study group, in chlorpromazine equivalents; f) Proportions of people taking anticholinergic medication; g) IQ measures.

Results

Overall effect size

The search for articles in Pubmed and PsycInfo led to the identification of 248 and 189 published studies respectively, with several papers overlapping both lists. From this pool of studies, 63 studies fulfilled the inclusion criteria. In addition, 21 articles were identified with the help of the references of the meta-analyses on memory in schizophrenia and from other retrieved papers. Thus, in total 84 studies offered independent data from which 87 effect sizes could be computed.

Effects sizes for recognition memory computed from each study ranged from -0.27 to 2.75. Figure 1 illustrates this variability using a funnel plot. Table 1 presents the results for the overall effect size for recognition memory on the first line and the results of several contrasts pertaining to cognitive variables. The mean weighted effect size of 0.76 is highly significantly different than zero ($p<0.001$). The probability associated with the homogeneity statistic was also highly significant, which points to the presence of moderator variables.

Effects of Cognitive variables

Table 1 presents the different statistics for the cognitive variables and Figure 2 illustrates four of the contrasts performed for the cognitive variables. A contrast for the material specificity revealed that the mean effect size for recognition memory was

significantly larger with figural material (d=1.00) as compared to verbal material (d=0.71), yielding a contrast of Z = 3.68, p<0.001. The contrast between the effect sizes for different figural stimuli (faces, patterns and pictures) did not elicit any significant difference (respectively d=0.93, d=1.07, and d=0.83, Z=1.01, ns).

The contrast between the combined effect size for tests assessing item memory and tests assessing associative memory did not reveal a significant difference (Figure 2, Z=0.14, p=0.46). The combined weighted effect size was 0.72 for the item tests and 0.71 for associative tests. When tests assessing associative memory were restricted to source memory and pair memory, the combined weighted effect size remained similar (d = 0.68) to the overall effect size for associative tests. Table 2 presents results from all the associative studies retrieved, with their respective effect sizes for verbal and figural material.

Contrasting the different recognition formats revealed that the combined effect size under the yes-no recognition format was significantly greater than the combined effect size under the FC recognition format (Z=2.15, p< 0.05). This difference was driven by the unweighted effect sizes, as the weighted effect sizes were similar for both conditions (0.73 and 0.75 for the yes-no and the FC recognition, respectively). However, an unbalanced distribution of studies per condition can be observed. Specifically, the majority of studies using figural stimuli reported the use of a FC recognition format, whereas most of the studies that used verbal stimuli featured tests in a yes-no recognition format. As a result, the effect size for the FC format may have been inflated by the fact that it had been extracted from proportionally more studies that used figural stimuli. In fact, when the contrast was restricted to studies using only

verbal stimuli, a significant difference emerged with the effect size under the yes-no condition being greater than the effect size under the FC condition ($Z=2.42$, $p< 0.01$; with a weighted effect size of 0.70 and of 0.62 for the yes-no and the FC condition, respectively). We were able to look at the difference between hit rate, d', and FA rate only for the yes-no format, as almost every study using FC reported only one measure. Hit rate and d' share the same effect size (respectively $d=0.71$ and $d=0.68$). Compared to these two measures, the FA rate, as reported in nine studies, were significantly smaller ($d=0.47$, $Z=1.99$, $p<0.05$).

Effects of Clinical variables

An important part of the variability of our effect sizes might also be explained by the presence of clinical variables. To increase the homogeneity within the studies, the contrasts were made after restricting the analyses to studies using verbal stimuli. The influence of clinical moderator variables restricted to studies using verbal stimuli is shown in Table 3. Effect sizes were significantly larger as a function of illness chronicity ($Z=5.67$, $p< .001$). No significant difference was observed between the effect sizes of studies including a majority of patients that were either drug naïve or off medication, receiving atypical neuroleptics, or receiving typical neuroleptics. In the latter, the effect size for recognition memory did not correlate with the mean dose of typical medication received. Table 3 also shows that the effect size did not correlate with the patient's status. The effects of clinical symptoms on recognition memory performance are difficult to examine because many different rating scales have been used, but also because the necessary information was often lacking. Table

4 summarizes the contrasts performed for several of the clinical scales that could be analyzed. Three different trends were observed overall. A trend was observed for the contrast of the total score of the PANSS, indicating that larger effect sizes were associated with higher scores on this test. Furthermore, a trend was observed for the contrast of the SANS global rating score and the PANSS positive subscale, indicating that both negative symptoms as measured by the global rating scores of the SANS and positive symptoms as measured by the PANSS likely moderate the effect size for recognition memory. It should be mentioned though that the total score of the PANSS encompasses the score on the PANSS positive subscale and thus the former is in part a function of the latter. Finally, effect sizes were grouped with regards to current mean IQ for each group. The overall mean IQ was 92.3, and sixteen out of twenty studies had a mean between 84 and 96. The contrast between the recognition memory effect sizes for studies with higher IQ compared to the recognition memory effect sizes for studies with lower IQ did not reveal significant differences ($Z=1.17$, $p>0.05$).

Discussion

Our meta-analysis reveals a significant association between schizophrenia and poor recognition memory, as indicated by the overall moderate effect size of $d = 0.76$. More importantly, our findings strongly suggest that recognition memory performance in schizophrenia is sensitive to cognitive and clinical moderator variables.

Item/Associative memory

The absence of a significant difference between the effect sizes for item recognition and associative recognition tests is an important finding of this meta-analysis and appears at first glance to contradict the results of recent studies (i.e. (Danion et al., 1999; Huron et al., 1995; Keefe et al., 2002)). This result might at first challenge the view that recollection is more impaired than familiarity in schizophrenia subjects when they are compared to control subjects. However, our inclusion criterion for the associative tests was admittedly broad, so that associative tests included frequency as well as recency judgment tests, which have been suggested to rely more on familiarity than on recollection (A. P. Yonelinas et al., 1998). When we separate the results of associative memory according to the type of test (as can be seen in Table 2), a numerical difference between pair memory (e.g. (Danion et al., 1999; J. D. Ragland et al., 1998; Russell, Bannatyne, & Smith, 1975) and source memory could be observed, with pair memory being more affected. Pair memory emphasizes interactions between prefrontal cortex and MTL (Simons & Spiers, 2003) and thus tests assessing this type of memory may be more sensitive to the connectivity problems in schizophrenia (P. Fletcher et al., 1999; Friston, 1998).

Several reasons might be advanced in order to explain the discrepancy between the results of our meta-analysis and those of investigations that specifically assessed patients' item and associative memory in the same study. First, the item memory tests administered in these experiments were often easier than most of the item memory tests that contributed to the calculations of the combined effect size in this meta-analysis. These easier item memory tests likely suffered from ceiling effects, thus reducing the size of the effect. For example, in the study conducted by

Danion and collaborators (Danion et al., 1999), subjects only had to remember ten items during the item memory test, while they had to remember seventy associations during the pair test. As a result, these researchers may have underestimated the magnitude of the item memory deficit.

With respect to source recognition, another reason for the apparent discrepancy between the results of our meta-analysis and those of several other empirical studies is that many of these studies did not measure item memory and source memory independently. Instead, most studies combined items remembered and items correctly guessed during item memory measurement, without controlling statistically for the guessed response (Keefe et al., 2002; Murnane & Bayen, 1996, 1998). However, because healthy subjects relied on guessing to a lesser extent than schizophrenia patients, the ratio of source judgements made on guessed items differed between groups. This statistical procedure inflates artificially the performance difference between item and source memory.

Finally, the lack of a significant difference in the present meta-analysis between item and associative recognition tests does not mean that associative recognition is unimportant. The present meta-analysis clearly shows that associative recognition memory is impaired. Furthermore, it is possible that measures of associative recognition correlate better with specific symptoms than measures of item recognition (Moritz, Woodward, & Ruff, 2003). Clearly, future studies that examine item and associative recognition memory and minimize the confounding effects of some of the variables previously described will provide a better measure of the difference between the two.

Other cognitive variables

An interesting result of the meta-analysis is that schizophrenia patients had greater difficulty, relative to controls, in yes-no format than in FC format. This result could suggest a deficit for schizophrenia patients to develop and maintain an appropriate criterion for evaluating memory characteristics (Nolde, Johnson, & Raye, 1998). Of interest, the memory performance of schizophrenia patients were more affected when measured either by the hit rate or by d' than when they were measured by false recognition. This result supports unexpected findings from recent studies showing that memory performance of schizophrenia patients were disproportionately less affected by false recognition than by correct recognition (Elvevag, Fisher, Weickert, Weinberger, & Goldberg, 2004; Huron & Danion, 2002); but see (Weiss et al., 2002) for a different result. It is not clear if these results are related methodologically to a reduced hit rate, or if they indicate, given the hypothesis that false alarms and hit rate reflect different aspects of recognition memory, that the cognitive and neural processes responsible for avoiding false recognition are less affected in schizophrenia (Elvevag et al., 2004). This issue clearly warrants further investigation.

The material specificity of the items to be remembered elicited a significant difference, with the effect size for the figural condition being significantly greater than the effect size for the verbal condition. This result suggests that people with schizophrenia have greater difficulty relative to control subjects on recognition tests when they studied figural stimuli than when they studied verbal stimuli. This result is

in contrast with other meta-analyses (Aleman et al., 1999; Heinrichs & Zakzanis, 1998). In the meta-analysis of Heinrichs and Zakzanis, the absence of a significant difference between verbal and non verbal stimuli is possibly undermined by the fact that the study used primarily measures of verbal and non verbal recall. However, the processes required to perform verbal recall are different from the processes needed to perform non verbal recall, a difference that is attenuated in the recognition format. Therefore, we believe that the recall format is not the most appropriate format to measure the difference in material specificity. In the meta-analysis of Aleman and al., the authors presented separate effect sizes for recall and recognition formats. For the recognition format, the authors identified 12 studies that used verbal stimuli and whose combined effect size for recognition was 0.61 and 8 studies for non verbal stimuli in which the combined effect size was 0.73. This numerical difference between the two effect sizes may have been reported to be non significant due to the lack of power. In our meta-analysis, we identified 68 studies that used verbal stimuli, for a combined effect size of 0.71, and 34 studies that used non verbal stimuli that combined to produce an effect size of 1.00. Our difference in interpretation is thus explained both by an increased dataset of studies and by an increase in power needed to detect a difference. Furthermore, our results suggest that the figural memory deficit is a more general deficit, not limited to either faces, objects, or more abstract drawings.

Although the meta-analysis did not specifically address the relation between brain activity and recognition memory, this difference in performance could be indicative of the neural correlates involved in verbal and non verbal recognition

memory deficits in schizophrenia. A lateralization effect with regards to brain activity hinges on the type of material used. Figural stimuli, particularly during encoding, prompt more activation in both hemispheres than verbal stimuli, which is associated with left hemisphere activation (Golby et al., 2001; Kelley et al., 1998). To the extent that brain activity and memory performance are associated, this meta-analysis provides no support for the hypothesis of a preferential left hemisphere normality in schizophrenia (Crow, 1990; A.J. Saykin et al., 1994). The deficit for figural stimuli in schizophrenia might also be explained by results in cognitive psychology that figural stimuli usually benefit from a dual-code encoding, an encoding that is verbal as well as non-verbal (Paivio & Csapo, 1973). It has been suggested that the laterality of activation observed for figural stimuli might indeed reflect the dual-code aspect of the figural stimuli (Grady, McIntosh, Rajah, & Craik, 1998) Taken together, and again to the extent that brain activity and memory performance are associated, our results suggest that schizophrenia subjects might suffer from disrupted interhemispheric connectivity, which in turn could drive down, relative to a control group, the performance of schizophrenia subjects for recognition memory of figural stimuli. One cannot, however, discard the hypothesis that a more generalized visuospatial impairment present with schizophrenia (Archer, Hay, & Young, 1992; Streit, Wolwer, & Gaebel, 1997)., such as visual scanning deficits (Kojima et al., 1990; Kurachi et al., 1994), for example, has affected the appropriate processes of information.

Clinical variables

One significant contrast emerged from the analyses of the clinical variables. The meta-analysis revealed that the mean effect sizes for groups with higher means of illness duration were greater than the mean effect sizes for groups with lower means of illness duration. This result suggests that chronicity may have a detrimental effect on recognition memory, a result that differs from many reports that have indicated that chronicity has no effect on memory performance (Heaton et al., 2001; Hoff et al., 1999) . However, most of these studies have relied on recall measures to assess memory. Compared to control subjects, schizophrenia patients have a greater deficit on recall measures than on recognition measures. Because recall differs from recognition in that it relies more on the effortful initiation of search and retrieval mechanisms (Paulsen, 1995), it is possible that recall tasks suffer from floor effects which would make the effects of chronicity on memory more difficult to detect. In contrast, the recognition format allows patients to demonstrate their acquired knowledge by relying more on monitoring processes (e.g. by correctly rejecting new items and accepting cues) (Cabeza, Locantore, & Anderson, 2003), thereby providing a measure that is more sensitive to the magnitude of the defects that could affect the acquisition of knowledge. Furthermore, given that all studies included a control group that was matched for age, it is unlikely that this effect of chronicity is due simply to age. It is possible though that the effect of chronicity is linked to a general intellectual decline. In the meta-analysis, current IQ measures, as a variable, did not reach significance, most probably because the groups in the meta-analysis share a similar

IQ mean. As a matter of fact, 80% of the studies had a group mean between 84 and 96.

Several clinical variables examined in this meta-analysis do not seem to have a significant influence on the magnitude of recognition memory impairment. Some, including the mean dose of typical medication and the patient's status (outpatient or inpatient), were also found in the meta-analysis by Aleman and collaborators (Aleman et al., 1999) to have no significant influence on recall memory impairment. Thus, we can infer that the finding of episodic memory impairment in schizophrenia is of considerable robustness. Furthermore, the proportion of people taking anticholinergic medication was not significantly correlated to the magnitude of the effect size of recognition memory. However, our measure, based on group means, is not a direct measure of the effect of anticholinergics on individual performance. Thus, it is likely that anticholinergics can impair memory performance, a result repeatedly reported in the literature on memory studies in schizophrenia (Fennig et al., 1987; Silver & Geraisy, 1995; Spohn & Strauss, 1989).

Many trends were found in the analysis of the effect of the different scales measuring positive and negative symptoms on recognition memory impairment. It should be noted however that the number of studies per contrast for the different scales was rather small. Consequently, not only is the power to find significant contrast reduced, but also there is no guarantee that the limited number of studies is representative of the overall dataset.

Methodological caveats

Several methodological and statistical limitations should be mentioned as they can potentially confound some of the findings. First, we observed some differences between the weighted and the unweighted effect size. For example, the weighted effect sizes for yes-no and FC tests were similar, while the contrast based on unweighted effect sizes revealed a significant difference. This result could be explained by the fact that some of the largest groups comprised patients that were quite functional. One study (C.D. Frith, Leary, Cahill, & Johnstone, 1991), in particular, tested 283 patients that were diagnosed prior to the introduction of the DSM-III and that had for the most part recovered from their illness. This study yielded a very small effect size. The combination of this small effect size to its large sample yields a large impact of this study on the overall effect size if we use the weighted effect size. For this reason, the use of unweighted effect sizes, which is more robust to outliers, may be more representative of the impairment in recognition memory observed in people with schizophrenia. Another caveat is that many studies suffered from ceiling effects, especially those studies with verbal item memory tests. Ceiling effects affect both the mean and the variance of data from control subjects. Consequently, verbal tests may not correctly account for the difference in performance between schizophrenia patients and healthy controls due to the upper limit that is imposed on the performance of such controls. Finally, because meta-analyses are based on group differences, they have less power to detect the influence of clinical moderating variables that share high within-group variability than they have to detect the influence of cognitive moderating variables that are only based on

between-group variability. This lack of power might explain some of the negative results reported by our meta-analysis for our clinical moderating variables.

The purpose of this meta-analysis was to identify the cognitive and clinical variables that account for the variability in the recognition memory performance of schizophrenia patients. Our meta-analysis revealed a significant association between schizophrenia and poor recognition memory. More importantly, the use of figural recognition memory tests dramatically increased the effect size relative to tests of verbal memory recognition. Another important finding was the lack of a significant difference in effect size between tests of item recognition and associative recognition, although some difference between memory for pairs and memory for source is possible. Among the clinical variables, the patients' duration of illness was found to influence recognition memory performance. Together, these findings strongly suggest that recognition memory performance in schizophrenia is moderated by cognitive and clinical variables that are likely to account for the high variability observed in the literature.

Episodic memory network

Before turning to the functional aspects of memory deficit in schizophrenia, and in order to provide a framework both for interpreting the neuroimaging literature on memory in schizophrenia and for the model in our effective connectivity analysis, we will first review the neural circuits involved in the current models of normal memory.

Neural substrates of memory

Researchers interested in the neural substrates of memory have explored three different but complementary avenues: clinical cases of amnesia, animal models of amnesia, and, more recently, the use of functional neuroimaging techniques (PET & fMRI) during the performance of memory tasks in healthy humans.

Anterograde amnesia is a deficit in which a subject is severely impaired in learning and remembering new episodes of her life, while other intellectual functions are preserved. A first lesson brought about by clinical cases of amnesia was that there were indeed specific regions playing a role of neural substrates of memory, that memory loss was not simply a gradient of the magnitude of the insults of the affected brain (Corkin, Amaral, Gonzalez, Johnson, & Hyman, 1997).

Diencephalic structures

Amnesia is likely to be produced by the atrophy of any of three following regions: diencephalic structures, basal forebrain, and MTL. From a historical perspective, the first of these regions known to be related to amnesia was the

diencephalic structures, particularly those identified with the onset of the Korsakoff syndrome. The Korsakoff syndrome is defined as a disproportionate impairment in memory, relative to other aspects of cognitive function, often resulting from thiamine depletion (Kopelman, 1995). Post-mortem studies on the neurodegeneration associated with the Korsakoff syndrome (Kopelman, 1995) as well as animal studies with lesions in diencephalic structures (S. M. Zola-Morgan et al., 2000) all suggests that lesions to the mammilary bodies, the anterior thalamus, and the mammillo-thalamic tract joining both structures all contribute to the memory loss to some extent. In fact, these three structures can be considered as working as one functional and cohesive unit, receiving dense inputs from hippocampus through the fornix and projecting mainly to the cingulate gyrus (Kandel et al., 2002). The anterior cingulate also receives direct projections from the hippocampus. It is not clear, though, how the diencephalic structure contributes specifically to memory.

Basal Forebrain

Amnesia caused by lesions in the forebrain area is the most recent to be uncovered. The structures in this area include the septal nuclei, nucleus accumbens, substantia innominata, and related pathways (Damasio, Graff-Radford, Eslinger, Damasio, & Kassell, 1985). These nuclei contain cholinergic neurons that provide cholinergic innervation to cortical structures. It is thus likely that this type of amnesia is caused in part by reduction of achetylcholine in the cortex. This reduction would then lead to a malfunction of the hippocampal system, a structure strongly interconnected to the basal forebrain structure.

Medial Temporal lobe

Finally, several cases of anterograde amnesia, including one, H.M., most notably exposed by Brenda Milner of the MNI, propelled the medial temporal lobe (MTL) to prominence in the cognitive brain research (Scoville & Milner, 1957). Figure 3 illustrates the anatomy of this region. In short, all polymodal associative cortices project to the MTL structures, converging onto the hippocampus. Parahippocampal cortex, which is situated posterior to perirhinal cortex, receives its main input from the associative areas of the parietal cortex, the ultimate processing region of the so-called "dorsal stream" (visual information about space and moving targets). The parahippocampal cortex also receives large projections from the superior temporal lobes (auditory information). The perirhinal cortex mostly receives projections from the inferior temporal lobe, the associative area part of the "ventral stream" (visual information about "what" is perceived). The projections of these two structures constitute the main input (approximately two-thirds) of the entorhinal cortex, which also receives input from the orbitofrontal cortex, cingulate cortex, insula, and superior temporal cortex. The major target of the entorhinal cortex is the hippocampus. Thus, the entorhinal cortex serves as a gateway for almost all entries into hippocampus. As for the latter, the main outputs are through the fornix, to regions that we have already discussed: the mammilary bodies, the anterior thalamic nuclei, and the anterior cingulate. Feedback projections to entorhinal cortex, and from there to perirhinal and parahippocampal cortex are also present. (Barbas, 2000; Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000b; Petrides &

Pandya, 1999). At first, it was believed that the hippocampus proper was the key structure in the amnesia induced in H.M. However, while several studies showed that lesions of the hippocampus bilaterally alone seem sufficient to produce a clinically significant anterograde amnesia, these lesions do not seem sufficient to obtain the severe deficit as observed in H.M (Kandel et al., 2002). Experimental studies in primates further indicated that it may be necessary for bilateral lesions to include the entorhinal and/or perirhinal cortices (as in H. M.) to witness an amnesic syndrome as severe as that in H. M. (Corkin et al., 1997). These mixed results have lead to a hotly debate around the precise role of each structure within the MTL.

Three models have been proposed about the roles of the MTL structures. One model rejects the hypothesis that functional differences exist between systems within MTL with regards to encoding and retrieval processes (Squire, Stark, & Clark, 2004; S. Zola-Morgan, Squire, & Ramus, 1994). According to this model, each region participates sequentially to the formation and retrieval of memories, and no difference for the level of treatment being processed (e.g. individual representations as opposed to relationships, or quick novelty vs enriched past memories) is taken into account by one MTL region. The special role of hippocampus, according to this view, would happen later, during the consolidation and storage of information, not during encoding. Authors supporting this view mainly point out that performance of animals and humans with partial lesions within MTL for memory is rarely intact when testing with either individual items or relationships (Reed & Squire, 1997).

In contrast, a second view postulates that functional differences exist within the MTL, mainly between hippocampus and the cortical regions from which it receives its main projections (Eichenbaum, Otto, & Cohen, 1994). Based on the anatomical evidence that hippocampus is a converging zone of projections whereas the perirhinal and parahippocampal cortices are structurally connected to specialized associative areas, this model proposes that hippocampal system-dependent memory mediates the storage of relationships among distinct items and the flexible expression of memory in novel contexts while the parahippocampal and perirhinal cortices mediates memory for individual representations. Compelling data for this model come from animal studies where different techniques to selectively lesion the hippocampus while sparing the parahippocampal region were used. Rats and monkeys that undergo such procedures are selectively impaired in tasks that encourage learning relationships among stimuli (Alvarez, Lipton, Melrose, & Eichenbaum, 2001; Sutherland et al., 2001).

A third model, proposed by Aggleton and Brown, resembles the first one, but reformulates the two postulated systems in one needed for relational information, centered on the hippocampus, and one needed for quick object recognition, centered on the perirhinal cortex (Aggleton & Brown, 1999). The perirhinal cortex, it is hypothesized, would bypass the hippocampus and project to the frontal lobes information for a quick detection of an already presented stimuli. Two lines of evidence support this model. Studies with monkeys have highlighted the role of the perirhinal cortex in object recognition (Bachevalier & Mishkin, 1994). For example,

in a delayed non-matching-to-sample (DNMS) procedure, the animal is first presented with a stimulus. After a delay, the animal is presented with the same object, along with a novel object, and the animal is rewarded if he selects the novel object. It has been shown that hippocampal-lesioned animals perform normally on DNMS task, while lesions of the perirhinal cortex lead to severe deficits on this task (Aggleton & Brown, 1999). A second line of evidence came from the first PET studies, which suggested a posterior/anterior functional separation within MTL, which lead to the proposition of the HIPER model (Hippocampal Encoding/Retrieval). This model refers to a then newly discovered pattern of an antero-posterior gradient of encoding and retrieval activations based on 54 activations extracted from 52 studies. The review paper revealed that encoding conditions produced activations on MTL sites located mostly (83%) anterior to y=-26 (x,y,z in Talairach coordinates)[3], while retrieval conditions produced activations almost exclusively (94%) to sites posterior to the same border (Lepage, Habib, & Tulving, 1998). The authors thus proposed that the anterior and posterior regions might serve as neural correlates for respectively encoding-related and retrieval-related processes. However, the model proposed by Aggleton and Brown calls for a reinterpretation of the data reviewed by Lepage and colleagues. Instead of focusing on a memory-process-oriented distinction, the model suggests to put the emphasis on a distinction based on the history of the stimuli. By definition, a stimulus presented during retrieval is a stimulus that is being presented to the subject at least a second time. Therefore, one may interpret the nearly absence of activations in anterior MTL for retrieval conditions as revealing that this region is not

[3] The (x,y,z) coordinates represents respectively the lateral-medial axis, the anterior-posterior axis, and the dorso-ventral axis.

specialized in signalling subsequent presentation of a new stimulus, but rather is specialized in signalling the novelty of a stimulus. Similarly, it is not simply any kind of encoding that should activate the anterior MTL. Instead, only encoding placing emphasis on the novelty of the stimulus is expected to produce activations there. In fact, in a re-analysis of the same data that lead to the proposal of the HIPER model, Schacter and colleagues showed that encoding sites could be found anywhere along the hippocampal axis (Schacter & Wagner, 1999). However, when we restrict the encoding condition to a contrast comparing novel stimuli to repeated/familiar stimuli, we can find that seven out of eight activations are in the anterior MTL are found within the border arbitrary chosen from Lepage and colleagues. While the landmark (y =-26) had been chosen purely arbitrarily by the authors, it has been since then demonstrated that this border is precisely the posterior limit of the perirhinal cortex in approximately 95% of normal subjects (Bohbot et al., 1998).

More recent studies have supported the notion of a separate functional difference between anterior and posterior MTL cortices. Many of the more recent studies have used a subsequent memory design, which enables one to isolate the activity during encoding associated to the stimuli that have been successfully retrieved. This procedure was used to show that left MTL, extending to fusiform gyrus, and left inferior frontal gyrus jointly contribute to the memory formation of verbalizable stimuli (Wagner, Desmond, Glover, & Gabrieli, 1998; Wiggs, Weisberg, & Martin, 1999). Davachi et al. (Davachi, Mitchell, & Wagner, 2003) innovated by manipulating the encoding tasks. In this experiment, subjects either formed an image

of a context that could be associated to the word presented, or read the word backward. The retrieval session, conducted outside the scanner, examined both the memory for the stimuli and for the source (Imagery vs Read). Their results showed engagement of hippocampus during the associative condition, and predicted subsequent memory for context recollection, but not for subsequent item recognition. In sharp contrast, the encoding activity in perirhinal cortex showed the opposite pattern (Davachi et al., 2003). One confound of this study was that the encoding procedure between making imagery contextualization and reading are different on many more dimensions than simply on the relational aspects. For example, it is quite certain that contextualized words received deeper level of semantic processing from subjects than words read. According to this objection, the activity in hippocampus would thus reflect the deeper level of processing rather than the making of associations. Evidence against this objection is mixed. Activations in the hippocampus have often been shown to modulate with semantic level of processing in contrast to non-semantic (eg. phonetic) encoding (Buckner & Koutstaal, 1998; Rugg et al., 1998) and by meaningful attributions (eg. actions as opposed to non-meaningful actions (Decety et al., 1997)). However, two recent studies provide a rebuttal to this objection. In one study, Otten and colleagues compared the activity in MTL during deep encoding with the activity in MTL during the creation of new semantic associations (Otten, Henson, & Rugg, 2001). The observed activity in hippocampus during creations of associations, but not during deep encoding, could predict subsequent memory. In the second study, investigators observed the activity in MTL during recombination of face-name pairing. Hippocampus was differently involved

during the formation of new face-name pairings, but not during observation of old face-name pairings (Kirwan & Stark, 2004). Further studies showed that activations in hippocampus and parahippocampal regions were more sustained during encoding and retrieval of associations (Dobbins, Foley, Schacter, & Wagner, 2002; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Henke, Buck, Weber, & Wieser, 1997; Henke, Weber, Kneifel, Wieser, & Buck, 1999; R. N. Henson, Cansino, Herron, Robb, & Rugg, 2003; Ranganath & Rainer, 2003; Ranganath et al., 2004; Small et al., 2001; R. Sperling et al., 2003; R. A. Sperling et al., 2001; A.P. Yonelinas, Hopfinger, Buonocore, Kroll, & Baynes, 2001) but see for contrary evidence : (Stark & Squire, 2001a, 2001c), Thus, it appears that the capacity for making memory associations between items implicates more posterior regions within MTL. In contrast, the perirhinal cortex appears to modulate its activity for simpler old-new contrasts. Supporting this view, one multi-study analysis of four fMRI studies showed that a familiar effect, defined as decrease activation during a repeated presentation of a stimulus, was observed in the right perirhinal cortex (R. N. Henson et al., 2003). This role of the perirhinal cortex can also be seen as a novelty assessment (Habib & Lepage, 2000; Tulving, Markowitsch, Kapur, Habib, & Houle, 1994). The role of the perirhinal cortex would thus be to receive inputs from inferior temporal cortices responsible for object recognition, and send a quick signal to the rest of the brain about the novelty of the stimulus.

While it appears that perirhinal cortex integrates a priming system, generating increased deactivation for subsequent presentations of the stimuli, the evidence from neuropsychology goes against this view, as subjects with large MTL have intact

priming (Hamann & Squire, 1997) . Functional studies have rather showed that activations associated to priming are located in more posterior occipito-parietal regions (Cabeza & Nyberg, 2000a).

In contrast to the controversial debate about the functional unity of the MTL, there is general agreement about a functional dissociation between left and right MTL, providing evidence for the lateralization of the MTL according to the type of information to encode. In most lesion-deficit studies, left, but not right, MTL lesions produce highly significant verbal memory deficits (Aggleton & Shaw, 1996). Both left and right MTL lesions, however, seem to produce deficits in non-verbal memory tests. This finding probably reflects the dual-code nature of non-verbal items or the importance of the left hemisphere for the use of strategies in better encoding in memory tests even in non-verbal items. In agreement with these theoretical considerations, a recent subsequent fMRI study examining the lateralization of memory encoding in MTL found that activation was left-lateralized for word encoding, bilateral for picture encoding, and right-lateralized for face encoding (Powell et al., 2005), see also (Golby et al., 2001) .

Frontal lobes

The prefrontal cortex lies in the anterior part of the frontal lobe. It consists of many areas that are distinct both at the level of cytoarchitecture and connectivity. There is no consensus on how these distinct cortical areas should be regrouped in subdivisions. The view we will adopt here is to separate the prefrontal cortex in five distinct regions (Stuss & Anderson, 2004). In the anterior prefrontal cortex, we find

the frontal pole (BA 10) and the orbitofrontal cortex (BA 11, 47). The lateral part is divided along a ventral-dorsal subdividision, leading way to ventrolateral (BA 44, 45), and dorsolateral (BA 8, 9, 46) prefrontal cortices. Finally, the medial part of the brain, including the cingulate gyrus, forms a last part of the prefrontal areas (BA 24, 25, 32). This subdivision, while still arbitrary, has the merit to be consequent with the connectivity the prefrontal cortex has with the rest of the brain.

A steady accumulation of data from neuropsychology, clinical psychology, and neuroimagery indicates that the contribution from the prefrontal cortex is necessary for an optimal performance on memory tests (P.C. Fletcher & Henson, 2001; Stuss & Anderson, 2004; Wheeler, Stuss, & Tulving, 1995) This contribution encompasses different specific cognitive processes including cue-generation, monitoring of information, organization strategies, and inhibition of non relevant information. According to Endel Tulving, the contribution of the frontal lobe also encompasses the subjective experience of remembering, of projecting oneself into the past (Tulving, 2002).

The first neuroimaging studies have indeed shown strong activation in prefrontal cortex related to memory activity. One of the most intriguing result provided by the first neuroimaging data was the lateralization of activations between encoding and retrieval mechanisms, with a left prefrontal activation, mostly in DLPFC BA 9/46 and in VLPFC (BA 45), for verbal encoding (and bilateral activation for non verbal encoding), and a right prefrontal activation, in all four parts of the prefrontal cortex, but with strong implication of the most anterior part (BA10), for retrieval. This lateralization of activations led to the formulation of the hemispheric

encoding retrieval asymmetry (HERA) model (Cabeza & Nyberg, 2000b; Tulving et al., 1994). However, many recent studies reveal that neural correlates for retrieval appear more bilaterally. In an analysis comprising several studies which identified different sites showing as much differential activation in testing of old and new items retrieval, the common activated sites included cingulate cortex (BA 32), bilateral anterior prefrontal cortex (BA10), bilateral VLPFC (BA 47/45), and right DLPFC (BA 8/9) (Lepage, Ghaffar, Nyberg, & Tulving, 2000). This study suggested the existence of a neural network representing a correlate for a "retrieval mode" that would be active regardless of the success of the retrieval search. Activations in the frontal pole have been relatively common when associative recognition is contrasted to item recognition (R. Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Nolde, Johnson, & D'Esposito, 1998; Nolde, Johnson, & Raye, 1998; Ranganath & D'Esposito, 2001; Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1996; A.P. Yonelinas, 2002). These activations have been interpreted as reflecting the intentional guidance underlying the retrieval mode (P.C. Fletcher & Henson, 2001; Simons, 2005). Many researchers have further functionally separated the contribution of the DLPFC from VPFC during retrieval. The left DLPFC region, for example, appears active in many retrieval conditions, mostly free recall and complex recognition memory (P.C. Fletcher & Henson, 2001; Petrides, 2002). These activations suggested that left DLPFC could reflect increases of complexity in evaluation (Nolde, Johnson, & D'Esposito, 1998), production of cues (Cabeza et al., 2003), or generation of memory responses and successful retrieval (Lepage, Brodeur, & Bourgouin, 2004). VPFC, on the other hand, is highly activated in retrieval after semantic encoding, particularly

when the encoding task stresses the association between words (Badgaiyan, Schacter, & Alpert, 2002; Kapur et al., 1996; Prince, Daselaar, & Cabeza, 2005). This has been interpreted to represent an involvement in searching the information to be recalled with the use of a specified cue (Petrides, 2002; Simons, 2005). Observations of orbitofrontal (OFC) activations are rare when associative recognition memory is contrasted to item memory. In contrast, the OFC appears highly active in old-new recognition tasks, particularly when the task has a non verbalizable component (Frey & Petrides, 2000). Finally, cingulate cortex has often been shown to be more involved during familiarity-based judgements than during recollection-based judgements (Achim & Lepage, 2005b; Lepage, Brodeur, & Bourgouin, 2003) . Cingulate cortex is involved in tasks which increases demands for error detection under self-monitoring guidance (van Veen & Carter, 2002). Given that decisions based on familiarity are assumed to reflect a signal detection process (A.P. Yonelinas, 2002), it is likely that item recognition requires some processes not needed for recollection-based decisions (e.g. judging the probability of a given signal), and the activity in anterior cingulate might reflect these processes.

The connectivity model

Anatomically, four bundles assure the communication between the temporal lobe and the prefrontal cortex. As we already mentioned, most of the projections from the hippocampus go either through the **fornix** or back to the MTL. As we have seen, the fibers in the fornix mostly project in the forebrain and in the medial nucleus of the thalamus, which densely innervates VPFC, DLPFC, and anterior cingulate (Squire et

al., 2004). Fibers directly from parahippocampal cortex are also found in the fornix (Lavenex, Suzuki, & Amaral, 2002). Returning fibers from prefrontal cortex to the hippocampus mostly take the **cingulate bundle**. The specific origin of the fibers passing through the cingulate bundle originates in DLPFC (most in BA 46, extending to 9/46,(Barbas & Blatt, 1995; Petrides & Pandya, 2002). This bundle projects mainly to posterior parahippocampal gyrus and into posterior presubiculum. Projecting fibers through the cingulate bundle from frontal pole and VPFC to these regions were markedly absent (Petrides & Pandya, 2002). A third pathway between the temporal and prefrontal cortices is the **uncinate fascicle**. Through it, we find mostly bidirectional fibres from the inferior temporal lateral to VPFC. We also find in this bundle fibers from perirhinal cortex that projects mostly to the orbitofrontal cortex (BA 11,12,13 in monkeys) (Barbas, Ghashghaei, Dombrowski, & Rempel-Clower, 1999; Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000a; Lavenex et al., 2002; Suzuki & Amaral, 1994a, 1994b) Finally, neurons in the superior temporal gyrus and in occipito-parieto-temporo junction send axons through the **arcuate fascicule** to a posterior dorsal region (BA 8/9) as well as to the expressive speech area known as the Broca area (BA44, and insula).

Aim and hypothesis

The general aim of our connectivity analysis was to investigate the possibility of exposing different regional networks for familiarity and recollection, and to observe if control subjects would activate different networks than schizophrenia subjects.

Familiarity and recollection were regarded as two bases of judgments that could operate differently with regards to the retrieval needs. To test this, our laboratory set up an fMRI experiment in which subjects would alternatively retrieve items, or associations of objects, in a "yes-no" recognition memory format. We made the hypothesis that only recollection could serve as a judgment basis for associative recognition memory while both recollection and familiarity could serve as a judgment basis for item memory. Therefore, we hypothesized that the connectivity network sustaining associative recognition in control subjects would reveal the network underlying recollection. While the MTL and the prefrontal cortex appear important for both recognition of items and associations, we made the hypothesis that associative recognition memory would require a greater connectivity between the prefrontal cortex and the MTL than memory for items. We were also interested in examining the model of Aggleton and al (Aggleton & Brown, 1999) which suggests that perirhinal cortex is specialized in quick detection of new items. In this respect, we were interested in finding a dissociation of activations between, on one hand, the posterior MTL and the DLPFC, and on the other hand, the anterior MTL and a more medial, orbitofrontal cortex.

Further, we made the hypothesis that schizophrenia patients would mostly be affected during associative recognition memory than during item memory. We thus hypothesized that their behavioural performance would be more affected for associative recognition, and that this result would be reflected by a reduced connectivity between the MTL and the prefrontal cortex during associative recognition. Because only correct responses were kept in the analysis, we could have

confidence that differences of connectivity would indicate a difficulty in the part of schizophrenia subjects to sustain a correct communication between the regions in the brain necessary for memory.

Familiarity and recollection are here conceived as two different cognitive modes that can serve for *recognition* judgements. During the encoding phase, single items and pairs of items were sequentially presented, and but it is not clear how differences of activations during this phase can relate to any difference between familiarity and recollection. While it could be interesting to explore this avenue, we prefer to limit ourselves to the recognition phase.

Methods

We obtained informed, written consent from all participants according to the institutional guidelines established by the Ethics Committee of the Montreal Neurological Hospital and Institute.

Subjects

Fifteen outpatients with DSM-IV-defined schizophrenia and eighteen age-matched healthy participants participated in the study. Confirmation of diagnosis was made by clinic psychiatrists using the Structured Clinical Interview for DSM-IV (SCID). Patients had chronic illness, with mean duration of illness of 10.3 (SD ±7.3) years, and were clinically stable at the time of assessment. All but one of the patients were taking antipsychotic medication (12 on second-generation antipsychotics, 3 on conventional antipsychotics, 4 taking a combination of both, and one was neuroleptic free), the mean dose of medication was equivalent to 453 mg/day of chlorpromazine

(Woods, 2003), and medication was not withdrawn for the purposes of the study. No patients were taking anticholinergic medication. (see table 5 for demographical and clinical data).

Healthy control participants were all in good health and free of any history of neurological and psychiatric disorders or substance abuse, as assessed using the non-patient edition of the Structured Clinical Interview for DSM–IV Axis I Disorders (SCID-I/P).

Stimuli

Stimuli consisted of 60 pairs of two different clipart images (referred to as pairs), 90 clipart images duplicated to have the same appearance as a pair (referred to as items) and one pair of two abstract images repeated through out the experiment that was used as a baseline. Clipart images were obtained from a Corel Draw picture library and depicted common objects and animals. Stimuli were divided into two.

Cognitive tasks

Participants were scanned during four runs, two encoding runs and two recognition runs. Half of the subjects began with encoding and recognition of list I while the other half started with list II. Stimuli were presented at a rate of one every 6.5 sec. A trial consisted of the presentation of an experimental stimulus for 2500 ms followed by a fixation cross presented for 4000 ms. When a response was required, subjects could answer at any point during the presentation of the stimulus or during the subsequent fixation cross. Presentation of the baseline stimulus during both the encoding and the recognition tasks was used to introduce some jitter in the design; the baseline stimulus was not used in the analyses.

During the encoding phase, subjects were presented with a study list of 90 consecutive stimuli (30 pairs, 30 items and 30 occurrences of the baseline). The order of presentation was pseudo-randomized so that each subject viewed the items in the same order. Subjects were instructed to memorize the images (both pairs and doubles) and their associations (pairs only). On each trial, subjects indicated with a mouse click whether a double or a pair was presented. No response was required for the baseline stimulus.

During the retrieval phase, subjects were presented with a list of 90 consecutive stimuli (15 old items, 15 new items, 15 intact pairs, 15 rearranged pairs and 30 occurrences of the baseline) and were required to make memory judgments as follows: 1) when items were presented (*item recognition*) subjects were required to indicate with a mouse click whether it was old (studied before) or new (never studied before), and 2) when pairs were presented (*associative recognition*) subjects were instructed to indicate with a mouse click whether it was intact (images presented in the same pairing as in the encoding session) or rearranged (images from previously studied pairs presented in new pairings). Again, no response was required for the baseline stimulus.

In order to minimize set shifting and make the task easier for the subjects, item and associative recognition trials were blocked. Eight to nine recognition judgments of the same type (item or associative) were answered in a row, intermixed with presentations of the abstract stimulus. Instructions were given at the beginning of each block in order to inform the subjects that a switch in the type of trials had occurred, as well as to remind them of how to respond. The order of presentation was

pseudo-randomized so that each subject viewed the items in the same order within each list.

Subjects performed a short version of the task comprised of similar stimuli prior to the scanning session to ensure that they understood the task. They were thus aware of the type of recognition task that they would have to perform following the encoding session.

Scanning and fmri analyses

Scanning was carried out at the Montreal Neurological Institute (MNI) on a whole body 1.5 Tesla Siemens Sonata system, using gradient echo EPI sequences. A vacuum cushion stabilized the subject's head. Stimuli were generated by a Pentium class PC Laptop computer and projected via a LCD projector and mirror system. A mouse connected to the computer recorded the subject's responses. Each scanning session began with a high-resolution T1-weighted three-dimensional volume acquisition for anatomical localization (voxel size 1x1x1 mm). This was followed by the acquisition of the functional images of the brain. T2*-weighted images were acquired with blood oxygenation level-dependent (BOLD) contrast (TR=3000ms TE=50ms) and covered the entire brain (25 slices, in plane resolution: 2x2 mm, thickness: 5 mm). Functional scans were acquired parallel to the anterior-posterior commissural plane. Each functional runs consisted of 230 scans. The first scan of each run triggered the start of the cognitive task.

All T_2* images were first co-registered and realigned to the fifth image in the first acquired run and spatially smoothed with a 6 mm (fwhm) isotropic Gaussian kernel. fMRI images were analyzed with fmristat (Worsley et al., 2002).

Normalization to standard space was done using the MNI_305 template (Cocosco, Zijdenbos, & Evans, 2003) as a reference. The design matrix of the linear model was convolved with a hemodynamic response function modeled as a difference of two gamma functions timed to coincide with the acquisition of each slice. Low frequency drifts were removed by including polynomial covariates, up to degree 3, in the design matrix. The correlation structure was modeled as an autoregressive process of degree 1. At each voxel, the autocorrelation parameter was estimated from the least squares residuals using the Yule-Walker equations. The autocorrelation parameter was first regularized by spatial smoothing with a 15 mm fwhm Gaussian filter, and then used to whiten the data and the design matrix. The linear model was then re-estimated using least squares on the whitened data to produce estimates of effects and their standard errors (Worsley et al., 2002).

Within-group maps of our contrasts of interests were computed in the full random effect model. For retrieval analysis, only the correct answers were entered in the analysis. These maps included all activations above a threshold of $p < 0.001$, uncorrected for multiple comparisons ($t(17) = 3.65$; and $t(14) = 3.79$) for the control and schizophrenia group respectively). In a third step, between-group interactions (with a significant threshold set at $t(31)=3.37$) were computed on the activations obtained in the within-group maps, only for clusters with a minimum of five significant voxels. Thus, unless specified otherwise, all significant between-group voxels discussed below showed a main for the contrast under study in addition to a significant group effect. This method was preferred for clarity of interpretation (J. D. Ragland et al., 2004). This being said, because we were ultimately interested in

examining the connectivity network among preselected regions, we did not hesitate to examine sub-thresholded voxels in regions of interest, notably in the MTL.

We were interested in calculating the connectivity for two networks: the network for associative recognition, and the network for item recognition. We also examine the network for detecting "new" items in an explorative way, but because item recognition encompasses detecting new items (as well as recognizing old objects), these two networks are not independent, and the "new" condition was not further explored. The nodes were selected as a function of the activations obtained in the univariate analysis and of the *a priori* ROI. We followed the usual strategy of selecting regions that appear significant in the contrasts under study, but we permitted a more liberal threshold. We further constrained the selection of voxels by choosing voxels that showed activations when contrasting recognition memory conditions to baseline. This had the effect of eliminating the hippocampus, the septum, and most of the anterior cingulate cortex from the analysis of the network (see the discussion section for more details). As a result, all the selected ROIs contributed to the activations observed during memory retrieval, some ROIs by being more active during the associative condition, some other by being more active during the item association. Only one ROI was selected per cluster of activation. The choice of the ROI within a large cluster was guided by the local maxima of the cluster and by the a priori interest in specific regions. Each node corresponds to a 6 mm3 cube centered on the selected voxel. The existing connections between these nodes were derived from the animal literature.

Despite our use of an event-related design, we did not calculate the correlations from the estimated value for each event. Instead, we used a similar logic as for the effective analyses performed on block design. Three principal reasons motivated this choice: the need to increase power in detecting connections for which group differences could be observed; the rationalization that it would be preferable, for the study of the schizophrenia group, to rely on subject-to-subject variability instead of on event-to-event variability for doing group comparisons, and the motivation to have results comparable to the published connectivity analyses which all used block designs.. Thus, we calculated the correlations from the parameter estimates for each subject, computed for each run, for every region of interest. Our analysis examined the activations across the runs without considering that every subject contributed for two runs. The rationale for this decision was to increase our degree of freedoms. This decision implies that the estimation of connectivity between two regions was based on 72 correlations for the control group and 60 correlations for the schizophrenia group respectively. This step was necessary for using the type of statistical analyses we wanted to examine. However, this decision has the negative outcome to potentially increase the value of correlations. To counter this side effect, we examined the Greenhouse-Geisser variable across runs for every subject in a variety of ROI, and we observed no group effect. Before calculating the correlations, the parameter estimates were standardized to have a standard deviation of 1 unit for all subjects. This is a mandatory condition with numbers of arbitrary units, such as parameter estimates for fmri activation, when they are entered in a multivariate correlational analysis (Howell, 1997). This operation also has the advantage to put the

focus on the change of variability in the activations across the brain rather than in the magnitude of the activations. The correlations between the nodes were expressed in a correlation matrix, which was used as input to compute path coefficients for the relevant connections in a structural equation modeling (Della-Maggiore et al., 2000; McIntosh & Gonzalez-Lima, 1994). In short, this mathematical modeling decomposes the covariance in the context of an anatomical network, and provides a paratemer estimate of the path coefficients between the nodes, which is interpretated as an indicator of the strength of the connectivity. The structural equation modeling was performed with LISREL 8 (Joreskog & Sorbom, 1996). We first explored the network for associative memory. Direct connections between regions within the model were unidirectional to ensure robust estimates (Maguire, Vargha-Khadem, & Mishkin, 2001). In addition to calculating the path coefficient, the Lisrel program calculates the t-statistic for all parameter estimates. We interpreted the parameter estimates that were significantly different from zero at $p<0.05$ as showing significant connectivity in the network under study. To insure the robustness of the result, we compared conditions using a variation of the stacked model in Lisrel (McIntosh & Gonzalez-Lima, 1994). Basically, we compared the network underlying associative recognition memory, reduced to its significant connectivity to a null model whose path coefficients were set to be equal between conditions, constraining the estimate of the path coefficients to be equal across item and associative recognition memory. These models were evaluated by comparing their respective goodness of fit index (as expressed by a chi-square (X^2) value), and the differential X^2 was compared to the X^2

critical at $p < 0.05$. Figure 4 illustrates all the path coefficients that were tested in the analysis.

One difficulty in examining the MTL is to distinguish the perirhinal cortex from the parahippocampal cortex, as they are both located on the parahippocampal gyrus, on the collateral sulcus, and partially overlap. For our purposes, we have closely followed the conclusions of Veronique Bohbot and colleagues (Bohbot et al., 1998). In one study, she carefully segmented this region and built a probabilistic map of the posterior limit of the perirhinal cortex. In 75% of the subjects, the perirhinal cortex did not extend y=-20. We have thus operationalized the perirhinal cortex as the part of the MTL cortex, ventral or lateral to the hippocampus, located anterior to y=-20, and the parahippocampal cortex as the part of the MTL cortex, ventral or lateral to the hippocampus, located posterior to y=-20. Given the smoothing applied to the data and the global registration, we purposely did not disentangle the enthorhinal cortex from the parahippocampal and perirhinal cortex. Hippocampus was determined by visual inspection.of the registered average brain of our control subjects.

Results

At the performance level, an ANOVA on recognition accuracy yielded a trend towards a significant Group X Recognition Test interaction ($F(1,31)=3.02$, $p=.09$). This trend was driven by a difference on the associative recognition test, with the schizophrenia group performing significantly lower than the control group ($t(31) = 2.12$, $p<.05$). The performance on detecting new items was similar in the two groups

($t(31)=0.37$, $p>.05$). This analysis also revealed a significant main effect of Recognition Test ($F(1,31)=105$, $p<.0001$). Table 6 displays the means of each group and the resulting probability as measured by individual t-tests during encoding, new item detection, and item and associative memory recognition.

Association vs item

We will first describe the results for control subjects. Results of the comparison between correct item recognition and correct associative recognition trials in control sujects are presented in Table 7 and Figure 5 (upper level). Associative recognition resulted in bilateral activation of the fusiform gyrus, bilateral parietal cortex (on the superior lobules), left DLPFC, left and right VLPFC, and the dorsal part of the anterior cingulate cortex. Left and right parahippocanpal cortex, significant at a lower threshold ($p=0.01$, uncorrected), as well as a right anterior part of the frontal pole that were close to significance, were also included in the network model for the associative condition. With the exception of the left parahippocampal cortex and the right anterior frontal poles, all active regions here were also significantly activated in the memory recognition condition contrasted to baseline. Activations in regions of interest not considered in the network included other parietal regions and insula.

Table 8 presents the results for item recognition. In contrast to associative recognition memory, item memory resulted in activation in left perirhinal cortex (and right perirhinal cortex and amygdala at a lower threshold), left and right inferior partietal lobules, extending to the temporal-parietal junctions, left and right insula,

left and right superior temporal lobes, medial frontal cortex (BA 8), the ventral part of cingular cortex, as well as the medial anterior and orbitofrontal PFC. It is interesting to note that these regions were quite differently activated in the memory vs baseline condition. The medial anterior PFC, the anterior cingulate, and the right superior temporal lobe were also massively deactivated when comparing memory to the baseline condition, while the left and right inferior parietal lobules contributed positively to the memory conditions. Other regions, like the perirhinal cortices and the medial orbitofrontal activated region remain largely neutral in the memory vs baseline condition.

As can be seen in Figure 5 (lower level), schizophrenia subjects displayed during associative recognition most of the increasing activity observed in the control group that were located in the occipitotemporal and parietal cortices. Activations in the anterior part of the brain were more disrupted, particularly in left DLPFC (BA 8 and BA 9 more precisely). Like control subjects, we noted activations in bilateral parahippocampal cortex (but not perirhinal cortex) that were slightly under the pre-selected threshold for significance.

We can observe the regions that were the most active in control subjects compared to a schizophrenia group in figure 6. Compared to control subjects, schizophrenia subjects showed decreased activity mostly in right and left superior parietal lobules, left DLPFC, and medial frontal cortex (BA8/9), with other few clusters, notably in right VLPFC (BA 47) and in left MTL (in the neighbour of fusiform gyrus). The numeric differences are detailed in table 9.

Selection of the model

As we mentioned, the first step consists in selecting the regions of interest that will serve as a network for associative recognition memory. We were mainly interesting in peaks of activity in the memory vs baseline condition, as well as in peaks that show a distinct pattern for either associative and item recognition memory. Several regions that we thought of interest for this network were not significant in either associative > item or item > associative contrasts, including the hippocampus and the cingulate cortex. Overall, healthy and schizophrenia subjects showed a similar pattern of activity, but healthy subjects have generally greater activation. In the following, we summarize the overall patterns of activity in the whole brain when memory was compared to the baseline

As it was already noted, the recognition of the stimuli produced robust activations in both dorsal and ventral stream originating from occipital lobes. Activity in the dorsal stream concludes with massive activations in the parietal precuneus, and in superior and inferior lobules. Activity in the motor cortex reflects the fact that subjects had to press buttons during the memory conditions, but had to remain still during presentation of the baseline. Activations in the ventral stream extend to the fusiform gyrus and to most of the MTL cortex underneath the hippocampus, however at lower thresholds, during recognition of the stimuli. In sharp contrast to the MTL cortex, the hippocampal axis shows consistent deactivations in the memory conditions. A few significant activations for the *baseline* condition were indeed found in the hippocampus. Other regions showing similar "active" state during the baseline presentation include most of the ventral part of the anterior cingulate. Lateral

temporal lobes extending to superior lateral temporal were mostly deactivated, during recognition. Subcortical structures mostly show very strong activation during the recognition, but the septal nuclei remained relatively neutral. The resulting network included the nodes shown in table 10.

Connectivity analysis

Six path coefficients appear significant in the analysis of the network for associative recognition memory in controls. The comparison of the differential goodness-of-fit between this model and the null model was significant ($X2$ (5) = 12.4, $p<0.05$). These significant path coefficients are exposed in the higher section of figure 7, with the significant path coefficients for schizophrenia subjects illustrated below. In the associative recognition network, the significant positive communications included the left and right fusiform gyri (0.30, $p<0.05$), the left fusiform and the left VLPFC (0.24, $p<0.05$), the right frontal pole and the left DLPFC (0.23, $p<0.05$), and the left DLPFC to the right parahippocampus (0.24, $p<0.05$). Compared to the controls, the network for associative recognition memory in schizophrenia only sustained significant connectivity between left VLPFC and left DLPFC (0.41, $p<0.05$). Because we were specifically interested in the differences between schizophrenia and control subjects in the temporo-prefrontal connectivity, we specifically tested if the connectivity between left VLPFC and left fusiform was significantly different between the two groups. This can be done by using a stacked model, this time by testing if the fit model improves by freeing the parameter measuring the pathway between left VLPFC and left fusiform in the control group

from forcing it to equal the value observed in the schizophrenia group. The fit improvement was marginally significant (X2 (1) = 3.14, $p<0.1$).

The network for item recognition memory shows a different pattern, as we can see in figure 8 (again, the figure above illustrates the significant pathways for control subjects, and the figure below displays the significant pathways for the schizophrenia group). The path coefficients were significant for connections between left parahippocampal cortex and left perirhinal cortex (0.32, $p<0.05$), left perirhinal and medial orbitofrontal cortex (0.22, $p<0.05$), left VLPFC and right frontal pole (0.33, $p<0.05$), left DLPFC to both right frontal pole and cingulate cortex (respectively 0.28 and 0.33, both $p<.05$. In schizophrenia subjects, only two of these path coefficient show significant correlations: left perirhinal and medial orbitofrontal cortex (0.53, $p<0.01$), and right anterior frontal cortex and left VLPFC (0.28, $p<0.05$). During item memory presentation, only two of the path coefficients observed in control subjects showed significant connectivity in the schizophrenia group: this was left perirhinal and medial orbitofrontal cortex (0.53, $p<0.01$), and right anterior frontal cortex and left VLPFC (0.28, $p<0.05$). The schizophrenia group also displayed significant connectivity between parahippocampal gyrus and perirhinal cortex, but contrary to control subjects, this connectivity was observed in the right hemisphere. In a post-hoc analysis, we reproduced the same network observed here in the item recognition condition, but only for the new condition. Both groups show strong connectivity between left perirhinal and medial orbitofrontal cortex (0.47 and 0.64 for the control and schizophrenia group respectively).

Discussion

We examined differences in connectivity between a control and a schizophrenia group using an fMRI study aimed to identify brain regions and underlying connectivity that are differentially activated when associations are retrieved and when new items are detected during episodic memory.

Behavioural and univariate analysis results

At the behavioral level, the schizophrenia subjects performed significantly worse than the controls during the associative recognition task, but not during item recognition memory. This result provides support to the hypothesis that schizophrenia subjects are impaired in associative recognition memory to a greater extent than in item memory, as it has been observed by other groups that have used a pair recognition memory design (Danion et al., 1999; J. D. Ragland et al., 1998; Weiss et al., 2002)

In our event-related fmri analysis, only activations for correct memory judgements were used to model the hemodynamic curve during memory. Despite this caution, the univariate analysis has demonstrated more active regions in control subjects than in people with schizophrenia during associative recognition memory compared to the item memory recognition. During associative recognition memory, the strongest differences of activations were found in left and right superior parietal lobules, left DLPFC and right VLPFC. A recent meta-analysis has shown that the left DLPFC is one of the common regions of group differences when a schizophrenia group is compared to a control group with a memory task (Achim & Lepage, In

press). The superior parietal lobules have often been reported to be active, particularly during associative recognition memory (Wagner, Shannon, Kahn, & Buckner, 2005). While its role in episodic memory is still not well understood, the importance of the superior parietal cortex during working memory suggests that this region contributes to episodic memory by providing additional working memory resources. Because the superior parietal lobules were also active in the schizophrenia group, albeit to a lesser degree these regions were incorporated in the connectivity modeling. In contrast, schizophrenia subjects did not demonstrate any modulation of activity in the left DLPFC and right VLPFC appear active in controls. We thus opted for a slightly more superior activation in the DLPFC, and for a left VLPFC, in order to test the connectivity with regions that showed active regions.

Results for the connectivity analysis

The major finding of our connectivity analysis is the presence of active connectivity during associative recognition memory between the temporal cortex and the prefrontal cortex in the control group, but not in the schizophrenia group. However, this result did not generalize to item recognition memory, as both group demonstrated significant connectivity between the left perirhinal cortex and a medial orbitofrontal area. These results suggest that abnormal communication between the prefrontal and temporal areas in schizophrenia are likely to contribute in the reduced performance observed during associative recognition memory.

One important region in the network for associative memory is the fusiform gyrus. In our experiment, the recognition of the pictorial objects shown to subjects

was a necessary step towards making a judgement about the past memory of the given object. In our task, the associative recognition memory differed from the item memory by forcing subjects to recognize two objects rather than only one object. It is thus likely that the contrast of associative memory to item memory can detect an important increase in activity of the neural correlates for recognizing objects. Many studies have shown that the fusiform gyrus, with extension to the lateral temporal cortex, is the most likely candidate to be this neural correlate (Murtha et al., 1999; Martin et al., 1996, Kosslyn et al., 1994; Whatmough et al, 2002). In our study, the fusiform gyrus produced the strongest activations during associative memory in both of our groups and thus responded extensively to object recognition.

What is less certain is if this region has also been implicated in the memory processing of associative recognition. First, studies using a subsequent memory effect have several times reported that active fusiform during encoding helps later retrieval (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Cabeza & Nyberg, 2000a; Wagner, Schacter et al., 1998). Many studies which have controlled for the number of object to recognize have found the fusiform to be active during memory. Simple memory tasks with verbalizable pictures of objects such as those we used often activate the fusiform gyrus as well as the MTL (Wagner, Poldrack et al., 1998; Wiggs et al., 1999). Strategies helping memory with objects, for example making a semantic decision on words referring to objects (e.g. category membership) also strongly activates the fusiform region (Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995; Moore & Price, 1999; Murtha, Chertkow, Beauregard, & Evans, 1999). Our subjects have perhaps used a similar strategy during encoding of objects in order to facilitate

the encoding and retrieval of associations between the objects which increased cognitive manipulations on these represented objects. The direct implication of the fusiform gyrus in memory has been directly tested in a recent study (Garoff, Slotnick, & Schacter, 2005). Using pictorial objects very similar to ours, the investigators demonstrated that fusiform activation during encoding predicted later successful recognition, and that stronger fusiform activation during recognition correlated with the better performance on memory tests. These experiments provide support to the idea that the significant connectivity associated with fusiform gyrus underlies a contribution to memory association of objects.

The fusiform gyrus is closely linked to the posterior parahippocampal gyrus, to which it is deeply connected. In schizophrenia subjects, when studies examined the fusiform gyrus along with the parahippocampal gyrus, it showed that the abnormalities in the two gyri are similar (Lee et al., 2002; McDonald et al., 2000). Importantly, schizophrenia subjects suffer from important (more than 10%) reductions of volume in the left fusiform gyrus (McDonald et al., 2000; Onitsuka et al., 2003), and this reduction is already important in first-episode schizophrenia subjects (Lee et al., 2002). Our data suggest that these abnormalities might have an impact on the quality of the connectivity with the parahippocampal regions as well as with the frontal lobe.

The fact that the left fusiform gyrus and the left VLPFC were significantly connected in the control subjects also suggests that this region participates into the memory network. The left VLPFC is a very active region in verbal fluency as well as in memory tasks, and its role has been interpreted as searching information notably in

networks found in temporal regions. Our data suggest that, as for semantic networks found in more anterior temporal lateral regions, an object-related network might retain information associated to objects in the fusiform gyri. The most recent evidence suggests that the left fusiform gyrus holds more conceptual information, whereas the right fusiform holds more perceptual information (Garoff et al., 2005). This evidence suggests that control subjects sustained a connectivity network between the left fusiform gyrus and left VLPFC suggests in order to retrieve conceptual information related to objects they have encountered. To the extent that this interpretation of the fusiform gyri is valid, the lack of connectivity shown by the schizophrenia subjects in our experiment is similar to the lack of connectivity observed in semantic processing tasks between the left VLPFC and the left temporal regions (Jennings et al., 1998; Lawrie et al., 2002).

Medial Temporal Lobe

Another temporo-prefrontal connection appear significantly active in the control group, but not in the schizophrenia group. A right posterior parahippocampal ROI exhibited during associative memory strong connectivity with the DLPFC. Several studies have reported greater activation in the posterior parahippocampal gyrus (as well as hippocampus) for recollection than familiarity decision (Simons & Spiers, 2003). Studies have also implicated the DLPFC in recollection (Dobbins et al., 2002), particularly when recollection is contrasted to an easier item memory condition. The DLPFC is connected to the parahippocampal gyrus in several ways, but the most dense projection links the DLPFC to the posterior MTL through the

cingulate bundle. The DLPFC is furthermore significantly connected to the right VLPFC, another region often shown for recollection (P.C. Fletcher & Henson, 2001). The frontal lobe has been associated to the self-initiation and guidance of memory. Altogether, our connectivity analysis suggests that the frontal pole recruited the DLPFC for initiating elaborative monitoring of associative memories, and that the DLPFC was a key region communicating with the parahippocampal cortex. We should mention that all connectivities between the nodes that we selected in our model have reciprocal connections. Our analysis could not determine the direction of flow between these nodes. It thus remains an open question whether the lack of connectivity between these regions in schizophrenia reflects bidirectional lack of communication or lack of top-down operation.

This result involving the parahippompal cortex has to be interpreted in the light of the overall pattern observed in the MTL during our experiment. In both groups, the activity in the MTL conveyed three different patterns. First, the hippocampus activated robustly during the presentation of the baseline. The baseline consisted in the repetition of two abstract stimuli. During the whole experiment, we presented the stimuli 120 times, a far greater number of repetitions than for any other stimulus in the study. The intense activity in hippocampus thus reflected the signaling of very familiar stimuli. Electrophysiological studies have shown that the hippocampus could increase linearly its activity with the increased repetitions of one stimuli to a very high level (Persson, Habib, & Nyberg, 2002). Our results thus appear to reflect the faculty of the hippocampus to increase activity as a function of increasing familiarity (Gabrieli et al., 1997). For this reason, the hippocampus showed

a different pattern of activity than from the rest of the MTL, and we therefore removed this region of interest from the connectivity network. That does not suggest however, that the hippocampus is unimportant for the memory tasks examined in this study.

Two other patterns in the MTL revealed by our study dissociated the parahippocampal cortex and the perirhinal cortex in response to the different demands conveyed by our experiment. Both of these regions showed positive activity for to-be-remembered stimuli during encoding and retrieval. However, they showed different patterns of activity when contrasting associative memory to item memory during retrieval. The parahippocampal cortex activity was modulated by an increased response to associative recognition when it was contrasted to item recognition. In contrast, the perirhinal cortex activity was modulated by an increasing response to the item recognition in contrast to associative recognition. Item recognition differs from associative recognition in that we present to subjects stimuli that have never been presented before, in addition to "old" stimuli that were studied during the encoding phase. During associative recognition, however, subjects are familiar with all stimili, only their pairings might be new. We thus interpret this modulation of activity in the perirhinal cortex as signaling the novelty of new stimuli during the item recognition. Consistent with this hypothesis, we observed that the connectivity between perirhinal and orbitofrontal was even stronger when the analysis was limited to the new condition. This greater activity for new items relative to old items reflects similar findings in anterior MTL (R. N. Henson et al., 2003; Persson et al., 2002; Rugg & Yonelinas, 2003). For example, Henson and colleagues have collapsed together data

from four studies examining activity in MTL for old and new items, and they found out that the regions showing a sharp modulation of activity were centered around a voxel (+22, -6, -28) almost identical to the one that modulated its activity the most for this contrast. In addition, the perirhinal cortex and the orbitofrontal cortex are often shown to be active during item retrieval (Frey & Petrides, 2000; R. N. Henson et al., 2003), and they are believed to be strongly inter-connected (Lavenex et al., 2002; Petrides & Pandya, 2002). Our result adds to the current knowledge in showing the functional participation of the perirhinal cortex to the activation of the orbitofrontal cortex in detecting new items. Furthermore, schizophrenia subjects behaviorally performed at the same level of as controls when they had to correctly reject new items. This result is supported by the findings we observed during the meta-analysis of recognition memory that we have surveyed in the earlier section. In this meta-analysis, the effect size for differential performance was at its lowest for the FA rate. Other studies have explained similarly their results (Elvevag et al., 2004; Huron et al, 2002).

Other investigators have noted however that schizophrenia was associated with failure to activate the proper network we have here identified when retrieving new stimuli. When Crespo-Facorro and colleagues contrasted "newly learned" items to well-learned items, they observed that the most deactivated regions in schizophrenia, compared to controls, were found in the orbitofrontal cortex and in clusters in the left and right neighbourhood of the anterior part of parahippocampal gyrus, in addition to anterior cingulate cortex (Crespo-Facorro et al., 2001). However, this study differed from ours in some important ways. First, it was a PET study, with

necessarily a block design. Therefore, the "newly learned" items that the investigators contrasted to a very familiar baseline included both correct new item detections and correct item retrieval (although in smaller proportion). Their results could therefore be explained by lower activations in schizophrenia subjects during the presentation of the target items, particularly for these activations found at the border of the anterior and posterior parts of the MTL. In a similar way, our results concerning the network underlying new item detection are not in contradiction with the findings of a study by Weiss and al (Weiss et al., 2004). In this study, the investigators demonstrated that increased false alarms rate in schizophrenia during a visual recognition memory task was associated with a failure to activate the right anterior hippocampus in schizophrenia subjects, and was inversely correlated with the volume of the right hippocampus. Our results differ in two ways. First, our results deal only with correct rejection of new items, since we have rule out of the fmri analysis any stimulus associated to an incorrect response. Therefore, we must remain silent about the neural correlates of false alarms (items that subjects falsely accepted as a target item). Second, the region identified in our network only concerns the perirhinal cortex and do not extend to hippocampus, which, in our data, demonstrated a wholly different pattern of results. Our result of a preserved network between perirhinal and orbitofrontal appears thus compatible with a disrupted involvement of the hippocampus in networks for memory, for example in network for associations.

Frontal regions

A common and robust observation in memory tasks with schizophrenia is the failure to recruit properly frontal regions (P. C. Fletcher et al., 1998, Weiss, 2001, Ragland, 2004; Ganguli et al., 1997; Nohara et al., 2000; Wiser et al., 1998; Wood & Flowers, 1990). In both the associative and item recognition memory network that we have unfolded, the network in schizophrenia subjects was characterized by a reduced connectivity within the frontal regions, particularly around the left DLPFC. However, the DLPFC and the VLPFC were more implicated in communication with temporal regions for associative recognition memory. We interpret these results as showing that, while schizophrenia subjects appear to suffer from reduced connectivity overall, because associative recognition memory relies on a greater integration of information than item recognition memory, the associative recognition memory is more likely to reveal that performance is affected by dysconnectivity. This interpretation would also explain why both DLPFC and VLPFC were inactive in the univariate analysis in the associative-item contrast relative to the control group. It thus appears that DLPFC and VLPFC are important regions for the integration of information during associative recognition memory as well as key regions in understanding the mnemonic deficit observed in schizophrenia. This interpretation is supported by several studies. For example, in a recent meta-analysis of neuroimaging studies of schizophrenia subjects, the left DLPFC was a significant common region that schizophrenia subjects failed to recruit during more difficult memory retrievals (Achim & Lepage, 2005a). In addition, many studies have pointed out that schizophrenia subjects failed to generate effective mnemonic strategies during retrieval (Bonner-Jackson, Haut, Csernansky, & Barch, 2005; Koh, 1978; J.D. Ragland et al., 2001). Our network analysis suggests a

neural correlate of this failed capacity. The low connectivity between frontal pole and DLPFC observed in schizophrenia during associative memory offers a neural substrate for explaining for the lack of self-initiation and generation of mnemonic strategies during retrieval.

It has been suggested that the faulty connectivity in subjects, particularly between frontal and temporal regions, is the result of the symptoms experienced by persons living with schizophrenia. It is unlikely that the lack of connectivity in our sample is the result of the acute state of the patients, as our subjects were clinically stable, with relatively few positive symptoms. While we do not deny the importance of faulty connectivity in the experiencing of symptoms, we think that our data suggest that the faulty connectivity might also reflect a trait-like condition, which affects the performance of subjects in challenging cognitive tasks, notably in retrieving memory for associations. One prediction from that is that first-degree relatives of schizophrenia subjects who are known to exhibit subtle episodic memory deficits and smaller MTL (O'Driscoll et al., 2001) could similarly show abnormal temporal frontal connectivity.

It should be noted that several caveats should be taken into consideration when interpreting these results. First, the goodness-of-fit of our model was relatively modest. This suggests that there are other regions important for the network of memory that we did not consider in our model. One important region was the hippocampus. It is likely that hippocampus, in addition to its connectivity with the rest of the brain during presentation of the baseline, might share connectivity also during the associative memory. Unfortunately, fMRI measures are always relative to

a baseline (Stark & Squire, 2001b), and so the use of our baseline hindered the detection of activity of hippocampus during associative memory. Another potential limitation of connectivity analyses is the relative arbitrariness in the selection of the nodes in our model, which could introduce a bias in the connectivity analysis against a specific group. In our study, we guided our selections of nodes by considering peaks in ROI that were higly significant in the memory vs baseline condition in both groups. An exception of this criterion was the selection of peaks in the MTL. Because the peaks in the MTL fell under the a priori statistical threshold, we selected peaks that showed opposite pattern of activations in item recognition and associative recognition memory. In order to limit the risk of introducing a bias, we made a direct comparison of the activitation maps between the schizophrenia and healthy, and no node in our model yielded a significant difference except the left superior parietal, which did not significantly participate in the memory networks. In addition, the higher activations observed in the healthy group were consistent throughout the nodes of our model, and so we are still left with an explanation to provide in order to explain the interaction effect that we observe between associative memory and prefrontal-MTL connectivity between the two groups. Still, to soundly resolve this issue, we should probably look for nodes in the ROI that do not show differences of fmri activation greater than t=1. A third limit in our interpretation is that all schizophrenia subjects but one were taking antipsychotic medication during our study. Therefore, one cannot discount the possibility that the reduced connectivity results from abnormal neuronal firing patterns caused by taking this medication rather than from altered anatomical connections. That being said, there was no significant correlation between overall

memory performance and the mean dose of antipsychotic medication taken and no influence of the type of medication (typical vs. atypical) on recognition memory performance. This suggests that these factors did not have a significant impact had on the present results. Finally, the majority of the chronic schizophrenia subjects that participated in the study presented with mild symptoms. It is thus possible that some of our results do not generalize to schizophrenia subjects experiencing positive symptoms, or with a greater severity of negative symptoms.

Conclusion

One guiding hypothesis in the recent years has been to explain the cognitive deficits and the paucity of functional activity in schizophrenia subjects as reflecting a lack of connecitivity between areas. In our review of the studies which have directly tested this hypothesis, we have found out that the results have been mixed. While schizophrenia subjects often display different network of connectivity, the few effective connectivity analyses have shown that several regions appear to present relative preserved connectivity. Furthermore, we have also observed that there was a lack of studies examining the connectivity between MTL and prefrontal cortex in a memory setting. In the meta-analysis of the recognition memory that we have performed, we observed that schizophrenia groups generally show great deficit for associative recognition of non-verbal objects in a pair memory experiment. In contrast, they show relative preserved correct rejection of new stimuli. This suggested the possibility of dissociation between the brain network subserving familiarity and recollection, with the latter likely to be more disrupted in schizophrenia. In accordance to this view, we show that schizophrenia subjects demonstrate a lack of MTL-DLPFC connectivity during associative recognition memory, as well as a lack of fusiform-VLPFC connectivity. However, they demonstrated a preserved anterior MTL-orbitofrontal cortex during item memory. These results suggest that recollective-based operations are likely to depend on a greater integration of information than familiarity-based operations, and thus likely to reveal a greater dysconnectivity in schizophrenia.

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APPENDIX

2. Method

2.1 Literature search

For this meta-analysis, Pubmed and PsycINFO databases were used to retrieve studies published between 1965 and July 2003 that reported measures of recognition memory. The key words used for the search were: « schizophrenia recognition memory ». References provided by meta-analyses on memory in schizophrenia and by the retrieved articles were also examined.

2.2 Criteria for inclusion

Three criteria guided the selection of the articles. First, to be included, a study needed both a group of patients with an established diagnosis of schizophrenia and a group of healthy comparison subjects. To include studies prior to DSM-III, any diagnosis of schizophrenia provided by psychiatric records was accepted. We rejected studies that included groups of schizophrenia subjects that had additional characteristics that could interfere with their performance (for instance geriatric patients (P. D. Harvey et al., 2000)). We accepted studies that included a minority of schizoaffective disorder patients (<20%) within the schizophrenia group (e.g. (Sullivan, Shear, Zipursky, Sagar, & Pfefferbaum, 1997)). One study was accepted even though one patient suffered from an unspecified psychotic disorder (Crespo-Facorro et al., 2001). Studies with schizophreniform subjects were accepted only if a diagnosis of schizophrenia was subsequently confirmed. When a study with schizophreniform subjects did not provide any indication as to the subsequent diagnosis, a search through Science Citation Index ® was carried out in order to

determine whether subjects of this group were diagnosed with schizophrenia in a subsequent study by the same authors. This procedure resulted in the rejection of only one study with schizophreniform subjects (Riley et al., 2000). In the case of twin studies, the control group that we selected for the calculation of effect size comprised normal twins instead of the unaffected discordant twins (Goldberg et al., 1995). Comparison of a schizophrenia group to standard normative scores generated by the California Verbal Learning Test (CVLT) (Delis, 1987) was included if scores were corrected individually for age and gender (e.g.(Mahurin et al., 1998; Tracy et al., 2001; Wilder-Willis, Shear, Steffen, & Borkin, 2002)). The overwhelming majority of studies had a control group that matched patients in age and gender, and when data were available for both a healthy group and a select group of healthy subjects matched to patients in age and gender, we selected the latter as the control group (e.g. (Paulsen, 1995)).

A second criterion for inclusion of the studies was the presence of a recognition test of episodic memory. To distinguish episodic memory tests from working memory tests, the encoding that preceded recognition testing had to include at least ten items. Acceptable tests included paradigms of yes-no recognition, forced-choice recognition and several paradigms of associative recognition memory.

Finally, studies had to provide sufficient data to compute the effect size value of the comparison of the schizophrenia group with the control group on the measure of recognition memory. We chose exact F values, t values, z values or p values to compute the effect size (Robert Rosenthal, 1995). When inferential statistics were not provided, we computed t values from the means and standard deviations displayed in

graphs or in tables. When significant or non-significant effects were reported in a study without any other information, it was excluded. This precaution limits the possibility of unwarranted guesses.

2.3 Meta-analytic techniques

A two-step strategy was applied for the meta-analysis (R. Rosenthal, 1991). First, we computed an overall mean effect size for all the studies reporting data on recognition memory performance. To insure independence in the data set, each study could contribute only once in the computation of the mean effect size. The second step consisted of estimating mean effect sizes for specific levels of variables in order to find out which variables played a moderator role in recognition memory. For these analyses we split the data, included the data pertaining to the level of the variable of interest, and contrasted levels of the variable using focused tests (R. Rosenthal, 1991). Focused tests measure the difference in effect sizes obtained under two conditions or under different levels of a same characteristic. This test yields a Z score, which indicates if the mean effect sizes between the different levels of a given variable differ statistically. For these contrasts, unweighted mean effect sizes were estimated, and one-tailed tests were used. For dichotomous variables, the split was categorical. For continuous variables, contrasts were performed by using Z scores of each study on this particular variable as an orthogonal coefficient (Mullen, 1989).

At each step, we performed a chi-square test to examine the homogeneity of the effect sizes included in the study. This procedure, as described by Rosenthal (R. Rosenthal, 1991), is perfectly equivalent to the calculation of Q_B as performed in

other meta-analytic strategies (Hedges & Olkin, 1985). A significant result is an indication of the presence of moderator variables within the dataset.

Effect sizes were calculated by estimating *r* (R. Rosenthal, 1991). When articles included several measures of the same variable, our preferred measure was first the discrimination score (be it *d'* or hit rate minus false alarms (FA) rate), and then the hit rate, but measures of FA rate were also registered. For FC tests, we also accepted the FA rate if results were reported for this measure only. The effect sizes *r* were then transformed in the Fisher *Zr* statistic, and all meta-analytical operations were performed on this statistic because of its superior distributional properties (R. Rosenthal, 1991). The indices of central tendency chosen were the unweighted and weighted (by the degrees of freedom) mean *r*'s. We then converted r to d values to facilitate comparisons with published meta-analyses on memory in schizophrenia. In addition, Stouffer's *Z* was calculated to provide an indication of the significance of the difference between the two groups of subjects. Standard errors and confidence intervals (established at 95%) were obtained for a fixed-model effect.

All data collection, computations and analysis were done with the Excel ® program. Funnel plots were obtained with SPSS ®.

2.4 Moderator Variables

The contrasts performed in this meta-analysis are listed below, with the number of levels and the operational definition assigned to each level in this meta-analysis. For cognitive variables, the following variables were selected: a) Material specificity, which included two levels: verbal stimuli, for all tests using words as stimuli, and figural stimuli, for all tests not using words. Hence, tests that we grouped

together under the term *figural* consisted of different stimuli, with some being more verbal than others. Furthermore, as previous studies suggested that there is a preferential impairment of face recognition in schizophrenia (Feinberg et al., 1986; Whittaker et al., 2001), a contrast between face stimuli, abstract designs and pictures of objects was also examined; b) Type of information retrieved, with two levels: item memory for all tests in which subjects must discriminate between target material and distracters, and associative memory for tests in which subjects must select the appropriate contextual information related to the item studied. Under this definition, associative tests included source (e.g. was item A presented in source 1 or source 2?) and pair tests (e.g. was item A associated with item B or item C?), as well as recency (e.g. did item A appear before/after item B?) and frequency judgment tests (e.g. did item A appear once/twice?). However, there are indications that recency and frequency tests are sensitive to functional deficits in planned processing rather than to deficits in the storage of associations (Mayes et al., 2001). Consequently, we were also interested in the contrasts between the different associative memory tests; c) The recognition format, with two levels: yes-no, for all tests with sequential displayed stimuli, and forced-choice for all tests assessing subjects by displaying the old stimulus among the foils; we also look at the type of measure (hit, d' or FA); d) Perceptual modality of the verbal item to memorize, also with two levels: auditory, for words that subjects hear, and visual, for words that subjects read.

As for clinical variables, we evaluated the contrast between levels of: a) Mean scores on the Scale for the Assessment of Negative Symptoms (SANS) (N. C. Andreasen, 1984a), on the Scale for the Assessment of Positive Symptoms (SAPS) (N. C.

Andreasen, 1984b), and on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987); b) Severity of psychopathology based on the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1980); c) Patient status (outpatients vs. inpatients); d) Chronicity, or the duration of illness (number of months since diagnosis); e) Antipsychotic medication, including the mean dose of typical neuroleptics per study group, in chlorpromazine equivalents; f) Proportions of people taking anticholinergic medication; g) IQ measures.

Table 1.

Mean effect sizes of overall recognition memory and effect sizes modulated by cognitive moderators from studies that compared schizophrenia people with control subjects on a recognition memory test.

	Mean effect size				Confidence intervals			Sample data		
	Weighted	Unweighted	SD	Stouffer	Lower	Upper	Hetero-geneity	studies	subjects	contrast
	d	d	d	z	d	d	X			Z
Overall recognition	0,76	0,83	0,03	21,9	0,68	0,84	183,6**	70	4161	-
Material specificity										
Verbal	0,71	0,73	0,03	22,2	0,64	0,77	117,6**	68	4374	3,68**
Figural	1,00	1,01	0,05	19,6	0,90	1,11	93,46**	34	1758	
Level of processing										
Item	0,72	0,79	0,03	22,6	0,66	0,78	172,29**	81	4848	0,14
Associative	0,71	0,79	0,05	13,4	0,61	0,81	40,00*	22	1418	
Recognition format										
Yes-No[a]	0,70	0,81	0,04	19,0	0,67	0,81	88,5**	56	3385	
FC[a]	0,62	0,58	0,06	13,6	0,51	0,74	21,1*	21	1465	2.42*
Figural										
faces[b]	0,93	0,90	0,06	14,1	0,80	1,06	27,50	21	1113	
pictures[b]	0,83	0,85	0,10	7,8	0,61	1,06	4,60	9	394	1,01
designs[b]	1,07	1,16	0,07	14,5	0,91	1,24	63,17**	12	767	

[a] *Indicates that the contrast was restricted to verbal item memory tests.*

[b] *Indicates that the contrast was restricted to figural memory tests.*

* $p < .01$

** $p < .001$

Table 2.

Mean effect sizes and confidence intervals from studies that compared schizophrenia people with control subjects on associative memory tests.

	Verbal			Figural		
Associative Tests	k	d	Confidence intervals	k	d	Confidence intervals
Source	11	0.48	0.41-0.55	4	1.09	0.78-1.42
Pair	1	1.29	0.64-2.05	3	1.15	0.80-1.52
Recency	4	0.75	0.50-1.01	1	0.56	0.14-1.00
Frequency	1	0.62	0.03-1.27	2	1.43	0.94-1.99

Table 3

Mean effect sizes of recognition memory modulated by clinical moderators from studies that compared schizophrenia people with control subjects.

	Mean effect sizes			Confidence intervals		Sample data		
	Weighted	Unweighted	SD	Lower	Upper	Studies	Subjects	Contrast
	d	*d*	*d*			*k*	*N*	*Z*
Medication :								
Free	0,78	0,80	0,07	0,63	0,93	8	811	
Typical neuroleptics	0,75	0,78	0,04	0,66	0,85	41	2108	0,36[a]
Atypical neuroleptics	0,85	0,83	0,08	0,68	1,02	14	689	0,68[b]
Anticholinergics	0,77	0,80	0,05	0,67	0,87	35	1974	0,64[b]
Duration of illness[c]								5,67**
≤ 10 years	0,76	0,71	0,06	0,64	0,89	21	1198	
> 10 years	0,96	0,95	0,05	0,81	1,04	22	1483	
Status of patient								0,22
Inpatient	0,67	0,70	0,06	0,51	0,78	20	1003	
Outpatient	0,64	0,68	0,06	0,51	0,74	15	1310	

[a] The *Z* score represents the contrast performed between effect sizes and the mean dose of the medication.

[b] The *Z* score represents the contrast performed between effect sizes and the proportion of people taking the medication.

c The Z score represents the contrast performed between effect sizes and the z-score for the average years of illness duration.

**p <.001

Table 4

Summary of the effects of different scales of clinical symptoms on effect sizes of recognition memory performance by schizophrenia subjects as compared to control subjects.

	k	*N*	*Z score*[a]	*p*
Positive symptoms				
SAPS Global Ratings	10	918	1,16	0,12
SAPS Total Items	7	370	0,14	0,44
PANSS positive scale	6	395	1,60	0,052
Negative symptoms				
SANS Global Ratings	10	918	1,44	0,07
SANS Total Items	8	374	0,43	0,34
PANSS negative scale	6	395	0,93	0,17
General symptoms				
BPRS	16	1158	1,13	0,13
PANSS overall	8	549	1.56	0.06

[a] A positive score indicates that high scores on a scale correlated with larger effect sizes.

Table 5: *Demographic and clinical data of the schizophrenia and control groups .*

Characteristic	**Schizophrenia Subjects** N=15			**Control Subjects** N=18			**Analysis** (p)
Demographic Characteristics	Mean	SD	Range	Mean	SD	Range	T-tests
Age	34.0	8.4	20-50	28.9	9.5	20-50	p=.118
Education	14.6	3.6	10-22	16.1	2.9	12-22	p=.191
Parental Education	12.4	2.7	8-17	12.7	2.7	9-17	p=.754
	N	%		N	%		Chi-square tests
Sex							
Male	10	67		10	56		p=.515
Female	5	33		8	44		
Language							
English	4	27		5	28		p=.943
French	11	73		13	72		
Dominant Hand							
Right	14	93		18	100		p=.266
Left	1	7		0	0		
Diagnosis							
Paranoid type	12						
Undifferentiated type	1						
Residual type	2						
Clinical Characteristics	Mean	SD	Range	Mean	SD	Range	T-tests
Duration of illness (years)	10.9	7.2	2-25	--			
PANSS Positive Scale	11.3	3.0	8-18	--			
PANSS Negative Scale	10.0	3.1	7-17	--			
PANSS General Psychopathology	24.1	5.3	17-37	--			
Abnormal Involuntary Movement Scale	2.2	4.3	0-16	0.0	0.0	-	
Global Assessment of Functioning	66.8	8.7	55-81	85.6	6.6	70-91	p<0.001

Table 6 Behavioural performance during encoding and recognition in the two groups.

	Schizophrenia Subjects N=15			**Control Subjects** N=18			**Analysis** (p)
Task	Mean	SD	Range	Mean	SD	Range	
Encoding	0.95	0.12	0.53-1.00	0.99	0.01	0.96-1.00	p=.226[a]
Recognition (overall)	0.73	0.08	0.63-0.92	0.80	0.10	0.62-0.98	p=.052
Recognition (item)	0.83	0.01	0.71-0.95	0.87	0.01	0.72-0.98	p=.183
Recognition (new)	0.89	0.08	0.69-1.00	0.90	0.05	0.82-1.00	p=.716
Recognition (asso)	0.62	0.08	0.50-0.88	0.72	0.08	0.46-0.98	p=.042*

[a] variance not assumed to be equal

* $p < .05$ (not corrected for multiple measures)

Table 7 Significant activations elicited by the associative recognition compared to the item memory task in control subjects.

Asso>Item for the Control group

peak activation	peak coordinates x	y	z		region	Brodmann Areas (BA)
6.27	-40	22	19	Left	Middle Frontal Gyrus	45/46
5.02	-30	19	1	Left	Claustrum	
5.46	-46	7	31	Left	Inferior Frontal Gyrus	9
7.08	0	-27	3	Left	Thalamus	
9.12	-26	-56	45	Left	Superior Parietal Lobule	7
4.08	-22	-58	1	Left	Lingual Gyrus	18
5.43	-42	-61	-7	Left	Fusiform Gyrus	37
6.12	-12	-70	44	Left	Precuneus	7
4.19	-2	-85	15	Left	Cuneus	18
4.47	2	33	39	Right	Medial Frontal Gyrus	8
3.94	28	25	-6	Right	Inferior Frontal Gyrus	47
5.84	2	20	43	Right	Medial Frontal Gyrus	8/32
4.33	2	-36	26	Right	Cingulate Gyrus	31
4.89	32	-51	-8	Right	Fusiform Gyrus	37
7.53	34	-62	49	Right	Superior Parietal Lobule	7
4.86	2	-69	11	Right	Cuneus	30
4.68	14	-71	16	Right	Cuneus	18
4.46	34	-72	42	Right	Superior Parietal Lobule	7
5.76	6	-76	-10	Right	Lingual Gyrus	18
4.34	16	-93	14	Right	Middle Occipital Gyrus	17/18

Table 8 Significant activations elicited by the item recognition compared to the associative recognition memory task in control subjects.

Item>Asso for the Control group

peak activation	peak coordinates x	y	z		region	Brodmann Areas (BA)
4.79	-8	56	12	Left	Medial Frontal Gyrus	10
4.09	-8	42	-18	Left	Medial Frontal Gyrus	11
5.17	-2	42	-2	Left	Anterior Cingulate	32
4.25	-20	38	46	Left	Superior Frontal Gyrus	8
4.32	-16	36	12	Left	Anterior Cingulate	32
4.41	-18	20	12	Left	Caudate	
4.66	-24	10	34	Left	Middle Frontal Gyrus	8
4.56	-12	8	38	Left	Cingulate Gyrus	32
4.74	-36	2	12	Left	Insula	13
3.85	-50	-2	0	Left	Superior Temporal Gyrus	22
4.09	-44	-2	10	Left	Insula	13
4.54	-32	-8	-18	Left	Amygdala/Perirhinal cortex	
4.66	-54	-10	14	Left	Precentral Gyrus	43
4.48	-40	-12	-14	Left	Inferior Temporal Gyrus	21
4.49	-62	-18	2	Left	Superior Temporal Gyrus	22
4.21	-12	-18	54	Left	Medial Frontal Gyrus	6
4.17	-54	-22	-10	Left	Middle Temporal Gyrus	21
4.97	-66	-26	12	Left	Superior Temporal Gyrus	42
5.88	-46	-34	12	Left	Superior Temporal Gyrus	41
4.26	-44	-34	0	Left	Superior Temporal Gyrus	22
7.26	-12	-38	54	Left	Paracentral Lobule	5
4.73	4	54	2	Right	Medial Frontal Gyrus	10
4.62	24	32	14	Right	Medial Frontal Gyrus	9
4.45	54	-4	12	Right	Precentral Gyrus	43
5.61	58	-8	-10	Right	Middle Temporal Gyrus	21
4.47	6	-10	46	Right	Paracentral Lobule	31
4.31	34	-16	6	Right	Claustrum	
5.16	40	-16	20	Right	Insula	13
4.93	62	-20	2	Right	Superior Temporal Gyrus	
4.63	32	-24	58	Right	Precentral Gyrus	4
6.4	58	-26	30	Right	Inferior Parietal Lobule	40
4.57	50	-28	60	Right	Postcentral Gyrus	2
4.33	38	-34	54	Right	Postcentral Gyrus	40
4.19	24	-36	68	Right	Postcentral Gyrus	2
4.27	58	-38	8	Right	Middle Temporal Gyrus	22
4.59	52	-64	8	Right	Middle Temporal Gyrus	37

Table 9a Significant interactions elicited by associative recognition memory task compared to item memory.

Interaction analysis: Control > Schizophrenia

peak activation	peak coordonates x	y	z			
2.87	-40	28	20	Left	Middle Frontal Gyrus	46
3.22	-30	-50	48	Left	Precuneus	7
2.90	-28	-64	46	Left	Superior Parietal Lobule	7
2.66	-44	-62	-8	Left	Middle Temporal Gyrus	37
3.41	28	26	-4	Right	Inferior Frontal Gyrus	47
3.05	2	18	48	Right	Medial Frontal Gyrus	8
3.63	4	-38	26	Right	Cingulate Gyrus	31
2.88	30	-58	48	Right	Superior Parietal Lobule	7
3.66	34	-74	52	Right	Superior Parietal Lobule	7
3.10	4	-76	-16	Right	Lingual Gyrus	18

Interaction analysis: Schizophrenia > Control
No significant activation was identified in this analysis

Table 9b significant interactions elicited by item memory task compared to associative memory.

Interaction analysis: Control > Schizophrenia

peak activation	peak coordonates x	y	z			
3.53	-18	16	30	Left	Cingulate gyrus	32
5.5	-18	10	30	Left	Cingulate gyrus	32
4.2	-14	-38	56	Left	Paracentral gyrus	4
4.76	-18	-52	-24	Left	Cerebellum	37
3.18	28	-2	20	Right	Claustrum	
3.16	44	-2	18	Right	Insula	13
3.84	30	-22	56	Right	Precentral Gyrus	4
4.17	64	-28	26	Right	Inferior Parietal Lobule	40
3.01	38	-34	54	Right	Postcentral Gyrus	3
3.67	50	-66	8	Right	Middle Temporal Gyrus	39

Interaction analysis: Schizophrenia > Control
No significant activation was identified in this analysis

Table 10. List of the nodes selected and their coordinates.

Region	**(Brodmann Area)**	**Coordinates (x y z)**		
Left fusiform gyrus (BA 37)		-32	-52	-18
Right fusiform gyrus (BA37)		32	-52	-14
Left posterior parahippocampal gyrus (BA36)		-28	-36	-16
Right posterior parahippocampal gyrus (BA 36)		30	-36	-18
Left perirhinal cortex (BA35)		-20	-8	-20
Right perirhinal cortex (BA35)		20	-12	-20
Left superior parietal lobule (BA7/40)		-28	-66	46
Right superior parietal lobule (BA7/40)		34	66	48
Cingulate cortex (BA32)		-1	16	42
Left DLPFC (BA9)		-42	20	28
Left VLPFC (VA45)		-28	20	6
Right anterior prefrontal cortex (BA10)		36	58	12
Medial orbitofrontal cortex (BA11)		-8	48	-18

Figure caption

Figure 1. *Funnel plot for the meta-analysis showing the 897 composite effect sizes of recognition memory performance by schizophrenia subjects as compared to control subjects.*

Figure 2. *Mean effect sizes for recognition memory between schizophrenia subjects and control subjects as a function of several cognitive variables.*

Figure 3. *Functional representation of the projections within the medial temporal lobe (reproduced from* Zola-Morgan, Squire & Ramus (1994)).

Figure 4. *Illustration of all the path coefficients tested in our connectivity analysis. The nodes in circles represent the actual location of the nodes, whereas the two box were located more anterior and are located for clarity only. Black lines represent reported neural connections between the neurons. The numbers refer to the Brodmann Areas (see table 10 for references to structures). PH stands for Parahippocampal cortex. PR stands for Perirhinal cortex.*

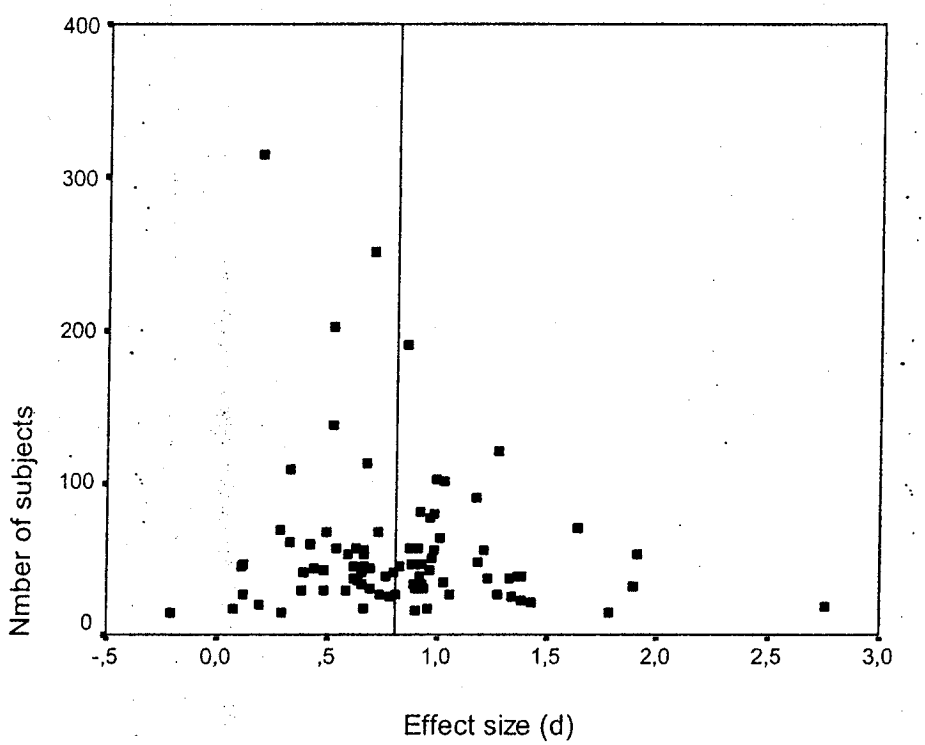
Figure 5. *Series of images along the anterior-posterior axis depicting activation for associative recognition memory in controls (above) and schizophrenia (below). Numbers below indicate the y coordinate according to the MNI template.*

Figure 6. *Images showing the most significant differences of activation in the interaction (associative vs item) for the contrast (controls vs schizophrenia)*

Figure 7. *Significant connectivity (up: in control subjects; below in the schizophrenia group) observed during associative recognition memory.*

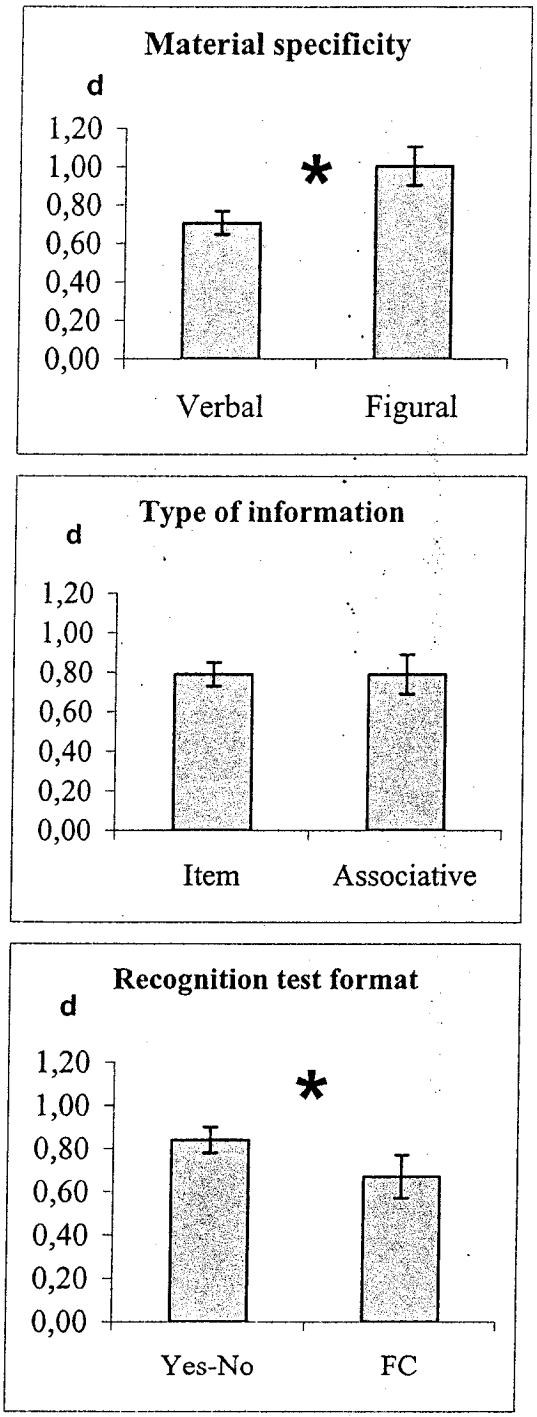
Figure 8. *Significant connectivity (up: in control subjects; below in the schizophrenia group) observed during item recognition memory.*

Figure 1.



Each dot corresponds to the effect size of one group comparison; the vertical line indicates the mean weighted effect size.

Figure 2


Material specificity
d
1,20
1,00
0,80
0,60
0,40
0,20
0,00
*
Verbal
Figural
Type of information
d
1,20
1,00
0,80
0,60
0,40
0,20
0,00
Item
Associative
Recognition test format
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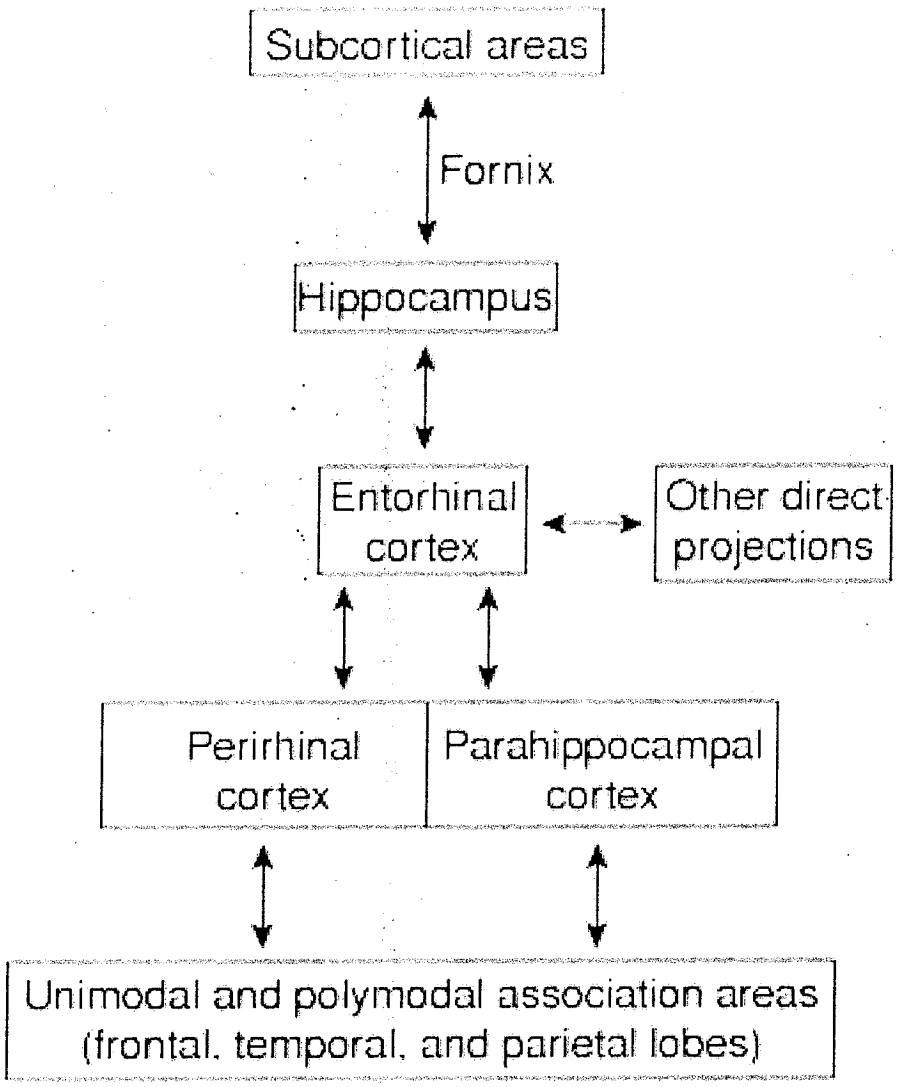
1,00
0,80
0,60
0,40
0,20
0,00
*
Yes-No
FC

Figure 3.



Zola-Morgan, Squire & Ramus (1994)

Figure 4

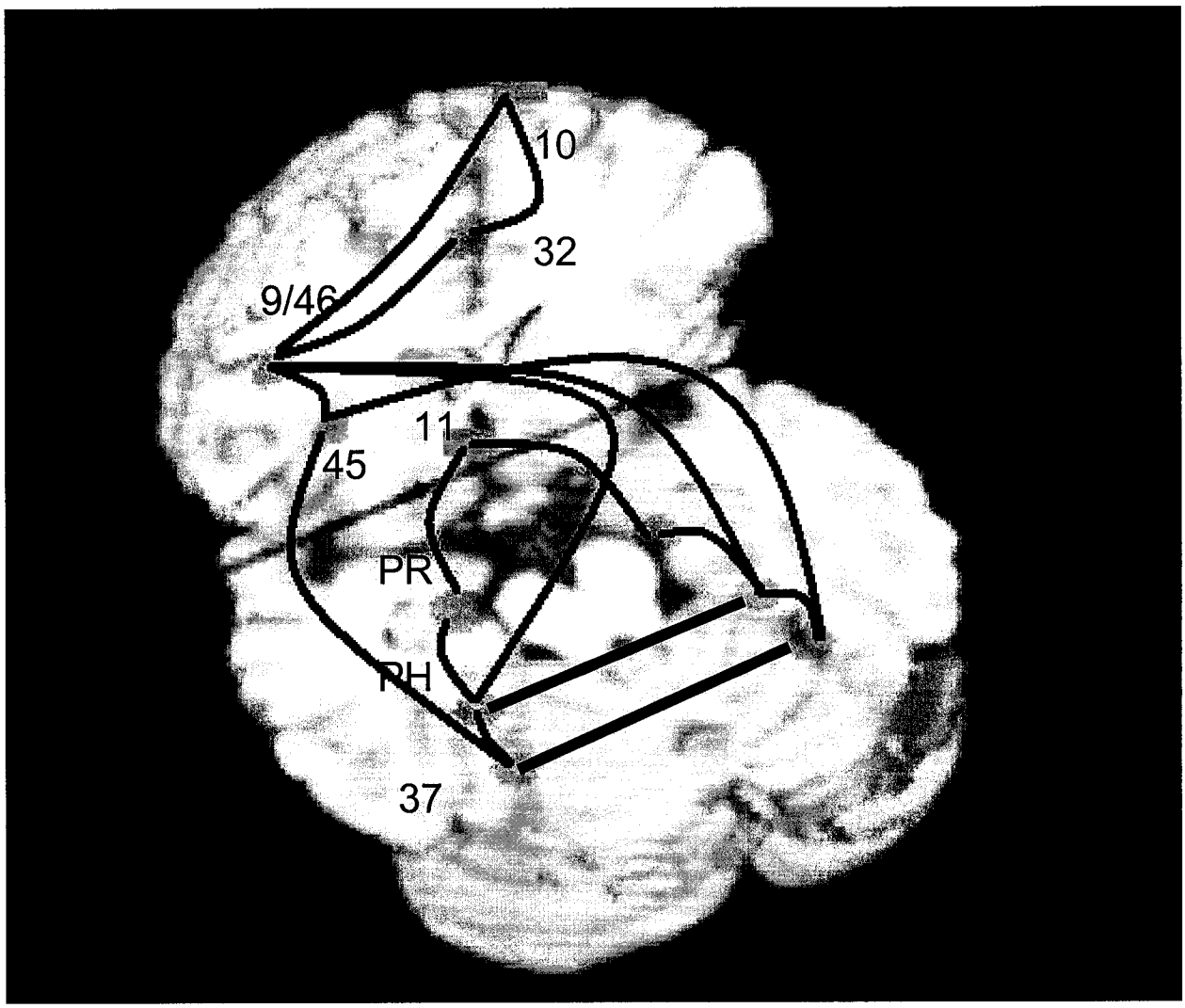


Figure 7

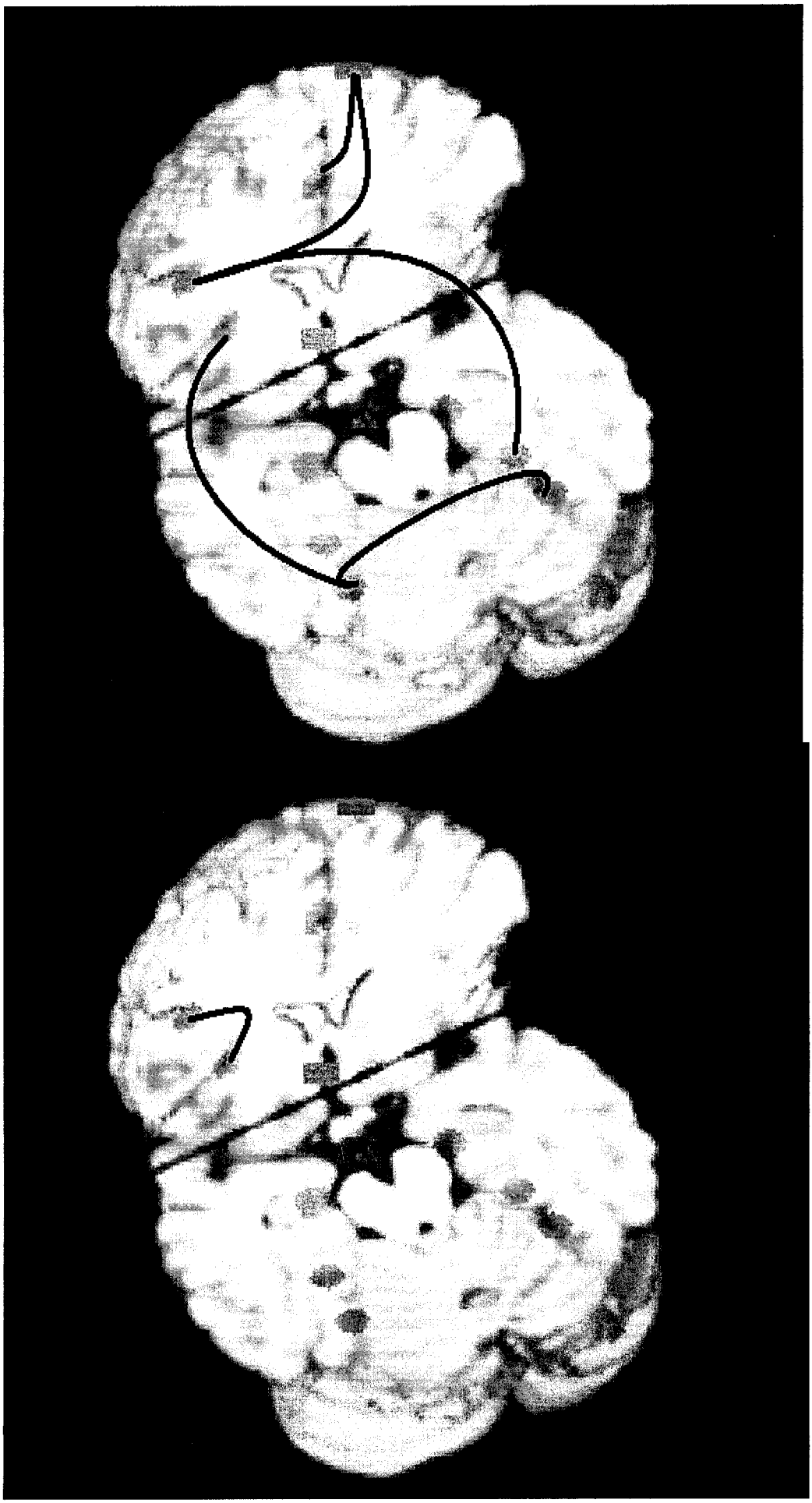
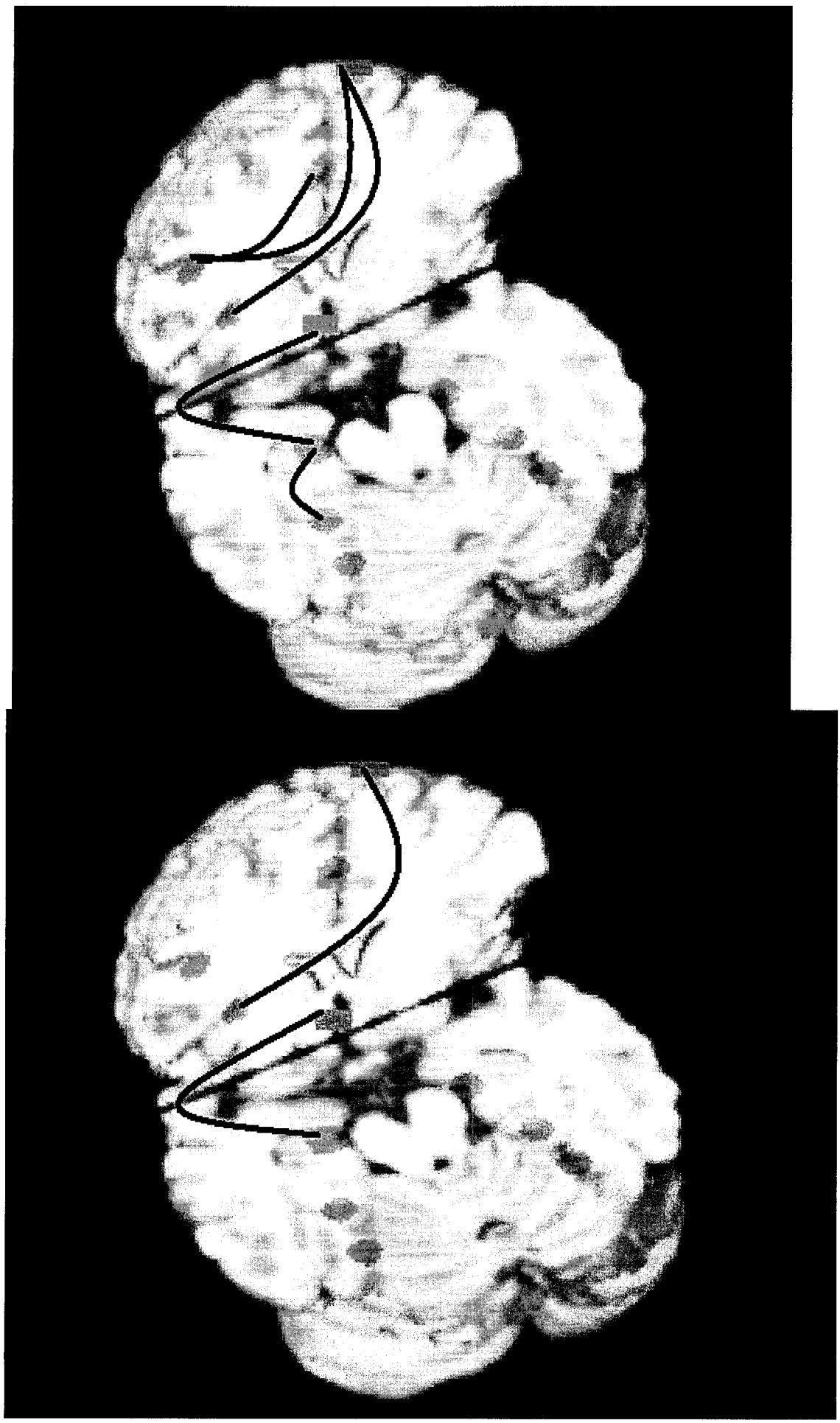


Figure 8



Appendix C : Compliance certification forms

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

1. **TITLE OF PROJECT:** An fMRI study of associative and item memory in healthy subjects and patients with schizophrenia

INVESTIGATORS: Martin Lepage Ph.D., Amelie Achim B.Sc., Alonso Montoya M.D., Samarthji Lal M.D., Bruce Pike Ph.D.

2. **REASON FOR THE STUDY**

The purpose of the study is to further our understanding of human memory works and particularly what happens in the brain when people try to encode new information or retrieve from memory some information. Specifically, functional Magnetic Resonance Imaging (fMRI) will be used to examine brain activity for memory for associations and memory for items.

3. **PROCEDURES**

During the experimental session which will last for 1.5 hour, you will undergo functional Magnetic Resonance Imaging (fMRI), a non-invasive test that uses a magnetic field and radiofrequency waves to visualize brain tissues and identify regions involved in performing a task. This second session will be divided in three successive tasks.

For the first task, you will view pairs of images. Some of these pairs will represent two identical objects whereas other pairs will represent two different objects. You will be required to memorize these items and the association between items. Your memory for these objects will be tested in another tasks alternating between two kinds of blocks. In the first type of block, we will present some objects that you have seen before and others that you have not seen during the study list. Your task will be to indicate which ones you have seen before. Another type of block will test your memory for associations. Pairs of two different objects will be presented. Some of these pairs will be identical as the ones you studied and others will be made of items you have already seen, but rearranged into new pairs. You will have to indicate which pairs are intact and which ones are rearranged.

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

4. CONTRAINDICATIONS

The following are contraindications for a magnetic resonance study:

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

5. ADVANTAGES OF THE PROPOSED STUDY

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

6. DISADVANTAGES OF THE PROPOSED STUDY

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

7. EFFECTS OF PARTICIPATION IN THIS STUDY

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

8. CONFIDENTIAL NATURE OF THIS STUDY

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

9. INCIDENTAL FINDINGS

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

10. DISCONTINUATION OF THE STUDY BY THE INVESTIGATOR

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

11. SUBJECT'S STATEMENT CONCERNING WITHDRAWAL FROM THE STUDY

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

12. COMPENSATION FOR PARTICIPATION IN THE STUDY

Upon completion of the study, you will receive $30 as compensation for your time and inconvenience.

An fMRI study of associative and item memory

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

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

1. Previous surgery (type and date)

_____

_____.

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

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

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

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

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

Imagerie Par Résonance Magnétique (IRM)
QUESTIONNAIRE ET DÉCLARATION DE CONSENTEMENT
INSTITUT ET HÔPITAL NEUROLOGIQUE DE MONTREAL
McConnell Brain Imaging Centre

1. **TITRE DU PROJET:** Une étude d'IRMf de la mémoire associative et de la mémoire des items chez les sujets sains et chez les schizophrènes

CHERCHEURS: Martin Lepage, Ph.D., Amélie Achim, B.Sc., Alonso Montoya M.D., Samarthji Lal M.D., Bruce Pike, Ph.D.

2. MOTIFS DE L'ÉTUDE

La présente étude est menée afin de mieux comprendre le fonctionnement de la mémoire et plus particulièrement ce qui se passe dans le cerveau quand une personne essaie d'acquérir de nouvelles informations ou de retrouver de l'information préalablement apprise. Afin d'identifier les régions du cerveau impliquées dans l'acquisition d'information et la récupération d'informations en mémoire, la technique d'Imagerie par Résonance Magnétique fonctionelle (IRMf) sera utilisée.

3. PROCÉDURE

Pendant la session d'IRMf, vous serez exposée à l'Imagerie par Résonance Magnétique fonctionelle (IRMf), un test non-invasif qui utilise un champs magnétique et des ondes de fréquence radio pour visualiser les tissus du cerveau et identifier les régions impliquées dans la réalisation de différentes tâches. Cette seconde session sera divisée en trois tâches successives.

Dans la première tâche, vous allez voir des paires d'images. La moitié de ces paires seront constituées de la duplication d'un même item et vous aurez à mémoriser l'item présenté. L'autre moitié de ces paires seront formées de deux items différents et vous aurez à mémoriser le pairage spécifique des deux items.

Dans la deuxième tâche, il y aura deux types de blocs. Dans un type de bloc, seulement des paires formées de la duplication d'un même item (items doubles) vous seront présentées. La moitié de ces paires seront nouvelles (jamais vues avant) et l'autre moitié seront les mêmes que celles présentées dans la première tâche (anciennes paires). Vous aurez à indiquer si les paires sont nouvelles ou anciennes.

Dans l'autre type de bloc, seulement des paires formées de deux items différents vous seront présentées. La moitié de ces paires seront présentées comme vous les avez vues dans la première tâche (pairage initial). L'autre moitié des paires sera formée d'items que vous avez déjà vu, mais ces items seront réarrangés entre eux de façon à ce qu'ils soient en un pairage jamais vu avant (pairage réarrangé). Vous aurez à indiquer si les paires sont présentées dans leur pairage initial ou en un pairage réarrangé.

L'IRMf est un scanner considérablement bruyant. Pour réduire le bruit, vous recevrez des bouchons pour les oreilles. On vous demandera de rester parfaitement immobile durant l'expérimentation et votre tête sera immobilisée. Vous serez en constante communication avec l'opérateur tout au long de l'expérimentation.

4. CONTRE-INDICATIONS

Les éléments suivants sont des contre-indications pour les études en Résonance Magnétique:
Stimulateur cardiaque
Clip d'anévrisme
Clip cardiaque ou vasculaire
Valve prothétique
Prothèses métalliques
Grossesse
Claustrophobie
Fragments de métaux dans le corps

5. AVANTAGES DE L'ÉTUDE PROPOSÉE

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

6. DÉSAVANTAGES DE L'ÉTUDE PROPOSÉE

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

7. EFFETS DE VOTRE PARTICIPATION

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

8. CARACTÈRE CONFIDENTIEL DE L'ÉTUDE

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

9. CONSTATATIONS FORTUITES

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

10. INTERRUPTION DE L'ÉTUDE PAR L'EXPÉRIMENTATEUR

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

11. DÉCLARATION DES PARTICIPANTS QUI SOUHAITENT SE DÉSISTER

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

12. COMPENSATION POUR PARTICIPATION À L'ÉTUDE

Après la réalisation de l'étude, vous recevrez 30$ en dédommagement pour votre temps et déplacement.

Une étude d'IRMf de la mémoire associative et de la mémoire des items

QUESTIONNAIRE ET DÉCLARATION DE CONSENTEMENT

McConnel Brain Imaging Centre

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

1. **Chirurgies antérieures (type et date)**

_____

_____.

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

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

3. Le sujet est-elle enceinte? _____ _____

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

J'ai parfaitement compris les procédures, les avantages et les inconvénients de cette étude. Je consens volontairement à y participer.

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

SIGNATURE _____ _____ _____
PARTICIPANT DATE N° DE CONTACT

SIGNATURE _____ _____ _____
EXPÉRIMENTATEUR DATE N° DE CONTACT

SIGNATURE _____ _____ _____
MÉDECIN DATE N° DE CONTACT