

Neurofunctional and neuroanatomical hippocampal deficits and connectivity differences in schizophrenia compared to healthy control participants tested on a virtual reality navigation wayfinding task: An fMRI, VBM and effective connectivity study

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Thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
In partial fulfilment of the requirements
For the Doctor of Philosophy degree in
Experimental Psychology, Behavioural Neuroscience

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Abstract

Episodic memory is a key feature in learning. One must remember past events to act upon a present situation. Episodic memory has been reported to be impaired in individuals with schizophrenia. In order to have an intact episodic memory the contextual features (context) must be bound to the content of the event; this mechanism is referred to as contextual binding. It is proposed that binding errors during the encoding process are responsible for episodic memory impairments in schizophrenia. Since the hippocampal formation is considered to be the central element for contextual binding, it is hypothesized that the synaptic disorganization described in this condition results in such a deficit. Moreover, the hippocampus mediates and influences other cognitive processes such as learning and executive functioning. Hence, a contextual binding deficit can have important consequences on cognition, behaviour and emotions. The object of this dissertation was to investigate the neurofunctioning, neuroanatomy and neurofunctional connectivity of the hippocampus while performing a task that utilized contextual binding mechanisms. Since spatial relational processing is part of contextual binding and is rooted in the hippocampal regions, visuospatial navigation, more precisely a wayfinding task, was used as a probe to activate the hippocampus and its associated regions in a group of patients with schizophrenia and matched healthy controls.

The following dissertation presents three original research papers contributing to our understanding of the contextual binding and hippocampal deficits in schizophrenia. The first paper investigates the neurofunctioning of the hippocampus with a wayfinding task. The second paper investigates the hippocampal structural abnormality in schizophrenia and how it relates to performance during the wayfinding task. The third paper explores effective connectivity of the hippocampus with other brain regions involved in navigation in schizophrenia with a particular interest in the prefrontal cortex. These three studies demonstrate significant neurofunctional, neuroanatomical, and neurofunctional connectivity deficits in the hippocampus of the patients with schizophrenia compared to a healthy control population. Results of all three papers are further discussed in terms of research and clinical implications.

Statement of Co-Authorship

The two first papers of this dissertation “Decreased fMRI activity in the hippocampus of patients with schizophrenia compared to healthy control participants, tested on a wayfinding task in a virtual town” and “Structural hippocampal anomalies in a schizophrenia population correlate with navigation performance on a wayfinding task” were collaborations with Jennifer Phillips, Alain Labelle, Andra Smith, Véronique Bohbot and Patrice Boyer. Jennifer Phillips assisted in the clinical assessments of the control and patient participants for this study; she also helped at the MRI scanning sessions. Alain Labelle referred patients with schizophrenia and confirmed that each patient qualified clinically for the first step of the study. Andra Smith advised on the conceptualization of the MRI acquisition, and participated with editing the manuscripts. Véronique Bohbot also provided guidance on the conceptualization of the navigation paradigm and MRI acquisitions. The experimental task was created in Dr. Bohbot’s lab and customized by the author. The author created the control task in Dr. Bohbot’s lab. Finally, Dr. Patrice Boyer provided guidance with the elaboration of the research questions. The contextual binding hypothesis stems directly from Dr. Boyer’s past research and hypotheses. The third paper entitled “Exploration of hippocampal effective connectivity in schizophrenia and control participants while performing a wayfinding task” were reviewed and edited by Drs. Smith and Boyer. I was the primary author on all three papers. As primary author, I was responsible for conceptualization of the research questions and methods, recruiting participants, assessing participants with the neurocognitive assessment, helping in clinically assessing patients with the PANSS, trained participants on the navigation paradigm, scanned and collected the data for structural and functional MRI scans. I was also entirely responsible for the planning and execution of statistical analyses, and preparation of manuscripts (planning and writing). Drs. Smith and Boyer provided guidance and assistance in all aspects of the project, especially in the refinement of study hypotheses, and editing of manuscripts.

Acknowledgments

Throughout this process many individuals have supported me. First I would like to extend my gratitude to my supervisor and advisor Dr. Andra Smith, for her valuable advice and discussions, for welcoming me to her lab, and for being a role model on attaining a sustainable work-life balance. To Dr. Boyer, I am grateful for your continued encouragements, for sharing your knowledge and offering me many good opportunities. I would also like to extend many thanks to Dr. Bohbot for her steady support and for sharing her expertise in the field of navigation. I would also like to thank my thesis committee: Dr. Patrick Davidson and Dr. Jean-Phillip Thivierge, and the external examiner Dr. Todd Girard.

Dear friends and family, it has been 6 long years of hard work, but you managed to support me through it all. I am grateful to my parents and brother who have supported me and encouraged me throughout this process. Finally I owe a special thanks to my spouse Benjamin, who's encouragements, support, computer programming skills and patience made it possible to complete this dissertation.

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List of Acronyms

AAL	Anatomical automatic labelling
AMPA	Alpha-amino-3-hydroxy-5-methylisoxazole-4 propionate acid
ANOVA	Analysis of variance
AUDIT	Alcohol Use Disorders Identification Test
BOLD	Blood oxygen level-dependent
CA	Cornu ammonis, subfields of the hippocampus proper
CDS	Calgary Depression Scale (CDS)
CSF	Cerebrospinal fluid
D2	D2 Test of Attention
d.f.	Degrees of freedom
DAST	Drug and Abuse Screening Test
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition
DTI	Diffusion tensor imaging
EC	Entorhinal cortex
ECT	Electroconvulsive therapy
EPI	Echoplanar images
EPS	Extrapyramidal symptoms
FA	Fractional anisotropy
fMRI	Functional magnetic resonance imaging
FP	Family Pictures
FWE	Family wise error
FWHM	Full width at half maximum
GM	Grey matter
HAMD	Hamilton Scale for Depression
ICBM	International Consortium for Brain Mapping (ICBM)
<i>k</i>	Cluster
K_E	Cluster size
KA	Kainate acid
L	Left
LM	Logical Memory
LTD	Long-term depression

LTP	Long-term potentiation
MANOVA	Multivariate analysis of variance
MNI	Montreal Neurological Institute
Nac	Nucleus accumbens
NART	National Adult Reading Test
NMDA	N-methyl-D-aspartate
NVHL	Neonatal ventral hippocampus lesion
<i>p</i>	<i>p</i> -value
PANSS	Positive and Negative Syndrome Scale
PPI	Psychophysiological interaction
PSC	Percent signal change
R	Right
ROI	Regions of interest
SCID-NP	Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Non-Patient Edition (SCID-P)
SCID-P	Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition
SD	Standard Deviation
sMRI	Structural magnetic resonance imaging
SPM	Statistical parametric mapping
SPSS	Statistical package for social sciences
SVC	Small volume corrections
TIV	Total intracranial volume
VBM	Voxel based morphometry
VLPFC	Ventrolateral prefrontal cortex
VPA	Verbal Paired Associates
WCST	Wisconsin Card Sorting Test
WM	White matter
WMS-III	Wechsler Memory Scale, 3rd edition
+	Positive
-	Negative

CHAPTER 1

Introduction

Schizophrenia

Schizophrenia is a psychiatric disorder with a prevalence of 1% and an annual incidence of 0.2-0.4% per 1000 individuals (Mueser & McGurk, 2004). Over the past two decades, the neurodevelopmental hypothesis has been one of the principal theories striving to explain the developmental course of schizophrenia. According to this theory, an adverse event (e.g. obstetrical complications) could disrupt the normal course of brain development and lead to brain anomalies. The interaction between the anomalies and normal maturation of the brain creates vulnerability in individuals susceptible to developing schizophrenia (Weinberger, 1987). In other words, the genetic makeup at conception can lead to a genetic liability for the disorder. The effects of these genetic predispositions may be compounded by a disrupted developmental process and environmental events occurring during specific phases of neurodevelopment.

The Relation Between Cognitive Impairment and Hippocampal Deficit in Schizophrenia

Clinical description of schizophrenia. Schizophrenia is characterized by positive and negative symptoms and cognitive impairment. Positive symptoms involve the loss of the sense of reality (Mueser & McGurk, 2004) and consist of delusional thinking, hallucinations, the association of incoherent ideas and disorganized behaviour. Negative symptoms are less evident, occurring mainly following disease onset, and are more difficult to detect. Common negative symptoms include blunt affect, monotonous voice, anhedonia (a loss of pleasure), avolition (a loss of energy or interest to accomplish different tasks) or apathy and alogia (a difficulty to converse) and social life withdrawal (Mueser & McGurk, 2004; Wing & Agrawal, 2007). Cognitive impairments include difficulties with attention and concentration, psychomotor, learning and memory deficits and executive functioning disturbances (Mueser & McGurk, 2004; Wing & Agrawal, 2007). The latter term defines a system that processes and

controls complex behaviour in humans. Executive functioning is responsible for planning, cognitive flexibility, abstract thinking, problem solving, initiating and inhibiting behaviours and monitoring oneself. Cognitive impairments have been shown to be present before the appearance of the first psychotic episode and to persist well into the chronic phase of the illness (Hughes et al., 2003; Rund, 1998). There is evidence that cognitive impairment in schizophrenia is at the core of the disorder (Elvevåg & Goldberg, 2000). These findings are validated by: 1) the fact that even though psychotic symptoms can be ameliorated, cognitive symptoms persist; 2) there is more homogeneity at the cognitive level compared to the symptomatic level, and 3) the fact that cognition is a reliable predictor of functional outcome (Elvevåg & Goldberg, 2000). These abnormalities in cognitive functioning have significant impacts in the daily lives of individuals with schizophrenia, hampering their educational pursuits and employability (Stip, Chouinard, & Boulay, 2005), and greatly impacting their social and independent living skills.

For many years, executive functioning (attention, planning, sequencing, decision making and initiating and inhibiting behaviour and working memory) was perceived as the primary cognitive deficit in schizophrenia while long-term memory impairments were considered secondary. However, emerging evidence (Aleman, Hijman, de Haan, & Kahn, 1999) seems to indicate, to the contrary, that the long-term memory profile in schizophrenia may be at the core of the disorder (Boyer, Phillips, Rousseau, & Ilivitsky, 2007) and may be responsible for other cognitive deficits observed in schizophrenia (Weinberger, Berman, Suddath, & Torrey, 1992).

Episodic memory and schizophrenia. Emerging research indicates other types of deficits more characteristic of this pathology, such as an episodic memory (a component of explicit memory) deficit related to the hippocampal formation (Aleman et al., 1999; Boyer et al., 2007). Episodic memory is defined as the capacity to acquire information about personal events along with its spatial and temporal context and “the ability to mentally ‘travel back’ in time” to retrieve these memories (Tulving, 1985). What distinguishes this class of memory from semantic memory (memory of facts) is the recollection of an event within its spatio-temporal context (i.e. a specific event versus facts in general; Burgess, Maguire, &

O'Keefe, 2002). It has been found that episodic memory is particularly impaired in schizophrenia (Aleman et al., 1999; Burglen et al., 2004; Gold, Poet, Wilk, & Buchanan, 2004; Lefèbvre et al., 2010; Rizzo, Danion, van der Linden, & Grange, 1996b).

Episodic memory plays an important role in autobiographical memory, the capacity of an individual to recollect personal events from their own lives (Riutort, Cuervo, Danion, Peretti, & Salame, 2003). Autobiographical memory is part of a person's personal identity and works with autonegic consciousness, which is defined as being aware of one's own identity and existence through time (Tulving, 1985). Therefore, autobiographical memory helps to develop personal identity. There is evidence that autobiographical memory is also impaired in schizophrenia (Danion, Rizzo, & Bruant, 1999).

Contextual binding and schizophrenia. It has been found that individuals with schizophrenia have difficulties learning new information or learning a new task (which requires specific encoding). On the other hand, it appears that for these patients, recalling an event (the retrieval component of the long term memory process) is more impaired than recognition (ability to identify different information that has been previously remembered) of the target information component of the memory (Boyer et al., 2007; Rizzo et al., 1996b; Rizzo, Danion, van der Linden, & Grange, 1996a). Furthermore, studies have demonstrated that patients with schizophrenia have an immediate recall deficit after the presentation of an associative memory task (Gold et al., 2004). These observations indicate that a deficit exists in the encoding stage (more precisely during the contextual binding phase) of forming a long-term memory (Holthausen et al., 2003); retrieval will necessarily be impaired if the encoding was incorrect or incomplete. In order to form a complete episodic or autobiographical memory, it is crucial that the information (content; the "what") is bound with the spatial and temporal information of the event (context; the "where" and "when"). During the encoding of a new event, the two elements of information are bound together: the event that occurs is bound with the contextual aspects of the situation, defined as the extrinsic features such as temporal or spatial information (Waters, Maybery, Badcock, & Michie, 2004). This process is referred to as contextual binding. These binding abilities are dependent not only on the encoding processes but also on the capability to reactivate similar information (common context),

providing the knowledge that the content and context have co-occurred (Chalfonte & Johnson, 1996). The literature suggests that schizophrenia patients have a deficit in binding the memory for an event with its contextual information to form an intact memory representation (Danion et al., 1999; Gold et al., 2004; Rizzo et al., 1996b, 1996a; Waters et al., 2004). The context-memory deficit theory proposes that schizophrenia patients store selected information normally but are unable to recognize this information because they are not able to associate it with its contextual (spatial or temporal) component (Rizzo et al., 1996a). As previously mentioned, it is thought that the memory deficit is located in the medial temporal lobe, more specifically in the hippocampal regions.

The hippocampus and contextual binding. The hippocampal formation is the main structure implicated in long-term memory, more specifically episodic memory. It is composed of the entorhinal cortex (EC), the dentate gyrus, the hippocampus (itself composed of 4 distinct subfields: CA1, CA2, CA3 and CA4), the presubiculum, the subiculum and finally the parasubiculum (Andersen, Morris, Amaral, Bliss, & O'Keefe, 2007).

It appears that the hippocampus plays a significant role in the most important mechanism that defines an episodic memory, namely, contextual binding. Presently, the dominant theory that attempts to determine the fundamental mechanism of the human hippocampus is the Cognitive Map Theory proposed in 1978 by O'Keefe and Nadel. The Cognitive Map Theory suggests that the main function of the hippocampus is to construct and maintain spatial maps (learned environment and their content) of the environment. As well, this theory postulates that the right hippocampus encodes spatial relationships and linear sense of time while the left hippocampus is involved in verbal memory. Pursuing this theory, Burgess, Maguire, Spiers, and O'Keefe (2001) suggested that the spatial characteristics of an event are encoded by place cells in the CA subfield of the right hippocampus, whereas the non-spatial features of the event, such as facts, activate the "event cells" located in the subiculum. When a cue about a non-spatial attribute of an event occurs, 'event cells' are recruited and the corresponding activation of place cells triggers the spatial configuration of the event (Burgess et al., 2001). Likewise, the representation of a location by place cells can cause the activation of event cells, which represent the content of the event

linked to that location. The result is a bi-directional association (caused by Hebbian learning i.e. synaptic plasticity), which corresponds to contextual binding.

It is now commonly accepted that the hippocampus plays a crucial role in learning and memory (Harrison, Law, & Eastwood, 2003). Memory and learning processes occur at the synaptic level in the neural circuits discussed above. It is at the glutamatergic excitatory synapses of the hippocampus that synaptic plasticity takes place. The action of glutamate is on ionotropic (N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methylisoxazole-4 propionate acid (AMPA)), kainite acid (KA) and metabotropic receptors. Synaptic plasticity occurs after repetitive trains of synaptic activity, or when presynaptic and postsynaptic firings are paired in a specific way (such as in Hebbian learning). The synaptic plasticity is called long-term potentiation (LTP) and long-term depression (LTD). A key feature in synaptic plasticity is the ionotropic NMDA receptor, which are necessary for potentiation to occur, (Rolls, 2010). NMDA receptors mediate slow excitatory postsynaptic potentials (EPSPs), where post-synaptic intracellular signaling proceeds over a protracted period. These slow EPSPs are critical for synaptic maintenance and synaptic plasticity, both important for the proper expression of complex behaviours, such as associative learning and memory, behavioural flexibility, working memory and attention (Daw, Stein, & Fox, 1993).

As previously discussed, it is thought that contextual-binding uses LTP, through the simultaneous firing of pre and post synapses (event and place cells). It has been shown in rats that during one-trial flavor-place association (a similar task as verbal paired associates used to test episodic memory in humans), the NMDA receptors of the pyramidal neurons of the CA3 field are necessary during the learning period to be able to complete the task (Day, Langston, & Morris, 2003; Rolls, 2010). This is evidence of LTP during contextual-binding.

Biological Abnormalities of the Hippocampal Region in Schizophrenia

It can be hypothesized that the episodic memory impairment is a direct consequence of the structural and molecular abnormalities found at the level of the hippocampal formation. More specifically, the contextual binding deficit would be a direct consequence of synaptic alteration found in the hippocampal subfields.

Structural abnormalities. One of the most robust findings in schizophrenia is the abnormal hippocampal structure (Weiss, DeWitt, Goff, Ditman, & Heckers, 2005). Abundant evidence from postmortem evaluations (Bogerts et al., 1990) and *in vivo* MRI studies has demonstrated a reduced volume of the hippocampal regions (Nelson, Saykin, Flashman, & Riordan, 1998; Wright et al., 2000). These MRI findings have also been observed in prodromal and first episode patients (Pantelis et al., 2003). Structural MRI studies have demonstrated that the hippocampal volume deficit is diffuse and not localized in the anterior or posterior parts of the hippocampus (Weiss et al., 2005). However, this result remains controversial. Further, studies have demonstrated shape differences in the hippocampal structure in individuals with schizophrenia compared to a healthy population (Shenton, Gerig, McCarley, Szekely, & Kikinis, 2002).

The number of neurons in the hippocampal formation does not seem to be affected (Heckers, Heinsen, Geiger, & Beckmann, 1991). Rather, changes are more morphological (size, organization and shape) in the hippocampal neurons. Post-mortem studies have demonstrated differences in the neuronal anatomy of the hippocampal region. Reduced neuronal size (Arnold et al., 1995; Benes, Sorensen, & Bird, 1991; Zaidel, Esiri, & Harrison, 1997) and pyramidal cell disarray (Luts, Jonsson, Guldborg-Kjaer, & Brun, 1998) in the hippocampus subfields CA1 (Arnold et al., 1995), CA2 and CA3 (Zaidel et al., 1997) and subiculum (Arnold et al., 1995; Kovelman & Scheibel, 1984) have been reported. Synaptic connectivity may be the cause of these morphological changes. The decrease in neuron size is hypothesized to be caused by a smaller number of axonal projections and synaptic connections (Harrison & Eastwood, 2001). In fact, there have been reports of decreased density of dendritic spines, and less extensive apical dendritic trees in the pyramidal neurons of the subiculum (Rosoklija G, 2000) and in the granule cells of the dentate gyrus (Lauer, Beckmann, & Senitz, 2003).

Neurochemical abnormalities. Pyramidal and granule cells (main cells of the dentate gyrus), both glutamatergic neurons of the hippocampal formation, are altered in schizophrenia. Glutamatergic involvement appears to differ between subfields and hemisphere. The left hippocampus has fewer binding sites than the right (Harrison et al., 2003). The CA4 subfield appears to be mostly affected and the CA1 field is thought to be

unaffected in schizophrenia (Harrison et al., 2003). The glutamatergic hypothesis stipulates a hypofunctioning of NMDA receptors in schizophrenia (Kim, Kornhuber, Schmid-Burgk, & Holzmüller, 1980; Krystal et al., 1994). The hypofunctioning of these receptors may lead to cognitive deficits in memory and in learning. Even though NMDA seems to be a key element in schizophrenia, the number of studies investigating NMDA receptor expression in the hippocampus has been limited. AMPA and KA have been the most widely studied in schizophrenia. Results consistently show a reduction of expression of AMPA and KA receptors (Harrison et al., 2003).

In summary to this section, it has been clearly demonstrated that contextual binding is the principal mechanism of episodic memory and works under the influence of the hippocampus. Further, it was elucidated that individuals with schizophrenia have a contextual binding deficit and also have anomalies in the hippocampal formation. One can hypothesize that the episodic memory deficit is a direct consequence of anatomical differences found in the hippocampal formation. More specifically, the contextual binding deficit would be a direct consequence of synaptic alteration in the hippocampal subfields. As stated, 'place' and 'event' cells are crucial for contextual binding and anatomical anomalies in the hippocampal formation can lead to contextual binding deficits. Memories influence learning and behaviour; if events are not encoded properly, this will have important consequences on other cognitive processes including executive functioning. Empirical evidence supports a connection involving the projection of information from the medial temporal lobe to the prefrontal cortex (Kawashima, Izaki, Grace, & Takita, 2006). More specifically this connection would begin at the level of the hippocampal formation (CA1 and subiculum fields) and project to the medial and orbital prefrontal cortices (Thierry, Gioanni, Degenetais, & Glowinski, 2000). The nucleus accumbens (NAc), part of the striatum, receives important glutamatergic afferent inputs from the amygdala, hippocampus and neocortex (Thierry et al., 2000). In fact, the CA1/subiculum regions send excitatory input to the NAc (Groenewegen, Vermeulen-Van der Zee, te Kortschot, & Witter, 1987). The hippocampal formation provides spatial and temporal information to the prefrontal cortex (Squire, 1992) and context-dependent information to the striatum region (Grace, 2000; Jarrard, 1995). It has

been observed that neonatal hippocampal lesions in animals produce important changes in the prefrontal cortex once adolescent (Bertolino et al., 1997), mimicking aspects of the pathology of schizophrenia. Further, it was demonstrated that neonatal lesions of the hippocampus in monkeys created a dysregulation in dopamine release at the level of the striatum (Saunders, Kolachana, Bachevalier, & Weinberger, 1998). Taking into account the contextual binding deficit, it is possible to postulate that abnormalities in the hippocampal formation can have significant implications on the information provided to the prefrontal cortex and striatum regions hampering learning and cognitive abilities.

Therefore, it is important to study the functioning of the hippocampus through a contextual binding task. No neuroimaging studies have yet explored the contextual binding deficit in schizophrenia with an ecological task that specifically targets the hippocampal formation and the contextual binding mechanism. Based on the information presented above, it appears that spatial knowledge of an event requires contextual binding. Hence, a visuospatial navigation task should be a valid surrogate for contextual binding and a good probe to activate the hippocampal formation.

The Role of the Medial Temporal Lobe and Visuospatial Navigation

Mental representation of the environment.

The cognitive map. The hippocampus plays a critical role in learning, long-term memory and spatial memory. When the hippocampus is selectively lesioned, humans present with severe spatial memory deficits (Bohbot et al., 1998). It has also been demonstrated that hippocampal lesions in rats produce difficulties in solving spatial navigation tasks (Morris, Garrud, Rawlins, & O'keefe, 1982). Visuospatial navigation tasks involving the construction of a cognitive map (mental representation of the environment) have been demonstrated to critically require the hippocampus (O'Keefe & Nadel, 1978; Pigott & Milner, 1993). Unitary cell recording in rats has shown that depending on the rat's spatial orientation (in a labyrinth), the 'place cells' (activated by different spatial orientations) fired in different ways in the hippocampal regions (O'Keefe, Burgess, Donnett, Jeffery, & Maguire, 1998; O'Keefe & Nadel, 1978). The place cells (located in the right CA1 and CA3 subfields) are activated or

correspond to different spatial locations.

The hippocampal formation and parahippocampal region are also thought to play a role in the acquisition of the cognitive map. The medial entorhinal cortex, composed of “grid cells”, are thought to provide an Euclidean space mapping of the environment in rats (Fyhn, Molden, Witter, Moser, & Moser, 2004). Grid cell maps seem to continuously re-organise themselves based on the self-position and direction of the animal, perhaps a system to optimise path integration (McNaughton, Battaglia, Jensen, Moser, & Moser, 2006). Eichenbaum, Sauvage, Fortin, Komorowski, and Lipton (2012) has suggested that these grid cells would provide spatial contextual information to the hippocampus. In their model, they stipulate that the perirhinal and lateral entorhinal cortices process object and event information and the medial entorhinal and parahippocampal cortices process spatial and temporal contextual information. These structures converge their information to the hippocampus where it maps events (e.g. landmarks) within a spatio-temporal contextual representation (Eichenbaum et al., 2012).

Egocentric and allocentric mental representations of the environment.

Navigation is a cognitively demanding task, and requires individuals to construct a mental representation of the environment within allocentric and egocentric frameworks. The allocentric representation of the environment is dependent on the cognitive map. In other words to be successful at a task one must learn the relations between landmarks (stimulus-stimulus association; Bohbot, Lerch, Thorndycraft, Iaria, & Zijdenbos, 2007; O’Keefe & Burgess, 1996). According to the Cognitive Map Theory the main function of the hippocampus is to construct and maintain spatial maps (learned environment and their content) of the environment (Kumaran & Maguire, 2005; O’Keefe & Nadel, 1978). Therefore, the cognitive map allows a target to be reached in a direct path from any given direction. In contrast, the egocentric representation is dependent on an individual’s viewpoint and can be associated to a stimulus-response learning (Packard, Hirsh, & White, 1989) for example using a single landmark as a reference (e.g. when facing the coffee shop turn left) or make decisions based on their body movement, independent of landmarks in their environment (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003). This type of learning will lead to a “route” strategy

(O'Keefe & Nadel, 1978). Patients with lesions at the level of the hippocampal formation are unable to complete spatial allocentric tasks but are capable of completing a stimulus response task (i.e eight-arm radial-maze; Bohbot et al., 1998).

Navigation strategies. Different strategies are used to find one's way in an environment. Individuals can use either wayfinding strategies or route following strategies in familiar environments (for example one's neighbourhood).

Wayfinding is defined as finding one's way in an unfamiliar environment or taking a new route to reach a familiar destination (Hartley, Maguire, Spiers, & Burgess, 2003; Allen, 1999). To engage in this type of navigation strategy it is essential for an individual to have a precise mental representation of the environment - to have a cognitive map representation of the environment. Furthermore, wayfinding requires good executive functioning, planning and decision making on the basis of one's knowledge of the environment (Allen, 1999).

In contrast, route following occurs when the individual is in a familiar environment following a familiar route (Hartley et al., 2003), for example following the route from one's home to place of employment. This strategy is based on a series of actions that are made automatically and unconsciously. When following the same route to work daily, one will always follow the same streets, turns, etc. This route following strategy is clearly independent from the cognitive map, and thus requires only an egocentric representation of the environment.

Wayfinding and route learning do not activate the same cerebral regions; and they have distinctive cognitive processes. Wayfinding is associated with the hippocampus (Hartley et al., 2003) while route learning is associated with the caudate nucleus (Bohbot et al., 1998). In other words, navigating in a new environment or taking a novel route requires the hippocampus; however, taking this route routinely will activate the caudate nucleus (Hartley et al., 2003).

Cerebral regions implicated in navigation. Navigation in large-scale environments requires individuals to make decisions about which way to go based on one's current goals, internal representations of the environment and perceptual cues. Many studies are attempting to find the cerebral regions implicated in navigation in complex environments

(Hartley, Burgess, Lever, Cacucci, & O'Keefe, 2000; Hartley et al., 2003; Maguire, 1997; Maguire, Burgess, et al., 1998; Maguire et al., 2000; Maguire, Frith, Burgess, Donnett, & O'Keefe, 1998a). The regions that are most often reported to be activated during navigation are the parahippocampal gyrus (implicated in encoding landmarks; Maguire, Frith, Burgess, Donnett, & O'Keefe, 1998b), the hippocampus (mnemonic processes of allocentric object location; Abrahams, Pickering, Polkey, & Morris, 1997; Bohbot et al., 1998; Maguire, Frackowiak, & Frith, 1996), medial prefrontal cortex (thought to play a role in attention, monitoring, planning potential movements and in strategic mediation between the hippocampal and striatal systems in controlling behaviour; Burgess, 2008), precuneus, retrosplenial cortex, posterior parietal cortex and the striatum (mostly used in egocentric representation of the environment, the striatum defines locations relative to local landmarks; Burgess, 2008).

In summary, during navigation, an individual is required to store related pieces of information together into a single memory, such as storing the location of a landmark along with the change in orientation that occurs there (e.g. making a turn at a certain location). This binding of event (change in orientation triggering the 'event cells') and its context (at the landmark triggering the 'place cells') is a feature of contextual binding. Therefore, the task mentioned in this project requires good functioning of the hippocampal formation. In order to succeed at the task, the hippocampal formation must be in communication with a network of brain regions. Visuospatial navigation serves as a probe to examine hippocampal functioning in schizophrenia.

Thesis Breakdown

The main purpose of this dissertation was to investigate 1) the neurofunctioning of the hippocampus while performing a wayfinding task, a task that requires similar mechanisms as in contextual binding, 2) the relation of the hippocampal morphology and performance at the wayfinding task and 3) explore the effective connectivity of the hippocampus and brain regions involved in visuospatial navigation in schizophrenia compared to control participants, while navigating in a wayfinding task.

This dissertation presents 3 original manuscripts. The first original paper of this thesis investigated hippocampal neurofunctioning in schizophrenia compared to control participants, while performing a wayfinding task. fMRI data collected during completion of a visuospatial navigation task were analysed by whole brain and region of interest (ROI) within and between group comparisons. Major findings revealed that controls performed better at the navigation task, finding target landmarks more often, in less time and making fewer errors. Additionally, controls had significantly more neural activity in the hippocampus compared to the patient group. The decreased hippocampal activity in schizophrenia patients might represent poor contextual binding, which may explain the episodic memory deficit observed in this population.

The second original paper investigated the morphology of the hippocampus in schizophrenia, and the relation between hippocampal morphology and performance at the wayfinding task. Furthermore, this paper explored the relation of hippocampal grey matter (GM) with other regions of the brain known to be anatomically linked to the hippocampus. Voxel based morphometry (VBM) methods were used to analyse whole brain and ROI between group comparisons. Major findings showed that individuals with schizophrenia have GM average differences in the hippocampus and prefrontal cortex compared to the control group. Furthermore, GM of the hippocampus was related to the performance of the wayfinding task, meaning that the more errors during the task the smaller the hippocampal GM. A second VBM regression analysis demonstrated that orbital frontal cortex did not relate with hippocampus GM in the patient group, a result congruent with the hippocampal-prefrontal connectivity hypothesis, which stipulates that lesions in the hippocampus could be the precursor for the prefrontal deficit seen in schizophrenia. Results of this study suggest that hippocampal abnormalities might be a key feature in the poor functioning of the hippocampus and henceforth the contextual binding deficit seen in schizophrenia. It is possible that directly targeting the hippocampal structure with intervention programs that use visuospatial navigation may increase hippocampal functioning and attenuate cognitive impairments.

The third and last original paper explored effective connectivity in schizophrenia, with

psychophysiological interaction (PPI) analyses. Major findings revealed differences in connectivity seeded in the right hippocampus in patients compared to the control group. Results indicated that the right hippocampus influences the medial prefrontal cortex and parahippocampal gyrus, both structures implicated in visuospatial navigation, in control participants. However, in patients the right hippocampus influenced the inferior frontal cortex and thalamus while performing the wayfinding task. The hippocampus of patients appears to be recruiting alternate regions to guide and help complete the wayfinding task. These findings also corroborate the hippocampal-prefrontal connectivity hypothesis.

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CHAPTER 2**Decreased fMRI Activity in the Hippocampus of Patients with Schizophrenia
Compared to Healthy Control Participants, Tested on a Wayfinding Task in a
Virtual Town**

Ledoux, A-A., Phillips, J.L., Labelle, A., Smith, A., Bohbot D.V., Boyer, P. (2013),
Psychiatry Research: Neuroimaging, 211, 47-56.

Abstract

Intact episodic memory requires the ability to make associations between the contextual features of an event, referred to as contextual binding. Binding processes combine different contextual elements into a complete memory representation. It has been proposed that binding errors during the encoding process are responsible for the episodic memory impairments reported in schizophrenia. Since the hippocampus is critical for contextual binding and episodic memory, it was hypothesized that patients with schizophrenia would show a deficit in information processing in the hippocampus, measured with fMRI. In the current experiment, 21 patients with schizophrenia and 22 healthy control participants were scanned while being tested on navigating in a virtual town (i.e. find the grocery store from the school), a task that was shown to be critically dependent on the hippocampus. Between-group comparisons revealed significantly less activation among patients relative to controls in the left middle frontal gyrus, and right and left hippocampi. We propose that the context and the content are not appropriately linked therefore affecting the formation of a cognitive map representation in the patient group and eliciting a contextual binding deficit.

Introduction

Episodic memory can be defined as memory for personal events in a spatial and temporal context (Tulving, 1983). Intact episodic memory requires the ability to make associations between the contextual features of an event, referred to as contextual binding. In binding processes, contextual elements are combined into a complete memory representation, providing the knowledge that the content and context have co-occurred (Chalfonte & Johnson, 1996). In order to form a complete episodic or autobiographical memory, the information (content; the “what”) gets bound with the spatial and temporal information of the event (context; the “where” and “when”) during a ‘deeper level’ of encoding (deeper semantic analyses of the stimuli involving meaning and implication compared to a more shallow sensory analyses of the stimuli e.g. form or color; Craik & Lockhart, 1972). These binding abilities are dependent not only on the encoding processes but also on the capability to reactivate similar information (common context; Chalfonte & Johnson, 1996).

It has been proposed that binding errors during the ‘deeper level’ of encoding process are responsible for the episodic memory impairments reported in schizophrenia (Boyer, Phillips, Rousseau, & Ilivitsky, 2007). The literature suggests that schizophrenia patients have difficulty binding the memory for an event with its contextual information to form an intact memory representation (Boyer et al., 2007; Danion, Rizzo, & Bruant, 1999; Gold, Poet, Wilk, & Buchanan, 2004; Rizzo, Danion, van der Linden, & Grange, 1996a, 1996b; Waters, Maybery, Badcock, & Michie, 2004). The context memory deficit theory proposes that schizophrenia patients encode and store selected information normally but are unable to link it with the contextual features (spatial or temporal) to form an intact memory representation (Rizzo et al., 1996a). Contextual binding is mediated by the hippocampus, which suggests that this brain area may be impaired in patients with schizophrenia.

One of the most robust findings in schizophrenia is the abnormal hippocampal structure (Weiss, DeWitt, Goff, Ditman, & Heckers, 2005). Evidence from postmortem evaluations (Bogerts et al., 1990) and *in vivo* magnetic resonance imaging (MRI) studies has demonstrated volume reductions (M. D. Nelson, Saykin, Flashman, & Riordan, 1998; Wright et al., 2000) and abnormal hippocampal shape (Shenton, Gerig, McCarley, Szekely, & Kikinis,

2002). Postmortem studies have demonstrated differences in the neuronal anatomy of the hippocampus. Reduced neuronal size (Arnold et al., 1995; Benes, Sorensen, & Bird, 1991; Zaidel, Esiri, & Harrison, 1997) and pyramidal cell disarray (Luts, Jonsson, Guldborg-Kjaer, & Brun, 1998) in the hippocampus CA1 (Arnold et al., 1995), CA2, and CA3 subfields (Zaidel et al., 1997), as well as the subiculum (Arnold et al., 1995; Kovelman & Scheibel, 1984) have been reported. It can be hypothesized that episodic memory impairment is a direct consequence of the structural and molecular abnormalities found in the hippocampal formation.

Visuospatial navigation has been shown to be critically dependent on the hippocampus. According to the cognitive map theory, the hippocampus is critical to construct and maintain spatial maps of the environment (O'Keefe & Nadel, 1978; Bohbot, Iaria, & Petrides, 2004; Kumaran & Maguire, 2005). The recollection of the spatio-temporal context of an event has been said to be the distinguishing factor between episodic memory and other types of memory such as semantic memory and the simple recollection of object familiarity (Burgess, Maguire, & O'Keefe, 2002). Spatial knowledge of an environment has been proposed as a good model of the acquisition of internal representations and is necessary for the storage and retrieval of events (Burgess et al., 2002; Kumaran & Maguire, 2005; Maguire, Burgess, et al., 1998; Maguire, Frith, Burgess, Donnett, & O'Keefe, 1998). Visuospatial navigation tasks involving the construction of a cognitive map have been proven to critically require the hippocampus (Pigott & Milner, 1993). These tasks test the capacity to bind an event (e.g. change of orientation) with its spatial context (e.g. at the landmark). Neuroimaging studies have greatly enriched the literature by providing supporting evidence that the hippocampus, together with the parahippocampal cortex, posterior parietal cortices, medial prefrontal cortex, and striatum (or caudate nucleus in humans), are engaged in visuospatial navigation (Shelton & Gabrieli, 2002; Burgess et al., 2002; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Kumaran & Maguire, 2005). It is also commonly accepted that the human hippocampus is involved in episodic memory (Burgess et al., 2002; Maguire & Frith, 2004).

The current research investigated hippocampal function in patients with schizophrenia and healthy control participants with functional MRI (fMRI) and a virtual visuospatial

navigation task called the wayfinding task, identical to the one used in Etchamendy and Bohbot (2007), modelled after Hartley, Maguire, Spiers, and Burgess (2003). To our knowledge, no neuroimaging studies have yet explored the hippocampal deficit in schizophrenia with an ecological task that specifically targets the hippocampus. The first step of this study was to demonstrate an episodic memory deficit in schizophrenia with the Wechsler memory tests (WMS-III; Wechsler, 1987), it was hypothesized that there would be a significant difference between groups for memory assessment. The second step was to correlate WMS-III Family picture (FP) scores, a measure that assesses visual context-content binding (considered as a component of episodic memory; Gold et al., 2004), with behavioural navigation variables to determine whether the virtual navigation task relates to the FP assessment within our sample. The third step was to test participants' ability to navigate within a virtual town while using fMRI. It was hypothesized that during the navigation task, participants with schizophrenia would take longer routes to reach the goal locations in the virtual town and would have less hippocampal activity when navigating compared to controls.

Methods

Participants

A total of 54 study participants (28 patients with schizophrenia and 26 control participants) were recruited for this study. Participants included right-handed (determined by the Edinburgh Handedness Inventory; Oldfield, 1971) men and women between 18 and 40 years old. Patients with a primary diagnosis of schizophrenia were recruited from the Outpatient Schizophrenia Clinic at the Royal Ottawa Mental Health Centre, Ottawa, Ontario. Controls were recruited via newspaper and advertisement. Controls were matched to schizophrenia patients in terms of age, sex, and education level. Current diagnosis of abuse or dependence during the preceding 12 months with alcohol (Alcohol Use Disorders Identification Test (AUDIT); Saunders, Aasland, Babor, de la Fuente, & Grant, 1993, score > 8 in men or > 7 in women) or drugs (Drug and Abuse Screening Test (DAST); Skinner, 1982, score > 6) were exclusion criteria for all participants. Participants with a history of neurological disease, head injury, cardiovascular disease, stroke, or contraindications to MRI (determined by Medical

Questionnaire) were also excluded.

Participants were paid a sum of \$75 to take part in the study. The Research Ethics Board of the Royal Ottawa Mental Health Centre approved this project. All participants provided written informed consent.

Inclusion and exclusion criteria specific to the patient group. Patients were clinically diagnosed with schizophrenia by a psychiatrist and met the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV-TR; American Psychiatric Association, 2000) criteria for schizophrenia determined by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition (SCID-P) interview (First, Spitzer, Gibson, & Williams, 2002b). Patients were clinically stabilized and had no significant change in symptom severity, medication, or therapeutic methods following a three-month retrospective chart review.

For feasibility purposes patients with an acute psychotic episode on the total Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) or two or more of the following four PANSS items having a score ≥ 4 : conceptual disorganization (P2), hallucinatory behaviour (P3), suspiciousness (P6), unusual thought content (G9) were excluded. Further patients exhibiting comorbid depressive symptoms (Calgary Depression Scale (CDS); Addington, Addington, & Schissel, 1990, score ≥ 7) were also excluded because depression has been linked to hippocampal atrophy. Participants taking typical antipsychotics, benzodiazepines, or receiving electroconvulsive therapy were excluded from this study. These medications are excluded due to their side effect profile, which may contribute to the worsening of cognitive performance. Finally, the presence of extrapyramidal symptoms, or overt signs of tremor or movement disorder (confirmed by clinician) were exclusion criteria.

Exclusion criteria specific to the control group. Exclusion criteria for controls included presentation of an Axis 1 DSM-IV TR diagnosis (using SCID Non-Patient interview; First, Spitzer, Gibson, & Williams, 2002a), report of a psychiatric history concerning participants' first-degree relatives (elicited by inquiry), or the presence of depressive symptoms (Hamilton Scale for Depression (HAMD); Hamilton, 1960, score > 10).

Material and Procedure

Clinical assessment. Participants underwent clinical interview during which the following assessments were administered: SCID, CDS or HAMD and the PANSS (for patients only) and the self-report AUDIT and DAST questionnaires.

Neurocognitive assessment. The following memory assessments of the Wechsler Memory Scale, 3rd edition (WMS-III; Wechsler, 1987) were administered to participants: logical memory (LM), verbal paired associates (VPA), and FP immediate and delayed components. Participants were also administered the National Adult Reading Test (NART; H. E. Nelson & Willison, 1991) to provide an estimate of premorbid intelligence.

MRI session. The behavioural and fMRI data for this study were generated during the performance of a virtual visuospatial navigation task called the wayfinding task. Briefly, this task required participants to navigate between specific landmarks in a previously encountered computer-generated virtual town. For the fMRI portion of the study, the contrast of interest was a comparison of brain activation in patients and controls during active navigation in the virtual town.

The MRI portion of this project occurred in two phases performed on the same day: the pre-scan training phase followed within 1 h by the scan phase. Since familiarity with first-person videogames may help in the virtual reality task performance, before the pre-scan training participants were asked about their video game habits (e.g. what type of video game played). During the pre-scan training, participants were first familiarized with the keyboard to ensure their ability to manoeuvre through the environment. This was done in a virtual environment different from the virtual town used for the fMRI experiment. They then navigated in the virtual town created with the game editor of a commercially available computer game (Unreal Tournament 2003; Epic Games, Raleigh, NC). The virtual town was a visually complex computer-based environment, which included several roads, intersections, and buildings, in addition to distinct landmarks (easily recognizable, labeled locations such as a school or a hospital). Participants engaged in a free exploration of the town for 20 - 30 minutes. During exploration, participants were required to encounter every landmark twice and to travel along all roads. The path taken and the amount of time participants visited

each landmark was recorded. The free exploration provided an opportunity for participants to encode and construct a cognitive map of the environment by building relations between landmarks in the town. Participants were not permitted sufficient exploration time to form habitual routes between landmarks. Creating the paradigm using a modified video game framework provided participants with a first-person perspective while navigating. Following the training outside the MRI, participants were scanned while performing tasks based on the navigation paradigm.

MRI scans were acquired using a 1.5 tesla Siemens Magnetom Symphony. An MRI-compatible virtual reality system, Silent Vision™ Model SV-7021 Fibre Optic Visual System with In Control Software (Avotec, Inc.), was acquired for this study, as well as a four-button fiber optic touch pad. Cerebral activation was measured with fMRI using blood oxygen level-dependent (BOLD) contrast. The International Consortium for Brain Mapping (ICBM) T1 protocol was used to acquire weighted structural images for coregistration with the echoplanar images (EPI). BOLD signals were obtained using the following T2* weighted EPI image parameters: 32 contiguous 4 mm axial slices, positioned parallel to the hippocampus (64×64 matrix, repetition time =3000 ms, echo time =50 ms, field of view =256 mm, flip angle =90°. A total of 160 volumes per run were used for the analysis).

Following a 12-min T1 structural scan, participants underwent an fMRI scanning session where they were required to complete the wayfinding (visuospatial navigation) task which consisted of an alternating series of eight navigation trials, and eight control conditions. In the task, participants were required to navigate between two landmarks in the previously explored town, taking the shortest possible route. For each navigation trial, participants were placed in front of one of the landmarks (e.g. school) and were required to navigate from there to another landmark (e.g. movie theater). For each trial, there were many different routes that could be taken to get to the target landmarks. Successful completion of this task required taking the shortest route by deriving it from a cognitive map, a task that critically requires the hippocampus. Once participants reached the target landmark, they initiated an automatic transition to the control task. If participants failed to find the target landmark during a predetermined time frame per probe (varying between 45 to 90 seconds; determined

by a pilot study), they were manually transported into the control town by the investigator. Since participants had not been previously exposed to the control town, it represented a novel, unfamiliar environment. The control task involved the completion of eight navigation routes during which participants followed different paths that were clearly indicated by arrows on the ground. This was thought to be an appropriate task to control for the visuo-motor components of the experimental task.

Participants navigated using their right hand to control an MRI-compatible touchpad. During completion of the navigation trials, participants were timed and their precise paths were recorded on a 2D aerial view of the town. This study used an fMRI block design with four fMRI BOLD scanning sessions of 8:06 min each, separated by 1-min rest periods. Each scan alternated between experimental and control tasks to control for scanner drift and a 6-s transition period between experimental conditions was used to allow the hemodynamic response function to normalize. Software was used to detect transition between experimental and control tasks, as well as frame times. The entire MRI and fMRI scan time was 60 min per participant.

Data Analyses

Participants were matched according to their age, sex, and education level for all analyses in this study. Behavioural data (demographics, cognitive assessment results, and navigation performance) were analyzed using Statistical Package for Social Sciences version 18 software (*SPSS*, 2008). Neuroimaging data were analyzed with Statistical Parametric Mapping software (Wellcome Department of Imaging Neuroscience, 2008).

Behavioural data. We hypothesized to find a significant difference between patient and control groups within the memory assessment and navigation performance. This hypothesis was tested using a multivariate analysis of variance (MANOVA). The memory variables considered for the analysis were (LM, VPA and FP) immediate and delayed scores. The navigation performance variables were accuracy (i.e. percentage of target locations reached) and percent error, time, distance travelled and sum of travelled and remaining distance.

$$\text{Percent error: } ((x + z) - y)/(x + z) * 100$$

(i.e. x = total distance travelled, z = distance remaining to reach the goal, y = shortest distance to goal). The z variable was included to account for incomplete trials where the target landmark was not reached. Since incomplete trials by definition are missing part of the way to the goal location, the z variable was made to include this missing distance, whereby the shortest distance from the end point at which the trial was interrupted to the goal location is added to the distance travelled.

Time, distance travelled (measured by the length in centimetres of the route drawn on the 2D aerial view of the town), sum of travelled and remaining distance (they include the same variables as the $x + z$ used in the percent error calculation) are additional variables used to quantify behaviour.

fMRI data. The second hypothesis, which predicts a significant difference in hippocampal BOLD activity between patient and control groups, was tested with the steps mentioned below.

Data quality assessment and preprocessing. DICOM images were converted to NIFTI format using SPM MRICONVERT. Data were preprocessed and analyzed with SPM8. Scans were realigned, co-registered, and spatially normalized to the ICBM EPI template. To improve the signal to noise ratio, data were spatially filtered with a Gaussian filter equal to twice the size of EPI voxels (full width at half maximum = $8 \times 8 \times 8$). The time series were high-pass filtered (minimum cutoff frequency of 1/128 Hz) to remove low-frequency artefacts.

Artefact detection. Preprocessed data were visually inspected and reviewed for artefacts and motion using custom software from the Massachusetts Institute of Technology (Mozes & Whitfield-Gabrieli, 2009, <http://web.mit.edu/swg/software.htm>). Functional data were subjected to artefact detection if motion exceeded 2 mm in any direction (absolute maximum). Unphysiological global signal changes were identified using a cutoff for global image mean of >2.5 standard deviations. Nuisance regressors (identifying movement and unphysiological global signal changes) were included as a covariate of no interest in the first level design matrix. No group differences on the measures related to artefact detection were found. Motion parameters were included in the single-subject General Linear Model to reduce

residual motion-related variance after realignment.

Statistical analysis of functional images. The first level subject-specific design matrices contained the following regressors: (1) two regressors encoding the average BOLD response at each of the two states (experimental task, following arrows); (2) a nuisance partition containing regressors modelling the individual scans that were identified as contaminated by movement and unphysiological global signal change (see Image Processing subsection above); and (3) a nuisance partition containing six regressors that encoded the movement displacement as estimated from the affine part of the image realignment procedure.

These subject-specific design matrices were estimated and for the purpose of this study, only images related to the experimental task were entered in a flexible factorial design (2×4 ANOVA). Experimental images were not contrasted with the control task, as the control task produced equal amounts of hippocampal activity. This did not affect between-group analyses as both groups had the same level of variance. This experiment was a 4 (runs) by 2 (groups) factorial design.

The statistical threshold was set to $p \leq 0.05$ family-wise error (FWE)-corrected for the entire brain volume, with no cluster limit. Predetermined regions of interest (bilateral hippocampi) were defined with an explicit structural mask of Pick Atlas extension (Maldjian, Laurienti, Kraft, & Burdette, 2003) using the AAL atlas (Tzourio-Mazoyer et al., 2002) and the statistical threshold was set to $p \leq 0.001$ uncorrected with a cluster-wise correction at $p_{FWE} = 0.05$, for the reduced search volume. In order to verify if the ROIs used a more liberal region than participants' hippocampi, a visual inspection of the active hippocampal region was performed on the whole brain analysis at a $p \leq 0.001$. Plots of percent signal change (PSC) were created using the `rfxplot` toolbox for SPM8 (Gläscher, 2009).

Results

Demographics

Twenty-eight schizophrenia patients and twenty-six healthy control participants were enrolled in the study. Complete datasets were available for 21 patients and 22 controls. Altogether, 20 pairs were successfully age, sex and education-matched. Only one patient (male, age 30) and

three controls (one female, age 22; two males, age 19 and 37) were matched with respect to the overall group. Altogether, there were no statistical differences between the two groups in terms of age, education or IQ, and experience with first person videogames, mean number of time participants visited the landmarks during the learning phase (visited landmarks), $p \geq 0.05$ (Table 1).

(Insert Table 1)

Episodic Memory

Episodic memory was measured with the WMS-III LM, FP, and VPA subtests. Comparison of groups on these assessments revealed significantly lower mean scores among schizophrenia patients relative to controls for the immediate and delayed component of these subtests (Table 2).

(Insert Table 2)

Behavioural Navigation Scores

Each group's accuracy, percent error, distance travelled, sum of travelled and remaining distances, and time are shown in Table 3. Each of the above-listed variables was significantly different between groups with controls outperforming patients. Since the percent error variable takes into consideration the error and the distance remaining to reach the goal for each participant, an ANOVA (2 groups \times 8 trials) was computed for this variable. After applying a Bonferroni correction, only trial 4 remained significantly different between groups $F_{(1,41)} = 12.07$, $p \leq 0.005$. Overall, as demonstrated in Figure 2, controls performed better than patients.

Pearson's correlations were calculated between FP (immediate and delayed) score and accuracy, time, and percent error. A significant positive relation was found between FP (immediate and delayed) memory scores and accuracy in the navigation task, and significant negative associations were found between FP (immediate and delayed) memory scores and time and percent error scores (Figure 1). When separating the groups and performing the same correlations, patient scores of FP immediate still correlated significantly with the

variables, time, accuracy and performance ($r = -.400$, $r = .470$, $r = -.431$; at a $p < 0.05$). Patient's FP delayed score just failed short of correlating significantly with the navigation variables. Control FP immediate and delayed scores still correlated with the variable time ($r = -.470$, $r = -.519$; $p < 0.05$). Control's FP delayed score came close to correlating significantly with percent error, though failed just below the statistical cutoff. For exploratory purposes, an investigation of discriminant validity was performed by correlating navigation performance scores with LM, VPA assessments, education and the NART. Since WMS-III assessments were significantly different between both groups, correlations were performed separately for both groups. Immediate and delayed score of VPA and delayed scores of LM correlated significantly with time, accuracy and percent error in the patient group. LM and VPA assessment did not correlate with navigation performance variables in the control group. NART and education did not correlate with navigation performance scores.

(Insert Table 3 and Figure 1)

fMRI Analyses

In order to determine between-group brain activity differences, a 2×4 flexible factorial analysis was performed. Results for the within-group analysis are shown in Tables 4 and 5. Both groups had similar regional activations, including the parietal lobe, precuneus, middle frontal gyrus, fusiform gyrus, insula, and hippocampus. All of these regions have been reported in previous visuospatial navigation studies with fMRI (Hartley et al., 2003; Iaria et al., 2003; Maguire, Frackowiak, & Frith, 1997; Maguire, Burgess, et al., 1998; Maguire, Frith, et al., 1998; Maguire et al., 2000).

(Insert Table 4 and 5)

Between-group analysis. The between-group analysis (Controls $>$ Patients) revealed significant differences in the left middle frontal gyrus and a trend in the right caudate when comparing controls to patients. When applying a small volume correction to the right caudate there was a significant between group difference. A region of interest in the bilateral hippocampus demonstrated significant between-group differences in the right and left posterior hippocampus (Table 6; Figure 1B). The analysis of the main effect of condition

revealed an average linear effect in both groups at the level of the right hippocampus ($F_{(1,121)} = 15.44$, FWE-corrected at $p \leq 0.05$). Furthermore, results of a between-group analysis (interaction group x condition) revealed differences in the linear effect of the left hippocampus across condition (time) ($F_{(1,121)} = 13.87$, FWE-corrected $p \leq 0.05$). The PSC graph revealed significant positive signal change in the controls' posterior hippocampus and the signal decreases over time. However, this was not the case in patients, where there seemed to be a different activity pattern in the posterior hippocampus (Figure 3). In fact, there was a significant positive signal change in the patient group only in Run 1.

(Insert Table 6 and Figure 2)

(Insert Figure 3a and 3b)

Since there were significant differences in the overall behavioural navigation performance between groups, to control for the behavioural aspect of the task a between-group analysis of only the successful trials was performed (Figure 4). Behavioural analysis revealed no significant differences between groups for accuracy, time and percent error. The FWE-corrected fMRI analysis demonstrated no significant whole brain differences between groups. However, a significant difference between controls and patients (controls > patients) in the right hippocampus was found at an uncorrected threshold of $p \leq 0.001$. Observation of the PSC graph (Figure 5) demonstrates that the evolution of the task over time was the same in both groups. However, the PSC graph clearly shows that the pattern of hippocampal involvement differed between groups, with controls having an increase in right hippocampal BOLD signal compared to patients. In fact, in the patient group, there was only one trial where the BOLD signal was significantly different from zero compared to controls where all trials were significantly different from zero.

(Insert Figure 4 and 5)

Discussion

The goal of the current research was to investigate the hippocampal deficit in schizophrenia. In order to test our hypotheses, it was necessary to use a task that is critically dependent on the hippocampus. The wayfinding task in the virtual town is a visuospatial navigation task

previously shown to involve the hippocampus (Hartley et al., 2003). Visuospatial navigation tasks explore the capacity to bind an event with its spatial context, using similar mechanisms as in contextual binding in episodic memory, thus it can be considered as a valid assessment for contextual binding and a good method to activate the hippocampus. The task was most efficiently solved by using an allocentric strategy. Allocentric representations are frameworks that are independent of the observer, and thus fixed to the environment so that the locations of objects can be found irrespective of the starting position of an individual in the environment. This mental representation forms the basis of flexible navigation (being able to take shortcuts) and permits long-term storage of complex spatial relationships.

Episodic memory was tested with the auditory LM and VPA, and visual FP assessments. Immediate and delayed scores of these assessments were significantly different between groups. These results are consistent with the contextual binding hypothesis (Danion et al., 1999; Gold et al., 2004; Rizzo et al., 1996a, 1996b; Waters et al., 2004), indicating a binding deficit in schizophrenia. FP assessment, which measures more adequately contextual binding, was significantly related to the wayfinding scores, indicating that participants who did poorest with respect to time and errors on the navigation task also performed poorly on the FP test. LM and VPA assessments are two measures of auditory memory, measuring the ability to associate context and content. These assessments were not related to the wayfinding task in the control group, however, VPA and LM delayed scores were related to the navigation performance in the patient group. This result is not surprising as these assessments also measure the ability to associate information together. On the contrary, the NART and education were not related to the navigation variables, indicating that the behavioural navigation variables do not measure a general cognitive factor.

The main purpose of this study was to evaluate hippocampal function in schizophrenia patients with fMRI and the wayfinding visuospatial navigation task. It was hypothesized that due to a contextual binding deficit, patients would have less hippocampal activity while navigating compared to controls. Behavioural navigation results demonstrated that controls did successfully complete the task more often than patients, took less time, and made fewer errors. Both groups showed hippocampal activity, however, controls had significantly more

posterior hippocampal activity while performing the task than the patient group. This was also demonstrated by the PSC graph where controls demonstrated significant signal change in the posterior part of their hippocampus whereas patients only had significant positive signal change in the first run.

In order to control for the level of difficulty of the task in both groups, the analysis was repeated on the successful trials only. As seen in Figure 4, an analysis of the successful trials resulted in no significant differences between groups, demonstrating that they performed equally well on the selected trials. However, the fMRI analysis revealed that the control group had significantly more BOLD activity in the hippocampus compared to the patient group. Hence, patients showed significantly lower activity in the hippocampus relative to matched controls even in successful trials. The PSC graphs demonstrated that these patients only had significant signal change for the first trial of the wayfinding task and no significant signal changes for the remaining trials.

Several studies have demonstrated allocentric spatial memory deficits in patients with schizophrenia (Hanlon et al., 2006; Weniger & Irle, 2008; Folley, Astur, Jagannathan, Calhoun, & Pearson, 2010; Girard, Christensen, DeGroot, & Rizvi, 2010). Weniger and Irle (2008) conducted a study in which healthy controls and patients with schizophrenia had to navigate in a virtual park and solve a virtual maze. These two tasks assessed allocentric and egocentric strategies, respectively. Interestingly, patients and controls did not differ significantly on navigation strategies used while performing both tasks (determined by a questionnaire). However, patients had difficulties learning their way in the allocentric virtual park, as their performance on the task differed significantly from controls. On the other hand, no significant differences were found between groups for the virtual maze that required egocentric strategies. Based on the results of Weniger and Irle (2008), one could not attribute the allocentric deficit in schizophrenia to impairment in navigational abilities, as the patient group was as efficient as the control group in the egocentric virtual maze task. In concordance with the Weniger study, differences observed in patients and controls are likely not due to impairments in navigational abilities in patients but to an impairment in the ability to bind together events and the spatial features of the environment.

Folley et al. (2010) investigated the function of the hippocampus in schizophrenia using a virtual Morris Water Maze task and fMRI. Behavioural results of their study are consistent with our results, as participants with schizophrenia made more errors, travelled greater distances, and spent more time in the task. Though they did not find significant differences in the activity of the hippocampus while patients were engaged in the task relative to controls, they did find a positive correlation between the hippocampal BOLD signal and the efficiency of the task in the control group but not in the patient group. Due to structural and functional anomalies of the hippocampus in schizophrenia, it would be interesting to investigate with fMRI the navigation strategies within this population. MRI studies with virtual navigation demonstrated that several strategies can be used, namely, spatial memory strategies dependent on the hippocampus and stimulus-response strategies that are dependent on the caudate nucleus (Bohbot, Lerch, Thorndyraft, Iaria, & Zijdenbos, 2007). In order to navigate successfully individuals with schizophrenia might be using a different strategy to compensate for the lack of neurofunctionality of the hippocampus.

The results of the current research demonstrates altered hippocampus functioning in schizophrenia during a wayfinding task whereby participants had to find a target location by the shortest route possible, even when the task was performed successfully. This may reflect a binding deficit, creating a recall impairment of the landmark relationships, as stipulated by the contextual binding hypothesis (Boyer et al., 2007). The study results are generalizable to a stable population on atypical antipsychotics. This may not be representative of the hippocampal deficit in a larger population. Nonetheless, abnormalities at the level of the hippocampal formation in schizophrenia have been demonstrated by converging evidence from neuropathological findings (Arnold et al., 1995; Benes et al., 1991; Harrison & Eastwood, 2001; Zaidel et al., 1997) and by different neuroimaging techniques (M. D. Nelson et al., 1998; Weiss et al., 2005; Wright et al., 2000). These studies have confirmed the reduced volume, decreased neuronal size, and neuron disarray in the hippocampus of individuals with schizophrenia. Based on this evidence, it can be hypothesized that the contextual binding deficit of schizophrenia is a direct consequence of structural and biochemical abnormalities in the hippocampus. Furthermore, these abnormalities may have a direct impact on other brain

regions, such as the prefrontal cortex. Memories influence learning and behaviour, therefore if events are not encoded properly, this will have important consequences on other cognitive processes, such as executive functioning. A contextual binding deficit can have important psychological repercussions. If the events are not bound properly, the information provided to other brain regions (e.g. prefrontal cortex) may be erroneous. Since past events influence the processing of new events, individuals with schizophrenia may not be able to use memories for past events with great flexibility to guide and control their behaviour, affect, and beliefs (Boyer et al., 2007; Danion et al., 1999; Gray, Feldon, Rawlins, Hemsley, & Smith, 1991).

The focus of this study was on the ability to bind information together during ‘deeper level’ of encoding. Since studies on contextual binding demonstrate that individuals with schizophrenia are capable of encoding the target information (e.g. landmark and orientation) adequately (Burglen et al., 2004; Rizzo et al., 1996a), but are unable to bind the target information together with its contextual features, we did not measure visuospatial working memory. However, the inclusion of a visuospatial working memory task (e.g. spatial span and visual reproduction) would be beneficial for future studies to determine whether visuospatial working memory can influence performance on a navigation task. In this study, the control task also produced significant hippocampal BOLD activity, therefore only the experimental task was reported and discussed. It is thought that the task of following the arrows on the ground may have been too simple, therefore participants had the chance to think of the experimental condition while doing the task or they could have learned spatial information about the control virtual town. Activity in the control task was previously noted (Etchamendy, Konishi, Pike, Marighetto, & Bohbot, 2012). In fact, Etchamendy et al. (2012) showed that asking participants to engage simultaneously in the control and in a mental task such as counting backwards from 1000 was sufficient to completely eliminate the significant fMRI activity observed in the hippocampus during the virtual navigation control task. It is also possible that the novelty of the environment in the control task of our study activated the hippocampus. Since, the virtual town was already familiar to participants, the conjunction of both tasks (virtual town task and control task) could explain why there was no difference in hippocampal activity between the two tasks. Having no control task should not

affect between-group analysis focusing on the hippocampus, as visuo-motor variance is the same in both groups.

Conclusion

It has been hypothesized that individuals with schizophrenia have an episodic memory deficit; more specifically a contextual binding deficit. Since the hippocampus is critical for contextual binding and episodic memory, it was hypothesized that patients with schizophrenia would show a deficit in information processing in the hippocampus, measured with fMRI. In this study it was proposed that visuospatial navigation is an appropriate measure of contextual binding because it precisely explores the capacity to bind an event with its spatial context. Behavioural results of the navigation task demonstrated that control participants successfully completed more trials than patients, took less time to achieve the task, and made fewer errors. fMRI results demonstrated that healthy control participants had significantly more hippocampal activity while performing the task than the patient group. This was also the case when only successful trials were considered. The decreased hippocampal activity in schizophrenia patients might be responsible for their contextual binding deficit, which may explain the episodic memory deficit observed in this population.

Acknowledgements

This study was funded by the Canada Foundation for Innovation, the University of Ottawa Medical Research Fund, the Ontario Ministry of Development and Trade, the Royal Ottawa Health Care Foundation and CIHR fund number 64381 to V.B. A-A Ledoux is supported by the Canadian Institutes of Health Research, and the University of Ottawa. We thank Philippe Fossati M.D., Ph.D., François Rousseau Ph.D., Catherine Smith M.A., Guylaine Veillette, Benjamin Deschamps, M.Sc.

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Table 1
Participant demographics

	Controls (<i>n</i> = 22; SD)	Patients (<i>n</i> = 21; SD)
Sex (F/M)	6/16	5/16
Age (years)	30.45 (1.25)	32.05 (1.08)
Education (years)	16.68 (2.64)	15.10 (2.09)
IQ (NART)	111.32 (1.67)	109.09 (1.47)
Played first person videogame (Yes/No)	13/9	13/8
Visited landmarks	20.64 (4.76)	21.38 (5.36)
Age of Onset (years)		20.52 (4.81)
Duration of Illness (years)		11.38 (4.93)
PANSS Total		64 (13.0)
PANSS Positive		15.14 (4.33)
PANSS Negative		18.14 (5.68)
PANSS General Score		30.71 (6.93)

Note: $p \geq 0.05$ on all measures.

Table 2
WMS-III episodic memory subtests

	Mean		d.f.	F-test
	Controls (SD)	Patients (SD)		
Logical Memory immediate	46.91 (10.74)	32.43 (9.38)	1	22.08***
Verbal paired Associates immediate	25.50 (5.59)	17.38 (8.10)	1	14.73***
Family Pictures immediate	48.73 (5.68)	41.95 (10.86)	1	6.66**
Logical Memory delayed	28.50 (6.91)	19.19 (7.72)	1	17.41***
Verbal paired Associates delayed	7.36 (1.00)	5.76 (2.36)	1	8.50**
Family Pictures delayed	48.59 (5.51)	41.19 (10.65)	1	8.31**

Note: ** $p \leq 0.01$, *** $p \leq 0.001$.

Table 3
Behavioural navigation performances

	Mean		d.f.	F-test
	Controls (SD)	Patients (SD)		
Accuracy (%)	82.95 (22.01)	53.57 (26.85)	1	15.47**
Percent error	33.16 (15.79)	48.34 (16.26)	1	9.64**
Additional variables				
Time (sec)	57.82 (15.06)	73.94 (15.09)	1	12.28**
Total distance travelled (cm)	12.88 (3.65)	15.06 (3.49)	1	3.98*
Sum of travelled and remaining distance (cm)	14.26 (5.18)	18.85 (5.05)	1	8.65**

Note: * $p \leq 0.05$, ** $p \leq 0.01$.

Table 4
Healthy control within-group analysis

[x,y,z]	Anatomical Location of Peak	Cluster Size	Z Equivalent
10,-68,58	Precuneus	1621	Inf
-14,-72,54	L Superior parietal lobule		Inf
18,-76,54	Superior parietal lobule		Inf
-26,0,62	L Middle frontal gyrus	95	7.54
-38,-28,54	L Postcentral gyrus		5.06
26,4,62	R Superior frontal gyrus	66	7.26
30,24,-2	R Insula	27	6.95
6,20,46	R Superior motor area	54	6.78
6,32,34	R Middle cingulate	54	5.73
-26,24,2	L Insula	18	6.16
42,44,22	R Middle frontal gyrus	16	5.95
-50,-24,38	L Inferior parietal lobule	7	5.28
6,-72,-2	R Lingual	4	5.05
ROI Hippocampus			
30,-36,-6	R Hippocampus	37	5.65
-14,-40,6	L Hippocampus	28	5.29

Note: Voxel-wise significance for the whole brain volume was set to FWE corrected $p \leq 0.05$. Statistical threshold for ROI was set to $p \leq 0.001$ uncorrected with a cluster-wise correction at $p_{FWE} = 0.05$

Table 5
Patient within-group analysis

[x,y,z]	Anatomical Location of Peak	Cluster Size	Z Equivalent
14,-68,54	R Superior Parietal lobule	258	Inf
-14,-76,50	L Superior Parietal lobule		Inf
-10,-60,66	L Precuneus		6.51
18,-56,18	R Calcarine	205	Inf
34,-84,26	R Middle occipital gyrus		7.10
26,0,54	R Superior frontal gyrus	70	7.25
26,-36,-14	R Fusiform	96	6.06
-22,-24,2	L Thalamus	59	6.37
-22,0,58	L Superior frontal gyrus	47	6.03
-30,20,-6	L Insula	11	5.84
10,28,34	R Middle cingulate	10	5.76
18,-16,10	R Thalamus	47	5.62
-50,-24,42	L Supramarginal gyrus	54	5.63
-38,-32,50	L Postcentral gyrus		5.56
-30,44,10	L Middle frontal gyrus	13	5.35
-14,-28,46	L Middle cingulum	8	5.16
-26,-84,30	L Middle occipital gyrus	7	5.22
ROI Hippocampus			
-26,-32,-2	L Hippocampus	31	5.25
30,-32,-10	R Hippocampus	12	4.97

Note: Voxel-wise significance for the whole brain volume was set to FWE corrected $p \leq 0.05$. Statistical threshold for ROI was set to $p \leq 0.001$ uncorrected with a cluster-wise correction at $p_{FWE} = 0.05$

Table 6
Between-group analysis Control > Patient

[x,y,z]	Anatomical Location of Peak	Cluster Size	T-Value
-38, 40, 30	L Middle frontal gyrus	3	4.98*
ROI			
14,-36,6	R Hippocampus	4	4.22*
-14, -36, 6	L Hippocampus	10	4.07*
SVC			
14, 16, 10	R Caudate	4	3.91*

Note: * FWE corr. $p \leq 0.05$.

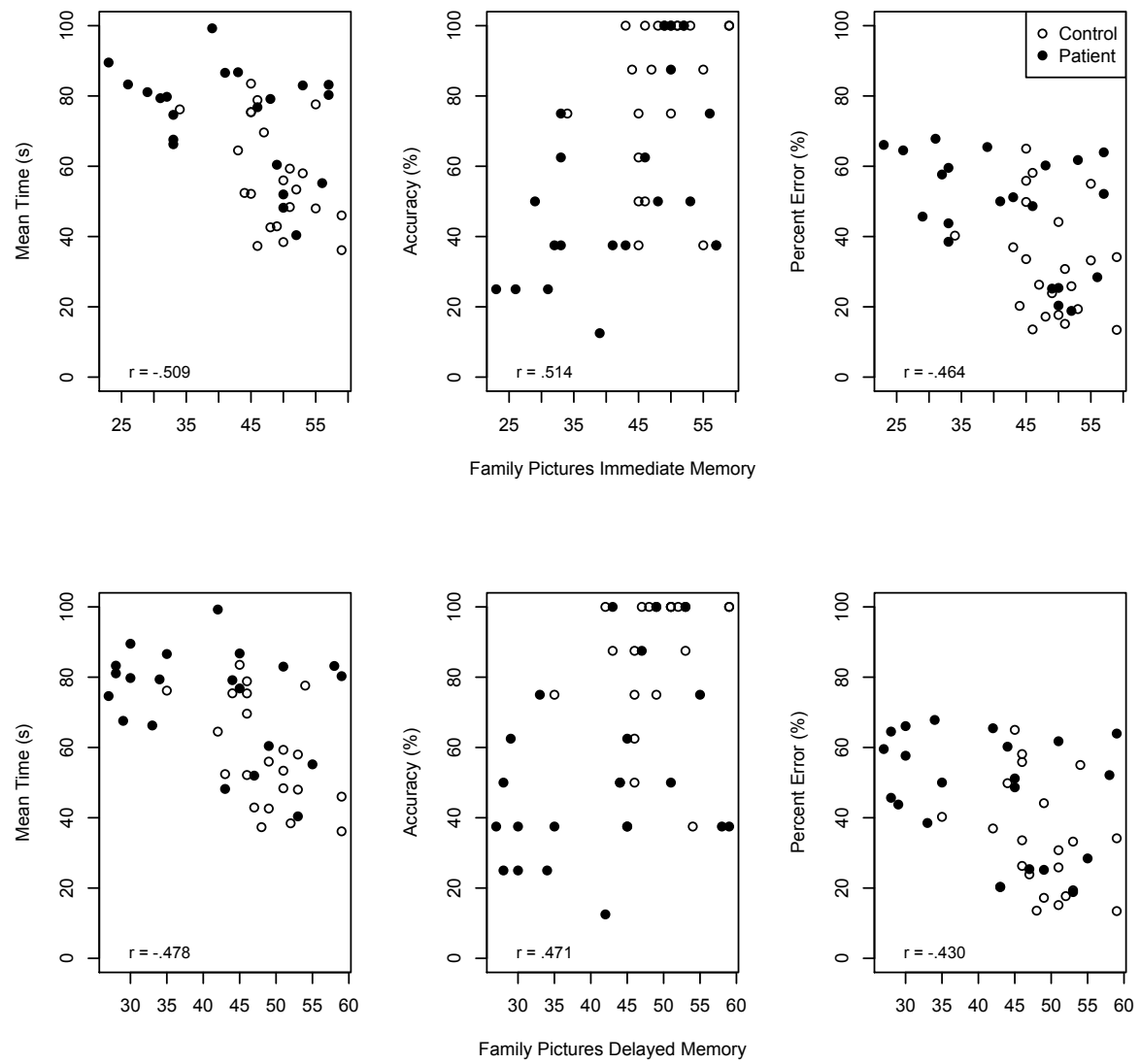


Figure 1. Group correlations between FP (immediate and delayed) scores and Time, Accuracy and Percent Error, $p \leq 0.005$.

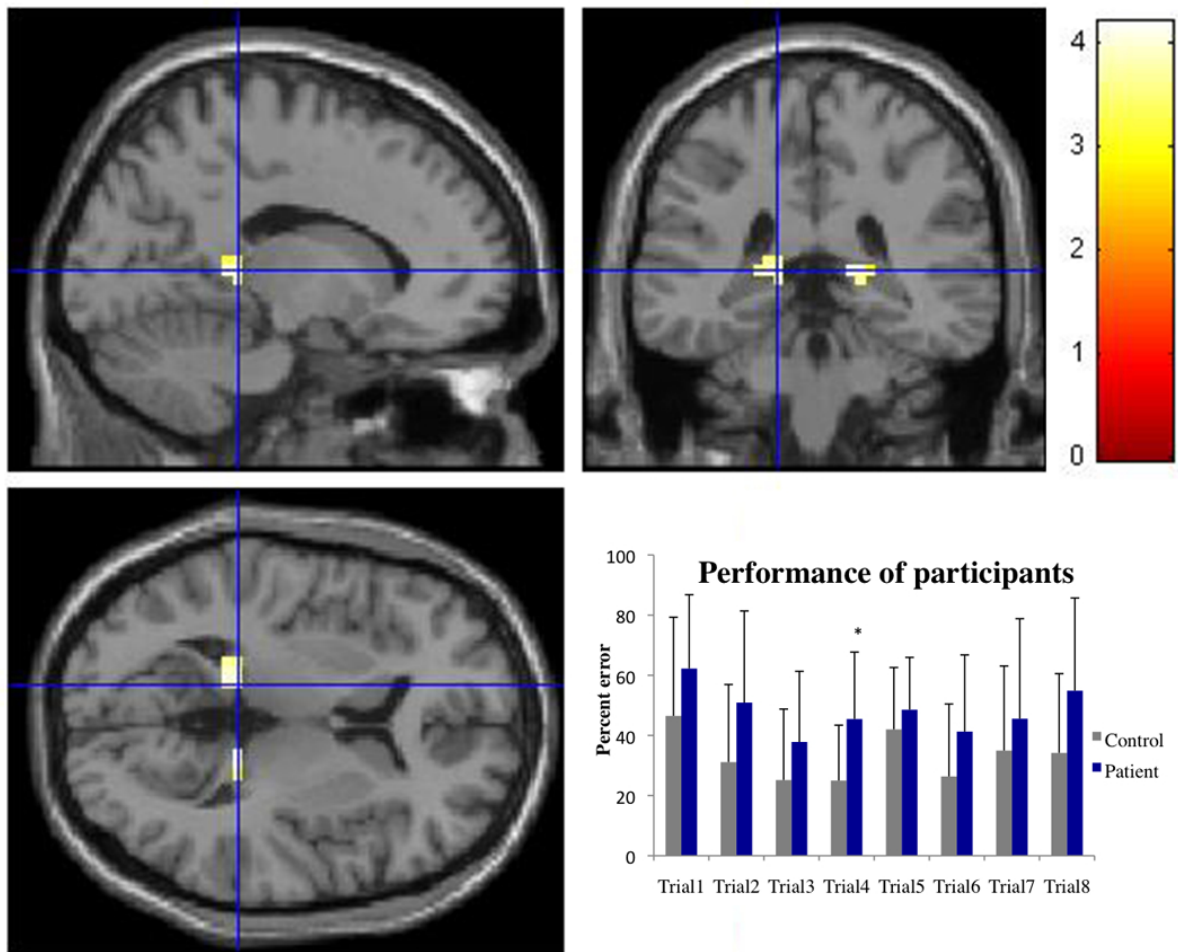


Figure 2. Between-group analysis. a) Differences (healthy controls > patients) in BOLD activity in the hippocampus. b) Difference between controls and patients for the percent error variable (i.e. total distance travelled + distance remaining to reach the goal compared to shortest distance needed to reach goal location), Bonferroni corrected, $p \leq 0.005$.

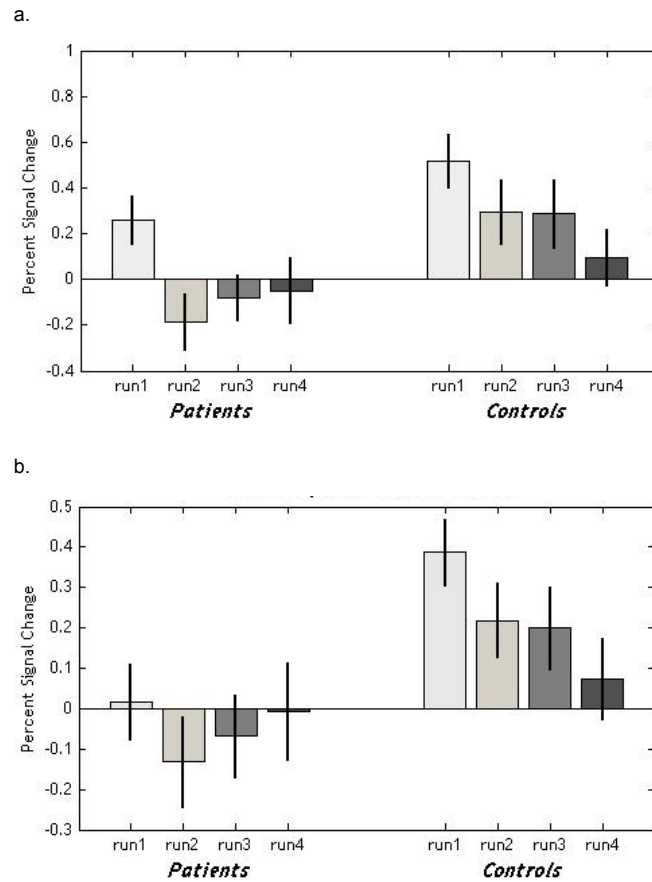


Figure 3. Percent signal change in the hippocampus, threshold p value ≤ 0.001 . a) Between-group analysis displaying percent signal change in right hippocampus (14, -36, 6). b) Between-group analysis displaying percent signal change in left hippocampus (-14, -36, 6).

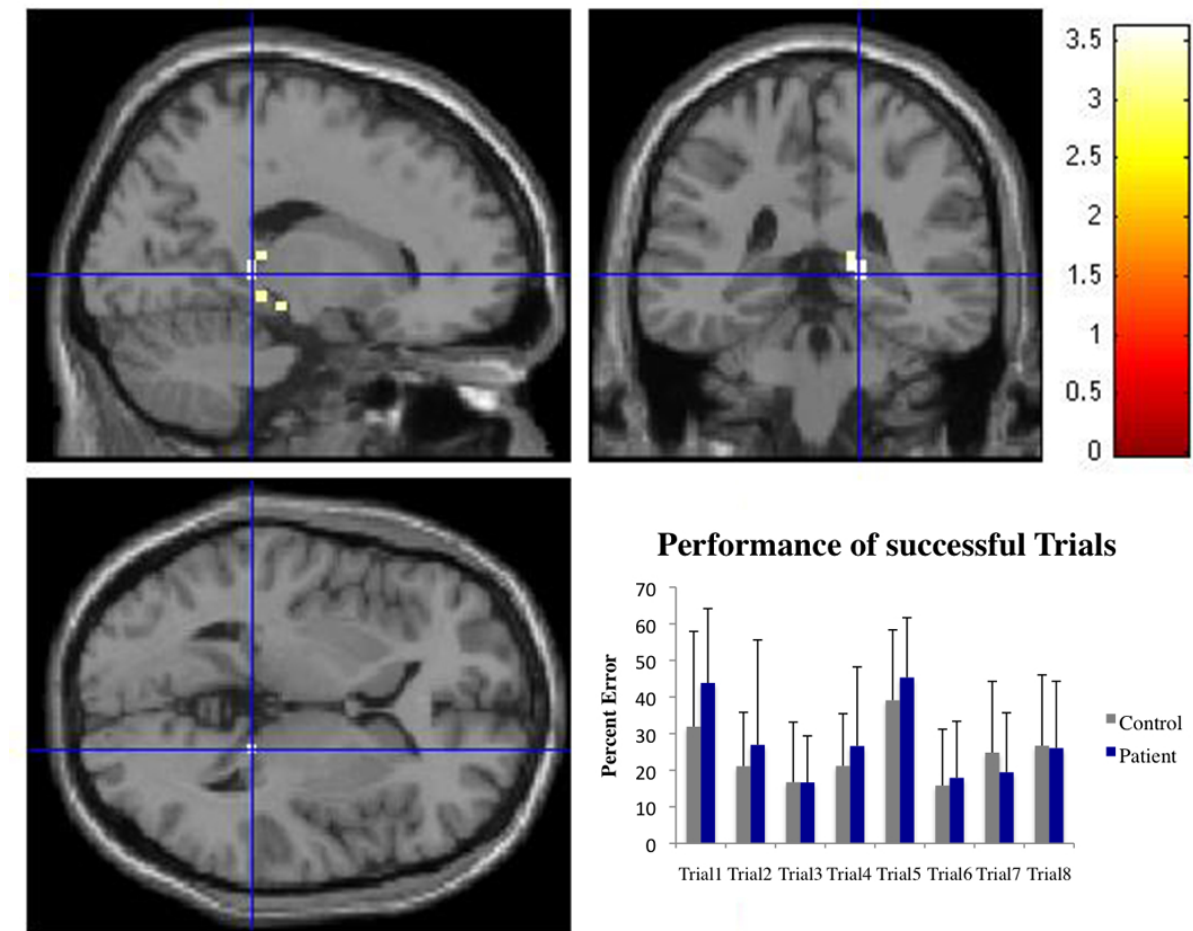


Figure 4. Between-group analysis of successful trials. a) Differences (healthy controls > patients) in hippocampal BOLD activity. b) Difference between controls and patients for the percent error variable (i.e. total distance travelled + distance remaining to reach the goal compared to shortest distance needed to reach goal location).

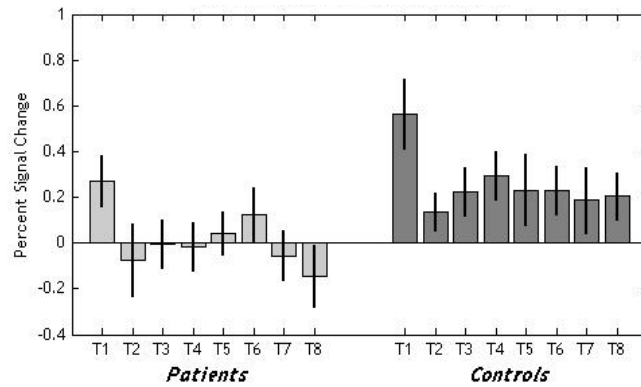


Figure 5. Percent signal change in the right hippocampus (18, -36, 2) threshold value 0.001, for successful trials in patients and controls.

CHAPTER 3

**Structural Hippocampal Anomalies in a Schizophrenia Population Correlate with
Navigation Performance on a Wayfinding Task**

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Brain Imaging and Behavior.*

Abstract

Episodic memory, related to the hippocampus, has been found to be impaired in schizophrenia. Further, hippocampal anomalies have also been observed in schizophrenia. This study investigated whether hippocampal grey matter (GM) would differentiate performance on a hippocampus-dependent memory task in patients with schizophrenia and in healthy controls. Twenty-one patients with schizophrenia and twenty-two control participants were scanned with an MRI while being tested on a wayfinding task in a virtual town (e.g., find the grocery store from the school). Regressions were performed for both groups individually and together using right hippocampal GM and performance on the wayfinding task. Results indicate that controls successfully completed the task more often than patients, took less time, and made fewer errors.

Additionally, controls had significantly more hippocampal GM than patients. Poor performance was associated with a decrease in the right hippocampus GM for both groups. Within group regressions found an association between right hippocampus GM and performance in controls and an association between the left hippocampus GM and performance in patients. A second analysis revealed that different anatomical GM regions, known to be associated with the hippocampus, such as the parahippocampal gyrus, amygdala, medial and orbital prefrontal cortices, covaried with the hippocampus in the control group. Interestingly, the cuneus and cingulate gyrus also covaried with the hippocampus in the patient group but the orbital frontal cortex did not, supporting the hippocampal-prefrontal cortex hypothesis in schizophrenia. These results present important implications for creating intervention programs aiming for measuring functional and structural changes in the hippocampus in schizophrenia.

Introduction

Cognitive dysfunction is believed to be among the core features of schizophrenia. Despite abundant evidence of a prefrontal impairment in schizophrenia, emerging research indicates that other types of cognitive impairments, such as a long-term episodic memory deficit thought to be related to a dysfunction at the level of the hippocampal formation, are as equally important in the neurocognitive disorder of schizophrenia (Aleman, Hijman, de Haan, & Kahn, 1999; Boyer, Phillips, Rousseau, & Ilivitsky, 2007).

One of the most robust findings in schizophrenia is the abnormal hippocampal structure (Weiss, DeWitt, Goff, Ditman, & Heckers, 2005). Abundant evidence from postmortem evaluations (Bogerts et al., 1990) and *in vivo* MRI studies has demonstrated a reduced volume of the hippocampal regions (M. D. Nelson, Saykin, Flashman, & Riordan, 1998; Wright et al., 2000). These MRI findings have also been observed in prodromal and first episode subjects (Pantelis et al., 2003). Structural MRI studies have demonstrated that the hippocampal volume deficit is diffuse and not localized in the anterior or posterior parts of the hippocampus (Weiss et al., 2005). Studies have demonstrated shape differences (Shenton, Gerig, McCarley, Szekely, & Kikinis, 2002) in the hippocampal structure but also morphological differences (size, organization and shape) in the hippocampal neurons. Postmortem studies have demonstrated reduced neuronal size (Arnold et al., 1995; Benes, Sorensen, & Bird, 1991; Zaidel, Esiri, & Harrison, 1997) and disorganized pyramidal cell (Luts, Jonsson, Guldborg-Kjaer, & Brun, 1998) in the hippocampus proper subfields CA1 (Arnold et al., 1995), CA2 and CA3 (Zaidel et al., 1997) and subiculum (Arnold et al., 1995; Kovelman & Scheibel, 1984). Further, there have been reports of decreased density of dendritic spines, and less extensive apical dendritic trees in the pyramidal neurons of the subicular complex (Rosoklija G, 2000) and in the granule cells of the dentate gyrus (Lauer, Beckmann, & Senitz, 2003).

It is now commonly accepted that the hippocampus plays a critical role in learning, long-term memory and spatial memory. When the hippocampus is selectively lesioned, humans present with severe spatial memory deficits (Bohbot et al., 1998). It has also been demonstrated that hippocampal lesions in rats produce difficulties in solving spatial

navigation tasks (Morris, Garrud, Rawlins, & O'keefe, 1982). Visuospatial navigation (wayfinding navigation) has been shown to be critically dependent on the hippocampus. Navigating is a cognitively demanding task, and requires individuals to construct a mental representation of the environment with allocentric and egocentric frameworks. The allocentric representation of the environment is dependent on the cognitive map. In other words to be successful at a task one must learn the relations between landmarks (stimulus-stimulus association; Bohbot, Lerch, Thorndyraft, Iaria, & Zijdenbos, 2007). According to the Cognitive Map Theory the main function of the hippocampus is to construct and maintain spatial maps (learning the relationship between environmental landmarks) of the environment (Kumaran & Maguire, 2005; O'Keefe & Nadel, 1978). Therefore, the cognitive map allows a target to be reached in a direct path from any given direction. In contrast, the egocentric representation is dependent on an individual's view point and his link to a stimulus-response learning (Packard, Hirsh, & White, 1989) for example using a single landmark as a reference (e.g. at the coffee shop turn left) or make decisions based on their body movement, independent of landmarks in their environment (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003). This type of mental representation of the environment is directly linked to a "route" strategy (O'Keefe & Nadel, 1978). Patients with lesions at the level of the hippocampal formation are unable to complete spatial allocentric tasks but are capable of completing stimulus response task requiring egocentric representations (Bohbot et al., 1998). Recently it was found in a behavioural study that individuals with schizophrenia exhibit impairments in allocentric memory while egocentric memory remained intact (Weniger & Irle, 2008). Similarly, patients with brain damage to the medial temporal lobe, which includes the hippocampus, are impaired when they spontaneously use an allocentric spatial memory strategy in a dual-solution task. However, similar patients who spontaneously use the stimulus-response strategy are not impaired (Bohbot, Iaria, & Petrides, 2004). Neuroimaging studies have greatly contributed to the literature by providing supporting evidence that the hippocampus, together with the parahippocampal gyrus, posterior parietal cortices, medial prefrontal cortex and striatum are engaged in visuospatial navigation (Burgess, Maguire, & O'Keefe, 2002; Kumaran & Maguire, 2005).

In a previous fMRI study that included the same research participants (schizophrenia patients and control groups) as those included in the current study (Ledoux et al., 2013), demonstrated an episodic memory deficit in the schizophrenia group. Further, controls performed significantly better on a virtual visuospatial navigation task called the wayfinding task and had significantly increased fMRI activity in the hippocampus compared to these patients while performing the navigation task. The wayfinding task used in Ledoux et al. (2013) and in the current study is identical to the one used in Etchamendy and Bohbot (2007), modeled after (Hartley, Maguire, Spiers, & Burgess, 2003). In this task participants are required to use allocentric frameworks in order to be successful at finding their way in the environment in a straight path. Therefore, in this study, we asked whether the wayfinding deficit found in patients with schizophrenia was associated with a GM reduction in the hippocampus.

The current study involved using voxel based morphometry (VBM) to investigate hippocampal GM in patients with schizophrenia and the healthy controls previously studied by Ledoux et al. (2013) and examined the relationship between the hippocampus and behavioural performance on the wayfinding task. In this study, we sought to investigate whether performance on the wayfinding task has a predictive relation with the morphological differences in the hippocampus of patients and control participants. Further, we investigated whether the different anatomical regions known to be anatomically connected to the hippocampus in a healthy population were associated to the hippocampal GM in the schizophrenia group. It was hypothesized that the patient group would have hippocampal GM differences compared to the control group and that the GM in the hippocampus would play a significant role in performance on the hippocampus-dependent spatial memory task in patients with schizophrenia and in healthy control participants.

Methods

Participants

A total of forty-three (43) study participants who comprised two groups: (1) 21 schizophrenia patients and (2) 22 control participants were recruited for this study. Participants were male

and female between 18 and 40 years old inclusively and right-handed (determined by the Edinburgh Handedness Inventory; Oldfield, 1971) due to documented differences in hippocampal areas linked to navigation skills associated with hemispheric dominance. Patients with a primary diagnosis of schizophrenia were recruited from the Outpatient Schizophrenia Clinic at the Royal Ottawa Mental Health Centre. Controls were recruited via newspaper and poster advertisement. The control group was closely matched to the schizophrenia patients in terms of age, sex and education level.

Inclusion criteria for the patient group. Participants of this group needed to be clinically diagnosed with schizophrenia by a psychiatrist, therefore they had to meet the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition criteria (DSM-IV-TR; American Psychiatric Association, 2000) criteria. Patients meeting the DSM IV criteria for schizophrenia, disorganized, undifferentiated or paranoid subtypes, were eligible; catatonia subtypes and schizoaffective patients were excluded. Patients needed to be clinically stabilized. Stabilization is defined as having had no significant change in symptom severity (i.e. level of severity), and no changes in medication type or dosage or therapeutic methods following a three-month retrospective chart review determined by their psychiatrist.

Exclusion criteria for patient group. Participants with an acute psychotic episode (determined by the Positive Negative Symptoms Scale (PANSS); Kay, Fiszbein, & Opler, 1987) or two or more of the following four PANSS items having a score ≥ 4 : conceptual disorganization (P2), hallucinatory behaviour (P3), suspiciousness (P6), unusual thought content (G9) were excluded. Also, participants exhibiting comorbid depressive symptoms (Calgary Depression Scale (CDS), score ≥ 7 ; Addington, Addington, & Schissel, 1990) were excluded. Participants taking typical antipsychotics, benzodiazepines or receiving electroconvulsive therapy (ECT) were excluded from this study. Finally, the presence of extrapyramidal symptoms (EPS), or overt signs of tremor or movement disorder could affect the quality of MRI image acquisition. Therefore, patients exhibiting those symptoms were also excluded from this study.

Exclusion criteria for control group. Presentation of a psychiatric condition corresponding to an Axis 1 DSM-IV TR diagnosis (using SCID-NP interview) was considered

an exclusion criteria. Also, participants reporting a psychiatric history concerning their siblings or other first-degree relatives did not qualify for the study. Finally, having depressive symptoms (Hamilton Scale for Depression (HAMD) score >10; Hamilton, 1960) excluded participants from the study.

Common exclusion criteria for patient and control groups. Current diagnosis of alcohol abuse or other kinds of dependence in the previous 12 months (Alcohol Use Disorders Identification Test (AUDIT); Saunders, Aasland, Babor, de la Fuente, & Grant, 1993, score > 8 in men or > 7 in women) or current diagnosis or history of drug abuse or dependence in the past 12 months (Drug and Abuse Screening Test (DAST); Skinner, 1982, score > 6) were exclusion criterion. Participants with neurological disease, history of head injury, cardiovascular disease or stroke (determined by Medical Questionnaire) were also excluded. The presence of any non-removable magnetic metal on or in the body (such as cardiac pacemakers, metal prostheses), as determined by the Medical Questionnaire, was also reason for exclusion from the study.

Participants were paid a sum of \$75 to take part in the study. The Research Ethics Board of the Royal Ottawa Mental Health Center approved this project.

Material and Procedure

Clinical and neurocognitive assessments. The clinical assessment was a two hour session separated into two parts. The first hour of the assessment was the clinical interview where the SCID, CDS or HAMD, PANSS (for patients only) were administered. The second part of the assessment consisted of self-report questionnaires answered by participants. Participants were required to assess themselves on the following questionnaires: AUDIT, DAST.

During the neurocognitive assessment session, participants were administered the National Adult Reading Test (NART; H. E. Nelson & Willison, 1991) to provide an estimate of premorbid intelligence and IQ.

MRI session. The MRI portion of this project occurred in two phases performed on the same day: the pre-scan training phase followed within one hour by the scan phase. Since

familiarity with first-person videogames may help in the virtual reality task performance, before the pre-scan training participants were asked about their video game habits (e.g. what type of video game played). During the pre-scan training, participants were first familiarized with the keyboard to ensure their ability to manoeuvre through the environment. This was done in a virtual environment different from the virtual town used for the experiment. They then navigated in the virtual town created with the game editor of a commercially available computer game (Unreal Tournament 2003; Epic Games, Raleigh, NC). The virtual town was a visually complex computer-based environment which included several roads, intersections, and buildings, in addition to distinct landmarks (easily recognizable, labeled locations such as a school or a hospital). Participants engaged in a free exploration of the town for 20 to 30 minutes. During exploration, participants were required to encounter every landmark twice and to travel along all roads. The path taken and the amount of time participants visited each landmark was recorded. The free exploration provided an opportunity for participants to encode and construct a cognitive map of the environment by building relationships between landmarks in the town. Participants were not permitted sufficient exploration time to form habitual routes between landmarks. Creating the paradigm using a modified video game framework provided participants with a first-person perspective while navigating. Following the training outside the MRI, participants were scanned while performing tasks based on the navigation paradigm. In the MRI, participants underwent a 15 minutes T1 structural scan. During fMRI scanning which followed, participants were required to complete the Navigation Task. For each of the 8 navigation trials, participants were placed in one location in the city (e.g. school) and were required to navigate from there to another landmark (e.g. movie theater) within the city. Successful completion of this task required taking the shortest route by deriving it from a cognitive map, a task that critically requires the hippocampus. During completion of the navigation trials, participants were timed and their precise paths were recorded on a 2D aerial view of the town.

MRI scans were acquired using a 1.5 tesla Siemens Magnetom Symphony. The protocol generated T1-weighted image volumes with a 1 mm isotropic resolution using a three-dimensional spoiled gradient echo acquisition with sagittal volume excitation (repetition

time, 22; echo time, 9.2; flip angle, 30°; field of view 256 mm; 160 1mm sagittal slices). An MRI-compatible virtual reality system, Silent Vision™ Model SV-7021 Fibre Optic Visual System with In Control Software (Avotec, Inc.), was acquired for this study, as well as a 4 button fiber optic touch pad.

Data Analyses

Participants were matched according to their age, sex and level of education for all analyses in this study. Behavioural data (demographics and navigation performances) were analyzed using SPSS (*SPSS*, 2008) software. Neuroimaging data were analysed with Statistical Parametric Mapping software (SPM8; Wellcome Department of Imaging Neuroscience, 2008, London, UK) and the VBM8 toolbox (<http://dbm.neuro.uni-ena.de/vbm.html>).

Behavioural data. The first hypothesis of a significant difference between patient and control groups within the behavioural navigation performance was analyzed with an ANOVA. Variables considered for the analysis of navigation performance were Accuracy (i.e. percentage of target locations reached), Percent error (i.e. percentage of extra distance travelled + distance remaining to reach the goal compared to shortest distance needed to reach goal location) and mean Time.

$$\text{Percent error: } ((x + z) - y) / (x + z) * 100$$

(i.e. x = total distance travelled, z = distance remaining to reach the goal, y = shortest distance to goal). The z variable was included to account for incomplete trials where the target landmark was not reached. Since incomplete trials by definition are missing part of the way to the goal location, the z variable was made to include this missing distance. Therefore, the shortest distance from the end point at which the trial was interrupted to the goal location is added to the distance travelled ($x + z$).

Voxel-based morphometry and statistical analysis. We applied VBM as implemented in the VBM8 toolbox with default parameters. Images were bias-corrected, tissue classified, and registered using linear (12-parameter affine) and non-linear transformations (warping), within a unified model (Ashburner & Friston, 2005). Subsequently, analyses were performed on grey matter (GM) and white matter (WM)

segments, which were multiplied by the non-linear components derived from the normalization matrix in order to preserve actual GM and WM values locally (modulated GM and WM volumes). Finally, the modulated volumes were smoothed with a Gaussian kernel of 12 mm full width at half maximum (FWHM). GM, WM, and CSF maps were combined for total intracranial volume (TIV). Voxel-wise GM and WM differences between schizophrenia patients and controls were examined using independent-sample t-tests. In order to avoid possible edge effects between different tissue types, we excluded all voxels with GM or WM values of less than 0.1 (absolute threshold masking).

For whole brain analysis voxel-wise significance was set at a threshold of $p_{FWE} = 0.05$. The purpose of our study was primarily focused on the hippocampal structure, and secondly the prefrontal cortex and caudate nucleus. Regions of interest (ROI) analyses were restricted to the hippocampus, parahippocampal gyrus, caudate nucleus, superior medial, and orbital prefrontal cortices. We created a mask for all specified ROI with the Pick Atlas extension (Maldjian, Laurienti, Kraft, & Burdette, 2003) using the AAL atlas (Tzourio-Mazoyer et al., 2002). This mask was then inserted as the explicit mask in the VBM analyses. Within the masks, significance was set at a threshold of uncorrected $p \leq 0.001$, with a cluster-wise correction at $p_{FWE} = 0.05$ and a set cluster size larger than 10 voxels.

A first regression was performed on GM and navigation performance to determine whether GM regressed with the percentage errors made during the task, Accuracy and Time. ROI used for this analysis were the same as the one noted above. To be noted due to the small sample size of the within group regressions trending results at an uncorrected threshold of $p \leq 0.01$ and $p \leq 0.05$ are also reported.

Pearson correlations were performed between subtracted hippocampal GM regions at the peak voxel (MNI space $x=24, y=-21, z=-15$ and $x=-24, y=-21, z=-18$) and the navigation behavioural variables in both groups.

Results of the first VBM regression were used to regress the GM value at the peak voxel (MNI space coordinates, $x=24, y=-21, z=-15$) in the hippocampus against the entire MRI volume in the control and patient groups. This second regression tested and compared whether GM in the network of regions known to be anatomically linked to the hippocampus

covaried with hippocampal GM in patients. This analytical method was based on Bohbot et al. (2007), showing that navigational strategies correlate with GM in the hippocampus or caudate of healthy participants. In turn, GM in the hippocampus correlated with a network of brain regions, known to be anatomically connected.

Results

Demographics

Twenty-one patients with schizophrenia and twenty-two healthy controls qualified and completed the study. All together 20 pairs were matched on age and sex and education. However, 1 patient (male age 30) and 3 controls (one female age 22 and two males age 19 and 37) were not matched because their respective matched partner was withdrawn from the study due to different problems (e.g. white matter abnormalities, experiencing excessive anxiety in the scanner). Therefore, no matching was possible; as a consequence we matched our samples by group. Participant's demographics are demonstrated in Table 1. No significant differences were found in the main matching criteria variables: age, sex, education and no significant differences were found in IQ scores, experience with first person videogames, or mean number of time participants visited the landmarks during the learning phase (visited landmarks), $p \geq 0.05$ (Table 1). Patients' PANSS global score of 64 represents a very moderate severity and slightly predominant but not marked negative symptoms (18.4 vs 15.4), in summary a moderate and stabilized population.

(Insert Table 1)

Behavioural Navigation Scores

Groups differed significantly for all 3 behavioural navigation variables, Figure 1.

(Insert Figure 1)

Structural Analysis

Regional GM reduction in patients compared to control participants. Groups did not differ in overall TIV ($t_{41} = -.96, p = .34$). In order to investigate whether there is

whole brain gray and white matter differences independent sample t-tests were performed. Since there was no significant difference in age and in TIV those variables were not used as covariables. Significant differences in GM (Table 2 and Figure 2) were found between groups (Controls>Patients). WM analysis showed significant differences between controls and patients in the right middle frontal cortex (MNI coordinates: 33, 18, 21; $t=4.48$) and right frontal inferior triangularis gyrus (MNI coordinates: 30, 39, 21; $t=4.02$), as well as in the ROI of the posterior left hippocampus (-12, -33, 9; $t=4.22$).

(Insert Table 2 and Figure 2)

First regression analysis: Association between GM and behavioural variables.

Whole group regressions were performed with GM and the behavioural variables. Results (Table 3) indicate an inverse association between the behavioral variables (Time and Percent error) and the right hippocampus and right parahippocampal gyrus GM. Along the same lines, a positive correlation was found between the right parahippocampal gyrus GM and Accuracy. Scatter plots of percent error against hippocampus GM derived from this analysis showed that the control group does not seem to form a homogenous population (Figure 3). A subsequent multivariate analysis confirmed a significant difference between both control groups for the variables percent error and right hippocampus GM ($F=40.88$, $p \leq 0.01$; $F=24.24$, $p \leq 0.01$). In addition, Figure 3 shows that patients have less hippocampal GM and poorer navigation performance. The within group regression analysis showed a significant negative correlation ($p_{uncorr.} \leq 0.001$) between selected brain areas including predominantly the right hippocampus, right parahippocampal gyrus and left caudate GM and Time and Percent error in controls. We also found a significant negative correlation ($p_{uncorr.} = 0.05$) between predominantly the left hippocampus and right parahippocampal gyrus GM and Time and Percent error in patients. A positive correlation was found between the right parahippocampal gyrus and Accuracy in controls and the right parahippocampal gyrus and left hippocampus and Accuracy for the patient group ($p_{uncorr.} \leq 0.01$). Bivariate Pearson correlations support these results where the right hippocampus seed region correlated significantly with Percent error and Time in controls ($r = -.484$, $p = .01$; $r = -.482$, $p = .01$) but not in patients ($r = -.318$, $p = .80$; $r = -.277$, $p = .11$) and the left hippocampus seed region

correlated significantly with Percent error and Time in the patient group ($r = -.401, p = .036$; $r = -.429, p = .026$) but not in the control group ($r = -.344, p = .06$; $r = -.235, p = .15$).

(Insert Table 3 and Figure 3)

Second regression: Regression at the seed voxel of the hippocampus. In the control group the regions covarying significantly with the right hippocampus were the parahippocampal gyrus, contralateral hippocampus, amygdala, frontal middle orbital cortex and frontal superior medial gyrus GM (Figure 4a). For the patient group, the parahippocampal gyrus, contralateral hippocampus, amygdala, cuneus, frontal superior medial gyrus, middle cingulate gyrus GM covaried with the right hippocampus (Figure 4b). To summarize, in the patient group the right hippocampus did not covary with the middle orbital cortex as within the control group but did covary with the cuneus and middle cingulate gyrus, which was not the case in the control group.

(Insert Figure 4)

Discussion

The goal of this study was to investigate whether grey matter in the hippocampus would predict performance on a hippocampus-dependent spatial memory task in patients with schizophrenia and in control participants. Furthermore, this study sought to explore whether regions known to be anatomically connected with the hippocampus covaried with the right hippocampus GM derived from the VBM regression analysis. To assess spatial memory, a wayfinding task was utilized where participants explored a virtual town and had to remember the location of several landmarks. Spatial memory was tested by asking participants to navigate from one landmark to another by taking the shortest route possible. It was hypothesized that the patient group would have a smaller hippocampal GM average compared to the control group and the size of the hippocampus could predict the performance on the navigation task.

During the navigation task individuals with schizophrenia reached the target goal less often, took more time and deviated from the shortest route possible significantly more than controls. When comparing controls to patients, GM volumetric analysis revealed significantly

lower GM average in the hippocampus of the patient group. This analysis also revealed GM average differences in the insula, middle and inferior frontal gyrus, gyrus rectus, caudate nucleus and frontal orbital cortex.

Whole group regression analysis revealed increased latency and deviation from the shortest route were associated with a decrease in the right hippocampus GM, indicating that more GM in the hippocampus is associated with better performance (finding the landmark by making fewer errors and taking less time to complete the task). The anterior right hippocampus has also been associated with performance in navigation in other studies. Bohbot et al. (2007) found that individuals using spontaneous spatial strategies had greater GM in the hippocampus compared to individuals using non-spatial strategies. As seen in the scatter plot (Figure 3) there appears to be two clusters in the control group, the good performers with greater right hippocampal GM and poor performers with lower right hippocampal GM. In support of these findings, Etchamendy and Bohbot (2007) found that approximately 50% of their participants used a spontaneous spatial strategy and those who maintained that strategy on the 4-on-8 virtual maze (the task used to dissociate spatial and response strategies) performed significantly better on the wayfinding task than participants who used a response strategy navigating from their starting position. Spatial learners on the 4-on-8 virtual maze also had significantly more grey matter in the hippocampus than response learners, which would be consistent with the current results. Head and Isom (2010) also demonstrated more GM in individuals who were better at the wayfinding task. Clearly, the current results show an association between hippocampus GM and the ability to learn the relations between the environmental landmarks in order to perform the task successfully.

Compared to controls participants, patients performed significantly worse at the navigation task and had smaller hippocampus. Low GM volumes have been previously reported in schizophrenia (Wright et al., 2000) and also in first episode groups (Pantelis et al., 2003). Lower GM volumes may be a risk factor for schizophrenia. These anatomical hippocampal anomalies may be the cause of encoding, spatial learning impairments and other important cognitive deficits seen in schizophrenia, such as an episodic memory deficit. We previously demonstrated significant differences between both groups, whereby patients made

more errors at the immediate and delayed recall of the family picture subtest of the Wechsler memory test (Wechsler, 1987) compared to the control group (Ledoux et al., 2013), which is, an assessment that specifically tests the ability to associate together the context and content of an event. The literature postulates that the episodic memory deficit seen in schizophrenia might be mediated by a contextual binding deficit (Boyer et al., 2007), the ability to make associations between the content (“what”) and the contextual features (the “where” and “when”) of an event. Since the hippocampus is critical for contextual binding in episodic memory (Burgess et al., 2002; Maguire & Frith, 2004), it seems appropriate to use the wayfinding task which assesses similar mechanisms (i.e. in order to reach the target location, participants are required to learn the relations between the environmental landmarks (association of the target information with its spatial context)).

Interestingly, the wayfinding-hippocampus grey matter relation in the patient group (Figure 3) shows a cluster, which overlaps with the poor performers in the control group, i.e. with the lower right hippocampus GM group. The controls overlapping with the schizophrenia group may suggest that they too may be at risk for neurological or psychiatric disorders. The current results suggest that the wayfinding task may be sensitive to abnormalities in the hippocampus for different types of population.

The prefrontal cortex, striatum and parahippocampal gyrus are all regions that have been implicated in previous visuospatial navigation studies (Bohbot et al., 1998; Burgess et al., 2002; Iaria et al., 2003; Kumaran & Maguire, 2005). In this study it was found that the GM average of these regions was also associated with the performance on the wayfinding task.

Regression between the seed region in the right hippocampus and the entire brain demonstrates that the parahippocampal gyrus, contralateral hippocampus, amygdala, frontal middle orbital cortex and frontal superior medial gyrus GM regions correlate with the hippocampus in the control group. In other words, when GM is greater in the hippocampus it will also be greater in the above mentioned regions. These regions are known to be anatomically related to the hippocampus and were also found to positively covary with the hippocampus in a similar navigation study (Bohbot et al., 2007). Contrary to the control group, in the patient group the cuneus and cingulate gyrus also covaried with the right

hippocampus but not the frontal orbital cortex. These regions might be recruited to compensate for the structural and functional deficit seen in schizophrenia while navigating. As previously mentioned the frontal orbital and hippocampal regions were found to have less GM in the patient group. Empirical evidence supports a connection involving neuroanatomical projections from the CA1 and subiculum fields to the medial prefrontal and orbital frontal cortices (Thierry, Gioanni, Degenetais, & Glowinski, 2000). The hippocampo-prefrontal pathway represents one of the major factors in learning and memory (Laroche, Davis, & Jay, 2000). These results provide support to the hippocampal-prefrontal connectivity hypothesis in schizophrenia, which suggests that the prefrontal deficit (such as executive functioning) may in fact be more closely linked to a temporal deficit or associated with connectivity deficits between the temporal lobe and the prefrontal cortex (Weinberger, Berman, Suddath, & Torrey, 1992).

Maguire et al. (2000), found that taxi cab drivers, whom have extensive navigation experience, had greater hippocampal volumes than the control group, and a recent study (Lerch et al., 2011) demonstrated in mice that spatial memory training causes neuroanatomical volume changes in the hippocampus (Lerch et al., 2011). The wayfinding task employed in this study seems to be particularly sensitive to the hippocampus. Training individuals with schizophrenia on hippocampal-dependent tasks, such as the wayfinding task, could potentially be used as a form of therapy to help improve the function and structure of the hippocampus, potentially alleviating cognitive deficits seen in this population such as episodic memory problems and executive dysfunction.

Conclusion

In the current study, we investigated whether performance in a wayfinding task could predictably be related to the GM in a healthy control group and in schizophrenia patient group and explore whether the same GM regions in both groups covaried with the hippocampus. Patients completed fewer trials than controls, took more time to achieve the task, and made more errors compared to controls. Patients also had a smaller hippocampal GM average than controls. Whole group performance was significantly related to the right

hippocampus. Patient's poor performance, contextual binding deficit, and reduced hippocampal activity while performing the wayfinding task, as demonstrated in our previous study, may be attributed to the hippocampal anomalies in the anterior portion of the hippocampus. The second VBM regression analysis demonstrated that orbital frontal cortex does not relate with the hippocampal GM in the patient group, a result congruent with the hippocampal-prefrontal connectivity hypothesis of schizophrenia. Results of this study demonstrate that individuals with schizophrenia have a hippocampal disorder and directly targeting the hippocampal structure might be important for improving the cognitive impairments.

Acknowledgement

This study was funded by the Canada Foundation for Innovation, the University of Ottawa Medical Research Fund, the Ontario Ministry of Development and Trade, the Royal Ottawa Health Care Foundation. A-A Ledoux is supported by the Canadian Institutes of Health Research, and the University of Ottawa. We thank François Rousseau Ph.D., Catherine Smith M.A., Benjamin Deschamps, M.Sc. and Guylaine Veillette.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Table 1
Participant demographics

	Controls (<i>n</i> = 22; SD)	Patients (<i>n</i> = 21; SD)
Sex (F/M)	6/16	5/16
Age (years)	30.45 (1.25)	32.05 (1.08)
Education (years)	16.68 (2.64)	15.10 (2.09)
IQ (NART)	111.32 (1.67)	109.09 (1.47)
Played first person videogame (Yes/No)	13/9	13/8
Visited landmarks	20.64 (4.76)	21.38 (5.36)
Age of Onset (years)		20.52 (4.81)
Duration of Illness (years)		11.38 (4.93)
PANSS Total		64 (13.0)
PANSS Positive		15.14 (4.33)
PANSS Negative		18.14 (5.68)
PANSS General Score		30.71 (6.93)

Note: $p \geq 0.05$ on all measures.

Table 2
*Reductions of GM average in patients with schizophrenia compared to healthy controls
 (Controls > Patients)*

Region	Side	MNI coordinates			K_E	Z value	T value
Insula	L	-28	20	-2	2950	5.98	7.61
Insula	R	34	15	-20	670	4.60	5.29
Middle Frontal gyrus	R	34	36	18	9	4.50	5.15
Gyrus rectus	L	-2	39	-18	69	4.49	5.15
Frontal Inferior Triangularis gyrus	R	39	33	3	4	4.48	5.12
<i>ROI</i>							
Hippocampus	L	-22	-22	-17	258	3.81	4.21
Hippocampus	L	-36	-12	-17		3.39	3.67
Hippocampus	R	38	-9	-15	109	3.80	4.18
Hippocampus	R	30	-15	-12		3.23	3.48
Caudate	R	22	24	-2	242	3.90	4.32
Frontal Inferior Orbital	L	-30	27	-5	1406	5.29	6.39
Frontal Superior Orbital	L	-26	14	-14		5.24	6.30
Frontal Superior Orbital	R	22	18	-14	542	4.91	5.78
Frontal Inferior Orbital	R	34	14	-20		4.51	5.16
Frontal Medial Orbital	L	-3	39	-15	2072	4.39	5.00
Frontal Medial Orbital	R	3	68	-2		4.20	4.73

Note: ROI investigation at threshold 0.001 uncorrected, $p_{FWE} = 0.05$ cluster-wise correction.
 (R= right, L= Left, (+)=positive, (-) = negative).

Table 3
Whole group regression

Condition	Region	MNI Coordinates			K_E	T value	Z value
Accuracy (+)	R Parahippocampal gyrus	33	-34	-15	80	3.89	3.57
	R Caudate	10	16	-11	80	4.00	3.65
	L Caudate	-10	18	-11	104	3.78	3.48
Time (-)	R Parahippocampal gyrus	33	-34	-15	274	4.62	4.12
	R Hippocampus	24	-21	-14	88	3.68	3.40
	R Caudate	10	15	-12	74	4.13	3.76
	L Caudate	-8	-16	-11	139	3.84	3.53
	L Frontal Inferior Orbital	-34	23	-9	760	4.27	3.86
	L Frontal Superior Orbital	-22	17	-15	760	4.20	3.80
	R Frontal Superior Medial	8	35	60	193	3.80	3.49
Percent Error (-)	R Parahippocampal gyrus	30	-31	-17	222	4.12	3.74
	R Hippocampus	24	-21	-15	78	3.82	3.51

Note: ROI investigation at threshold 0.001 uncorrected, $p_{FWE} = 0.05$ cluster-wise correction and $k > 10$, (R= right, L= Left, (+)=positive, (-) = negative).

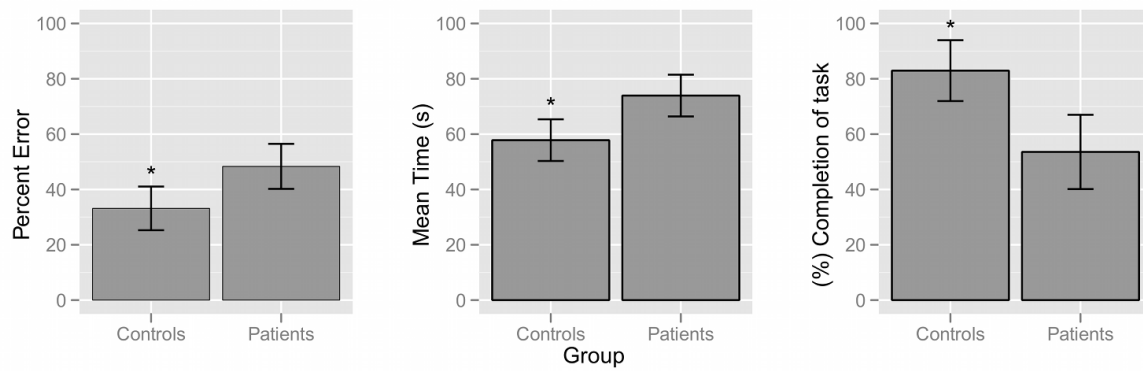


Figure 1. Between group differences for the behavioural navigation variables: Accuracy ($F_{(1,41)} = 15.47$, $p = .000$); Percent Error ($F_{(1,41)} = 9.639$, $p = .003$) and Time ($F_{(1,41)} = 12.28$, $p = .001$)

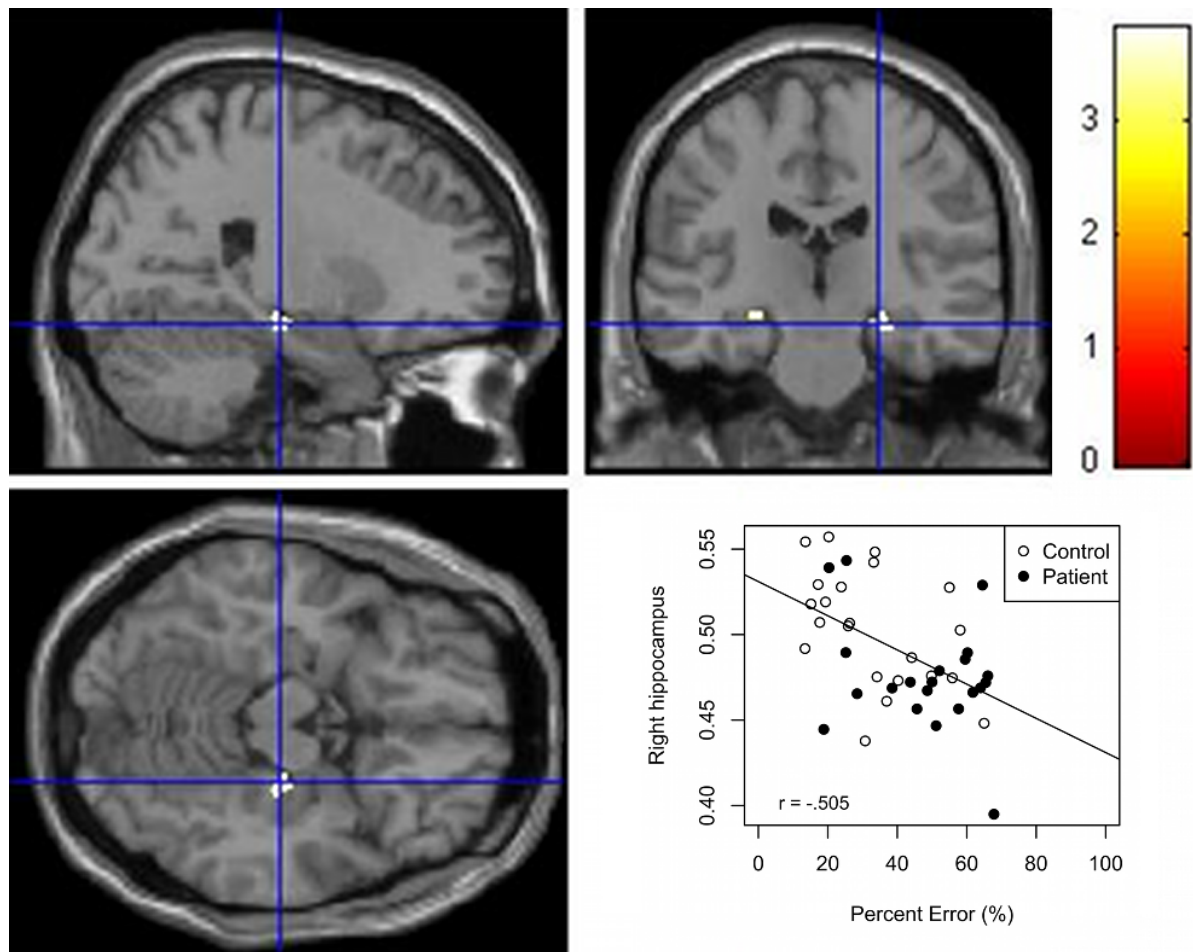


Figure 3. VBM Regression analysis with percent error at the wayfinding task ($pFWE_{corr.} \leq 0.05$). Scatter plot regression of right hippocampal cluster at seed voxel (24, -21, -15; $p < 0.001$) with Percent error at the navigation task. Pearson correlation for the control group ($r = -.484$, $p = .01$) and patient group ($r = -.318$, $p = .08$).

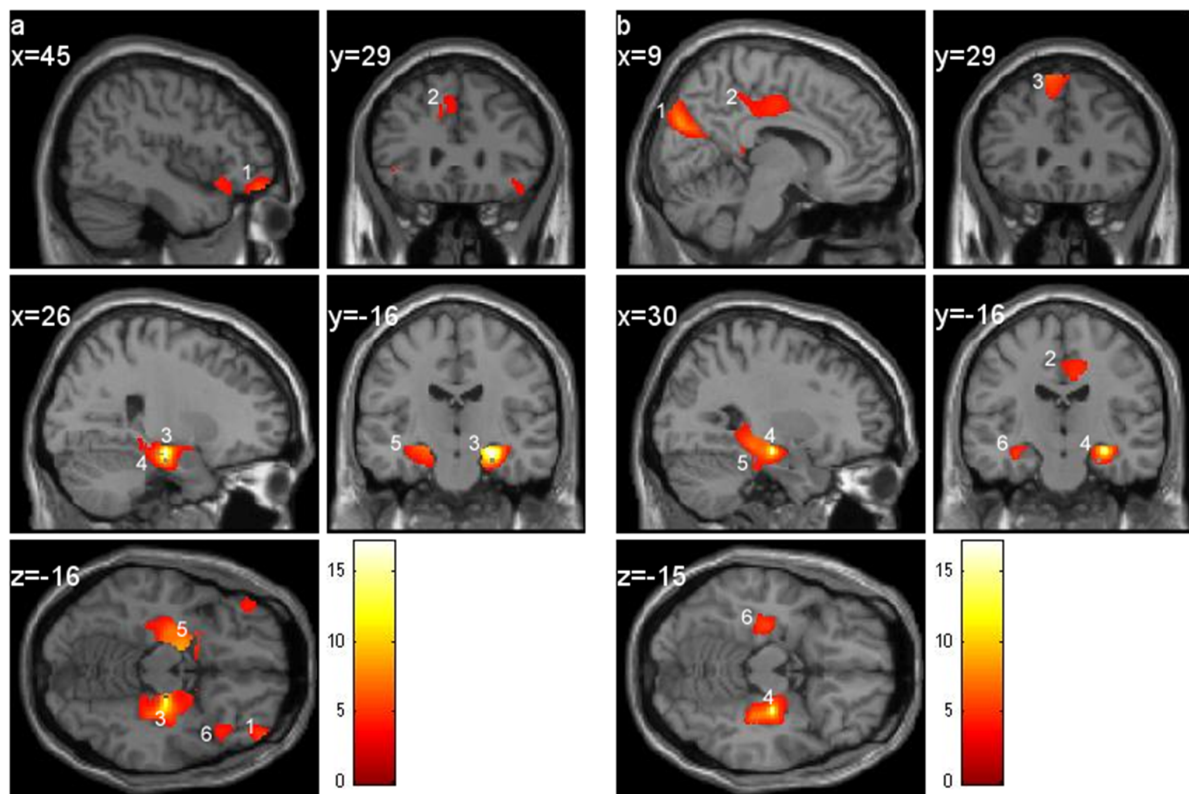


Figure 4. Regression at the seed voxel of the right hippocampus (24, -21, -15) in controls (Fig 4a) and in patients (Fig 4b). Fig.4a. Controls right hippocampus (region 3) covaries significantly with the 1 frontal middle orbital cortex, 2 Superior medial gyrus, 4 Right parahippocampal gyrus, 5 left hippocampus. Region 6, the inferior orbital cortex, is not significant. Fig. 4b. Patients right hippocampus (region 4) covaries significantly with the 1 cuneus, 2 middle cingulate gyrus, 3 Superior medial frontal gyrus, 5 Parahippocampal gyrus and 6 left hippocampus.

CHAPTER 4

**Exploration of Hippocampal Effective Connectivity in Schizophrenia and Control
Participants While Performing a Wayfinding Task**

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to Brain Connectivity.*

Abstract

It has been hypothesized that the contextual binding (content-context association) mechanism of episodic memory (memory for personal events), is impaired in schizophrenia. Many studies have shown that the hippocampus is structurally and functionally impaired in this illness. Since contextual binding is mainly related to hippocampal functions, evidence of both impairments appears to corroborate the central role of the hippocampus in the deficits observed in the domains of memory, learning and behaviour in schizophrenia. Moreover the hippocampo-prefrontal hypothesis stipulates that the alteration found in the hippocampus in schizophrenia could also impact the prefrontal functions (poor executive functions) observed in this illness. This study explored effective connectivity of the hippocampus in schizophrenia and healthy control participants, with a hippocampus-dependent wayfinding task.

Twenty-one patients with schizophrenia and twenty-two controls were scanned, with MRI, while performing the navigation task. Between-group analysis revealed the medial prefrontal cortex in controls and the inferior frontal cortex in patients covaried with the right hippocampus while performing the wayfinding task. Patients' hippocampus appears to be recruiting alternate pathways and regions to guide and help complete the wayfinding task. These results might be a consequence of altered hippocampal functioning due to a contextual binding deficit observed in schizophrenia.

Introduction

The cognitive profile in schizophrenia is at the core of the disorder. Various cognitive impairments have been convergently reported in the last three decades, especially in the domain of attention, executive functions and memory (working memory and long-term memory). Studies coupling neuropsychological exploration, cognitive assessments and neuroimaging techniques have shown evidence of working memory, executive functions and prefrontal deficits in schizophrenia (Callicott & Weinberger, 1999; Goldman-Rakic, 1999; for meta-analysis see: Minzenberg, 2009). This evidence is consistent with the role attributed to the prefrontal cortex for these higher cognitive functions. Both structural and physiological frontal abnormalities have been reported in most of the neuroimaging studies conducted in schizophrenia (even if the finding of a reduced volume of the frontal lobe has not been consistently replicated; Wible et al., 2001). There have also been reports of reduced volume of neuronal soma and neuropil and abnormalities in the synaptic architecture in the frontal region (Weinberger et al., 2001). It has been shown that when performing executive tasks reliant on the prefrontal cortex (e.g. Wisconsin card sorting test) there is a physiological hypofunctioning (reduced blood flow) in this precise area (Weinberger, Berman, & Zec, 1986). Despite abundant evidence for a prefrontal impairment in schizophrenia, this deficit is not the primary neurocognitive disorder. Emerging research indicates that other types of deficits are more characteristic of this pathology, such as an episodic memory deficit related to the hippocampal formation (Aleman, Hijman, de Haan, & Kahn, 1999; Boyer, Phillips, Rousseau, & Ilivitsky, 2007).

Episodic memory can be defined as the acquisition of memory for personal events in a spatial and temporal context (Tulving, 1983). Contextual binding (i.e. the ability to link the content of an event “what” with the contextual features of the event “when” and “where”) related to the hippocampal formation has been proposed to be the main mechanism for the formation of a complete episodic memory (Eichenbaum, 2000). Consequently, it has been proposed that the binding of encoded events with their context, is impaired in schizophrenia (Danion, Rizzo, & Bruant, 1999; Gold, Poet, Wilk, & Buchanan, 2004; Rizzo, Danion, van der Linden, & Grange, 1996; Waters, Maybery, Badcock, & Michie, 2004). Ledoux et al. (2013)

have demonstrated that while navigating in a wayfinding task (i.e. finding a way from point A to B by the shortest route possible), a task that uses a similar mechanism as in contextual binding, the hippocampus was functionally impaired in a group of schizophrenia patients. Furthermore, Ledoux et al. (n.d.) demonstrated, with the same participants, that the schizophrenia group had a decrease in grey matter average in their right and left hippocampus, superior medial frontal and orbital frontal cortices, caudate and insula. Converging evidence from many studies suggests that the prefrontal deficits (such as executive dysfunction) may in fact be more closely linked to a temporal deficit or associated with connectivity deficits between the temporal lobe and the prefrontal cortex (Weinberger, Berman, Suddath, & Torrey, 1992).

Empirical evidence supports a connection involving the projection of information from the medial temporal lobe to the prefrontal cortex (Kawashima, Izaki, Grace, & Takita, 2006). More specifically this connection would begin at the level of the hippocampal formation (CA1 and subiculum fields) and project to the medial prefrontal and orbital frontal cortices (Laroche, Davis, & Jay, 2000; Thierry, Gioanni, Degenetais, & Glowinski, 2000). Evidence from electrophysiological studies in rats has shown that low frequency stimulation of the ventral CA1 and subicular region produces excitatory responses in the neurons of the prefrontal cortex (Laroche et al., 2000). Because of their anatomical relation, it can be deduced that both structures are functionally associated (Thierry et al., 2000). A review on synaptic plasticity concluded that the hippocampo-prefrontal pathway represents one of the major factors in learning and memory (Laroche et al., 2000). In fact, it is thought that hippocampo-prefrontal cortex communication plays an important role in cognitive functioning (Squire, 1992), and that the hippocampus guides and influences the motor output regulated by the prefrontal cortex in learning (Laroche et al., 2000; Rolls, 1989).

To explain the concomitant dysfunction of the prefrontal and the medial and inferior temporal regions in schizophrenia it was hypothesized that the interaction existing between the hippocampus and the prefrontal cortex might be disturbed in this pathology (Berman, Weinberger, Shelton, & Zec, 1987; Weinberger et al., 1992). Several models of disconnectivity have been proposed, one of which explains the complex clinical feature of the disease as a

disruption in communication between multiple regions (Friston & Frith, 1995). This functional connectivity or disconnectivity would be due to altered synaptic connection strength rather than abnormalities in single regions (Friston et al., 1997). Agreeing with this hypothesis is the Bullmore, Frangou, and Murray (1997) model, the *dysplastic net hypothesis*, which argues that the disruption in the anatomical connections seen in schizophrenia may occur in part during prenatal development. Bertolino and colleagues demonstrated that neonatal lesions of the ventral hippocampus (NVHL) in rhesus monkeys induced postpubertal changes in the prefrontal cortex and its regulation of dopaminergic activity (Bertolino et al., 1997, 2002). A series of studies have corroborated that NVHL in rats produce “schizophrenia symptom-like” behaviour (which can be cautiously considered as “positive-like”, “negative-like” and “cognitive” deficits; Chambers, Moore, McEvoy, & Levin, 1996; Lipska, Jaskiw, & Weinberger, 1993; Tseng, Chambers, & Lipska, 2008), and cellular, molecular and morphological changes similar to those of schizophrenia emerge once the rats are adolescent. These animals show deficits in social behaviours, in self-grooming (Flores, Silva-Gomez, Ibanez, Quirion, & Srivastava, 2005), and difficulties with spatial learning and memory tasks (Le Pen et al., 2000).

Consistent with the hypothesis that early hippocampal damage results in abnormal connectivity at the level of the prefrontal cortex, a meta-analysis of MRI studies indicated that in schizophrenia white matter abnormalities are more pronounced in the frontal and temporal lobe regions (Wright et al., 2000). Diffusion tensor imaging (DTI) studies (a method that measures fractional anisotropy (FA), i.e. white matter tract integrity), have shown that the uncinate fasciculus (a tract connecting the temporal pole of the amygdala/hippocampus and the orbital prefrontal/ventrolateral prefrontal cortex) is smaller in individuals with schizophrenia (Kubicki et al., 2002; Szeszko et al., 2008). Correlation studies between neuropsychological tests and FA values in the uncinate fasciculus tract showed an association between decreased FA and negative symptoms in schizophrenia (Szeszko et al., 2008). Lower FA has also been correlated with impaired verbal episodic memory deficits (Nestor et al., 2004).

Finally the disconnectivity hypothesis can be dynamically tested. It has been demonstrated that the hippocampus, together with the parahippocampal gyrus, posterior parietal cortices, medial prefrontal cortex and striatum regions are involved in visuospatial navigation (Burgess, Maguire, & O'Keefe, 2002; Kumaran & Maguire, 2005). In order to be successful in the wayfinding task individuals must learn the relations between landmarks (stimulus-stimulus association; Bohbot, Lerch, Thorndycraft, Iaria, & Zijdenbos, 2007), a similar mechanism as in contextual binding. Learning and memory have an impact on executive functioning; it can be hypothesized that the inaccurate recollection of a landmark association (because they were not bound together accordingly) can result in a significant disturbance of the planning and decision making abilities during the wayfinding task. Further, it can be hypothesized that due to a connectivity impairment between the hippocampus and prefrontal cortex, the recruitment of the prefrontal cortex while doing the task might be impaired. The purpose of this exploratory study was to investigate effective connectivity of the hippocampus and anatomically connected regions in individuals with schizophrenia and control participants while performing a wayfinding task, with a particular interest in the prefrontal cortex. To investigate the functioning of the hippocampus and its connectivity patterns, the same MRI data collected in Ledoux et al. (2013) study was used.

Methods

Participants

A total of 54 study participants (28 patients with schizophrenia and 26 control participants) were recruited for this study. Participants included right-handed (determined by the Edinburgh Handedness Inventory; Oldfield, 1971) men and women between 18 and 40 years old. Patients with a primary diagnosis of schizophrenia were recruited from the Outpatient Schizophrenia Clinic at the Royal Ottawa Mental Health Centre, Ottawa, Ontario. Controls were recruited via newspaper and advertisement. Controls were matched to schizophrenia patients in terms of age, sex, and education level. Current diagnosis of abuse or dependence during the preceding 12 months with alcohol (Alcohol Use Disorders Identification Test (AUDIT); Saunders, Aasland, Babor, de la Fuente, & Grant, 1993, score > 8 in men or > 7 in

women) or drugs (Drug and Abuse Screening Test (DAST); Skinner, 1982, score > 6) were exclusion criteria for all participants. Participants with a history of neurological disease, head injury, cardiovascular disease, stroke, or contraindications to MRI (determined by Medical Questionnaire) were also excluded.

Participants were paid a sum of \$75 to take part in the study. The Research Ethics Board of the Royal Ottawa Mental Health Centre approved this project. All participants provided written informed consent.

Inclusion and exclusion criteria specific to the patient group. Patients were clinically diagnosed with schizophrenia by a psychiatrist and met the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV-TR; American Psychiatric Association, 2000) criteria for schizophrenia determined by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition (SCID-P) interview (First, Spitzer, Gibson, & Williams, 2002b). Patients meeting the DSM IV criteria for schizophrenia, disorganized, undifferentiated or paranoid subtypes, were eligible; catatonia subtypes and schizoaffective patients were excluded. Patients were clinically stabilized and had had no significant change in symptom severity, medication, or therapeutic methods following a three-month retrospective chart review.

For feasibility purposes patients with an acute psychotic episode as reflected by the total score on the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) or by two or more of the following four PANSS items having a score > 4: conceptual disorganization (P2), hallucinatory behaviour (P3), suspiciousness (P6), unusual thought content (G9) were excluded. Further patients exhibiting comorbid depressive symptoms (score ≥ 7 on the Calgary Depression Scale (CDS); Addington, Addington, & Schissel, 1990) were also excluded since depression has been linked to hippocampal atrophy. Participants taking typical antipsychotics, benzodiazepines, or receiving electroconvulsive therapy were excluded from this study: the side effect profiles of these medications are considered to contribute to the worsening of cognitive performances. Finally, the presence of extrapyramidal symptoms, or overt signs of tremor or movement disorder (confirmed by clinician) were exclusion criteria.

Exclusion criteria specific to the control group. Exclusion criteria for controls included presentation of an Axis 1 DSM-IV TR diagnosis (using SCID Non-Patient interview; First, Spitzer, Gibson, & Williams, 2002a), report of a psychiatric history concerning participants' first-degree relatives (elicited by inquiry), or the presence of depressive symptoms (Hamilton Scale for Depression (HAMD); Hamilton, 1960, score > 10).

Material and Procedure

Clinical assessment. Participants underwent clinical interview during which the following assessments were administered: SCID (P or NP), CDS (for patients only), HAMD (for controls only), PANSS (for patients only) and the self-report AUDIT and DAST questionnaires.

Neurocognitive assessment. The neurocognitive battery was comprised of several tools to determine the level of prefrontal and temporal deficits in schizophrenia and meant to be used as supporting evidence.

Neuropsychological assessments of anterior regions (prefrontal and cingulate cortices) functions. The following tests were administered: D2 Test of Attention (Brickenkamp & Zillmer, 1998), Wisconsin Card Sorting Test (WCST; Heaton, 1981), Wechsler memory subtest digit span forward and backward, Letter Number sequencing; the two latter assessments forming the composite score for working memory.

Neuropsychological assessments of temporal functions. The following episodic memory assessments of the Wechsler Memory Scale, 3rd edition (WMS-III; Wechsler, 1987) were administered: logical memory I and II, verbal paired associates I and II (both assessment form the auditory memory composite score) and Family Pictures I and II (visual memory).

Finally, during this session, participants were also given the National Adult Reading Test (NART; Nelson & Willison, 1991) to provide an estimate of premorbid intelligence and IQ.

MRI session.

The wayfinding task. The behavioural and fMRI data for this study were generated during the performance of a virtual visuospatial navigation task called the wayfinding task, the same task as in Etchamendy and Bohbot (2007). Briefly, this task required participants

to navigate between specific landmarks in a previously encountered computer-generated virtual town. For the fMRI portion of the study, the contrast of interest was a comparison of brain activation in patients and controls during active navigation in the virtual town.

The MRI portion of this project occurred in two phases performed on the same day: the pre-scan training phase followed within one hour by the scan phase. Since familiarity with first-person videogames may help in the virtual reality task performance, before the pre-scan training participants were asked about their video gaming habits (e.g. the type of video game played). During the pre-scan training, participants were first familiarized with the keyboard to ensure their ability to manoeuvre through the environment. This was done in a different virtual environment than the virtual town used for the fMRI experiment. They then navigated in the virtual town created with the game editor of a commercially available computer game (Unreal Tournament 2003; Epic Games, Raleigh, NC). The virtual town was a visually complex computer-based environment that included several roads, intersections, and buildings, in addition to distinct landmarks (easily recognizable, labelled locations such as a school or a hospital). Participants engaged in a free exploration of the town for 20 to 30 minutes. During exploration, participants were required to encounter every landmark twice and to travel along all roads. The path taken and the amount of time participants visited each landmark was recorded. The free exploration provided an opportunity for participants to encode and construct a cognitive map of the environment by building relationships between landmarks in the town. Participants were not permitted sufficient exploration time to form habitual routes between landmarks. Creating the paradigm using a modified video game framework provided participants with a first-person perspective while navigating. Following the training outside the MRI, participants were scanned while performing tasks based on the navigation paradigm.

MRI acquisition parameters. MRI scans were acquired using a 1.5 tesla Siemens Magnetom Symphony. An MRI-compatible virtual reality system, Silent Vision™ Model SV-7021 Fibre Optic Visual System with In Control Software (Avotec, Inc.), was used for this study, as was a 4-button fiber optic touch pad. Cerebral activation was measured with fMRI using a blood oxygen level-dependent (BOLD) contrast. The International Consortium for

Brain Mapping (ICBM) T1 protocol was used to acquire weighted structural images for coregistration with the echoplanar images (EPI). BOLD signals were obtained using the following T2* weighted EPI image parameters: 32 contiguous 4 mm axial slices, positioned parallel to the hippocampus (64×64 matrix, repetition time =3000 ms, echo time =50 ms, field of view =256mm, flip angle =90 degrees. A total of 160 volumes per run were used for the analysis).

Block-design and control task. Following a 12-minute T1 structural scan, participants underwent an fMRI scanning session where they were required to complete the wayfinding (visuospatial navigation) task which consisted of an alternating series of eight navigation trials, and eight control conditions. In the task, participants were required to navigate between two landmarks in the previously explored town, taking the shortest possible route. For each navigation trial, participants were placed in front of one of the landmarks (e.g. school) and were required to navigate from there to another landmark (e.g. movie theater). For each trial, there were many different routes that could be taken to get to the target landmarks. Successful completion of this task required taking the shortest route by deriving it from a cognitive map, a task that critically requires the hippocampus. Once participants reached the target landmark, they initiated an automatic transition to the control task. If participants failed to find the target landmark during a predetermined time frame (determined by a pilot study), they were manually transported into the control town by the investigator. Since participants had not been previously exposed to the control town, it represented a novel, unfamiliar environment. The control task involved the completion of eight navigation routes during which participants followed different paths that were clearly indicated by arrows on the ground. This was thought to be an appropriate task to control for the visuo-motor components of the experimental task.

Participants navigated using their right hand to control the MRI-compatible touchpad. During completion of the navigation trials, participants were timed and their precise paths were recorded on a 2D aerial view of the town. This study used an fMRI block design with 4 fMRI BOLD scanning sessions of 8:06 minutes each, separated by one-minute rest periods. Each scan alternated between experimental and control tasks to control for scanner drift and

a six-second transition period between experimental conditions was used to allow the hemodynamic response function to normalize. Software was used to detect transition between experimental and control tasks, as well as frame times. The entire MRI and fMRI scan time was 60 minutes per participant.

Data Analyses

Participants were matched according to their age, sex and level of education for all analyses in this study. Behavioural data (demographics, cognitive assessment results and navigation performances) were analyzed using Statistical Package for Social Sciences (*SPSS*, 2011) software. Neuroimaging data were analyzed with Statistical Parametric Mapping software (Wellcome Department of Imaging Neuroscience, 2008).

Behavioural data.

Neurocognitive and behavioural assessments. Composite scores were created for assessments measuring similar cognitive functions. We hypothesized that there would be a significant difference between patient and control groups within the neuropsychological assessments of their prefrontal and temporal regions. This hypothesis was tested using a multivariate analysis of variance (MANOVA). The variables considered for the analysis were Working memory, Attention and WCST (anterior regions of the frontal lobe), Immediate and Delayed auditory and visual memory scores (temporal regions). Differences between groups for the behavioural navigation task were computed in (Ledoux et al., 2013). To reiterate, the navigation performance variables were accuracy (i.e. percentage of target locations reached), percent error and time.

$$\text{Percent error: } ((x + z) - y) / (x + z) * 100$$

(where x = total distance travelled, z = distance remaining to reach the goal, y = shortest distance to goal). The z variable was included to account for incomplete trials where the target landmark was not reached. Since incomplete trials by definition are missing part of the way to the goal location, the z variable was made to include this missing distance. As a consequence the shortest distance from the end point at which the trial was interrupted to the goal location was added to the distance travelled ($x + z$).

Psychophysiological interaction. Tests of significant psychophysiological interactions (PPI) with the right hippocampus was conducted for each group of participants. PPI analysis reveals changes in the interaction between brain regions in relation to the experimental paradigm (Friston et al., 1997). More precisely, PPI is an effective connectivity technique based on linear regression, where the main BOLD effect signal is deconvolved to obtain the “neural” signal and is combined with the main effect of the task. PPI analyses aimed to detect regions that showed changes in their interaction with the hippocampus, in response to the navigation task (and not the experimental task minus control task, as per (Ledoux et al., 2013), with a particular focus on the prefrontal cortex. Anatomically, the hippocampal projections to the medial orbital cortex are located along the rostral-caudal extent of the hippocampus (Barbas & Blatt, 1995). Since the hippocampus has a curved shape and the projections are distributed along the entire anterior-posterior axis, the seed region for the analysis was respectively the entire right hippocampus. To perform PPI analyses, the first eigenvariate time series was extracted from the right hippocampus (thresholded at an uncorrected p value inferior to 0.05 to ensure its presence in all participants). The PPI function in SPM8 was used to construct an interaction variable representing the interaction between the time series and the psychological variable (wayfinding task). The effect of this interaction term was evaluated individually for each subject in each group. The individual contrast images of each group were then taken to the second level analysis in order to perform a flexible factorial design of the PPI pattern. The statistical threshold was set to $p \leq 0.05$ family-wise error (FWE) corrected for the entire brain volume, with no cluster limit. Small volume corrections (SVC) was applied on regions that were trending for significance; these results appear in the “trend” sections of the tables ($p \leq 0.05$ FWE-corrected). Predetermined regions of interest (ROI) including the left hippocampus, parahippocampal gyrus, prefrontal cortex (superior medial and orbital cortex), parietal lobe and caudate nucleus were defined with a structural mask from the Pick Atlas extension (Maldjian, Laurienti, Kraft, & Burdette, 2003) using the AAL atlas (Tzourio-Mazoyer et al., 2002) and the statistical threshold was set to $p \leq 0.001$ uncorrected with a cluster-wise correction at $p_{FWE} = 0.05$ for the reduced search volume.

Results

Demographics

Twenty-eight schizophrenia patients and twenty-six healthy control participants were enrolled in the study. Complete datasets were available for 21 patients and 22 controls with 20 pairs successfully matched by age, sex and education. Only one patient (male, age 30) and three controls (one female, age 22; two males, age 19 and 37) were matched with respect to the overall group. There were no statistical differences between the two groups in terms of age, education, IQ, experience with first person videogames or mean number of time participants visited the landmarks during the learning phase (visited landmarks), $p \geq 0.05$ (Table 1).

(Insert Table 1)

Behavioural Results

Neurocognitive assessments. Significant differences exist between groups for the neurocognitive assessments of prefrontal (and anterior regions) functions and the neurocognitive assessments of temporal (and related regions) functions (Table 2). While there was a difference between both groups for the D2 test of attention, the patients' mean score when compared to a normalized population ($N = 900$; Brickenkamp & Zillmer, 1998), did not indicate an attention deficit.

Behavioural navigation results. Since there was a significant difference between both groups for working memory, it was added as a covariate in the MANOVA to verify if it had an impact on navigation performance (Table 3). Results demonstrated significant differences between both groups on the behavioural navigation performance task.

(Insert Table 2 and 3)

Effective Connectivity Results

A 2×4 flexible factorial analysis was performed on the PPI regressors. Within-group analyses of the regions interacting with the right hippocampus are shown in Table 4 and 5.

Between-group analysis with the seed region in the right hippocampus, showed differences (Control > Patient) in the right superior medial frontal cortex (SVC, cluster FWE $p \leq 0.05$;

Figure 1a) and a trend in the right parahippocampal gyrus, and (Patients > Control) in the right inferior triangular pars of the frontal cortex (SVC, cluster FWE $p \leq 0.05$; Figure 1b) and trends for significance in the thalamus and right middle temporal gyrus.

(Insert Table 4 and 5 and Figure 1)

Discussion

The hippocampo-prefrontal connectivity hypothesis stipulates that anomalies in the hippocampus may play a central role in the prefrontal deficit observed in the schizophrenia population (Weinberger et al., 1992). The goal of this exploratory study was to gain support for this hypothesis by investigating effective connectivity associated with the hippocampus while performing a wayfinding task, with a particular interest in the prefrontal cortex. As demonstrated in this study, and in agreement with the literature, patients with schizophrenia have cognitive deficits related to prefrontal and temporal regions.

Ledoux et al. (2013) observed a deficit related to the temporal region (medial and inferior temporal lobes, hippocampus and parahippocampal gyrus) within the same schizophrenia group. Further, these same individuals displayed a significant decrease in the ability to link context and content as evidenced by the Family Picture assessment of the WMS-III suggesting a contextual binding deficit. Furthermore, Ledoux et al. (2013) revealed that while navigating in the wayfinding task patients with schizophrenia made more errors and took more time to complete the task. Structural and functional results revealed that patients with schizophrenia had less GM average in the orbital, middle and medial superior prefrontal cortex compared to the control group and less neurofunctional activity in the right and left hippocampus Ledoux et al. (n.d.). Even when controlling for performance, patients had less hippocampal activity than the control group. Given these results and the structural connectivity results of Ledoux et al. (n.d.), specifically the covariation with different structures for patients and controls, it was important to investigate effective connectivity, particularly in the prefrontal cortex.

While learning the task, the hippocampus plays an important role in binding locations (O'Keefe & Nadel, 1978). The hippocampus is also recruited during the planning of navigation routes through learned environments (Spiers & Maguire, 2006). The hippocampus

connects to the prefrontal cortex, i.e. the orbital and medial prefrontal cortices, also involved in navigation and thought to play important roles in the decision-making process (for instance, the evaluation of predicted future states and the ability to translate decisions into behaviour). Within-group analysis with the seed region in the right hippocampus in patients revealed that the caudate and thalamus covaried with the hippocampus while performing the navigation task. Differences between groups revealed that the hippocampus in controls influences the medial prefrontal cortex and parahippocampal gyrus and in patients influences the inferior part of the prefrontal cortex, as well as the thalamus/striatal regions while performing the task. Hence, one can conclude that the connectivity patterns employed by the patient group are different than the control group. As the ability to bind context and content is impaired in schizophrenia (Boyer et al., 2007; Danion et al., 1999; Gold et al., 2004; Ledoux et al., 2013; Rizzo et al., 1996; Waters et al., 2004), and the hippocampus and the hippocampo-prefrontal pathway have been found to be altered, different pathways might be used by the patients to compensate for this deficit. According to the results of this study and the results from our previous navigation studies, controls are using network regions more specifically related to allocentric navigation (i.e. medial prefrontal cortex, parahippocampal gyrus). Where the parahippocampal gyrus is implicated in the recognition of detailed visual scenes and is a crucial structure for the recall of specific and non-specific landmarks (Maguire, Frith, Burgess, Donnett, & O'Keefe, 1998)). It has been proposed that the parahippocampal gyrus provides "spatial scene information" to the hippocampus (Bohbot et al., 1998). Patients appeared to be making use of a shared network of the hippocampo-striatal-prefrontal cortices.

The hippocampus does not influence the medial prefrontal cortex in patients as it does in controls, rather their hippocampus influences the triangular part of the ventrolateral prefrontal cortex (VLPFC), which has been implicated in the cognitive control of memory and more specifically in episodic retrieval (Badre & Wagner, 2007; Buckner, 2002). This control mechanism is thought to control the cues that serve to trigger pattern-completion (Polyn, Natu, Cohen, & Norman, 2005) and event reconstruction (Addis, Wong, & Schacter, 2007; Badre & Wagner, 2007). Past fMRI studies have supported that the recollection of visual perceptual details about a past episode, elicited activation in right VLPFC (Dobbins &

Wagner, 2005). It is possible that in patients this region works with the hippocampus to retrieve and reconstruct the event to compensate for the impairment of the contextual binding mechanism.

Many potential scenarios can be derived from these results. It can be postulated that individuals with schizophrenia recruit the striatum and the triangular pars of the prefrontal cortex to compensate for hippocampal anomalies. The hippocampus connects indirectly to the prefrontal cortex through the nucleus accumbens (NAc), the main structure of the ventral striatum, receiving important glutamatergic afferent inputs from the amygdala, hippocampus and prefrontal cortex (Thierry et al., 2000). It is postulated that the CA1/subiculum, through the indirect ventral pallidum-thalamocortical circuit, can activate the prefrontal cortical neurons through a disinhibitory process (Thierry et al., 2000). The main inputs to the NAc play an important role in cognition, more precisely in context-dependent processing (Jarrard, 1995).

As previously noted the connection of the hippocampo-prefrontal cortex is hypothesised to be altered in schizophrenia, which may explain why the hippocampus covaries significantly with the superior medial frontal gyrus in controls when compared to patients. Further, this disconnectivity may explain why the striatum trends to 'work' more actively with the hippocampus in patients than in controls. As a consequence, patients might be using another strategy to navigate. In fact, the caudate portion of the striatum has been reported to be active in egocentric representation (dependent on an individual's view point) while performing a stimulus-response learning task such as the four on eight task (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Bohbot et al., 2007). The representations of the environment within an egocentric framework is supported by a network of thalamic/striatal and parietal and temporal cortices (Burgess, Maguire, Spiers, & O'Keefe, 2001). Recently it was found that individuals with schizophrenia exhibit impairments in allocentric memory while egocentric memory remained intact (Weniger & Irle, 2008), although it has been reported that the hippocampus and caudate support competing strategies in spatial navigation (Bohbot et al., 2007; Hartley, Maguire, Spiers, & Burgess, 2003; Iaria et al., 2003). Certain studies in navigation have shown that the hippocampus and caudate contribute in a noncompetitive,

cooperative manner in navigation tasks (Voermans et al., 2004). In Huntington patients, it was observed that the hippocampus compensates for the functional degradation of the caudate nucleus while performing a route recognition task (Voermans et al., 2004).

Furthermore, in a more recent connectivity study with a navigation task it was demonstrated that the hippocampus and caudate are “strongly engaged” with one another while navigating successfully in overlapping mazes (i.e. familiar environment; Brown, Ross, Tobyne, & Stern, 2012).

Limitations and future direction

In this study, only the experimental task was analyzed for effective connectivity. As discussed in Ledoux et al. (2013), the control task also produced significant hippocampal BOLD activity. Since the seed region was located in the hippocampus and the analysis used was based on “neural signal” (where the BOLD signal was deconvolved) paired with the main effect of the task, we do not believe this impacted our results. Another limitation and for future studies, connectivity patterns can differ over time, in our study not all individuals had significant hippocampal activity in each run, hence making it difficult to interpret within and between group connectivity patterns over time. Also, it is important to note that this study was exploratory, hence the use of PPI methods over other techniques. PPI methods are simple to implement making them suitable for exploratory studies, however, it is impossible to infer directionality with this family of methods: it must be pre-specified on the knowledge of anatomy or on other results. Techniques such as dynamic causal modelling (a model-driven analysis that brings more precision concerning the directionality and causality of the connectivity patterns) paired with DTI should be considered to pursue the investigation of connectivity of hippocampo-prefrontal and hippocampo-striatal in schizophrenia since they can provide different information than the interpretations possible with PPI.

Finally, it would be important to investigate, with fMRI, non-spatial strategies related to egocentric frameworks in schizophrenia, a topic that has not yet been explored.

Understanding non-spatial strategies in schizophrenia might shed light on the spatial connectivity patterns seeded in the hippocampus.

Conclusion

The current exploratory study investigated effective connectivity in schizophrenia and control participants while performing a wayfinding task. Results indicated that while performing the task the right hippocampus influences or regresses with the medial prefrontal cortex and with the parahippocampal gyrus in controls, and with the inferior prefrontal cortex and with the thalamus/striatum in patients. Since contextual binding is impaired in schizophrenia, other regions might be implicated for navigating through the wayfinding task such as the striatum and inferior prefrontal cortex. These results support the hippocampo-prefrontal pathway deficit in schizophrenia and suggest that compensatory networks may assist in the completion of the wayfinding task.

Acknowledgment

This study was funded by the Canada Foundation for Innovation, the University of Ottawa Medical Research Fund, the Ontario Ministry of Development and Trade, the Royal Ottawa Health Care Foundation. A-A Ledoux is supported by the Canadian Institutes of Health Research, and the University of Ottawa. We thank Benjamin Deschamps M.Sc., François Rousseau Ph.D., Catherine Smith M.A., and Guylaine Veillette.

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Table 1
Participant demographics

	Controls (<i>n</i> = 22; SD)	Patients (<i>n</i> = 21; SD)
Sex (F/M)	6/16	5/16
Age (years)	30.45 (1.25)	32.05 (1.08)
Education (years)	16.68 (2.64)	15.10 (2.09)
IQ (NART)	111.32 (1.67)	109.09 (1.47)
Played first person videogame (Yes/No)	13/9	13/8
Visited landmarks	20.64 (4.76)	21.38 (5.36)
Age of Onset (years)		20.52 (4.81)
Duration of Illness (years)		11.38 (4.93)
PANSS Total		64 (13.0)
PANSS Positive		15.14 (4.33)
PANSS Negative		18.14 (5.68)
PANSS General Score		30.71 (6.93)

Note: $p \geq 0.05$ on all measures.

Table 2
Between group differences on the prefrontal and temporal assessments

	Mean		d.f.	<i>F</i> -test
	Controls (SD)	Patients (SD)		
Prefrontal Assessments				
Wisconsin % Perseverative error	10.50 (5.82)	22.76(16.00)	1	11.366**
Attention - concentration	204.04 (38.59)	156.24 (38.17)	1	16.67**
Working memory	32.9 (5.20)	28.14 (6.22)	1	7.46*
Temporal Assessments				
Auditory immediate memory	72.40 (13.20)	49.80 (14.53)	1	28.54**
Visual immediate memory	48.73 (5.68)	41.95 (10.86)	1	6.66*
Auditory delayed memory	35.86 (7.07)	24.95 (8.98)	1	19.69**
Visual delayed memory	48.59 (5.50)	41.19 (10.65)	1	8.31**

Note: * $p \leq 0.01$; **Bonferroni $p \leq 0.007$

Table 3
Behavioural navigation performances controlled for working memory

	Mean		d.f.	<i>F</i> -test
	Controls (SD)	Patients (SD)		
Accuracy (%)	82.95 (22.01)	53.57 (26.85)	1	10.78*
Percent error	33.16 (15.79)	48.34 (16.26)	1	6.56*
Time (sec)	57.82 (15.06)	73.94 (15.09)	1	7.29*

Note: * $p \leq 0.01$.

Table 4
Patients PPI within group analysis

Seed region	[x,y,z]			Anatomical Location of Peak	K_E	Z Equiv- alent
Right Hippocampus	38	-24	10	R Heschl's gyrus	43	4.93
	10	-4	10	R Thalamus	143	4.43
	-18	8	2	L Putamen		3.74
	58	-28	-6	R Middle temporal gyrus	37	4.21
ROI	10	0	14	R Caudate	9	3.74
	-34	-28	-10	L Hippocampus	3	3.72
	30	-40	-6	R Parahippocampal gyrus	4	3.49
Trends	-38	-36	6	L Postcentral gyrus	18	4.13
	-58	-24	-6	L Middle temporal gyrus	20	3.91

Note: Voxel-wise significance for the whole brain volume was set to FWE corrected $p \leq 0.05$. Statistical threshold for ROI was set to $p \leq 0.001$ uncorrected with a cluster-wise correction at $p_{FWE} = 0.05$

Table 5
Controls PPI within group analysis

Seed region	[x,y,z]			Anatomical Location of Peak	K_E	Z Equiv- a- lent
Right Hippocampus	30	-4	-30	R Parahippocampal gyrus	26	4.61
ROI	-18	24	-10	L Hippocampus	8	3.58
	2	44	34	R Superior medial frontal cortex	9	3.57
Trends	6	6	26	R Anterior cingulate	11	4.21
	-54	-12	10	L Heschl's gyrus	13	4.07
	38	-12	-2	R Insula	25	3.86
	-6	-12	34	L Middle cingulate	13	3.58
	-50	-36	6	L Middle temporal gyrus	11	3.45
	-50	-12	-6	L Superior temporal gyrus	10	3.44

Note: Voxel-wise significance for the whole brain volume was set to FWE corrected $p \leq 0.05$. Statistical threshold for ROI was set to $p \leq 0.001$ uncorrected with a cluster-wise correction at $p_{FWE} = 0.05$

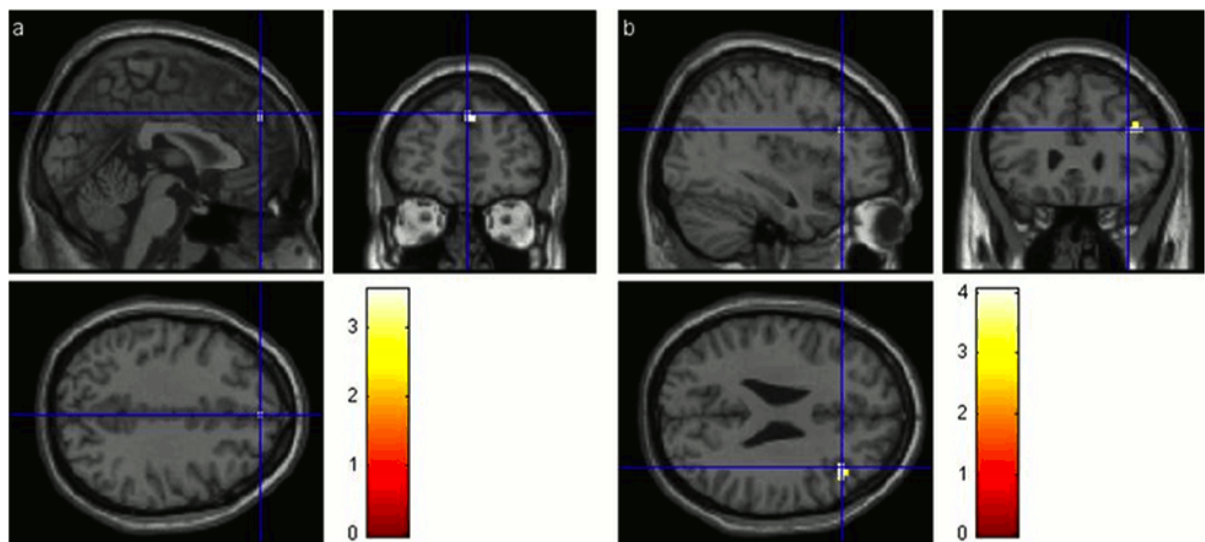


Figure 1. 1a. Uncorrected view $p \leq 0.001$ of differences between controls and patients. 1a. Difference between control and patients (controls > patients), controls having significant superior medial prefrontal connectivity with the right hippocampus (MNI coordinates: 2 48 38, SVC, $t = 3.55$, $pFWE_{corr.} = 0.05$). 1b. Differences between patients and controls (patients > controls), patients having a significant difference in the inferior triangular part of the prefrontal cortex (MNI coordinates: 38 28 26, SVC, $t = 4.05$, $pFWE_{corr.} = 0.05$)

CHAPTER 5

Discussion

Episodic memory is believed to be at the core of the cognitive disorder in schizophrenia. More specifically, individuals with schizophrenia have a deficit in binding the content of an event with its contextual features, a mechanism known as contextual binding, one of the central mechanisms in episodic memory. Learning and memory influences higher order cognitive processes, and the inaccurate recollection of an event can have tremendous impacts on planning and decision making. Hence, a contextual binding deficit can hamper the daily lives of individuals with schizophrenia. This dissertation was designed to improve our understanding of this cognitive disorder by studying the neurofunctioning and structural anomalies of the hippocampus, the main structure involved in contextual binding. Furthermore, this dissertation attempts to better understand the impact of such deficits and anomalies on other brain regions. Many studies have demonstrated a behavioural contextual binding deficit in schizophrenia (Burglen et al., 2004; Danion, Rizzo, & Bruant, 1999; Gold, Poet, Wilk, & Buchanan, 2004; Rizzo, Danion, van der Linden, & Grange, 1996b, 1996a; Waters, Maybery, Badcock, & Michie, 2004), but the neurofunctioning, structural anomalies and functional neuroconnectivity related to a contextual binding deficit and the hippocampus have not been the subject of any known ecological studies, especially using a visuospatial navigation task.

In order to study contextual binding it was necessary to design a task that targets content-context association, which involves the hippocampus. Visuospatial navigation tasks, more specifically wayfinding tasks, precisely call on the capacity to bind an event with its spatial context. In the wayfinding task, the role of the hippocampus is to bind locations and orientation together (content-context association). This is achieved by place cells in the CA subfields and event cells of the subiculum in the hippocampal formation (Burgess, Maguire, Spiers, & O'Keefe, 2001). When navigating on a novel route, the hippocampus is recruited in the recall of the bound information (locations) and in the planning of an adequate route. For these reasons, wayfinding navigation was considered as a valid surrogate for contextual

binding and a good probe to activate the hippocampal formation. Therefore in the first study, the author investigated the behavioural and neurofunctionality of the contextual binding deficit in schizophrenia with a wayfinding navigation task. The second study examined the structural deficits in schizophrenia and how these deficits can relate to wayfinding performance. The last study explored the effective connectivity of the hippocampus and other brain regions while performing the wayfinding navigation task. The findings and limitations of each study are presented, followed by the implications of this research for future investigation and clinical practice.

Study 1. Decreased fMRI Activity in the Hippocampus of Patients with Schizophrenia Compared to Healthy Control Participants, Tested on a Wayfinding Task in a Virtual Town

The first original paper of this study demonstrated that individuals with schizophrenia have a deficit in binding contextual information with the content of the event. This was demonstrated behaviourally and neurofunctionally. Patients made more errors on the Family Picture measure (a visual assessment of content-context association) compared to the control group, indicating a contextual binding deficit. While performing a wayfinding task, individuals with schizophrenia found the landmarks less frequently, made more errors and took more time to complete the task. Furthermore, they exhibited hypofunctioning of the posterior part of the hippocampus. These results are supported by many behavioural studies that investigated contextual binding in schizophrenia (e.g. Rizzo et al., 1996b; Burglen et al., 2004). This study brings a significant contribution to the literature, as neurofunctioning differences in the hippocampus while performing an ecological navigation task encompassing contextual binding have never been reported.

Limitations. In fMRI, a control task is used to control for visuo-motor and baseline activity in the brain. In our task the control task yielded hippocampal activity. Although there were lower levels of hippocampal activity in the control task than in the experimental task, when comparing the experimental task to the control task the weight of the activity in the control task reduced the significance of the activity in the experimental task. The same

problem was observed in Etchamendy, Konishi, Pike, Marighetto, and Bohbot (2012), where hippocampal activity was seen in the control task while navigating. Having no control task does not affect the between-group results as the visuo-motor activity is similar in both groups. Furthermore, this study focused on the hippocampus and not the occipital and motor cortices.

Future considerations. A limitation in schizophrenia research and in our study is the potential confounding effects of medication on the BOLD signal. Little is known about the effect of long-term treatment with antipsychotics and antidepressants on the BOLD signal. Results are inconclusive and vary from being region-specific with regards to the distribution of receptors and also to the sub-processes of the task. According to Röder, Dieleman, van der Veen, and Linden (2013), who undertook a systematic review of the literature, there was no general effect of antipsychotics on the BOLD-signal. However, effects of antipsychotics that have a specific affinity to the dopamine receptor (D2-receptors; haloperidol, olanzapine, quetiapine and risperidone) may reduce the BOLD-signal. To date, no studies have shown evidence of a reduced BOLD signal in the hippocampus due to the long-term use of antipsychotics. As for antidepressants, certain studies have shown that they can normalize hippocampal volumes in depressed populations (Sheline, Gado, & Kraemer, 2003). Since the effect of antipsychotics and antidepressants may be different in different regions of the brain, subsequent studies should account for the type and amount of medication administered with the BOLD signal by including them as covariates.

Study 2. Structural Hippocampal Anomalies in a Schizophrenia Population Correlate with Navigation Performance on a Wayfinding Task

The second paper of this dissertation explored structural brain differences in schizophrenia and investigated whether behavioural navigation performance could predict GM volume of the hippocampus in the overall group and the patient and control groups, individually. This paper also explored the structural relation between brain regions (i.e. the parahippocampal gyrus) known to be associated with the hippocampus, in both groups. Results indicated that controls had significantly more hippocampal GM and WM average than patients, a result that is consistent with the literature (Wright et al., 2000). Poor performance at the

wayfinding task was associated with a decrease in the right hippocampal GM for the overall group. Separated group regressions showed an association between right hippocampal GM and navigation performance in controls and an association between the left hippocampal GM and navigation performance in patients. A second analysis revealed that different GM regions known to be associated with the hippocampus, such as the parahippocampal gyrus, amygdala, medial and orbital prefrontal cortices, covaried with the hippocampus in the control group. In other words, greater hippocampal GM is related to greater GM in these associated regions. Interestingly, the cuneus and cingulum gyrus also covaried with the hippocampus in the patient group but not with the orbital frontal cortex, supporting the hippocampal-prefrontal cortex hypothesis in schizophrenia, which stipulates poor connectivity between both regions (Weinberger, Berman, Suddath, & Torrey, 1992). These results present important implications for creating intervention programs aiming for structural (and subsequently functional) changes in the hippocampus in schizophrenia.

Limitations. In this study a 1.5 tesla MRI was used, however, to obtain better resolution, a more powerful MRI would have been more adequate, and would have allowed the precise anatomical identification of lower density regions in the hippocampus. Another limitation is the sample size for each group was not sufficient to obtain significant results at the individual group level. A study with 40 participants in each group would be adequate to support the separated group results obtained and would be more representative of the larger population (Steen, Hamer, & Lieberman, 2007).

Study 3. Exploration of Hippocampal Effective Connectivity in Schizophrenia and Control Participants While Performing a Wayfinding Task

The third paper of this dissertation is a direct continuation of the preceding papers, and explored effective connectivity seeded in the right hippocampus while performing the wayfinding task in both groups of participants. Between-group analysis revealed that the medial prefrontal cortex and parahippocampal gyrus in controls and the triangular part of the inferior frontal cortex and thalamus in patients covaried with the right hippocampus while performing the wayfinding task. This signifies that the hippocampus influences and/or

recruited these regions while completing the wayfinding task. Previous studies have found activity in the medial prefrontal cortex (Hartley, Maguire, Spiers, & Burgess, 2003) and parahippocampal gyrus (Bohbot et al., 1998; Burgess, Maguire, et al., 2001; Epstein & Kanwisher, 1998; Hartley et al., 2003) while performing a wayfinding task. Interestingly, the medial prefrontal cortex is not influenced or recruited by the hippocampus in the patient group, a result that supports the hippocampo-prefrontal pathway hypothesis in schizophrenia (Weinberger et al., 1992). Most importantly, the triangular part of the inferior prefrontal cortex, part of the VLPFC, and implicated in episodic retrieval, is recruited by the hippocampus in patients. Therefore, it can be hypothesized that this is part of a compensatory mechanism due to a contextual binding deficit. Moreover, in patients, the hippocampus recruited alternate regions to help complete the wayfinding task. More specifically the triangular part of the inferior frontal cortex (as discussed), the striatum and thalamus regions worked in-synchrony with the hippocampus while performing the task. The two latter regions have been found to be active in egocentric mental representation of the environment (Burgess, Maguire, et al., 2001). These results may reflect a compensatory mechanism, a consequence of altered hippocampal functioning, due to the contextual binding deficit seen in schizophrenia.

Limitations. As within the first study of this dissertation, it would be important to have an adequate control task to precisely understand what regions are influenced by the hippocampus while navigating. However, the control task described in the first study would not be adequate for an effective connectivity study. In Etchamendy et al. (2012) and Ledoux et al. (2013), the control task was a route following task, meaning that participants employ the same route over and over again. This task has been shown to activate striatal regions (i.e. caudate nucleus; Bohbot, Lerch, Thorndyraft, Iaria, & Zijdenbos, 2007). Hence, using such a control task would not be beneficial in an effective connectivity study, were it is possible that participants use both allocentric and egocentric mental representations of the environment (both network regions).

PPI analyses are used to investigate connectivity of a single region with the rest of the brain, to precisely study two or more regions that are hypothesized to share a common

network (e.g. hippocampus to medial prefrontal cortex). Dynamic Causal Modelling would be a more suitable technique. Hence, using PPI prevented certainty when concluding that all regions mentioned above are part of the same network or that they are part of two different networks working simultaneously together.

Summary and Integration of Results

As demonstrated in these studies, episodic memory was impaired in the schizophrenia group. More importantly there seemed to be a contextual binding deficit as demonstrated by the WMS-III family picture assessment and the wayfinding task. The immediate recall deficit results support the hypothesis of a contextual binding encoding deficit. Contextual binding neural correlates are thought to stem from the hippocampal formation, more precisely in the posterior part of the hippocampus proper (i.e. CA3 field of the hippocampus; Rolls, 2010). As demonstrated by the two first studies the hippocampus in the schizophrenia group is impaired structurally and functionally. More specifically patients demonstrated less neurofunctional activity in the posterior part of the bilateral hippocampus while performing the wayfinding task, and only in the right posterior hippocampus when controlling for performance. The posterior right hippocampal activity in the control group is supported by numerous studies performed in the field of visuospatial navigation and neuroimaging (Bohbot et al., 2007; Etchamendy et al., 2012; Hartley et al., 2003; Maguire et al., 2000). Our results demonstrate poor neurofunctionality in the posterior part of the hippocampus in the schizophrenia group, supporting the contextual binding hypothesis. The left hippocampus was also found to be more active in controls than in patients. The left hippocampus is implicated in verbal and non-verbal context-dependent episodic memory, i.e. a more general episodic memory (Burgess, Becker, King, & O'Keefe, 2001; Spiers, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001; Spiers, Burgess, Maguire, et al., 2001). The implication of the left hippocampus in the recall of episodic and autobiographical memories has been confirmed with several neuroimaging studies (Burgess, Becker, et al., 2001; Chadwick, Hassabis, Weiskopf, & Maguire, 2010; Maguire & Mummery, 1999). This result also supports the episodic memory deficit theory in schizophrenia.

Interestingly, the right hippocampus GM average differences between patients and controls are more anterior than the functional differences seen in study 1. The anterior hippocampal region (i.e. dentate gyrus) is thought to play a significant role in encoding. The reduced GM average in the anterior hippocampal region in the patient group may impair encoding and hence create the retrieval deficit seen during the wayfinding task (i.e. poor performance and poor functioning of the posterior hippocampus). It was also shown that the right anterior hippocampus also regresses with performance. Although there is a difference in locality between the fMRI and VBM results, the anterior right hippocampus cluster is the same as the one reported in Bohbot et al. (2007) and overlaps with the hippocampal region found to regress with navigation performance in Maguire et al. (2000).

Another important result in neurofunctional and GM average difference is in the prefrontal cortex when comparing both groups. Patients have less prefrontal activity while performing the task and also less GM in the prefrontal cortex, notably in the orbital prefrontal cortex. These results are supporting Weinberger et al. (1992) hippocampo-prefrontal connectivity hypothesis, which suggests that lesions to the hippocampus could lead to prefrontal cortex dysfunction.

When investigating connectivity patterns in both groups, lower WM average difference in the patient group compared to the controls was observed in the hippocampal region and in the prefrontal cortex. Two analyses were conducted to explore connectivity patterns (respectively structural and functional connectivity analysis) in schizophrenia and control participants. The superior medial GM average covaries positively with the right hippocampus GM in both groups, e.g. when the right hippocampus has greater volume, the superior medial prefrontal cortex will also have greater volume and when the right hippocampus has a lesser volume, the GM in the superior medial prefrontal cortex is smaller. It was also found that patients' GM of the right hippocampus does not correlate with the orbital prefrontal cortex as in the control group. The functional connectivity results corroborate these results, as the right hippocampus does not seem to recruit or influence the medial prefrontal cortex in schizophrenia but the triangular part of the inferior frontal cortex. Once again, the results of both analyses support Weinberger's hippocampo-prefrontal hypothesis. Taking into account

that the hippocampo-prefrontal pathway (connecting the CA1 and subiculum to the medial and orbital prefrontal cortex) plays an important role in learning and memory, by providing spatial and temporal information. The anomalies in the hippocampus might create a structural and functional deficit in the hippocampus but also in the prefrontal cortex.

Interestingly, the results seem to indicate that patients are recruiting other brain regions to perform the task. As mentioned in the third study this might be a compensatory mechanism. The derived structural and functional network in the schizophrenia group and in a previous study (i.e. Weniger & Irl, 2008) lead to the hypothesis that patients might be using egocentric representations to accomplish the task. This is thought to be due to a lack of hippocampal functioning (i.e. contextual binding) and or a lack of hippocampal connectivity.

Research and Clinical Implications

It is important to study the hippocampus in schizophrenia, as it is believed that long-term memory might be at the core of the disorder. Contextual binding is an important feature in episodic memory but also in autobiographical memory, the capacity of individuals to recollect personal events from their own lives (Riutort, Cuervo, Danion, Peretti, & Salame, 2003). Autobiographical memory has also been found to be impaired in schizophrenia (Danion et al., 1999). The contextual binding deficit can have important repercussions on the daily lives of these individuals hampering cognition, behavioural and emotional levels.

As discussed earlier, insults to the developing hippocampal region can have important repercussions on the prefrontal cortex and striatal regions. The disconnectivity theories are appealing since they tap into the neurodevelopmental theory of schizophrenia, which stipulates that prenatal insults can alter the neurodevelopmental course of the brain (Bertolino et al., 1997; Saunders, Kolachana, Bachevalier, & Weinberger, 1998) and increase the risk of developing schizophrenia in the future. In addition, lesions to the hippocampus can have altering effects on behaviour. Many researchers are hypothesizing that early hippocampal damage can result in abnormal connectivity with the prefrontal cortex (Weinberger et al., 1992). This could lead to negative symptoms and impairments in learning and cognitive abilities in the prefrontal cortex. Within the same context, insults to the

developing hippocampal region can have important repercussions on the striatal region. There is evidence that glutamatergic transmission induces several types of time-dependent modifications within the dopaminergic systems (Grace, 2000). It is believed that the connection between the hippocampal formation and ventral striatum plays a central role in schizophrenia, especially in positive symptoms (Gray, Feldon, Rawlins, Hemsley, & Smith, 1991). Gray and colleagues hypothesized a dysfunctional communication between the hippocampal formation and striatal region in schizophrenia, creating difficulties in monitoring whether the expected outcome of a motor task (e.g. the next word to be said in a sentence) matches the actual outcome (Gray et al., 1991). Along the same lines, many authors have postulated that cognitive deficits in schizophrenia are due to the inability to construct and maintain internal representations of context (Cohen & Servan-Schreiber, 1992). Considering the role of the hippocampus in memory and the fact that contextual binding is impaired in schizophrenia, one can speculate that new motor outcomes cannot be monitored or compared adequately with past or expected outcomes. This dysfunctional system (based on contextual binding creating a context-dependent processing deficit) may be at the basis of positive symptoms (e.g. disorganized thought processes and delusions; Boyer, Phillips, Rousseau, & Ilivitsky, 2007; Grace, 2000; Gray et al., 1991).

Hence, to better understand the cognitive disorder and its clinical profile in schizophrenia it would be interesting to investigate positive- and negative-symptomatic individuals with the wayfinding task and non-spatial task such as route-learning tasks. Since individuals with prominent negative symptoms tend to have more prefrontal cognitive deficits it can be hypothesized that these individuals have altered communication pathways between the hippocampal region and prefrontal cortex, resulting in poor prefrontal functioning. Likewise, the alteration of the hippocampal formation may have a direct impact on the striatum region and its functions, characterizing individuals with prominent positive symptoms. These two groups might be using different strategies within the navigation paradigm eliciting different connectivity patterns. It is important to note that this aspect did not affect the results of the third study of this dissertation since patients were stable. Nonetheless both patient groups have a hippocampal deficit compared to the healthy control population; hence training the

hippocampus in navigation paradigms might be the key for better treatment.

It is now well documented that the hippocampus is very plastic and is an ideal environment for neuroplasticity and neurogenesis. Virtual navigation training seems to be an ideal tool to increase the neuronal volume and functional abilities of the hippocampus. A well-known example is the study by (Maguire et al., 2000) which has shown that the hippocampus is larger in taxi drivers than in non-taxi drivers. Furthermore, in more recent studies Lerch et al. (2011) have shown in rats that navigation training increases the neuroanatomical volume of the hippocampus. These findings suggest that rehabilitation programs with visuospatial navigation targeting the hippocampus might be the key to increase the volume and consequently the functioning of the hippocampus. It would be important to investigate the modifications brought to the hippocampus with navigation training in a longitudinal study using sMRI, DTI and fMRI, and whether these modifications help improve the mnemonic abilities, symptoms and cognition. If such results prove to be successful these navigation training program could become part of behavioural cognitive therapy programs. Demonstrating that individuals with schizophrenia have a functional deficit in the hippocampus while performing the wayfinding task is a step forward for improving rehabilitation programs and targeted drug development.

Conclusion

In conclusion, in this dissertation it was demonstrated behaviourally, neurofunctionally and neuroanatomically that contextual binding mediated by the hippocampus is impaired in schizophrenia. Furthermore, while performing the wayfinding task, connectivity patterns seeded in the hippocampus in patients with schizophrenia were shown to be different than in the control group. All three studies support a hippocampal deficit in schizophrenia, indicating the importance to study and target this structure and connected regions (prefrontal cortex and striatum) in order to ameliorate behavioural-cognitive and pharmaceutical therapies. Lastly, in order to better understand this disorder it would be important to establish a body of positive research on the disorder. Focusing on the similarities of the functions of the brain with a healthy population rather than the differences might bring a different perspective on the disorder and help dispel societal stigma.

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