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White matter correlates of episodic memory encoding and retrieval in schizophrenia

Amity E. Green [a,*], Rodney J. Croft [b,c], Jerome J. Maller [a], Paul B. Fitzgerald [a]

[a] Monash Alfred Psychiatry Research Centre, Central Clinical School, Monash University and the Alfred Hospital, Australia
[b] Illawarra Health & Medical Research Institute, University of Wollongong, Australia
[c] School of Psychology, University of Wollongong, Australia

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ABSTRACT

Episodic memory (EM) impairments in schizophrenia (SZ) are predictive of functional outcome and are a potential endophenotype of the disorder. The current study investigated the neuroanatomical correlates of EM encoding and retrieval in SZ with structural magnetic resonance and diffusion tensor imaging (DTI) measures in 22 patients with SZ and 22 age- and gender-matched healthy controls. Tract-based Spatial Statistics (TBSS) was used to investigate microstructural alterations in white matter (WM), while FreeSurfer surface-based analysis was used to determine abnormalities in grey matter (GM) and WM volumetrics and cortical thickness. Compared to controls, patients demonstrated GM deficits in temporal and parietal regions and lower fractional anisotropy (FA) of WM in diffuse brain regions. Patients also demonstrated reduced functioning in both encoding and retention of auditory-verbal EM. Among patients but not controls, EM encoding correlated with WM volume in the orbitofrontal cortex and increased radial diffusivity in the fornix, whereas EM retrieval correlated with WM volume in posterior parietal cortex. These findings suggest a differential role for frontal and parietal WM in EM encoding and retrieval processes, while myelin integrity of the fornix may play a specific role in mediating EM encoding processes in SZ.

1. Introduction

Cognitive abnormalities in schizophrenia (SZ) are considered a core feature of the illness (Elvevag and Goldberg, 2000). Among cognitive domains affected, specific deficits in declarative episodic memory (EM) are consistently reported (Cirillo and Seidman, 2003; Pelletier et al., 2005; Valli et al., 2012). EM impairments do not appear to be related to age, medication, symptom severity or illness duration (Aleman et al., 1999; Keefe et al., 2006; Rund, 1998; Saykin et al., 1994; Thornton et al., 2006). They have been dissociated from impairments in other cognitive functions such as executive functioning and general IQ measures, suggesting that they most likely reflect inefficiencies in EM processing itself (Kopald et al., 2012). Impairments specific to EM have been reported in genetic high-risk, prodromal and first episode psychosis (Agnew-Blais and Seidman, 2013; Brewer et al., 2005; Haut et al., 2015; Whyte et al., 2006), indicating that EM impairments may be a marker for the disorder. Furthermore, EM more than any other cognitive function has been suggested to have potential as a predictor for future transition to psychosis in at-risk individuals (Valli et al., 2012). Despite relative improvement of positive symptoms with antipsychotic medications, enduring impairments in memory continue to impact patients' overall functioning and quality of life (Green, 1996; Green et al., 2000). As such there is a great deal of interest in identifying the neural mechanisms underlying memory impairment in SZ.

The formation of EM depends on successful encoding, storage and retrieval, and while EM impairment in SZ is thought to be related mainly to deficits in encoding (Cirillo and Seidman, 2003; Danion et al., 2007), the relative contribution of these sub-processes and their neural underpinnings are not well understood. In healthy subjects, the hemispheric encoding retrieval asymmetry (HERA) model suggests a differential role for left prefrontal cortex during episodic encoding and semantic retrieval, and right prefrontal cortex for episodic retrieval (Tulving et al., 1994). Further to this, positron emission tomography (PET) studies have demonstrated a specific role for hippocampal subregions during episodic encoding and retrieval, with the rostral portion of the hippocampus subserving EM encoding processes, and the caudal portion differentially associated with EM retrieval, known as the

* Correspondence to: Monash Alfred Psychiatry Research Centre, Level 4, 607 St Kilda Rd, Melbourne, Victoria 3004, Australia.
E-mail address: amity.green@monash.edu (A.E. Green).

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Hippocampal Encoding/Retrieval (HIPER) model (Lepage et al., 1998).

Several functional imaging studies have investigated episodic encoding and retrieval in SZ, providing evidence that processes within these models may be dysfunctional in the disorder. For example, in a study that used PET to measure cerebral blood flow during verbal encoding and recognition, control participants showed extensive frontal activation (including activation in the left frontal pole, left dorsolateral prefrontal cortex (DLPFC) and bilateral Broca's area) and activation in posterior cingulate during encoding, with a similar pattern of frontal activation observed during recognition (Ragland et al., 2004). Patients however, displayed bilateral frontal deficits with no significant activation in the same frontal areas that were demonstrated in healthy controls during encoding. Furthermore, during retrieval patients showed normal right prefrontal activation while impairments in left hemisphere activation were observed (Ragland et al., 2004). Thus it could be concluded that EM impairment in SZ may be the result of a failure to adequately encode stimuli as demonstrated by a lack of frontal activation during the encoding process.

Conventional MRI techniques have demonstrated regional grey matter (GM) changes in subcortical structures in the medial temporal lobe (MTL), in addition to abnormal activity in functionally related MTL and frontal structures that have been associated with EM impairments in SZ (Achim and Lepage, 2005; Eldridge et al., 2005; Mathew et al., 2014; Yonelinas et al., 2005). In addition to regional brain abnormalities, a leading hypothesis suggests that it is a dysfunction in communication and connectivity in anatomical WM among these brain regions that underlies functional abnormalities seen in SZ (Friston, 1999).

Magnetic resonance diffusion tensor imaging (DTI) is a non-invasive technique for measuring the microstructural properties of WM by detecting the direction and diffusion of water molecules along major WM fibre bundles in the brain (Pierpaoli et al., 1996). There are several ways in which the microstructural properties of WM can be measured. Fractional anisotropy (FA) is an index of the degree to which water diffuses in a specific and consistent direction (Basser et al., 1994), whereas radial diffusivity (RD) measures are thought to reflect microstructural properties of myelin (Song et al., 2005). Similarly, axial diffusivity (AxD) measures the primary vector of the diffusion and has been suggested as an index of axonal damage (Sun et al., 2006).

DTI studies in SZ have demonstrated widespread abnormalities in WM projection, commissural, and association fibres (for review see Fitzsimmons et al., 2013). Moreover, widespread alterations in WM have been associated with clinical symptomatology and poorer neurocognitive performance (Roalf et al., 2015). Studies using DTI have specifically demonstrated WM abnormalities in SZ that are related to measures of EM, including FA abnormalities in bilateral anterior limbs of the internal capsule (ALIC) (Levitt et al., 2012; Rosenberger et al., 2012), and in inferior longitudinal fasciculus (ILF) and inferior fronto-occipital (IFO) tracts (Liu et al., 2013). Other studies have shown microstructural alterations of major WM bundles of the limbic system, including uncinate fasciculus and fornix, that are associated with deficits in visual and verbal learning and memory, in both recent onset and chronic SZ (Nestor et al., 2004, 2007, 2008; Szeszko et al., 2008; Takei et al., 2008). These findings suggest that EM impairments in SZ may be the result of disrupted connectivity between MTL and frontal cortex, however, how the structures connecting these brain regions differentially subserve encoding and retrieval processes in EM is not known. Therefore the aim of the present study was to investigate the neuroanatomical correlates of EM encoding and retrieval in SZ. It was hypothesised that compared to healthy controls, patients would demonstrate regional GM deficits and abnormalities in WM diffusion measures in frontal and MTL areas, and that these deficits would be differentially associated with EM encoding and retrieval performance in a pattern that diverged from healthy controls.

2. Materials and methods

2.1. Participants

Twenty-two patients with SZ (n=18) or schizoaffective disorder (n=4) and 22 age- and gender-matched healthy comparison subjects were recruited for this study (Table 1). Patients were recruited through outpatient clinics of the Alfred Hospital, the Monash Alfred Psychiatry Research Centre participant database, and from the general community. Patients were clinically stable with no current hospitalisation and no change to medication for at least 4 weeks prior to inclusion in the study. Current clinical symptoms were assessed using the Positive and Negative Symptom Scale (PANSS; Kay et al., 1987) and the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1990), and diagnosis was confirmed using the MINI International Neuropsychiatric Inventory (MINI; Sheehan et al., 1998). All patients were receiving antipsychotic medication at the time of testing (risperidone 5; olanzapine 3; aripiprazole 4; quetiapine 1; amisulpride 2; ziprasidone 1; zuclopenthixol 4; flupenthixol 1; haloperidol 1). Healthy control participants were recruited from the general community and were screened for Axis I psychiatric disorders using the MINI screen. Patients and controls were excluded on the basis of history of serious head injury (defined as having caused loss of consciousness), neurological conditions, or contraindication to MRI scanning. Two participants were excluded from the final analysis. We excluded data from one patient with SZ due to the finding of an incidental abnormality, and from one healthy control participant due to head size being beyond the field of view of the receiver array. All participants provided written informed consent and the protocol was approved by the Alfred Hospital and Monash University Human Research Ethics Committees.

2.2. Assessments

EM assessment included Prose Passages (PP) immediate and delayed recall (Sullivan, 2005). PP stories are prose-recall passages for the assessment of auditory-verbal EM. The psychometric properties of the PP stories test has been demonstrated to be comparable to the Logical Memory subscale of the Wechsler Memory Scale-Revised (Wechsler, 1997). PP delayed recall was assessed approximately 40 min after administration and assessment of immediate recall. Demeaned scores for PP immediate recall were used as an index of encoding. In order to dissociate deficits in memory that result from impairments in storage and retrieval processes, as opposed to those that result from impairments in encoding, retention ratio for delayed recall was calculated by dividing immediate recall scores by delayed recall scores (Maller et al., 2007). A retention ratio of 1 suggests perfect retrieval, and that no forgetting has occurred during the retention interval, whereas ratios <1 indicate some impairment in storage or retrieval processes.

Additionally, neuropsychological assessment included the CogState Schizophrenia Battery (CSSB) (Pietrzak et al., 2009) from which composite z scores were derived, as a measure of overall cognitive functioning. The CSSB has been developed to provide a brief computerised measurement of the cognitive domains considered important in determining the presence of treatment effects in schizophrenia (Nuechterlein et al., 2004). In order to calculate composite scores for CSSB data, first standardised scores were calculated for each participant on each test (participant$_x$ score on test$_y$ – control mean for test$_y$/control group standard