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Examining hippocampal function in schizophrenia using a virtual reality spatial navigation task

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ABSTRACT

Background: Structural pathology in the hippocampus is well-documented in schizophrenia, but brain functional changes have not been consistently found. We used spatial navigation in a virtual reality environment, a task that is known to produce robust hippocampal activation in healthy subjects, to examine task-related activations and de-activations in the disorder.
Methods: Twenty-seven DSM IV schizophrenia patients and 32 healthy controls underwent fMRI while they navigated to a goal through a virtual reality town. Activations and de-activations were examined at the whole brain level and also using a region-of-interest (ROI) in the hippocampus.
Results: Spatial navigation was associated with activation in the posterior hippocampus and parahippocampal gyrus plus widespread neocortical areas. The patients showed reduced activation compared to the controls in the left dorsolateral prefrontal cortex (DLPFC) and the left occipital/temporal cortex. No differences in hippocampal activation were seen either at the whole-brain level or in the ROI analysis. The patients showed failure of de-activation affecting some but not all subregions of the default mode network.
Conclusions: Schizophrenia is associated with task-related hypoactivation in the DLPFC during spatial navigation, but not with functional changes in the hippocampus. The failure of de-activation also found adds to evidence for default mode network dysfunction in the disorder.

1. Introduction

Several lines of evidence have implicated the hippocampus and related medial temporal lobe structures such as the entorhinal cortex/parahippocampal gyrus in schizophrenia. Structural MRI studies have found that the hippocampus is one of the areas of greatest areas of volume reduction in the disorder (Haijma et al., 2013). Although claims for microscopic structural changes in the hippocampus and parahippocampal gyrus have not stood the test of time (Harrison, 1999), synaptic pathology in the former structure is a well-replicated finding (Harrison, 2004). Finally, the hippocampus is crucial for long-term memory which, along with executive impairment, is one of the major areas of neuropsychological impairment in schizophrenia (Palmer et al., 2009; Reichenberg and Harvey, 2007).

Whether the hippocampus shows functional brain abnormality in schizophrenia is less clear. A meta-analysis of 18 functional imaging studies examining patients during performance of episodic memory tasks (Achim and Lepage, 2005) identified the left inferior prefrontal cortex as the main area of difference from controls; reduced activation in the right hippocampus was also found, but only during encoding and not during retrieval. A subsequent meta-analysis that pooled data from a somewhat different set of studies (Ragland et al., 2009) failed to confirm the finding of reduced hippocampal activation, but instead found greater activation in the parahippocampal gyrus during encoding and retrieval. Most recently, a large study of 62 schizophrenia patients and 181 healthy controls by Rasetti et al., (2014) using an incidental memory encoding paradigm found reduced activation in the parahippocampal gyrus in the patients, among other regions. In a subsequent region-of-interest (ROI) analysis in a subsample of 54 patients and controls reduced activation was also seen in the hippocampus.

Following O'Keefe and Nadel's (1978) demonstration of place cells in the hippocampus and the more recent finding of grid cells in the

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entorhinal cortex (Moser et al., 2008), there is a consensus that these structures mediate spatial navigation in animals. In humans, functional imaging studies using navigation tasks, particularly those using so-called allocentric tasks, where the subject has to find his/her way through an environment using landmarks as cues, have regularly found activation in the hippocampus (Gron et al., 2000; Hartley et al., 2003; Igloi et al., 2010; Maguire et al., 1998; Orban et al., 2006; Parslow et al., 2004; Peigneux et al., 2004; Rauchs et al., 2008; Xu et al., 2010) and/or the parahippocampal gyrus (Aguirre et al., 1996; Gron et al., 2000; Hartley et al., 2003; Marsh et al., 2010; Orban et al., 2006; Parslow et al., 2004; Shipman and Astur, 2008; Xu et al., 2010), along with other areas such as the retrosplenial cortex, the parietal lobe and the prefrontal cortex (for a meta-analysis see Boccia et al., 2014). To date, only one study has employed the navigation paradigm to examine hippocampal/parahippocampal activation in schizophrenia: Ledoux et al. (2013) compared 21 patients and 22 healthy controls while they navigated towards a goal in a previously explored virtual reality town by means of landmarks such as a school and a hospital. Whole-brain analysis revealed reduced activation in the left dorsolateral prefrontal cortex (DLPFC) in the patients, but not in the hippocampus. Reduced hippocampal activation was detected, however, when the voxel-based analysis was repeated within an area masked to this structure bilaterally.

Since 2001 it has been recognized that some brain regions de-activate rather than activate during performance of attention-demanding cognitive tasks (Gusnard and Raichle, 2001; Raichle et al., 2001). These regions, collectively known as the default mode network, include the medial prefrontal cortex, the posterior cingulate cortex/precuneus, parts of the parietal and temporal lobe cortex and also the hippocampus (Buckner et al., 2008). According to an increasing body of evidence, failure of default mode network de-activation is a feature of schizophrenia, where it has been documented during performance of working memory tasks (Dreher et al., 2012; Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009), and also during attentional (Mannell et al., 2010), response inhibition (Schneider et al., 2011) and facial emotion (Salgado-Pineda et al., 2011) tasks. The failure is seen particularly the medial frontal cortex, but has also sometimes been found to affect the posterior cingulate gyrus/precuneus (Salgado-Pineda et al., 2011; Schneider et al., 2011) and in one study the hippocampus (Dreher et al., 2012). The behaviour of the default mode network during spatial navigation in schizophrenia is unknown, but is of interest given that this task normally activates rather than de-activates the hippocampus; and also because another area activated by navigation tasks, the retrosplenial cortex, overlaps substantially with another part of default mode network, the posterior cingulate cortex (Vann et al., 2009).

This study used a virtual reality spatial navigation task to examine activations and de-activations in schizophrenia. We carried out analyses at the whole-brain level and also examined the hippocampus using a region of interest (ROI) approach. We hypothesised that patients with the disorder would show evidence of reduced activation in the hippocampus and/or related structures like the parahippocampal gyrus, as well as in the prefrontal cortex, given that this region is a traditional site of abnormality in schizophrenia and has been found to activated by spatial navigation. We anticipated that performance of the task would lead to de-activation in all or part of the default mode network in the healthy controls, and that a failure of de-activation would be evident in the patients with schizophrenia.

2. Method

2.1. Participants

The patient sample consisted of 27 right-handed patients with schizophrenia, recruited from hospitals of the Hermanas Hospitalarias Group in Barcelona, and 32 healthy controls. These sample sizes have revealed robust activation and de-activation differences between patients with schizophrenia and healthy controls in our previous studies using other paradigms (e.g. Guerrero-Pedraza et al. 2012; Ortiz-Gil et al. 2011; Pomarol-Clotet et al. 2008); additionally, power calculations

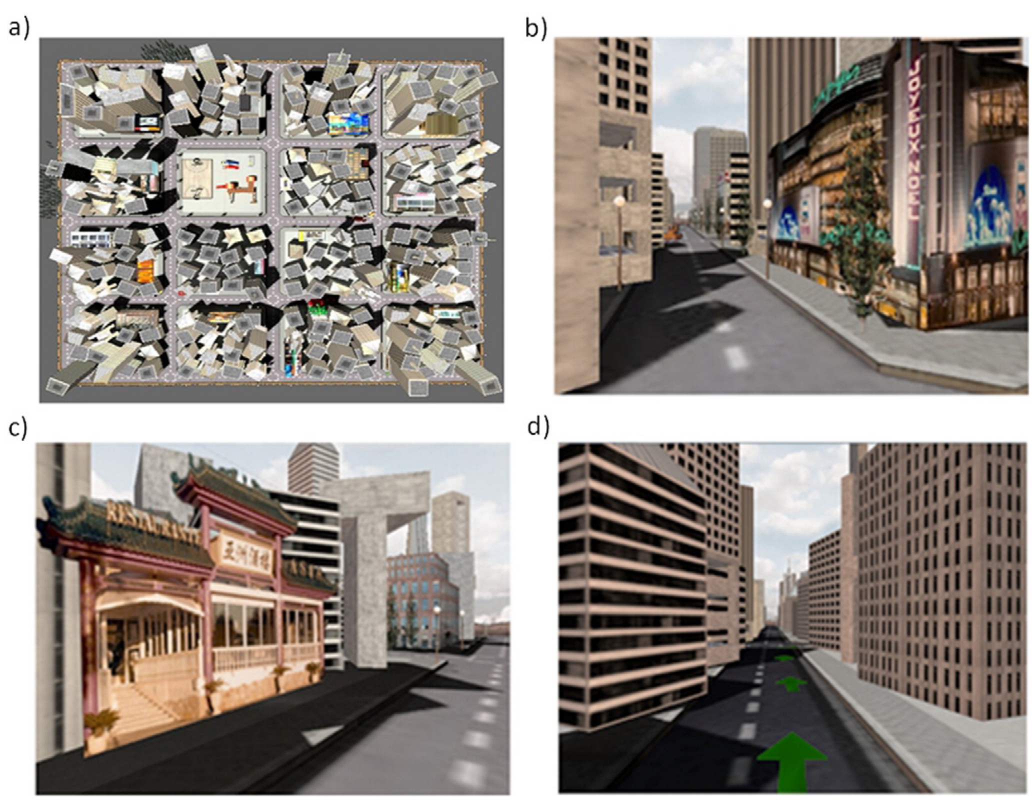

Fig. 1. The spatial navigation task: (a) view of the town from above; (b) example of cue-guided navigation; (c) the goal; (d) example of the control condition.