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Hippocampal volume in subjects at clinical high-risk for psychosis: A systematic review and meta-analysis

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ABSTRACT

Several magnetic resonance imaging studies have reported reductions in hippocampal volume in patients with psychosis. It is unclear whether structural abnormalities predate illness onset.

We conducted a detailed, systematic literature search for studies reporting hippocampal volume in subjects with clinical high-risk, compared to healthy controls. The overall sample size comprised 1429 subjects.

Meta-analysis revealed no difference for left, but a small, albeit significant, difference for right hippocampal volume, such that clinical high-risk patients had slightly smaller hippocampal volume than healthy controls ($g = 0.24$, $p = 0.0418$). Meta-regression indicated a moderating effect of manual tracing approach, due to one outlying site. The small difference on the right side did not remain significant ($g = 0.14$, 95%CI = [−0.03–0.32], $p = 0.11$) after removal of this outlier.

This meta-analysis suggests that there is no reduction in hippocampal volume before transition to psychosis and hippocampal volume cannot be used as a biomarker in clinical high-risk individuals.

Contents

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1. Introduction

The hippocampus is a key brain region in the pathophysiology of psychosis and structural and functional changes in the hippocampus have been consistently reported in psychotic patients (Adriano et al., 2012; Shenton et al., 2001; Tamminga et al., 2010; van Erp et al., 2015).

The hippocampus is especially involved in the constructive process of spatial and declarative memory – the ability to learn, store, and retrieve information (Loureiro et al., 2012). The latter is of particular interest in psychosis and deficits are widely recognised as a consistent and critical component of schizophrenia (Heckers, 2001; Ragland et al., 2015; Rasetti et al., 2014).

Several subregions have been differentially associated with deficits associated with psychosis. The anterior or ventral parts of the hippocampus seem to be involved in affective and cognitive deficits (Gothelf et al., 2000), as well as other complex behaviours such as stress, emotion (mediating anxiety-related behaviours), sensory–motor integration and goal-directed activity (Small et al., 2011; Strange et al., 2014). Several different studies have demonstrated that the posterior or dorsal hippocampus is more likely to be involved in memory and cognitive processing (Small et al., 2011). There is considerable evidence for abnormalities in the posterior hippocampus in schizophrenia (Lipska et al., 1993). It has also been hypothesised that dopaminergic psychotic features may be driven by abnormally heightened hippocampal activity (Grace, 2012; Tamminga and Zukin, 2015).

Meta-analysis in patients with diagnosed schizophrenia found significant bilateral reduction in hippocampal volume compared to healthy controls (Adriano et al., 2012; van Erp et al., 2015). However, in other neuropsychiatric disorders too, including major depressive disorder, anxiety disorder, bipolar disorder, and schizophrenia, meta-analysis of the relation between hippocampal volume and the BDNF rs6265 genotype revealed that patients had smaller hippocampal volume than healthy controls, regardless of the genotype (Harrisberger et al., 2015).

Many factors are likely to underlie hippocampal abnormalities in patients with psychosis (including dose and duration of antipsychotic treatment, and numerous other confounding factors associated with the experience of the disorder). This is the reason why it is crucial to define whether these abnormalities are already present in patients with clinical high-risk for psychosis.

Multivariate models incorporating risk factors from clinical, demographic, neurocognitive, and psychosocial assessments achieve high levels of predictive accuracy in help-seeking high-risk individuals (Cannon, 2015). An individualised risk calculator that could improve clinical decision making is available (Cannon, 2015). Unfortunately, these assessments are sophisticated and time-consuming. There is therefore a strong imperative to develop a biomarker for clinical high-risk that can be easily and objectively obtained as part of a routine screening exam and with minimum discomfort or risk to the patient. Measurement of hippocampal volume meets all these criteria.

A review of hippocampal volume considering all types of high-risk subjects (Ganzola et al., 2014), and using three different classes of subjects, based on (1) the sole presence of psychotic symptoms, (2) all kinds of risk factors (including low IQ, and high scores in either the Structured Interview for Schizotypy and Child Behavior Checklist or both), and (3) presence of combined risk symptoms, did not systematically assess patients with established criteria of clinical high-risk for psychosis (Fusar-Poli et al., 2015), and furthermore did not consider overlapping samples (Ganzola et al., 2014). Thus, no conclusive results could be achieved, aside from some vague evidence for hippocampal abnormalities preceding schizophrenia onset. In this meta-analysis, we wanted to focus on clinical high-risk individuals categorised by established criteria (Häfner et al., 1992; Miller et al., 2003; Riecher-Rössler et al., 2007; Schultze-Lutter, 2009; Yung et al., 2005, 1996), as these patients have about a 18%-36% risk of developing psychosis after 6 months to 3 years (Fusar-Poli et al., 2012a). Furthermore, research on the clinical high-risk for psychosis has progressed exponentially and preventive therapy is now possible (Fusar-Poli et al., 2013a).

A range of neuroimaging techniques showed alterations in brain structure (DeLisi, 2008; Kempton et al., 2010; Mechelli et al., 2011), function (Fusar-Poli et al., 2007), and neurochemistry (Howes et al., 2007) in patients with clinical high-risk for psychosis (Borgwardt et al., 2011; DeLisi, 2011; Fusar-Poli and Borgwardt, 2012). These neuroimaging studies have shown that alterations in brain anatomy found in established psychosis are also present in people with a clinical high-risk (Smieskova et al., 2010). Overall, these patients exhibit qualitatively similar, but less pronounced, structural brain abnormalities than patients with established psychosis.

Individual MRI studies in clinical high-risk individuals may be biased because they are typically obtained in small samples, are heterogeneous and may contain contradictory results. Thus, a meta-analytic study should be useful to clarify whether hippocampal volume is reduced in patients with a clinical high-risk for psychosis. This could support the neurodevelopmental theory of psychosis (Lewis and Levitt, 2002; Rapoport et al., 2012) and would be a putative biomarker. On the other hand, if there is no reduction in hippocampal volume, this would tend to support the neurodegenerative theory of psychosis (Lieberman, 1999), according to which, hippocampal volume is only reduced around or after the transition to psychosis.

One important issue is the MRI technique used to measure hippocampal volume. We wished to focus on hippocampal volume, which is obtained using the region of - interest (ROI) method. The volume of the structure (in mm^3) is considered by accurately identifying its boundaries (Spoletini et al., 2011; Velakoulis et al., 1999). Investigators commonly use the measurement of manually delineated, anatomically defined ROI to assess and localize grey matter disruptions. The main advantage of manually selecting ROI is that the method is not susceptible to artefacts deriving from interfaces between bone, brain and air in the orbitofrontal areas. Although manually delineate anatomical regions might bear some inaccuracy when very small areas are investigated, ROI analyses were in general praised to enjoy substantial anatomic validity (Perlini et al., 2012). As the manual segmentation is highly time consuming, automated methods introduce substantial gains. On the other hand, the implementation of those methods is a challenge because