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Hippocampus and amygdala volumes in children and young adults at high-risk of schizophrenia: Research synthesis

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ABSTRACT

Background: Studies have reported hippocampal and amygdala volume abnormalities in schizophrenic patients. It is necessary to explore the potential for these structures as early disease markers in subjects at high risk (HR) of schizophrenia.
Methods: We performed a review of 29 magnetic resonance imaging (MRI) studies measuring hippocampal and amygdala volumes in subjects at HR for schizophrenia. We reclassified subjects in 3 new HR categories: presence of only risk symptoms (psychotic moderate symptoms), presence of only risk factors (genetic, developmental or environmental), and presence of combined risk symptoms/factors.
Results: Hippocampal volume reductions were detected in subjects with first episode (FE) of psychosis, in all young adults and in adolescents at HR of schizophrenia. The loss of tissue was mainly located in the posterior part of hippocampus and the right side seems more vulnerable in young adults with only risk symptoms. Instead, the anterior sector seems more involved in HR subjects with genetic risks. Abnormal amygdala volumes were found in FE subjects, in children with combined risk symptoms/factors and in older subjects using different inclusion criteria, but not in young adults.
Conclusion: Hippocampal and amygdala abnormalities may be present before schizophrenia onset. Further studies should be conducted to clarify whether these abnormalities are causally or effectually related to neurodevelopment. Shape analysis could clarify the impact of environmental, genetic, and developmental factors on the medial temporal structures during the evolution of this disease.

Contents

Abbreviations: AG, amygdala; AHC, amygdala–hippocampal complex; HC, hippocampus; FE, first episode; HR, high risk; HRp, high risk subject psychotic at follow-up; HRnp, high risk subject non-psychotic at follow-up; MRI, magnetic resonance imaging; IQ, Intelligence Quotient; y.o., years old.

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1. Introduction

Several studies in the literature focus on finding early disease markers of schizophrenia, with the goal to detect subjects in a preclinical phase in order to plan pre-onset interventions. One such putative marker is structural neuroimaging, as, for example, measurements obtained from magnetic resonance imaging (MRI). Authors have reported reduced total brain and gray matter and increased ventricular volumes in schizophrenic patients compared to controls (Shenton et al., 2001; Steen et al., 2006). Reductions have also been observed in the hippocampus (HC), amygdala (AG), and superior temporal gyri (Lawrie and Abukmeil, 1998; Nelson et al., 1998), in the prefrontal cortex and thalamus (Konick and Friedman, 2001), in the anterior cingulate gyrus (Baiano et al., 2007), and the corpus callosum (Woodruff et al., 1995) between these two groups. Total brain volume reductions are subtle and close to the detection thresholds of current MRI methods however (~3%) (Wright et al., 2000), while changes are larger in the hippocampus (~8%) (Wright et al., 2000) and in the amygdala (6–10%) (Lawrie and Abukmeil, 1998; Nelson et al., 1998; Wright et al., 2000).

It has been shown that medial temporal lobe reductions correlate with memory impairment (Antonova et al., 2004) and that structural, functional, and neurochemical abnormalities in the hippocampus have been related to impairment in declarative memory function in schizophrenic patients (Weiss and Heckers, 2001), as well as an important vulnerability indicator for this disorder (McCarley et al., 1993; Seidman et al., 2002, 2003; Tamminga et al., 2010). Further, smaller amygdala volumes seem to be related to reduced emotional expression and emotion recognition in schizophrenic subjects (Aleman and Kahn, 2005). Hippocampal and amygdala volume reductions are also seen in the unaffected relatives of schizophrenic probands (Seidman et al., 1999; O'Driscoll et al., 2001; Van Erp et al., 2002; Boos et al., 2007) and in first-episode (FE) of schizophrenia (Joyal et al., 2003; Vita, 2007; Adriano et al., 2011).

1.1. High risk subjects

Many recent studies have analyzed HC and AG volumes in young subjects at high risk for schizophrenia, based on the dual hypotheses that within this group of subjects, many are, in fact, in a prodromal period, and that later changes in MRI measures would be apparent in that prodromal period.

Thus, in recent years, 'high-risk' strategies have been helpful in assessing brain structural and functional changes surrounding the onset of psychosis and schizophrenia. These have largely been undertaken in two ways, one based around genetic risk, and a second based on the identification of prodrome from clinical symptoms (Olsen and Rosenbaum, 2006).

Within the genetic risk paradigm, Boos et al. conducted a meta-analysis of family studies in schizophrenia and showed that first-degree relatives had lower hippocampal, total gray matter, and ventricular volumes, compared with healthy volunteers (Boos et al., 2007). Other studies considering only genetic risk provide an overview of brain changes in subjects with high risk for schizophrenia (Keshavan et al., 1997, 2002; Whalley et al., 2005; Lawrie et al., 2008; Moran et al., 2013) reporting abnormalities mainly in the frontal and temporal regions.

To our knowledge, only Jung et al. have proceeded with systematically reviewing the literature for MRI studies considering all type of HR subjects (Jung et al., 2010). The authors concluded that abnormalities in prefrontal, temporal and anterior cingulate cortices occur before illness onset, but they did not report their findings from a neurodevelopmental perspective, but rather simply as differences between controls, HR and patients.

2. Objective

We aim to review published evidence regarding HC and AG volumetric differences in HR subjects for schizophrenia.

The objective was to determine if hippocampal and amygdala volumes differ in HR individuals in order to understand whether these volumes can help in the early detection and clinical intervention of schizophrenia.

As is the case with many major neuropsychiatric illnesses, the typical age of onset for schizophrenia is late adolescence or early twenties, with a slightly later onset in females (Hafner et al., 1994). Neuroimaging studies that focus on this age range may provide unique insights into the onset and course of psychosis. Based on this finding, we examined evidence from studies spanning ages from early childhood to young adulthood.

We chose to focus our review solely on the hippocampus and amygdala because: (i) they are both part of the limbic circuit involved in schizophrenia pathology; and (ii) there is evidence that they are both affected in schizophrenia. Our intent was to address issues of heterogeneity in the HR concept, including age, and to analyze results taking into account different risk factors and neurodevelopmental stages.

3. Methods

Studies were included in our research synthesis if they met the following criteria:

(1) Papers had to be drafted in English;
(2) Papers were original works (i.e. no review);
(3) Subjects were defined as "high risk", "ultra-high risk" or "at-risk mental state" to develop schizophrenia;
(4) High risk subjects were between 8 and 30 years of age (group mean age). As we stated earlier, the aim of the present review is to provide an overview of hippocampal and amygdala changes between childhood and young adult period;
(5) Structural magnetic resonance imaging techniques analyzing cerebral gray matter were used to obtain information specifically on the HC, AG or both (HC/AG complex).

We conducted an extensive PUBMED search for online listings from 1990 until January 2014 using the following keyword combinations: "schizo* [ti] AND risk [ti] AND MRI"; "schizo* [ti] AND offspring* [ti]