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# Neuroimaging hippocampal subfields in schizophrenia and bipolar disorder: A systematic review and meta-analysis

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ABSTRACT

The hippocampus is a complex structure consisting of subregions with specialized cytoarchitecture and functions. Magnetic resonance imaging (MRI) studies in psychotic disorders show hippocampal subfield abnormalities, but affected regions differ between studies. We here present an overview of hippocampal anatomy and function relevant to psychosis, and the first systematic review and meta-analysis of MRI studies of hippocampal subfield morphology in schizophrenia and bipolar disorder. Twenty-one MRI studies assessing hippocampal subfield volumes or shape in schizophrenia or bipolar disorder were included (n 15–887 subjects). Nine volumetric group comparison studies (total n = 2593) were included in random effects meta-analyses of group differences. The review showed mixed results, with volume reductions reported in most subfields in schizophrenia and bipolar disorder. Volumetric studies using ex-vivo based image analysis templates corresponded best with the shape studies, with CA1 as the most affected region. The meta-analyses showed volume reductions in all subfields in schizophrenia and bipolar disorder compared to healthy controls (all $p < .005$; schizophrenia: $d = 0.28$-$0.49$, bipolar disorder: $d = 0.20$-$0.35$), and smaller left CA2/3 and right subiculum in schizophrenia than bipolar disorder. In conclusion, the hippocampal subfields appear to be differently affected in psychotic disorders. However, due to the lack of control for putative confounders such as medication, alcohol and illicit substance use, and illness stage, the results from the meta-analysis should be interpreted with caution. Methodological subfield segmentation weaknesses should be addressed in future studies.

## 1. Introduction

Recently, studies from the Enhancing Neuroimaging Genetics through Meta-Analysis Consortium (ENIGMA; http://enigma.ini.usc.edu) have in the hitherto largest magnetic resonance imaging (MRI) studies of patients with schizophrenia (Okada et al., 2016; van Erp et al., 2016) and bipolar disorder (Hibar et al., 2016) reported the hippocampus to be the most reduced of all subcortical brain structure volumes in both disorders. In the few studies that directly compared across the two disorders, the magnitude of the hippocampus volume reduction was greater in schizophrenia than in bipolar disorder (Arnold et al., 2015; Rimol et al., 2010).

Over the last years, methods for automated hippocampal subfield segmentation have been developed, offering possibilities for detailed and valid characterizations of anatomically and functionally distinct parts of the hippocampus. This hold promises for identifying signatures for subregion involvement in different clinical conditions, including schizophrenia and bipolar disorder, and allow for hypotheses about mechanistic biological explanations of the role of hippocampus in these disorders, which etiologies remain to be elucidated.

### 1.1. Hippocampal anatomy

The neuroanatomy of the hippocampus is complex and reflects a

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high degree of specialization of cellular layers, circuitry and function. Histologically, the hippocampal formation consists of the hippocampus proper with its distinct subfields (Cornu ammonis (CA) 1–3) and dentate gyrus (DG) (including the CA4 as polymorph layer), and the other regions within the hippocampal formation; the subiculum complex and the entorhinal complex, and extends into the perirhinal and parahippocampal medial temporal lobe cortices (Amaral and Lavenex, 2007). The subfields are demarked based on distinct cytoarchitectonic differences with functional specialization and overlap (Schultz and Engelhardt, 2014). The subfields consist mainly of one pyramidal cell layer, but CA1 has two cell layers and a poorly defined border with CA2. The pyramidal cell layer of CA1 overlaps that of the subiculum forming a complex transitional zone. The DG is densely packed with granule cells. Myelinated axons originating in the pyramidal neurons of the hippocampus and subiculum, travel in the alveus, merge into the fimbria, continue in the fornix and fuses in the corpus callosum. The hippocampus itself has a relatively low degree of myelination (Berger and Frotscher, 1994).

In schizophrenia and bipolar disorder, histological postmortem studies of the hippocampus have shown several abnormalities compared to healthy controls, including smaller pyramidal neuron bodies (Harrison, 2004; Liu et al., 2007), and reduced dendritic spine density (Kolomeets et al., 2007), number of oligodendrocytes (Falkai et al., 2016a; Schmitt et al., 2009), and interneuron density and number (Konradi et al., 2011a, 2011b; Wang et al., 2011). The findings differ between subfields. In schizophrenia, CA4 has been found to show more prominent pyramidal soma reduction than CA1 (Konradi et al., 2011a), there is decreased number of mossy fiber synapses in the CA3 (Kolomeets et al., 2007), and hippocampal CA4 and dentate gyrus volumes have been found to be smaller in post-mortem studies (Falkai et al., 2016a; Schmitt et al., 2009). In bipolar disorder, significant reductions of somatostatin-positive neurons in CA1 only and parvalbumin-positive neurons in CA1 and CA4 have been found (Konradi et al., 2011b). Cytoarchitectonic differences between the two disorders have been reported in the presubiculum, with reduced somatostatin positive neuron density in schizophrenia compared to bipolar disorder (Wang et al., 2011). Compared to controls, patients with bipolar disorder had significantly more neurons in the cornu ammonis subfield 1 (CA1) and the subiculum, while the number of oligodendrocytes was higher only in CA1 (Malchow et al., 2015). Increased cell numbers could suggest a denser packing of neurons and oligodendrocytes as a result of a decreased neuropil.

### 1.2. Hippocampal function

Hippocampus is involved in multiple cognitive functions, but plays a key role in learning and episodic memory (Squire and Wixted, 2011). There is however a functional division between the ventral/anterior hippocampus, which appears to be important for emotion regulation and stress responses, and the posterior parts, which seem to be more important for visuospatial orientation and memory (Fanselow and Dong, 2010). The process of pattern completion (i.e. the ability to retrieve a complete pattern of activity or memory from incomplete input), has been associated with the CA3, whereas pattern separation (i.e. the ability to distinguish and store similar inputs in a distinct, non-overlapping fashion) mainly takes place in the DG (Knierim and Neunuebel, 2016; Yassa and Stark, 2011).

The role of the hippocampus in schizophrenia or bipolar disorder neuropathology is not understood, but it has been suggested that connectivity disruptions in local and external hippocampal circuits are important to the formation of psychotic symptoms and thought content (Tamminga et al., 2010). An animal model of psychosis showed that hippocampal hyperactivity leads to hyperdopaminergia in the striatum which may affect correct salience attribution and play a role in the development of hallucinations and delusions (Lodge and Grace, 2011). Subjects with an ultra high risk for developing psychosis have a disrupted relationship between hippocampal glutamate levels and striatal dopamine levels (Stone et al., 2010). Moreover, reduced glutaminergic signaling in the DG has been associated with diminished pattern separation, which in combination with increased CA3 associational activity and accelerated pattern completion has been suggested to cause delusions and thought disorders (Tamminga et al., 2012). In addition, lower oligodendrocyte number in CA4 has been associated with cognitive deficits in schizophrenia patients (Falkai et al., 2016b).

### 1.3. Hippocampal plasticity

The hippocampus displays prolonged high neuroplasticity relative to most other brain structures. The subgranular layer of the DG of the hippocampus is a neurogenic zone showing adult neurogenesis with increased granule cell proliferation in response to stimulation such as aerobic exercise (Kandola et al., 2016), alcohol (Stragier et al., 2015), ischemia (Ortega-Martinez, 2015) and medication (Rajkowska et al., 2016). The adult neurogenesis is likely to be important for learning and memory, but has also been suggested to play a significant role in neurodegenerative and psychiatric disorders (Balu and Lucki, 2009; Ortega-Martinez, 2015). A recent post mortem study showed reduced number of neurons in the DG of patients with schizophrenia (Falkai et al., 2016a), which supports previous findings of decreased hippocampal stem cell proliferation in schizophrenia (Allen et al., 2016; Reif et al., 2006). Animal and human translational studies have characterized an immature DG with elevated calretinin and reduced calbindin expression in schizophrenia and bipolar disorder (Kohen et al., 2014; Walton et al., 2012), which further supports impaired neurogenesis to be of importance in both diseases. However, despite the fact that the adult born hippocampal neurons have enhanced synaptic plasticity and that neurogenesis may affect hippocampus related functions (Spalding et al., 2013), it is not clear to which extent the hippocampal neurogenesis affects subfield volume or shape.

### 1.4. MR imaging of hippocampal subregions

Advances in neuroimaging methods, including high-resolution MRI and continuously developing analysis software, allow for non-invasive *in vivo* visualization and quantitative macro-anatomical characterization based on differences in tissue properties of specific brain structures. Since the hippocampus is sideways rolled up like a Swiss roll, it is difficult to visualize and segment into subcomponents. The MRI resolution alone has not been sufficient to reliably differentiate hippocampal subfields, but there are studies that have combined cyto- and chemoarchitectural features with macroscopic landmarks in order to better separate across different subfields on MR-images (Ding and Van Hoesen, 2015). As there is an increasing push towards larger samples to obtain adequate statistical power (Button et al., 2013), manual delineation of hippocampal subfields, which is time-consuming to master and perform, is becoming less viable. Moreover, although manual segmentation certainly has its advantages, it involves some degree of subjectivity and such variability poses a challenge for replication (Schlichting et al., 2017). Over the last years, several automated MRI hippocampal subfield segmentation protocols have been developed (Iglesias et al., 2015; Pipitone et al., 2014; Van Leemput et al., 2009; Yushkevich et al., 2010, 2015) (Fig. 2).

Here, we give a systematic overview of existing MRI studies of hippocampal subfield morphology (i.e. volume or shape characteristics) in schizophrenia and bipolar spectrum disorders. In addition to case-control differences, we review results on longitudinal changes, clinical and cognitive associations, and medication use. Secondly, we present a meta-analysis of subfield volumes from a subset of group comparison studies of non-overlapping samples (total n = 2593). In addition to comparing schizophrenia and bipolar disorder patient groups to healthy controls, we will also compare the two to each other in search for diagnosis specific patterns. Finally, we discuss important methodological