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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: $d=.28$-$.49$, bipolar disorder: $d=.20$-$.35$), 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.

Key words: MRI; Neuroanatomy; Psychosis; Cornu ammonis; Subiculum; Hippocampus; Hippocampal subregions

Main text

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.

Hippocampal anatomy

The neuroanatomy of the hippocampus is complex and reflects a 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, 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; Konradi et al., 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.

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).

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 placticity 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.

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., 2015; Yushkevich et al., 2010) (Figure 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 issues and limiations, and point toward directions forward.

Methods

The systematic review is based on the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) 27 item checklist and flow diagram (Moher et al., 2009). The literature search was performed in September 2017 in PubMed with the search phrase "hippocampal subfields AND (schizophrenia OR bipolar disorder OR psychosis)". All abstracts were read for screening, and the eligibility criteria were: 1) original studies in English 2) using MRI to assess hippocampal subfield morphology 3) in patients with schizophrenia, bipolar disorder, psychosis, or their relatives. Post mortem-, animal-, and other imaging modality-studies or studies conducted on other patient groups were excluded, as were reviews. References were cross-checked for relevant studies. The screening and selection procedure is detailed in Figure 1. All eligible studies were read in full by two of the authors (UKH, CKT) and inclusion was made by consensus.

For the meta-analysis, volumetric studies including case-control comparisons were selected. The authors of one study were contacted to obtain additional data (Ota et al., 2017). We

used The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses (oxford.asp). NOS includes evaluation of the selection, comparability, and exposure (in this study: MRI aquisition and analysis) of cases and controls. Mean values and standard errors or deviation for each of the five subfields CA1, CA2/3, CA4/DG, subiculum and presubiculum for the tree groups schizophrenia, bipolar disorder, and healthy controls were extracted. These five subfields were selected based on the possibility for comparison across segmentation protocols. The meta-analysis was performed using adjusted z-scores (d-scores) of differences in mean hippocampal subfield volumes between cases and controls (schizophenia and bipolar disorder versus controls) and between schizophrenia and bipolar disorder. The data were analyzed by weighted one- and two-sample t-tests. A random effects model was selected with the inverse variances as weights (Field and Gillett, 2010; Schmidt et al., 2009), and heterogeneity was assessed with Q statistics and I^2 calculations (Huedo-Medina et al., 2006). Computations were performed in Microsoft Excel 2000 (version 9.0.2720) using macros. Bonferroni adjustment for multiple comparisons of the subfields was applied (i.e. five subfields in each hemisphere, adjusted p=0.05/5= 0.01).

Results

Study selection

The literature search returned 64 articles. All abstracts were read for screening. A total of 17 (Aas et al., 2014; Bearden et al., 2008; Buchy et al., 2016; Cao et al., 2017; Francis et al., 2013; Hartberg et al., 2015; Haukvik et al., 2015; Ho et al., 2017a; Ho et al., 2017b; Hyza et al., 2016; Kawano et al., 2015; Kuhn et al., 2012; Mathew et al., 2014; Orfei et al., 2016; Ota et al., 2017;

Papiol et al., 2017; Simonetti et al., 2016) studies fulfilled the inclusion/eligibility criteria. By cross-checking of references, three more studies were found (Elvsashagen et al., 2013; Narr et al., 2004; Zierhut et al., 2013), and one more by cross-referencing in PubMed (Mamah et al., 2016). Of the 21 studies included in the systematic review, 18 studied hippocampal subfield volumetry and three studied shape deformities. Sample sizes varied greatly, from the smallest study including 15 first episode schizophrenia patients (Buchy et al., 2016) to the largest including 887 subjects (from different sites) across the psychosis spectrum and healthy controls (Mathew et al., 2014). The main characteristics and findings from each study are summarized in Table 1.

For the meta-analysis, 10 studies fulfilled the eligibility criteria (Cao et al., 2017; Elvsashagen et al., 2013; Haukvik et al., 2015; Ho et al., 2017b; Hyza et al., 2016; Kawano et al., 2015; Mathew et al., 2014; Orfei et al., 2016; Ota et al., 2017; Simonetti et al., 2016). One of these presented the sum of left and right hemisphere subfield volumes (Ota et al., 2017), and was excluded since we did not succeed in obtaining separate volume estimates after writing to the authors. The nine remaining studies included healthy controls (n=1089) and two patient groups (n=1504; schizophrenia patients (n=909) and bipolar disorder patients (n=625)). Four studies used 3T data, 4 used 1.5T, and one multi-site study did not report field strength. All nine studies used the FreeSurfer software to obtain automatic measures of the hippocampal subfields; two used the new *ex vivo* atlas based segmentation (Iglesias et al., 2015), and the rest used the older *in vivo* atlas based segmentation protocol (Van Leemput et al., 2009). All the studies were classified as moderate to high quality according to the NOS (Supplemental Table 1). Mean volumes of hippocampal subfields, standard deviation and error, and effects sizes from the included studies are listed in Supplemental Table 2.

Systematic review and qualitative analysis

Hippocampal subfields in schizophrenia

Patients with schizophrenia had smaller hippocampal subfields compared to healthy controls in five of six volumetric studies comparing the two groups (Haukvik et al., 2015; Ho et al., 2017b; Hyza et al., 2016; Kawano et al., 2015; Mathew et al., 2014; Ota et al., 2017). The two largest studies (Haukvik et al., 2015; Mathew et al., 2014) both reported widespread volume reductions in the CA2/3, CA4/DG, presubiculum, subiculum, and CA1. Ho *et al* reported the most prominent volume reductions in the CA1 in first episode and chronic schizophrenia patients, with more widespread reductions in the chronic patients(Ho et al., 2017b). The findings are in line with results by Ota *et al*, reporting reduced CA1 and DG volumes (Ota et al., 2017). In contrast, Hyza *et al* found larger CA1 in first episode schizophrenia (Hyza et al., 2016). Kawano *et al* found that CA4/DG volume varied with illness duration found and in addition CA2-3 volume reductions in chronic schizophrenia (Kawano et al., 2015). With regard to hippocampal shape abnormalities, Narr *et al* reported CA1 and CA2 deformities (Narr et al., 2004), and Mahmah *et al* found shape deformities in the CA1 and subiculum (Mamah et al., 2016) compared to healthy controls.

Hippocampal subfields in bipolar disorder

Four studies have investigated hippocampal subfield volumes in bipolar disorder compared to healthy controls. Mathew *et al* found smaller CA2/3 bilaterally, left presubiculum, and right CA4/DG and subiculum in bipolar disorder (Mathew et al., 2014), whereas Haukvik *et al* found bilateral CA2/3, CA4/DG, subiculum, and right CA1 volume reductions (Haukvik et al., 2015). Elvsåshagen *et al* reported smaller CA4/DG and fimbria volumes in bipolar II disorder

(Elvsashagen et al., 2013). Recently, Cao *et al* reported smaller left CA4, granular cell layer, molecular layer, and bilateral tail volumes in bipolar disorder, mostly driven by patients with bipolar disorder I (Cao et al., 2017). With regard to hippocampal shape deformities, Bearden *et al* found CA2-4 and DG contraction and CA1 expansion in psychotic bipolar disorder compared to controls (Bearden et al., 2008).

Longitudinal changes

Two studies reported greater hippocampal subfield volume changes over time in schizophrenia patients compared to healthy controls. Ho *et al* found the most pronounced differences in the bilateral CA1 and the granular layer of the DG, and the right CA2/3 and the molecular layer of the CA4 and subiculum (Ho et al., 2017b), while Kawano *et al* found the largest difference in the CA4/DG (Kawano et al., 2015). In addition, Hyza *et al* performed a longitudinal clinical follow-up, and reported no associations between baseline subfield volumes and relapse, number of psychotic episodes or residual symptoms in first episode schizophrenia patients (Hyza et al., 2016). In a study of youth at ultra-high risk for psychosis (Ho et al., 2017a), Ho *et al* found greater volume decline of the CA1 in subjects with persistent subthreshold psychosis symptoms and conversion to psychosis than in subjects who remitted. Papiol *et al* studied longitudinal change over 3 months in schizophrenia patients with and without an aerobic exercise intervention and found changes in the CA4/DG related to polygenic risk scores in the exercise group (Papiol et al., 2017). There are to date no longitudinal studies of hippocampal subfield volumes in bipolar disorder patients.

Clinical and cognitive associations

To address the functional relevance of the hippocampal subfield volumes or shape abnormalities, eight studies reported on associations with psychosis symptoms. Negative psychosis symptoms (e.g. apathy, anhedonia) were associated with smaller CA2/3 and CA4/DG volumes (Kawano et al., 2015), and subicular volume (Haukvik et al., 2015) and contraction (Mamah et al., 2016). Positive psychosis symptoms (e.g. hallucinations, delusions) were associated with CA1 deformity (Zierhut et al., 2013) and contraction (Mamah et al., 2016), larger CA1 volume (Hyza et al., 2016), and smaller CA1 and CA2/3 (Kuhn et al., 2012), and CA2/3, CA4/DG, presubiculum, and subiculum (Mathew et al., 2014) volumes. One study reported no associations between subfield volumes and psychosis symptoms (Ho et al., 2017b). Directly comparing the results across studies is challenging since the psychosis symptom profiles (i.e. positive or negative symptoms or specific single symptoms) and the investigated subfields differed between studies.

Cognitive impairment is a core feature of both schizophrenia and bipolar disorder (Simonsen et al., 2011), and three studies investigated associations between subfield morphometry and performance on various cognitive tasks. Haukvik *et al* found smaller subiculum volume to be associated with poorer verbal memory in patients with bipolar disorder and healthy controls, but not in the schizophrenia patients (Haukvik et al., 2015). Mathews *et al* found several subfields in the left hemisphere to be positively correlated with verbal memory, and all subfields to a composite cognitive score in patients across the psychosis continuum (Mathew et al., 2014). Francis *et al* found a positive association between subiculum volume and verbal recall in relatives at high risk for schizophrenia (Francis et al., 2013). Taken together, although the reported associations between subfield morphometry and clinical and cognitive

characteristics differ, the results suggest a link between CA1 and positive psychosis symptoms, and the subiculum and negative psychosis symptoms and cognitive impairments.

Medication use

None of the reviewed studies reported on associations between antipsychotic medication and hippocampal subfield morphometry in schizophrenia. An important question regarding bipolar disorder is whether Lithium use has an effect on hippocampal subfield morphometry. Simonetti *et al* found smaller CA2/3, CA4/DG and subiculum volumes in bipolar disorder patients who never used lithium or had less than 24 months use compared to patients who used more than 24 months and healthy controls (Simonetti et al., 2016). In a larger subject sample, Hartberg *et al.* reported smaller right CA1 and subiculum-, and bilateral CA2/3, CA4/DG subfields in non-lithium users as opposed to lithium users, compared to controls (Hartberg et al., 2015). Similarly, Bearden *et al* found volume deficits corresponding to the right CA1 in non-lithium users compared to lithium users and healthy controls (Bearden et al., 2008). Notably, the differences were not restricted to the CA4/DG, which is the most important region for neurogenesis and the region thought to be the most affected by lithium (Ferensztajn-Rochowiak and Rybakowski, 2016).

Meta-analysis

The random effects meta-analysis showed significant volume reductions in all investigated subfields in both schizophrenia and bipolar disorder patients compared to healthy controls (all $p<.005$, Table 2), with effect sizes from 0.28 (right CA1) to 0.49 (left CA4/DG) in schizophrenia and 0.20 (left CA1) to 0.35 (left subiculum) in bipolar disorder. When directly compared,

schizophrenia patients had significantly smaller left CA2/3 (z=-2.63, p=.0086, *d*=0.15) and right presubiculum (z=-3.20, p=.0014, *d*=0.13) than bipolar disorder patients (Table 2) after conservative Bonferroni multiple comparisons correction. At trend level (nominal p-values <.05), schizophrenia patients also had smaller left CA1 (z=-2.20, p=.028), left CA4/DG (z=-2.49, p=.013), and right subiculum (z=-2.36, p=.018) than bipolar disorder patients. The heterogeneity among studies varied between subfields, from Q=1.9-29.5 and I^2= $1.0x10^{-7}$%-72.9% (Table 2).

Discussion

The main finding from this review and meta-analysis is that there are extensive hippocampal subfield volume reductions in both schizophrenia and bipolar disorder. Our meta-analysis revealed widespread subfield volume reductions in both disorders. The results indicate that the hippocampal volume reductions observed in schizophrenia and bipolar disorder are not restricted to specific subfields. Compared to bipolar disorder patients, schizophrenia patients had smaller left CA2/3 and right presubiculum. However, methodological concerns regarding the most used segmentation protocol (Freesurfer 5.3) have been raised, and the results from the limited number of studies not using this protocol point toward reduced CA1 volumes to be most prominent in schizophrenia.

Although the meta-analysis showed group differences in all investigated subfields, the results from the individual studies varied. This could reflect selection bias in the inclusion criteria or heterogeneity within or across the diagnostic categories. Based on the NOS, all studies included in the meta-analysis had robust inclusion criteria of participants, although only one study reported consecutive inclusion of patients (Simonetti et al., 2016). The hippocampus could

also be differently affected in early as compared to chronic illness stages. Indeed, three of the studies specifically included first episode schizophrenia patients (Bearden et al., 2008; Buchy et al., 2016; Hyza et al., 2016) and one study included subjects at ultra-high risk (Ho et al., 2017a). These studies, however, addressed different aspects, i.e. hippocampal shape (Bearden et al., 2008), associations to cognitive function (Buchy et al., 2016), longitudinal change (Ho et al., 2017a), case-control differences and associations to psychosis symptoms (Hyza et al., 2016) (Table 1). As such, only the two last studies (addressing case-control differences) were included in the meta-analysis together with studies of patients with longer illness duration, and in chronic stages (Supplemental table 2). Despite the heterogeneity in the results from the above-mentioned studies, first episode schizophrenia patients in general show less brain changes compared to chronic patient groups (Dietsche et al., 2017; Torres et al., 2016; Vita et al., 2012). This could account for some of the variation between the individual studies. In addition, studies of typically developing individuals suggest that the subfields develop differently (Tamnes et al., 2018), and further longitudinal studies of hippocampal subfield morphometry before and during the course of psychotic disorders are needed as there is a dearth of available data on this

With regard to diagnostic heterogeneity, some studies used ICD-10 and others DSM-IV for classification, and there was a mix of hospitalized and out-patients. Moreover, there is increasing evidence that psychotic disorders are dimensional, with shared genetics, biomarkers, physiological and clinical characteristics (Javitt, 2016). The development of research domain criteria (RDoC) adresses the diagnostic heterogeneity and dimensional characteristics of psychotic disorders and can facilitate the understanding the of the neurobiological underpinnings of specific psychosis symptoms unrestricted by diagnostic categories (Cuthbert and Insel, 2013). A recent study reporting three different neuroimaging- and neurophysiological based biotypes

across the psychosis spectrum, provide empirical evidence for the dimensional characteristics of psychotic disorders (Clementz et al., 2016). By using diagnostic criteria for categorization, the included studies – and the reported meta-analysis – did not address this aspect.

The heterogeneity of volumetric differences between diagnostic groups could also reflect methodological differences in MRI acquisition and weaknesses in hippocampal segmentation protocols. Hippocampal subfield segmentation from MRI is methodologically challenging given the complexity of the hippocampal anatomy and cellular morphology which cannot be optimally captured on standard 1.5T and 3T scanners (Kirov et al., 2013). In this review, all volumetric studies except two (Bearden et al., 2008; Ota et al., 2017), used the FreeSurfer software for automated hippocampal subfield segmentation (Iglesias et al., 2015; Van Leemput et al., 2009). Of these, 12 studies used the earlier van Lempuut (FreeSurfer 5.3) segmentation version (Van Leemput et al., 2009). This version has, when compared to results from histological studies, been criticized for underestimating CA1 volumes (51), at the expense of a relative enlargement of subiculum in the hippocampal head where the boundary between the two subfields is difficult to delineate (Lim et al., 2013; Schoene-Bake et al., 2014). A new FreeSurfer version was therefore developed, based on *ex vivo* (post mortem fixated) scans. This facilitates more accurate subfield annotations and a delineation protocol better suited for hippocampal head and tail distinction (Iglesias et al., 2015). With this protocol, prominent CA1 volume reductions in schizophrenia were found (Ho et al., 2017b), in contrast to the results from the two largest studies which used the earlier FreeSurfer protocol (Haukvik et al., 2015; Mathew et al., 2014). Moreover, a study that used a different segmentation protocol, developed by Yushkevich and colleagues (Yushkevich et al., 2010) only found reduced CA1 volumes in schizophrenia patients (Ota et al., 2017). Notably, the recent findings correspond better with the results from the shape deformity

analyses, in which CA1 abnormalities were the most pronounced (Mamah et al., 2016; Narr et al., 2004). As such, one could argue that by using newer and more valid segmentation protocols the CA1 appears to be the most affected subregion of the hippocampus in schizophrenia.

Other methodological issues include the use of 1.5T versus 3T scanners, and multi-site versus same-scanner studies, as well as scanner upgrades. Six of the studies acquired data using 1.5T scanners (Aas et al., 2014; Cao et al., 2017; Hartberg et al., 2015; Haukvik et al., 2015; Hyza et al., 2016; Kawano et al., 2015), while one multisite study did not state field strengths (Mathew et al., 2014). This may have decreased sensitivity to disease-related and regional variability. Future studies should counteract these methodological limitations with robust designs and updated protocols (Wisse et al., 2017).

Although associations between CA1 and positive symptoms and the subiculum and negative symptoms were reported in more than one study, the relationships between hippocampal subfield volumes and clinical and functional characteristics clearly warrant further research. An inherent limitation to understanding how the links have biological meaning in psychosis is the difficulty in developing adequate animal models for negative or positive symptoms. In a model study (Schobel et al., 2013), individuals at risk for psychosis showed hypermetabolism in the CA1 field which spread to the subiculum after psychosis onset. In parallel, a model of ketamine was used to mimic acute psychosis in mice and reproduced a similar regional pattern of hypermetabolism in the hippocampus. Animal studies of memory functions have suggested an involvement of CA3 and DG in memory encoding and early retrieval and an involvement of CA1 in late retrieval, consolidation and recognition, and preliminary results from human MRI studies have corroborated such division (Mueller et al., 2011). To date, there is a lack of innovative studies on memory formation and hippocampal

subfields specifically in psychiatry. To see this area extensively researched in severe mental disease is of great interest considering the crucial role of the hippocampus in memory function and the fact that cognitive impairment is a stable finding at group level in patients with schizophrenia and have also been demonstrated in bipolar disorders (Simonsen et al., 2011).

All the reviewed studies were of medicated patients. Lithium is known to have neurotrophic effects on the structure of the cerebral cortex (Hibar et al., 2017). In a human stereological post mortem study (Rajkowska et al., 2016), lithium treatment increased the numbers of neurons and glia in the DG, but the volumes of the hippocampus and its subfields and areas of the neocortex were not altered by lithium. As reviewed above in bipolar disorder, the CA1, subiculum-, and CA2/3, CA4/DG subfields in non-lithium users were smaller than observed in lithium users and healthy controls. Experimental stem cell data on the effects of lithium on neurogenesis shows that Lithium increases progenitor cell proliferation in the DG which connects with the neuroprotective and neurotrophic effects of lithium observed in clinical studies (Ferensztajn-Rochowiak and Rybakowski, 2016). Anti-depressant medication (selective serotonin reuptake inhibitors) has been shown to increase angiogenesis and neurogenesis in the DG in major depression (Boldrini et al., 2012). With regard to anti-psychotic medication, elevated hippocampal neurogenesis following olanzapine treatment, and increased cell-proliferation after clozapine treatment (Balu and Lucki, 2009) have been reported. In post-mortem rat brains, 6 months of oral haloperidol or clozapine treatment increased kainate receptor binding in all hippocampal subfields (Schmitt et al., 2003), and another animal study showed effects of haloperidol, but not clozapine on hippocampus volume (Schmitt et al., 2004). Nevertheless, none of the studies reported effects of antipsychotics on the hippocampal subfield morphometry. However, we cannot rule out the possibility that although although there were no

effects of anti-psychotic medication in the individual studies, medication use could have confounded the results from the meta-analysis.

Other factors that may confound the results from brain imaging studies in psychiatric populations are alcohol or substance use. Although beyond the scope of this review, and not addressed in any of the included studies, both alcohol dependence (Lee et al., 2016) and cannabis exposure (Beale et al., 2018) have been showed to affect the hippocampal subfield volumes differently. As such, substance use could be a confounder both in the individual studies and in the current meta-analysis.

Limitations

This study has some notable limitations. At first, due to the lack of control for putative confounders such as medication and substance abuse as well different stages of the illness, the results from the meta-analysis should be interpreted with caution. Moreover, as discussed above, a recognized limitation of this review and meta-analysis is the differences between the hippocampal subfield segmentation protocols and their validity. In particular, there is a systematic segmentation bias towards larger subiculum and smaller CA1-volumes in the Freesurfer 5.3 protocol (which was used by the majority of the studies in this review and meta-analysis)(Wisse et al., 2017). Acknowledging this limitation, we present the literature review differences between the studies using the 5.3 protocol and studies using the Freesurfer 6.0 version or other segmentation protocols. We hope that by carefully discussing these studies and informing the research community about important shortcomings we will stimulate to further research using newer and more robust methods.

Suggestions for future studies

Future studies using the newer protocols in larger subject samples should be conducted. Using higher field strengths (minimum 3T), higher resolution, and adding T2 weighted images, could meet some of the methodological challenges. In addition, studies of typically developing individuals suggest that different subfield develop differently (Tamnes et al., 2018), and further longitudinal studies of hippocampal subfield morphometry before and during the course of psychotic disorders are needed. The influence on adult neurogenesis from different drug treatments such lithium, antipsychotic or antidepressants could be systematically tested in both animals and stem cell model experiments (Ihunwo et al., 2016) with implications of behavior (Goncalves et al., 2016) and then investigated in humans using the MRI-hippocampal subfield methods.

Conclusion

Hippocampal subfield morphology is affected in psychotic disorders, and the results from the present systematic review and meta-analysis indicate widespread effects in both schizophrenia and bipolar disorder, with greater magnitude in schizophrenia. Heterogenous diagnostic categories and methodological weaknesses may explain differences between studies. Despite the shortcomings, the current methodology has great advantages and future potentials to elucidate on some of the enigma of hippocampal involvement found in severe mental illness.

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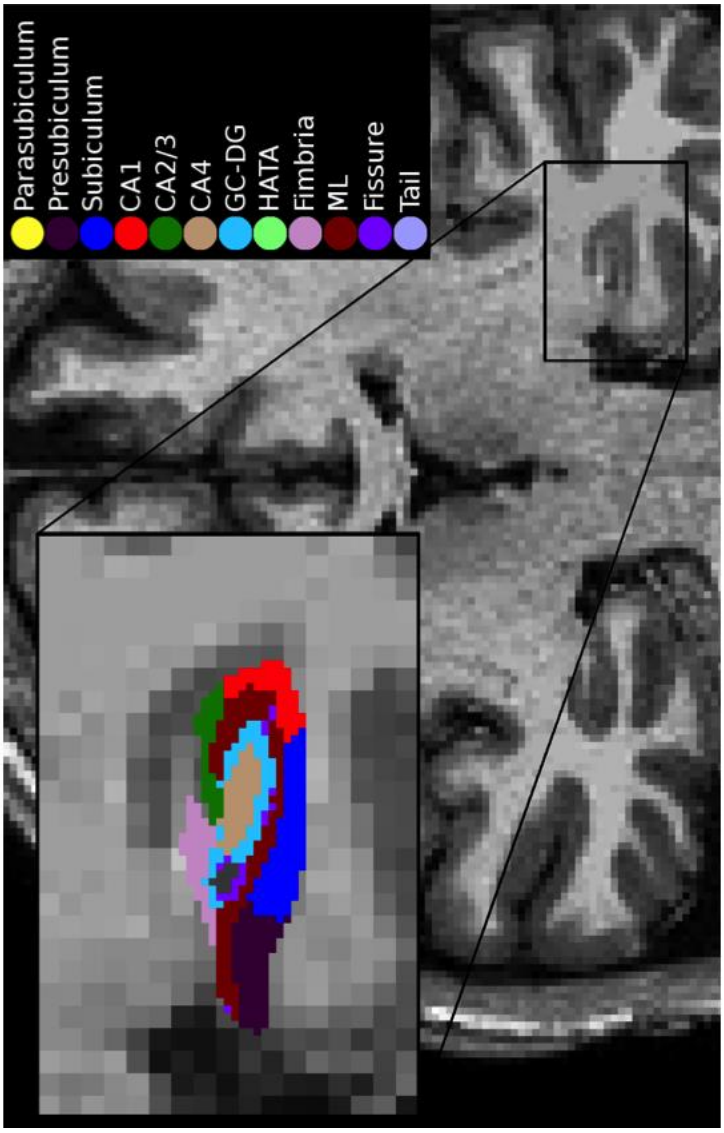
Figure legends

Figure 1. Search and selection procedure according to the PRISMA criteria.

Figure 2. Illustration of the automated hippocampal subfield segmentation using the new FreeSurfer protocol using a 3T T1-weighthed MRI scan from a healthy adult. Abbreviations: CA = Cornu ammonis, GC-DG = granule cell layer of the dentate gyrus, HATA = hippocampus-amygdala transition area, ML = molecular layer.


Parasubiculum
Presubiculum
Subiculum
CA1
CA2/3
CA4
GC-DG
HATA
Fimbria
ML
Fissure
Tail

Tables

Table 1. MRI-studies of hippocampal subfields in schizophrenia, bipolar disorder, and psychosis

*Abbreviations: SCZ- schizophrenia patients; HC- healthy controls; CA – cornu ammonis; feSCZ- first episode schizophrenia; scSCZ- subchronic schizophrenia; cSCZ- chronic schizophrenia; DG- dentate gyrus; BD- bipolar disorder patients; Li- lithium; SCA- schizoaffective disorder; FHR – persons with familial high risk for schizophrenia; pBD- psychotic bipolar disorder; npBD- non-psychotic bipolar disorder; SCA- schizoaffective disorder; UHR – ultra high risk for psychosis; * studies of the same cohort; 1: age and gender not listed*

	Year	Subjects (n) (%male, mean age)	MRI (field strength, subfield segmentation)	Design	Findings
Aas et al.*	2014	SCZ+BD=108 (48%, 32)	1.5T, automatic (FreeSurfer 5.3)	Cross sectional, cohort, childhood trauma,	Smaller CA2/3 and CA4/DG in BDNF val66met met carriers with childhood trauma
Bearden et al.	2008	BD=33 (52%, 34) HC=62 (53%, 33)	1.5T manual hippocampus surface shape delineation	Cross sectional, case-control, lithium effects,	Deficits in right CA1 in BD(Li-) vs BD(Li+) and HC
Buchy et al.	2016	feSCZ=15 (87%, 23)	3T, automatic (FreeSurfer 5.3)	Cross sectional, cohort, cognitive insight	No associations
Cao et al	2017	BD=133 (31%, 39) HC=152 (37%, 35)	1.5T, automatic (FreeSurfer 6.0)	Cross sectional, case-control	BD< left CA4, GCL, ML and bilateral tail than HC
Elvsashagen et al.	2013	BD II=37 (30%, 33) HC=42 (41%, 33)	3T, automatic (FreeSurfer 5.3)	Cross sectional, case-control,	BDII < DG/CA4 and fimbria than HC
Francis et al.	2013	FHR=46 (30%, 25) HC=31 (42%, 24)	3T, automatic (FreeSurfer 3.5)	Cross sectional FHR-controls	Smaller subiculum in FHR, correlated with verbal recall
Hartberg et al.*	2015	BD=181(38%,35) HC= 300 (53%, 35)	1.5T, automatic (FreeSurfer 5.3)	Cross sectional, case-control, lithium effects	BD (Li-) < right CA1 and subiculum subfields, bilateral CA2/3, CA4/DG, but not BD(Li+) than HC
Haukvik et al.*	2015	SCZ= 210 (59%, 32) BD= 192 (40%, 36) HC=300 (53%, 35)	1.5T, automatic (FreeSurfer 5.3)	Cross sectional, case-control	SCZ and BD <CA4/DG, CA2/3, subiculum and right CA1 than HC. SCZ< subiculum and presubiculum than BD. Smaller subiculum: poorer verbal memory in BD and HC, negative symptoms in SCZ
Ho et al	2017	UHR=93 (68%, 21) HC=54 (50%, 21)	3T, automatic (FreeSurfer 6.0)	Longitudinal, UHR-control	No baseline difference, non-remitting UHR >CA1 longitudinal reduction
Ho et al.	2016	SCZ = 201(71%, 35) HC= 125 (69%, 35)	3T, automatic (FreeSurfer 6.0)	Cross sectional, case- control, Longitudinal in a sub-cohort, multisite	SCZ < CA1 than HC. Greater longitudinal volume loss in SCZ. Negative association between CA1 volume and illness duration
Hyza et al.	2016	feSCZ = 58 (100%, 23) HC=58 (100%, 24)	1.5T, automatic (FreeSurfer 5.3)	Cross-sectional, case-control	SCZ> CA1 than HC, positive correlation between CA1 volume and PANSS positive
Kawano et al.	2016	SCZ=34 (53%, 28) HC= 15 (66%, 25)	1.5T, automatic (FreeSurfer 5.3)	Cross sectional, case- control, Longitudinal in a sub-cohort	SCZ < CA4/DG than HC, cSCZ < CA2/3 than HC, inversely correlated with negative symptoms. Longitudinal reduction in CA4/DG in feSCZ
Kuhn et al.	2012	SCZ=21 (76%, 34)	3T, automatic (FreeSurfer 5.3)	Cross sectional, cohort	Negative correlation between positive symptoms score and CA2/3 and CA1 volume

Mamah et al	2016	SCZ=52 (73%, 26) BD=73 (38%, 26) HC=40 (50%, 25)	3T, automatic shape delineation	Cross sectional, case-control,	Subiculum and CA1 contraction in SCZ, CA2-4 + dentate contraction and CA1 expansion in pBD, Negative symptoms: subiculum- and positive with CA1 contraction
Mathew et al.	2014	SCZ= 219 (66%, 35.1) SCA=142 (44%, 35.7) BD= 188(30%, 36.1) HC=337(45%, 37,2)	Not specified field strength, automatic (FreeSurfer 5.3)	Cross sectional, case-control multi-site	All patient groups <, CA2/3. left CA4/DG, presubiculum, and subiculum than HC. Right subiculum: negatively with PANSS positive
Narr et al.	2004	feSCZ=62 (73%, 25) HC=60 (50%, 26)	1.5T, manual shape delineation	Cross sectional, case-control,	FeSCZ shape differences in CA1 and CA2
Orfei et al.	2017	SCZ=45 (67%, 40) HC=45 (67%, 40)	3T, automatic (FreeSurfer 5.3)	Cross sectional, case-control	Smaller presubiculum volumes - poorer self-confidence
Ota et al.	2016	SCZ=20 (75%,37) HC=35 (52%, 39)	3T, automatic (ASHS)	Cross sectional case-control	SCZ < CA1 than HC and < DG than HC
Papiol et al.	2017	SCZ=20[1] HC=23	3T, automatic (FreeSurfer 5.3)	Longitudinal, cohort, genes and exercise	Negative effect of high polygenic risk score on CA4/DG changes over 3 months
Simonetti et al.	2016	BD =45 (58%, 42) HC=15 (60%, 42)	3T, automatic (FreeSurfer 5.3)	Cross sectional, case-control, lithium effects	Li- and Li<24 had smaller subfield volumes than Li>24 and HC.
Zierhut et al	2013	SCZ= 32 (66%, 34) HC=34 (59%, 31)	3T, manual shape delineation	Cross sectional, case-control	Different inward deformity of left CA1, CA1 deformity correlated with positive symptom severity (PANSS positive scores)

Table 2. Meta-analysis results

a. Schizophrenia vs healthy controls

Left	*Mean diff. (d)*	*SE*	*lower CI*	*upper CI*	*Effect size (z)*	*p z*	*Heterogeneity (Q)*	*p Q*
CA1	-0,304	0,102	-0,504	-0,104	-2,983	0,003	29,540	*
CA2/3	-0,450	0,089	-0,624	-0,275	-5,052	***	7,806	0,253
CA4/DG	-0,493	0,109	-0,708	-0,279	-4,513	***	26,621	****
Presubiculum	-0,286	0,061	-0,405	-0,167	-4,700	***	7,231	0,300
Subiculum	-0,394	0,046	-0,485	-0,303	-8,488	****	7,010	0,428
Right								
CA1	-0,282	0,056	-0,391	-0,173	-5,066	****	8,649	0,279
CA2/3	-0,328	0,065	-0,455	-0,201	-5,045	****	12,204	0,058
CA4/DG	-0,364	0,056	-0,474	-0,253	-6,446	****	8,779	0,201
Presubiculum	-0,349	0,060	-0,468	-0,231	-5,774	****	7,163	0,306
Subiculum	-0,375	0,046	-0,466	-0,284	-8,091	****	5,558	0,592

b. Bipolar disorder vs healthy controls

Left	*Mean diff. (d)*	*SE*	*lower CI*	*upper CI*	*Effect size (z)*	*p z*	*Heterogeneity (Q)*	*p Q*
CA1	-0,200	0,054	-0,305	-0,094	-3,725	*	5,151	0,523
CA2/3	-0,304	0,071	-0,443	-0,166	-4,310	**	1,931	0,859
CA4/DG	-0,340	0,075	-0,486	-0,194	-4,550	***	8,699	0,191
Presubiculum	-0,285	0,061	-0,405	-0,166	-4,673	***	5,506	0,357
Subiculum	-0,354	0,095	-0,540	-0,168	-3,733	*	12,686	0,048
Right								
CA1	-0,243	0,054	-0,348	-0,138	-4,528	***	5,078	0,534
CA2/3	-0,349	0,060	-0,467	-0,231	-5,794	****	5,673	0,339
CA4/DG	-0,328	0,054	-0,434	-0,223	-6,111	****	2,396	0,880
Presubiculum	-0,219	0,051	-0,327	-0,111	-3,970	**	3,496	0,624
Subiculum	-0,284	0,069	-0,420	-0,149	-4,108	**	7,862	0,248

c. Schizophrenia vs bipolar disorder

Left	*Mean diff. (d)*	*SE*	*lower CI*	*upper CI*	*Effect size (z)*	*p z*

CA1	-0,105	0,047	-0,197	-0,012	-2,205	0,027
CA2/3	-0,145	0,055	-0,254	-0,037	-2,627	0,009
CA4/DG	-0,153	0,062	-0,274	-0,032	-2,487	0,013
Presubiculum	-0,001	0,043	-0,085	0,084	-0,016	0,987
Subiculum	-0,040	0,042	-0,122	0,042	-0,957	0,339
Right						
CA1	-0,039	0,039	-0,115	0,037	-1,007	0,314
CA2/3	0,021	0,044	-0,066	0,108	0,477	0,633
CA4/DG	-0,035	0,039	-0,111	0,041	-0,903	0,367
Presubiculum	-0,130	0,041	-0,210	-0,050	-3,196	0,001
Subiculum	-0,091	0,038	-0,166	-0,015	-2,362	0,018

*p<.001, **p<.0001, ***p<.00001, ****p<.00000; *SE- standard error, CI – confidence interval*