Reduction in Hippocampal Subfield Volumes in Psychosis

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INTRODUCTION

PSYCHOSIS

Psychosis is a broad term encompassing problems in reality testing. It presents across many psychiatric conditions, including core psychotic disorders such as schizophrenia but also as a qualifier in other (non-core) disorders such as mood disorders.

HIPPOCAMPUS

The hippocampus, located in the medial temporal lobe, has an S-shaped structure consisting of two histologically distinct parts separated by the hippocampal fissure: the hippocampus proper or cornu ammonis (CA) region and the dentate gyrus[1]. The CA region is divided into four regions (CA1-4). While focus was initially placed on investigating its ability to form new, declarative memory, with emerging findings of differences in the hippocampus in psychiatric disorders, it has shifted towards its role in emotion regulation. The hippocampus is linked to a number of regions through its output tracks in a unidirectional information flow: from the external sensory and internal cortical/subcortical, information funnels through the entorhinal cortex to the dentate granule cells; and from the dentate, information flows to the CA regions and on to the subiculum.

Smaller hippocampal volumes have been consistently shown in psychotic disorders such as schizophrenia[2] and schizoaffective disorder[3]. Recent advances in MRI, such as increased fields strengths, development of sophisticated pre-processing techniques and improved computational power, allow imaging of the smaller functional hippocampal substructures.

AIM

Although there have been disorder-specific reviews of hippocampal substructures in psychosis, **no study to date has focused on substructures in psychosis independent of diagnosis.** This systematic review aims to identify common hippocampal substructures impacted across the psychosis spectrum.

METHODS

SEARCH STRATEGY

PubMed, Google Scholar, MEDLINE and EMBASE were searched using the keywords: (Hippocampus AND psychosis) OR (Hippocampal subfield AND psychosis) OR (Cornu ammonis AND psychosis) OR (Subiculum AND psychosis) OR (dentate AND psychosis).

ELIGIBILITY SELECTION

The studies included in this review encompassed MRI neuroimaging studies of patients with a definitive diagnosis of psychosis and comparisons with healthy control participants. The studies which segmented the subfields of the hippocampus using either automatic or manual means were included. All the studies included will have been peer-reviewed. Studies where illicit drug use is documented, or those with history of other significant psychiatric comorbidities or medical psychosis were excluded.

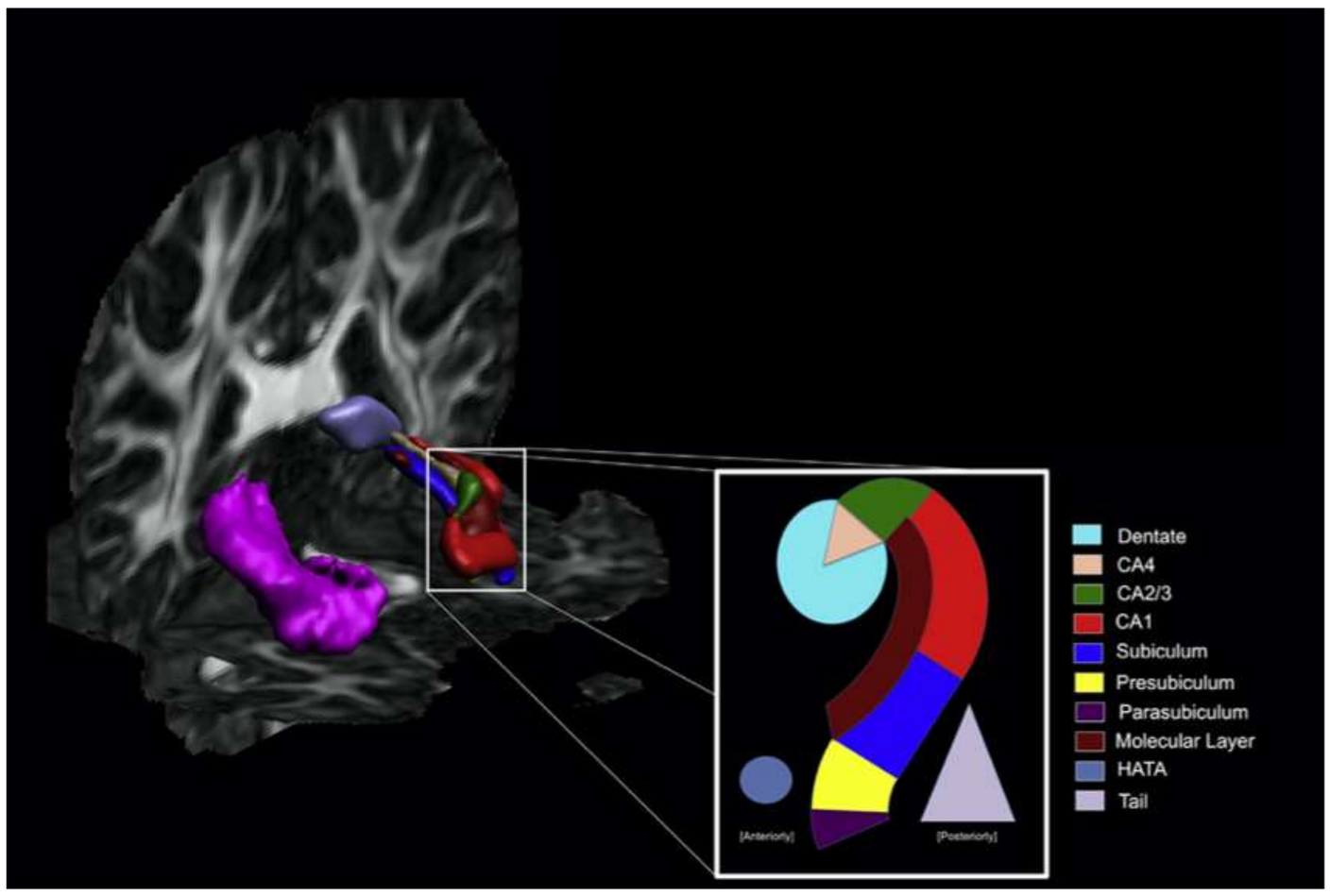

Figure 1. FreeSurfer output showing left and right hippocampi and their subfields. (Roddy *et al*. 2019)

RESULTS

Substructure	Volume decrease	No change	Volume increase
CA1	Baglivo *et al.* 2017, Briend *et al.* 2020, Hartberg *et al.* 2015, Ho *et al.* 2016, Lenka *et al.* 2018, Luckhoff *et al.* 2020, Mathew *et al.* 2014, McHugo *et al.* 2018, Nakahara *et al.* 2018, Rhindress *et al.* 2017, Schobel *et al.* 2009, Teicher *et al.* 2012, Tesli *et al.* 2020, Vargus *et al.* 2017, Wannan *et al,* 2018		Haukvik *et al.* 2015
CA2/3	Mathew *et al.* 2014, Hartberg *et al.* 2015, Haukvik *et al.* 2015, McHugo *et al.* 2018, Vargus *et al.* 2017, Lenka *et al.* 2018, Wannan *et al.* 2018, Baglivo *et al.* 2017		
CA4/DG	Hartberg *et al.* 2015, Haukvik *et al.* 2015, Lenka *et al.* 2018, Mathew *et al.* 2014, McHugo *et al.* 2018, Vargus *et al.* 2017, Wannan *et al.* 2018		
Subiculum	Mathew *et al.* 2014, Haukvik *et al.* 2015, Briend *et al.* 2020, Wannan *et al.* 2018, Lenka *et al.* 2018, Vargus *et al.* 2017	McHugo *et al.* 2018	Rhindress *et al.* 2017
Presubiculum	Hartberg *et al.* 2015, Haukvik *et al.* 2015, Teicher *et al.* 2012, Vargus *et al.* 2017, Briend *et al.* 2020		
ML of DG	Baglivo *et al.* 2017, Lenka *et al.* 2018, Tesli *et al.* 2020		
Fimbria	Teicher *et al.* 2012, Tesli *et al.* 2020	Haukvik *et al.* 2015	

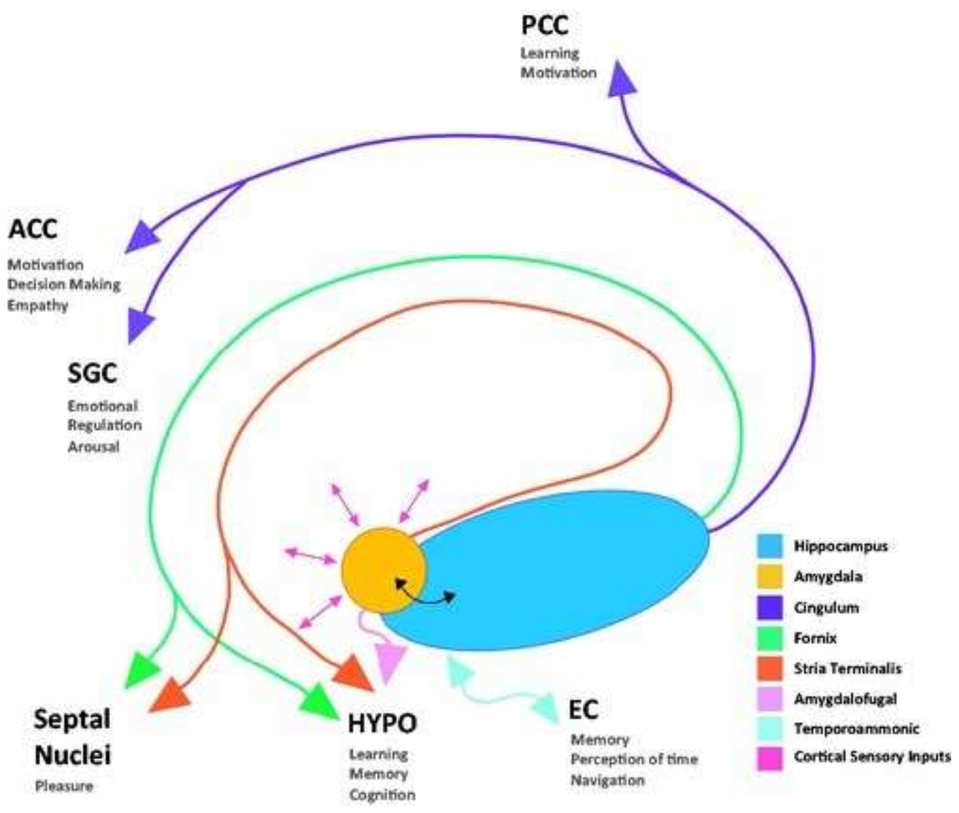

Figure 2. Hippocampal output tracks and amygdala functional connectivity. ACC: anterior cingulate cortex; EC: entorhinal cortex; Hypo: hypothalamus; PCC: posterior cingulate cortex; SGC: subgenual cortex. (Nolan *et al*. 2020)

We extracted 16 papers which studied hippocampal subfields in psychosis. A summary of the results can be found in the table above. The most commonly studied psychotic condition was schizophrenia, with bipolar depression being the second most common. Schizoaffective and major depressive disorder with psychosis were also represented.

CA1 reduction was the most reported finding almost every study (15/16) across the psychosis spectrum, with its adjacent subfields on either side (CA2/3 and dentate/CA4) also commonly reported. Other structures were found to be affected in fewer studies.

Many studies also assessed neighbouring amygdala and parahippocampal regions in which reduced volumes were also observed in patients with psychosis spectrum and associated disorders. Finally, another important region apparently impacted is the hippocampal fissure in which multiple studies have observed widening of the fissure (indicating adjacent nonspecific tissue atrophy) in patients.

CONCLUSION

This is the first systematic review of hippocampal substructures differences in psychosis, independent of primary psychiatric diagnosis. The CA1 region was found to be smaller in the overwhelming majority of studies. Involvement of the adjacent CA4/dentate and CA2/3 regions on either side suggests a potential CA1 locus for pathology in psychosis with lesser involvement of neighbouring and functionally aligned subfields. This study hints at the possibility of the hippocampal CA1 substructures as a biomarker for psychosis, independent of diagnosis. A meta-analysis is underway.

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