

Cornu Ammonis Changes Are at the Core of Hippocampal Pathology in Depression

Darren Roddy¹  and Veronica O'Keane²

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The hippocampus is considered a key cognitive hub that has been implicated in the pathogenesis of major depressive disorder (MDD). Although hippocampal volume reductions are commonly observed in neuroimaging, such findings lack consistency in the literature due to diagnostic and other clinical differences (e.g. age, treatment states, chronicity of illness etc.).¹ A further cause of heterogeneity between studies may lie with the actual definition of the hippocampus used, with over 60 different anatomical guidelines in use to estimate hippocampal volumes.² The human hippocampus consists of interrelated yet anatomically diverse substructures within the medial temporal lobe. These substructures include both the classic hippocampal regions (i.e. dentate, cornu ammonis (CA) and subiculum) that combine organizationally to form the traditional functional unit, as well as more peripheral supporting substructures including the pre-/parasubiculum, periamygdalar and parahippocampal areas. Differing hippocampal descriptions have plagued both clinical and preclinical hippocampal research since it was first described by Arantius in the 16th century with classifications ranging from restrictive (CA only) to broad (all classic hippocampal and extra hippocampal structures).

In a recent study,³ we used advanced automated magnetic resonance hippocampal segmentation (Freesurfer 6.0) to investigate substructure differences between 80 patients with MDD and 83 healthy controls. Individual hippocampal substructure volumes were smaller, mostly on the left in the MDD group, but these were only confined to the classic hippocampal regions (dentate, CA1–4 and subiculum). By dividing our depressed group into first presentation (mean MDD duration 10 months) and recurrent (mean MDD duration 60 months), we found pathology localized to the CA2–4 regions in the

first presentation group, whereas the recurrent group demonstrated much more widespread changes. Even though this study is a cross-sectional case–control sample and as such pathology progression cannot be inferred (unlike a longitudinal study), these results hint at a potential CA2–4 region locus for an initial hippocampal insult in MDD, with further disease process with extension to the other substructures. A novel finding was that the CA1 region demonstrated lateralization of pathology exclusively to the left side and this region was predictive of MDD disease duration.

The main strength of our study is the novel reassembly of the individual computed substructures into 'composite' groups. These composite groups were formed simply by summing the substructural volumes according to known anatomico-functional regions within the hippocampus. By creating three alternative whole hippocampal characterizations, we were able to explore the effects of differing hippocampal definitions in MDD. We found that as we restricted our definitions of hippocampus from broad (all substructures), through functional (dentate, CA1–4 and subiculum only) and finally to conservative (CA regions only), the significance of the changes in MDD increased considerably ($p = 0.005 \rightarrow p = 0.003 \rightarrow p = 0.0002$). This shows for the first time that hippocampal changes seen in MDD depend on the hippocampal definition but also that MDD pathology seems to have a greater impact on the core CA processing regions.

Additional exploratory composite measures were used to further investigate the volumes of anatomical subregions within the hippocampal complex. These included a more refined dentate (dentate and CA4) and CA composites (CA1–3) (with CA4 actually being the hilum of the dentate, rather than a true CA region) as well as a combined total dentate/CA composite. Using these

¹Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland

²Department of Psychiatry, Trinity College Dublin, Dublin, Ireland

Corresponding Author:

Darren Roddy, Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin 2, Ireland.
Email: dwrodny@tcd.ie

To further investigate hippocampal circuitry, we propose here, previously unpublished, three further composites to explore the course of information flow through the hippocampus. In a *highly* simplified form, information flows in to the hippocampus through the dentate/CA4 to the CA2/3 (*mossy fibre path*), then CA2/3 to the CA1 (*Schaffer collaterals*) and then CA1 to subiculum before exiting out from the hippocampus (Figure 1). By using novel composites to evaluate the volumes of each of these three steps (Input, Middle and Output), we may gain insight into the effects of MDD on each component of this circuit (see original paper for methods). We found within each section highly significant volume reductions in depressed compared to controls (Input $p=0.0004$ ($\eta^2=0.07$), Middle $p=0.0002$ ($\eta^2=0.09$) and Output $p=0.0004$ ($\eta^2=0.06$)) suggesting that MDD impacts each part of the central circuit pathways across the hippocampus. This reinforces our hypothesis that MDD impacts the core processing activities of the hippocampus, resulting in well-documented cognitive and memory problems associated with the condition.⁵

In summary, MDD is not a disease of the wider hippocampus, but a disease of the hippocampal core, which impacts the basic processing circuitry that is fundamental to most higher order brain activities. Pathology localized in the hippocampal core may account for the diverse and wide-ranging symptoms often experienced in depression.

Declaration of Conflicting Interests

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ORCID iD

Darren Roddy  <https://orcid.org/0000-0001-7070-5469>

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