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Subregional hippocampal deformations in major depressive disorder

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Abstract

Background—Hippocampal atrophy is a well reported feature of major depressive disorder, although the evidence has been mixed. The present study sought to examine hippocampal volume and subregional morphology in patients with major depressive disorder, who were all medication-free and in an acute depressive episode of moderate severity.

Methods—Structural magnetic resonance imaging scans were acquired in 37 patients (mean age 42 years) and 37 age, gender and IQ-matched healthy individuals. Hippocampal volume and subregional structural differences were measured by manual tracings and identification of homologous surface points to the central core of each hippocampus.

Results—Both right ($P = 0.001$) and left ($P = 0.005$) hippocampal volumes were reduced in patients relative to healthy controls ($n = 37$ patients and $n = 37$ controls), while only the right hippocampus ($p = 0.016$) showed a reduced volume in a subgroup of first episode depression patients ($n = 13$) relative to healthy controls. Shape analysis localised the subregional deformations to the subiculum and CA1 subfield extending into the CA2-3 subfields predominantly in the tail regions in the right ($p = 0.017$) and left ($p = 0.011$) hippocampi.

Limitations—As all patients were in an acute depressive episode, effects associated with depressive state cannot be distinguished from trait effects.

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Contributors Author CF designed the study and wrote the protocol. Authors SC, JC, CH, and PT undertook the statistical analysis, and author JC wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest All authors declare that they have no conflicts of interest.

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Conclusions—Subregional hippocampal deficits are present early in the course of major depression. The deformations may reflect structural correlates underlying functional memory impairments and distinguish depression from other psychiatric disorders.

Keywords

depression; hippocampus; morphology; shape; MRI

Introduction

Reduced hippocampal volume is the most consistently observed structural abnormality in major depressive disorder (MDD) (reviewed in: Campbell et al., 2004; Videbech and Ravnkilde, 2004; McKinnon et al., 2009), with some conflicting reports (Rusch et al., 2001; Posener et al., 2003; Hastings et al., 2004; Vythilingam et al., 2004). Subregional deformations though may be discernible in the hippocampus, which are not captured by volumetric measures alone (Posener et al., 2003). Measures of regional brain structural morphology quantify the dimensions of the structure in its entirety as well as subregional features, providing an output of both the structural volume and morphological shape (Thompson et al., 2004). Analysis of hippocampal morphology have identified distinct and potentially characteristic subregional deformations in schizophrenia (Narr et al., 2004), late-life depression (Ballmaier et al., 2008) and adolescent bipolar disorder (Bearden et al., 2008).

In the present study, we sought to examine hippocampal volume and shape in mid-life depression. We applied manual tracing of each hippocampus for each subject and point-by-point statistical comparisons at each surface location (Thompson et al., 2004). In late-life depression, Ballmaier et al. (2008) observed significant hippocampal atrophy and localised deficits to the anterior CA1-CA3 regions and subiculum bilaterally. However, in mid-life depression, reports of hippocampal atrophy have been mixed (Rusch et al., 2001; Posener et al., 2003; Zou et al., 2010), perhaps reflecting a greater number of episodes or duration of illness in late-life depression (Campbell et al., 2004; Videbech and Ravnkilde, 2004; McKinnon et al., 2009). The present sample consisted of mid-life, adult MDD patients with a history of 2 or fewer episodes, all were suffering from an acute depressive episode and were medication-free (Costafreda et al., 2009). We expected to find similar deformations in the subiculum and adjacent hippocampal subfields, although perhaps less extensive than that observed in late-life depression.

Methods

Participants

Thirty-seven right-handed patients were recruited meeting DSM-IV criteria for major depressive disorder (APA, 1994) by Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995) and clinical interview with a consultant psychiatrist (Costafreda et al., 2009). Inclusion criteria were an acute episode of unipolar major depression and a minimum score of 18 on the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960). Exclusion criteria were a history of neurological trauma resulting in loss of consciousness, current neurological disorder, current co-morbid Axis I disorder including bipolar disorder or an anxiety disorder, history of substance abuse within 2 months of study participation, and a lifetime history of substance dependence. All patients were medication-free for a minimum of 2 weeks prior to the scan (4 weeks if the previous treatment had been fluoxetine). Eight patients had received previous antidepressant medications, which included citalopram, fluoxetine and paroxetine. Thirty-seven age, sex, and IQ matched, right-handed healthy controls were recruited with no history of psychiatric disorder, neurological

disorder, or head injury resulting in a loss of consciousness and an HRSD score < 7 (Table 1). All subjects were recruited by advertisement from the local community, and all patients were outpatients. All participants provided written informed consent to participate in this study in accordance with the guidelines of the Institute of Psychiatry and South London and Maudsley NHS Trust Ethics (Research) Committee.

Image acquisition

Structural MRI brain scans were acquired using a 1.5 T GE NV/i Signa system (General Electric, Milwaukee WI, USA) at the Maudsley Hospital, London. Head movement was limited by foam padding within the head coil and a restraining band across the forehead. 3D spoiled gradient recalled (SPGR) T1-weighted scans were obtained with the acquisition parameters: TE = 8, TR = 24ms, flip angle = 30° , field of view = $25\text{cm} \times 25\text{cm}$, slice thickness = 1.3 mm, number of partitions (slices) = 124, image matrix = $256 \times 256 \times 124$, voxel size = $0.97\text{ mm} \times 0.97\text{ mm} \times 1.3\text{ mm}$. Image requisition parameters are consistent with most MRI acquisition protocols that have been used for defining the hippocampus (reviewed in: Konrad et al, 2009) and is a standard resolution for many structural studies (<http://www.loni.ucla.edu/ADNI/Research/Cores/>). Image contrast for datasets was chosen with the aid of a software tool for optimising image contrast (Simmons et al, 1996).

Image pre-processing and analysis

Pre-processing steps consisted of removal of non-cortical tissue, linear alignment to standard space, and reslicing into the anterior-posterior orientation. Each hippocampus was outlined manually in MultiTracer (Woods, 2003) by a trained investigator (JC) blind to diagnosis. Inter and intra-rater reliability (intra-class correlation coefficient = 0.91) was calculated based on established protocols (Narr et al., 2004; Thompson et al., 2004). Outlines were traced in the coronal orientation, from anterior to posterior along contiguous image slices, and included all hippocampal grey matter including the dentate gyrus and subiculum. Volumetric measures were calculated from the centre of the first slice to the centre of the last, 1 mm sampling along the axis, with the square root of areas varying linearly from slice to slice. The sum of these areas generated the hippocampal volume. Intra-cranial volume (ICV) was calculated with the Brain Extraction Tool (BET) (Smith, 2002) which removes all non-brain matter from MR images. The original unprocessed images were BET-segmented, then manually checked to ensure accurate identification of grey matter, white matter and cerebrospinal fluid. Measures of volume, in mm^3 , were generated from the extracted images. Subgroup analyses of hippocampal volume were also conducted with the patient group divided into patients in their first episode of depression ($n = 13$) and those with recurrent episodes of depression ($n = 24$) (Table 1).

Morphological analysis

Surface mesh modelling analysis was performed as described in Thompson et al. (2004). Briefly, parametric surface meshes were computed from the manually-derived hippocampal outlines. Surface meshes were combined to form a mean shape representing each group in three dimensions. In each individual, the medial core, a central 3D curve threading down the long axis of the structure, was computed. From each point on the hippocampal surface, a radial distance measure was derived to the medial core. As the same surface grid was imposed on all subjects' hippocampi in the same coordinate space, statistical comparisons were made at each hippocampal surface point between the groups to index contrasts on a local scale. Probability values from these statistical comparisons were mapped onto an average hippocampal shape for the entire sample to generate a 3D representation of the structural differences between the groups. Permutation testing was performed in order to correct for the 30,000 simultaneous comparisons made for each hippocampus. Each subject was randomly assigned to a diagnostic group 150,000 times with a statistical threshold of p

< 0.05 , and the area of the hippocampus with suprathreshold statistics in each group comparison was compared with its null distribution, thus deriving an overall corrected significance value for the pattern of effects for each hippocampus

Results

There was an expected significant difference in HRSD ratings between healthy controls and patients ($F = 1611.34$, $df = 2, 71$, $P < 0.001$), in which post-hoc Tukey's test showed a significant difference between healthy controls and patients with recurrent episodes of depression ($p < 0.001$), healthy controls and patients in their first episode ($p < 0.001$), and a trend towards significance between patients with recurrent episodes and those in their first episode ($p = 0.055$).

There was no significant difference in intracranial volume (ICV) between healthy controls and patients ($F = 0.95$, $df = 2, 71$, $P = 0.39$). Left hippocampal volume showed a significant difference between patients and healthy controls ($F = 5.64$, $df = 2, 71$, $P = 0.005$), and post-hoc Tukey's test revealed a significant difference between healthy controls and patients with recurrent episodes of depression ($p = 0.005$), but not between healthy controls and patients in their first episode or between the patient subgroups. Right hippocampal volume also showed a significant difference between patients and healthy controls ($F = 7.58$, $df = 2, 71$, $P = 0.001$), and post-hoc Tukey's test revealed significant differences between healthy controls and both patient subgroups: patients with recurrent episodes of depression ($p = 0.003$) and patients in their first episode ($p = 0.016$), but there were no differences between the patient subgroups. There were no significant correlations with right or left hippocampal volume and the number of previous episodes, duration of illness, or severity of illness as measured by the HRSD score. There were no significant differences between males and females in terms of age, IQ, right or left hippocampal volumes, or corrected hippocampal volumes, all p -values > 0.3 .

Morphological analysis revealed distinct hippocampal deformations in the subiculum and CA1 extending into the CA2-3 subfields predominantly in the tail regions in both the left (corrected $p = 0.011$) and right (corrected $p = 0.017$) hippocampi in patients relative to healthy controls (Figure 1).

Discussion

We found significant bilateral hippocampal atrophy in medication-free patients with major depression of a moderate severity. Morphological analysis localised the atrophy to distinct subregions within the hippocampi. Marked deformations were evident in the subiculum and CA1 subfield extending into the CA2-3 subfields largely in the tail regions of both hippocampi in depressed patients relative to healthy controls. The findings indicate that subregional hippocampal deficits are not confined to late-life depression (Ballmaier et al., 2008), but are evident early in the illness.

The hippocampal deformations observed from MRI scans are supported by neuropathological findings (Rosoklija et al., 2000). Neumister et al. (2004) reported decreased hippocampal volume in its whole and more pronounced in the posterior region, and Maller et al. (2007) found localised volume reductions in the most posterior region of the tail of the hippocampus in patients with treatment-resistant depression. Posener et al. (2003) noted specific abnormalities in the subiculum in patients with similar demographic features to those in the present study, but half the patient group was receiving psychiatric medications. In the present study, all patients were medication-free, right-handed, and had 2 or fewer episodes of depression. In late-life depression, Ballmaier et al. (2008) observed

extensive morphological abnormalities in the subiculum and CA1 subregions which extended into the CA2-3 subfields. In the late-life depression group, those patients with a comparable age of onset to our sample had an average of 5 previous episodes of depression at the time of their scan (Ballmaier et al., 2008). Our findings revealed that the main hippocampal body was relatively intact while deformations were evident particularly in the tail region within the subiculum and CA1 subfield but as well in the CA2-3 subfields. Together, these data suggest that the subregional hippocampal abnormalities present at early stages in the illness may become more extensive with recurrent episodes, contributing to the hippocampal atrophy that is particularly evident in recurrent and treatment-resistant depression (reviewed in: Campbell et al., 2004; Videbech and Ravnkilde, 2004; McKinnon et al., 2009).

The posterior portion of the hippocampus is engaged by memory retrieval (Lepage et al., 1998), and the subiculum has been specifically implicated in the retrieval of episodic memories (Gabrieli et al., 1997; Zeineh et al., 2003; Eldridge et al., 2005). Memory impairments are associated with hippocampal atrophy in depression (Hickie et al., 2005). In particular, deficits in episodic memory are a commonly reported feature (Golinkoff and Sweeney, 1989; Ilsley et al., 2005), which may be greater in the retrieval, as opposed to the encoding, aspects of the memory trace (Fossati et al., 2002). These deficits are not evident in the first episode of depression, but become more prominent in recurrent depression (Fossati et al., 2004). A main component of autobiographical memory is the recall of episodes in one's life (Brewer, 1986). It is widely recognised that individuals with depression have difficulty in recalling specific autobiographical events (Williams and Broadbent, 1986; Williams and Scott, 1988), instead they tend to produce an overgeneralised memory, which may be more pronounced with negative incidents (Williams and Scott, 1988).

Although we observed a right lateralised deficit in hippocampal volume in first-episode patients, bilateral hippocampal atrophy has been reported in medication-naïve, first-episode patients with depression (Zhou et al., 2010), in medication-free patients with recurrent depression (Neumister et al., 2004), and a recent meta-analysis indicates a 4% aggregate loss in hippocampal volume in depression with no significant lateralisation effects (McKinnon et al., 2009). A left lateralised reduction in hippocampal volume has been noted in first-episode male patients (Frodl et al., 2002) and in late-life depression of a mean age of onset of 35 years (Ballmaier et al., 2008). The reason for the right lateralised effect that we have observed is unclear, but we did not find any significant correlations with right or left hippocampal volume and the number of previous episodes, duration of illness, or severity of illness.

However, hippocampal atrophy is not specific to depression as it has been observed in other psychiatric disorders, such as schizophrenia (Sumich et al., 2002), obsessive-compulsive disorder (Atmaca et al., 2008), and borderline personality disorder (Driessen et al., 2000). The present study may help to distinguish between hippocampal abnormalities found in depression and other psychiatric disorders. For example, both depression and schizophrenia have been associated with global hippocampal volume reductions (Sumich et al., 2002). Morphological analysis revealed localised deformations in the anterior regions in schizophrenia (Narr et al., 2004), while we found greater alterations in posterior tail regions. Furthermore, in schizophrenia the deficits were generally bilateral, more extensive, and clearly evident in patients in their first-episode (Narr et al., 2004). In depression, the hippocampal deformations were more circumscribed in mid-life depression and volumetric atrophy was only found in the right hippocampus in first-episode depression. This dissociation between psychiatric disorders may have important aetiological and diagnostic implications, and the specificity of the morphological changes will require further investigation.

A caveat to the interpretation of morphological analysis though is limited anatomical accuracy. Hence, local deficits identified with shape mapping and MRI would be characterized with greater precision by neuropathological examination. Furthermore, the present study did not address possible causative mechanisms, such as hippocampal apoptosis and decreased neurogenesis, which may be driven by hypercortisolemia or diminished neurotrophin levels (Czeh and Lucassen, 2007). Posener et al. (2003) examined hippocampal morphology by delineating the boundaries of the hippocampus based on specific landmarks, reporting no difference in hippocampal volume but deficits in the subiculum region. The method though consisted of a limited number of anatomical landmarks to define hippocampal morphology which may have minimised gross and local irregularities. Moreover, we did not observe a correlation between hippocampal volume and the number of depressive episodes. The present group though consisted of patients with none or few previous episodes of depression, which may have limited the observation of any correlations as they may become evident in a larger sample with a greater range of episodes.

In summary, hippocampal deformations localised to the subiculum and CA1 subregion extending into the CA2-3 subregions were observed in patients with major depression. Subregional hippocampal deformations may distinguish depression from other psychiatric disorders.

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Figure 1. Morphological analysis of bilateral hippocampi in major depressive disorder. Top panel presents a schematic figure of the hippocampi *in-situ*. In the middle panel, regional subfield deformations are depicted on hippocampal surface maps. Smaller p-values reflect greater medial distance reductions in patients with depression ($n = 37$) relative to healthy controls ($n = 37$). Reference shapes are presented in the lower panel depicting the hippocampal subfields based on the subfield definitions used by Bearden et al. (2008). Hippocampi are presented left to right in the following order: Right hippocampus, Superior view; Left hippocampus, Superior view; Left hippocampus, Inferior view; Right hippocampus, Inferior view. CA = cornu ammonis.

Table 1

Demographic features and hippocampal volumetric data

	Healthy Controls		Depressed Patients	
		All Patients	First Episode	Recurrent
Number of subjects	37	37	13	24
Mean age (years)	42.2 (9.0)	41.9 (8.9)	38.1 (7.9)	44.0 (9.4)
Sex (male/female)	9/28	9/28	2/11	7/17
HRSD	0.2 (0.6)	20.7 (2.2) *	21.5 (2.7) *	20.2 (1.7) *
Verbal IQ	114.5 (13.2)	108.7 (17.1)	103.1 (20.3)	111.6 (15.0)
L hippocampus	1.98 (0.29)	1.77 (0.26) *	1.81 (0.29)	1.75 (0.24) *
R hippocampus	2.08 (0.28)	1.86 (0.22) *	1.85 (0.21) *	1.84 (0.24) *
Intracranial volume	1501.57 (137.73)	1459.45 (125.30)	1464.24 (105.54)	1456.86 (136.91)

Data presented as mean and standard deviation in parenthesis. Volume measures are in mL units. HRSD = Hamilton Rating Scale for Depression; L = left, R = right.

* Indicates data showing a significant difference from healthy controls