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Short Communication

Hippocampal volume in vulnerability and resilience to depression

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ABSTRACT

Background: Reduced hippocampal volume has been associated with clinical depression. However, it remains unclear whether these changes are a biological vulnerability marker or a consequence of this disorder.
Methods and results (Study 1): We first compared hippocampal volumes between (i) never-depressed individuals with elevated risk for depression by virtue of high neuroticism (ii) recovered depressed individuals with matched levels of neuroticism; and (iii) individuals with low neuroticism and no history of depression. We replicated the finding of reduced hippocampal volume in the recovered group; unexpectedly however, the never-depressed high-risk group showed an *increase* in volume. One hypothesis is that this group had a mean age above the typical onset age for depression; hence, these participants who have remained euthymic despite their personality risk might in fact possess some resilience.
Methods and results (Study 2): A subsequent study was therefore carried out to compare hippocampal volume between high-neurotic vs. low-neurotic volunteers in a younger sample. No group difference was found.
Limitations: The present findings are limited by a small sample size; the cross-sectional design precluded us from makineg definitive conclusions about causal effect.
Conclusion: Our overall results suggest that reduced hippocampal volumes is a neural marker for the scar effect of depression, although this structural impairment could also be seen as a vulnerability marker for the development of future recurrent episodes. By contrast, larger hippocampal volumes could be a biological marker of resilience. These findings have clinical implications regarding treatment development for the prevention of illness onset and recurrent depressive episodes.

1. Introduction

There is much interest in the role of disturbed neuroplasticity in the biological basis of depression (Czeh and Lucassen, 2007). Significant reduction (typically around 10%) in hippocampal grey matter volume has been reported in depressed (Campbell et al., 2004; Colla et al., 2007; Videbech and Ravnkilde, 2004) and remitted patients (Neumeister et al., 2005; Sheline et al., 1996), suggesting that this impairment may represent a trait characteristic of depression. However, the causal and temporal nature of this volume change is unclear.

The neurotoxicity hypothesis posits that these volumetric changes occur as a neurodegenerative reaction to prolonged periods of stress and associated heightened glucocorticoid levels in depression (Sheline, 2011). Consistent with this, hippocampal volume loss is correlated with the length and number of recurrent episodes (MacQueen and Frodl, 2011; Sheline et al., 1999, 2003).

However, smaller hippocampal volume has also been illustrated in individuals at the first depressive episode (Cole et al., 2011) and adolescent depressed patients (Rao et al., 2010). Therefore, it is possible that vulnerable individuals may have a pre-existing difference in hippocampal volume. Supporting this vulnerability hypothesis, never-depressed individuals with familial risk of depression were shown to have significantly smaller hippocampus than matched control participants (Baare et al., 2010; Chen et al., 2010), and predictive of depressive episode in five years (Rao et al., 2010). However, contradictory findings should be

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noted (den Heijer et al., 2011). Furthermore, the evidence was limited to familial risk and may not be generalisable to other risk factors. Finally, the neurotoxicity and vulnerability hypotheses are not mutually exclusive. It is possible that smaller hippocampus predisposes individuals to depression, and the illness itself leads to further volume reduction.

The current study therefore examined whether differences in hippocampal volume occur as a function of vulnerability to depression. Neuroticism is a robust risk factor for depression (Kendler et al., 2006). We recruited participants with high neuroticism who had never experienced depression or had recovered from at least one depressive episode. Hippocampal volumes were compared to a control group with low neuroticism. We predicted that hippocampal volume would be lower in the volunteers recovered from depression. We further hypothesised reduced hippocampal volume in never-depressed volunteers at risk for depression, but to a lesser extent, suggesting that reduction occurs both as a predisposing factor and a consequence of depression.

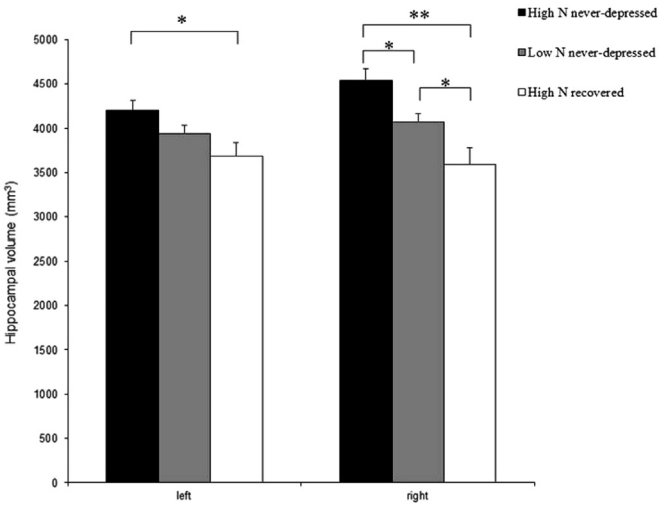

Fig. 1. Hippocampal volumes of the high *N* never-depressed, high *N* recovered depressed and low *N* control participants in Study 1. *Note.* Values represent group mean ± S.E.M. Asterisks indicate significant group difference, $^{*}p < .05$, $^{**}p < .01$.

2. Study 1

2.1. Methods (Study 1)

2.1.1. Participants and psychological measures

Thirty-six participants (aged 19–62) gave informed consent to the study, which was approved by the local psychiatric ethics committee. Selection was based on their extreme scores for high or low neuroticism (*N*) on the Eysenck Personality Questionnaire (EPQ; Eysenck and Eysenck, 1975) from a cohort of 20,427 families collected as part of a larger investigation (Fullerton et al., 2003). We contacted unrelated individuals with high neuroticism scores ($\geq$ 17/23; Mean 21.0, SD 1.3) who had never suffered from depression or other axis I disorder ($n=12$); matched high *N* volunteers ($\geq$ 17/23; Mean 20.5, SD 1.6) who had recovered from at least one episode of depression ($n=12$); and healthy volunteers scoring at the low end of neuroticism ($\leq$ 4/23, Mean 1.5, SD 1.7; $n=12$).

Using the Structured Clinical Interview for DSM-IV (SCID-I; First et al., 1995), all participants were confirmed to be free of current axis I psychiatric disorder. They had no current physical illness and had been free of medication for at least one month. Those volunteers who had been depressed had suffered an average of 1.8 episodes (range 1–6) and had been euthymic for at least three months before the study. Beck Depression Inventory (BDI; Beck et al., 1961) was administered.

The three groups were matched in gender (6:6 in each group), age (high *N* never-depressed 40.0 ± 14.3 vs. high *N* recovered 48.9 ± 6.9 vs. low *N* 40.6 ± 12.9) and years of education (15.0 ± 4.0 vs. 15.2 ± 3.1 vs. 16.6 ± 3.2) (all *p*'s > .15). As expected, the recovered depressed (10.9 ± 5.5) and never-depressed high *N* (9.3 ± 5.1) groups had higher BDI compared to the low *N* group (2.0 ± 2.3) ($F(2,35)=13.1$, $p < .001$). These two high *N* groups did not differ from each other ($p=.47$).

2.1.2. MRI acquisition

Anatomical images were acquired with a 1.5T Siemens-Sonata scanner (Siemens Medical Solutions, Bracknell, UK). A T1-weighted scan was acquired (3D FLASH sequence, TR=5.6 msec, flip angle 19°) with 1 mm^2 in-plane resolution and 1 mm slice thickness.

2.1.3. MRI analysis

Hippocampal volumes were obtained using FIRST (FMRIB's Integrated Registration and Segmentation Tool), part of FSL (FMRIB's Software Library: www.fmrib.ox.ac.uk/fsl). FIRST uses Bayesian active appearance models, which are based on both shape and intensity priors constructed from a training set of 139 datasets that were manually segmented at the Centre for Morphometric Analysis, Boston, USA. See Patenaude et al. (2007) for details on the procedure.

2.1.4. Statistical analysis

A repeated measures ANOVA was carried out for hippocampal volumes, with group as between-subjects factor and hemisphere as the within-subjects factor. Significant interactions were further analysed using one-way ANOVAs and *t* tests. All tests were two-tailed with statistical significance $p < .05$.

2.2. Results (Study 1)

There was a significant main effect of group ($F(2,33)=9.1$, $p=.001$) and a hemisphere by group interaction ($F(2,33)=3.4$, $p=.044$, see Fig. 1). In the right hemisphere, group difference ($F(2,35)=10.24$, $p < .001$) was driven by an increased volume in the high *N* never-depressed group compared with both the low *N* control ($t(22)=2.8$, $p=.010$) and the recovered group ($t(22)=4.0$, $p=.001$). The recovered group also showed a reduced volume compared with the low *N* control group ($t(22)= 2.2$, $p=.039$). In the left hemisphere, the group difference ($F(2,35)=4.6$, $p=.017$) was driven only by an increased volume in the high *N* never-depressed group compared with the recovered depressed group ($t(22)=2.7$, $p=.013$). There were no differences between the high *N* never-depressed and low *N* control group ($t(22)=1.7$, $p=.097$) or between the recovered depressed and low *N* control group ($t(22)=1.5$, $p=.14$). Due to the small sample size, non-parametric tests were conducted; same results were yielded.

2.3. Discussion (Study 1)

Reductions in hippocampal volume have been reported during and following remission from depression (Neumeister et al., 2005; Sheline et al., 1999). This effect was replicated here with the recovered depressed group showing reductions of 12% and 26% in the right hippocampus compared to the low *N* and high *N* never-depressed groups, respectively. Our results further suggested that such volume reductions are apparent even compared with participants matched in risk by neuroticism.

Contrary to our predictions however, never-depressed high *N*