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ORIGINAL ARTICLE

Hippocampal volume as marker of daily life stress sensitivity in psychosis

D. Collip†, P. Habets†, M. Marcelis, E. Gronenschild, T. Lataster, M. Lardinois, N. A. Nicolson and I. Myin-Germeys* for G.R.O.U.P.

Department of Psychiatry and Psychology, School for Mental Health and Neuroscience, EURON, Maastricht University Medical Centre, Maastricht, The Netherlands

Background. Reduced hippocampal size and increased stress sensitivity are associated with psychotic disorder and familial risk for psychosis. However, to what degree the hippocampus is implicated in daily life stress reactivity has not yet been examined. The current study investigated (i) whether familial risk (the contrast between controls, patients and siblings of patients) moderated the relationship between hippocampal volume (HV) and emotional daily stress reactivity and (ii) whether familial risk (the contrast between controls and siblings of patients) moderated the relationship between HV and cortisol daily stress reactivity.

Method. T1-weighted magnetic resonance imaging (MRI) scans were acquired from 20 patients with schizophrenia, 37 healthy siblings with familial risk for schizophrenia and 32 controls. Freesurfer 5.0.0 was used to measure HV. The experience sampling method (ESM), a structured momentary assessment technique, was used to assess emotional stress reactivity, that is the effect of momentary stress on momentary negative affect (NA). In addition, in the control and sibling groups, cortisol stress reactivity was assessed using momentary cortisol levels extracted from saliva.

Results. Multilevel linear regression analyses revealed a significant three-way interaction between group, HV and momentary stress in both the model of NA and the model of cortisol. Increased emotional stress reactivity was associated with smaller left HV in patients and larger total HV in controls. In line with the results in patients, siblings with small HV demonstrated increased emotional and cortisol stress reactivity compared to those with large HV.

Conclusions. HV may index risk and possibly disease-related mechanisms underlying daily life stress reactivity in psychotic disorder.

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Key words: Cortisol, genetic predisposition to disease, hippocampus, hypothalamo-hypophyseal system, magnetic resonance imaging, psychological stress, schizophrenia, stress.

Introduction

Patients with psychotic disorder generally display reduced hippocampal size (Wright *et al*. 2000; Geuze *et al*. 2005; Steen *et al*. 2006; Vita *et al*. 2006). Studies have shown that similar alterations in hippocampal volume (HV) may be present in first-degree relatives of patients with schizophrenia (Boos *et al*. 2007; Lawrie *et al*. 2008), suggesting that HV alterations constitute part of the liability to psychosis. The hippocampus plays a pivotal role in regulating emotional responses to stressful stimuli and in the negative feedback mechanism controlling hypothalamic–pituitary–adrenal (HPA) axis activity (Jacobson & Sapolsky, 1991; Sapolsky, 2000; Corcoran *et al*. 2003; Buchanan *et al*. 2009). Because the hippocampus has an inhibitory influence, a smaller HV might be associated with increased HPA axis reactivity to stress. Indeed, in clinical and aged samples, studies have reported an inverse association between HV and cortisol levels (Lupien *et al*. 1998; Knoops *et al*. 2010). Similarly, in patients with a psychotic disorder, smaller left HV was associated with higher salivary cortisol levels (Mondelli *et al*. 2010*b*).

By contrast, findings in (younger) healthy volunteers show mixed results. One study, examining the association between HV and cortisol response to experimental psychological stress and also to awakening (Pruessner *et al*. 2010), found a positive association between HV and cortisol reactivity in young healthy volunteers, whereas a negative association between HV and the cortisol response to a physiological

* Address for correspondence: I. Myin-Germeys, Ph.D., Department of Psychiatry and Neuropsychology, Maastricht University, PO Box 616 (VIJV1), 6200 MD Maastricht, The Netherlands.
(Email: i.germeys@maastrichtuniversity.nl)
† These authors contributed equally to this work.

challenge was found in another sample (Tessner *et al*. 2007). These findings indicate that the association between HV and stress reactivity may be different in healthy and clinical populations.

Familial vulnerability for psychosis has been associated with amplified emotional and cortisol responses to stress in daily life. Patients with a psychotic disorder and their unaffected first-degree relatives have been found to display increased negative emotions and an increase in psychotic experiences (Myin-Germeys *et al*. 2001, 2005). A recent study showed that siblings of patients compared to controls responded with increased cortisol secretion to minor everyday stressors (Collip *et al*. 2011). However, the neural mechanisms underlying this augmented stress sensitivity have not yet been identified.

In the current study we investigated whether HV is associated with emotional and cortisol reactivity to daily life stress, as indexed by momentary variation in negative affect (NA) and momentary cortisol levels. Given the reported discrepancy between clinical and non-clinical samples in the association between HV and cortisol (Pruessner *et al*. 2007), we examined whether this association was moderated by genetic risk for psychosis. Because some earlier studies suggest that cortisol levels are primarily associated with the left HV (Mondelli *et al*. 2010*b*), analyses also investigated hemispheric differentiation; that is differences in the HV stress reactivity. Analyses thus examined (i) to what degree HV was associated with emotional (for patients, siblings and controls) and cortisol (for siblings and controls) reactivity to daily stress, (ii) whether genetic/familial risk (the contrast between controls, patients and siblings of patients) moderated the relationship between HV and emotional daily stress reactivity and (iii) whether familial risk (the contrast between controls and siblings of patients) moderated the relationship between HV and cortisol daily stress reactivity.

Method

Participants

The sample included patients with a diagnosis of non-affective psychotic disorder, their siblings, and controls from the general population, in the context of the Dutch national Genetic Risk and Outcome of Psychosis (GROUP) project (Kahn *et al*. 2011). In selected representative geographical areas in The Netherlands and Belgium, patients were identified by clinicians whose caseload was screened for inclusion criteria. Subsequently, a group of patients presenting consecutively at these services, either as out-patients or in-patients, were recruited for the study. First-degree relatives were recruited through participating patients. Control subjects were recruited from the same population as the patients, through random mailings in the geographic region and advertisements in newspapers. All interviews were conducted by trained psychology graduates. From the wider sampling frame, the following subgroups were selected: 20 patients with a diagnosis of non-affective psychotic disorder, 37 siblings of patients with a diagnosis of schizophrenia and 32 controls. As the sibling group was recruited by asking the patients to inform their brothers and sisters about the study, participants were clustered within families. Inclusion criteria were: (i) age between 16 and 55 years and (ii) sufficient command of the Dutch language. Exclusion criteria were: (i) use of steroid medication, (ii) a current Axis I disorder, (iii) a lifetime history of psychotic disorder, and, for the controls, (iv) a family history of psychotic disorder as assessed by the Family Interview for Genetic Studies (FIGS; Maxwell, 1992; NIMH Genetics Initiative, 1992).

Diagnosis (lifetime) was based on DSM-IV criteria (APA, 2000) assessed with the Comprehensive Assessment of Symptoms and History (CASH) interview (Andreasen *et al*. 1992). Patients were diagnosed with: schizophrenia ($n=11$), schizo-affective disorder ($n=2$), schizophreniform disorder ($n=1$), brief psychotic disorder ($n=2$) and psychotic disorder not otherwise specified ($n=4$). The CASH was also used to confirm the absence of a lifetime diagnosis of psychotic disorder or any current affective disorder in the siblings and in the healthy controls. Prior to magnetic resonance imaging (MRI) acquisition, participants were screened for the following exclusion criteria: (i) brain injury with unconsciousness for >5 min, (ii) meningitis or other neurological diseases that might have affected brain structure/function, (iii) respiratory or cardiac disease and (iv) severe claustrophobia. In addition, subjects with metal corpora aliena were excluded from the study, along with women with an intrauterine device or (suspected) pregnancy. To prevent interference, the MRI scan was not taken during the week when the experience sampling method (ESM) technique was used (discussed later). MRI scans were conducted between several weeks and months after ESM. The study was approved by the standing ethics committee, and all the subjects gave written informed consent in accordance with the committee's guidelines.

Measures

The Positive and Negative Syndrome Scale (PANSS; Kay *et al*. 1987) was used to measure psychotic symptoms over the past 2 weeks.

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Antipsychotic medication (AP) was determined from reports of the participant's psychiatrist. Best-estimate lifetime (cumulative) AP use was determined by multiplying the number of days of AP use by the corresponding haloperidol equivalents and summing these scores for all periods of AP use (Cahn *et al*. 2002).

Estrogen exposure was estimated by multiplying the number of months of oral contraceptive use by micrograms of estrogen (of the corresponding oral contraceptive) per month.

Substance use was assessed using the Composite International Diagnostic Interview (CIDI) sections B–J–L (WHO, 1990). Cannabis use and other drug use [stimulants, sedatives, opiates, cocaine, PCP, psychedelics, inhalants, or other (e.g. XTC, poppers)] was assessed as reported frequency of use (i) during the past 12 months and (ii) lifetime. Alcohol and tobacco use was defined as the reported number of weekly consumptions during the past 12 months.

ESM

The ESM is a random time-sampling self-assessment technique; studies have demonstrated the feasibility, validity and reliability of ESM in general and patient populations (Csikszentmihalyi & Larson, 1987; Myin-Germeys *et al*. 2009). Subjects received a digital wristwatch that emitted a signal 10 times a day on six consecutive days, at unpredictable moments between 07:30 and 22:30 hours. After each 'beep', subjects completed ESM self-assessment forms concerning current context, thoughts, emotions and psychotic experiences.

ESM measures

Event stress. In accordance with previous work, stress was conceptualized as the subjectively appraised unpleasantness of distinctive events (Myin-Germeys *et al*. 2001). After each beep, participants were asked to report the most important event that had happened between the current and the previous report and then to rate this event on a seven-point scale (−3 = very unpleasant, 0 = neutral, 3 = very pleasant). For the current analyses, all positive responses were recoded as 0, and the negative responses were recoded so that high scores reflect more unpleasant and potentially stressful events (0 = neutral, 3 = very unpleasant) (Jacobs *et al*. 2007).

NA. In line with previous reports (Myin-Germeys *et al*. 2001), ESM NA was assessed as the mean score on six ESM items, rated on seven-point Likert scales (1 = not at all to 7 = very): 'I feel insecure', 'I feel lonely', 'I feel anxious', 'I feel down', 'I feel guilty' and 'I feel angry/ irritated' (Cronbach's $\alpha = 0.84$).

Salivary cortisol sampling

After each ESM beep, siblings and controls collected a saliva sample with a cotton swab (Salivette; Sarstedt, The Netherlands), replaced the swab in the salivette tube and recorded the exact collection time. No saliva was collected in the patient group because AP could have affected cortisol levels and brain structures (Meltzer *et al*. 1989; Wik, 1995; Pariante, 2008). Samples were stored in subjects' home freezers until transport to the laboratory, where uncentrifuged samples were kept at −20 °C until analysis. Saliva samples collected more than 15 min after the beep were excluded from the analysis.

MRI acquisition and processing

MRI scans were acquired using a 3-T Siemens scanner and the following acquisition parameters: for the modified driven equilibrium Fourier transform (MDEFT) sequence: 176 slices, 1 mm isotropic voxel size, echo time (TE) 2.4 ms, repetition time (TR) 7.92 ms, flip angle 15°, total acquisition time 12 min 51 s; and for the magnetization prepared rapid acquisition gradient echo (MP-RAGE): Alzheimer's Disease Neuroimaging Initiation (ADNI) sequence: 192 slices, 1 mm isotropic voxel size, TE 2.6 ms, TR 2250 ms, flip angle 9°, total acquisition time 7 min 23 s. For both sequences the matrix size and field of view were 256 × 256. Two sequences were used because of a scanner update during data collection. The MP-RAGE and MDEFT sequences are very similar, but to prevent any systematic bias, the total proportion of MP-RAGE scans (around 1/3) was balanced between the groups (for more detail see Habets *et al*. 2011).

MRI preprocessing

Scans were processed and analyzed using Freesurfer stable release version 5.0.0. Technical details of these procedures are described in previous publications (Dale *et al*. 1999; Fischl *et al*. 1999, 2002; Fischl & Dale, 2000; Segonne *et al*. 2004; Han *et al*. 2006; Jovicich *et al*. 2006).

Volume measures

The automated procedures for volumetric measures of the different brain structures are described by Fischl *et al*. (2002). These procedures automatically assign a neuroanatomical label to each voxel in an MRI volume based on probabilistic information automatically estimated from a manually labeled training set.

The accurate labeling of subcortical structures is achieved through the use of both global and local information. The global information is based on an atlas that makes the labeling robust to variations

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in contrast properties of the anatomical structures. Local information is incorporated by modeling the classification as a non-stationary anisotropic Markov random field. The introduction of non-stationarity and anisotropy into the classical Markov random field model allows spatial relationships of anatomical classes to enter into the segmentation procedure. For instance, the probability that a voxel labeled hippocampus will have its inferior neighbor labeled as amygdala provides a strong set of spatial constraints.

The training set included healthy persons in the age range 18–87 years and a group of patients with Alzheimer's disease in the age range 60–87 years, and the classification technique uses a registration procedure that is robust to anatomical variability, including the ventricular enlargement typically associated with neurological diseases and aging. The technique has previously been shown to be comparable in accuracy to manual labeling (Fischl *et al*. 2004). The segmentations were visually inspected for accuracy.

Statistical analyses

ESM and cortisol data were analyzed using multilevel regression techniques, which take the hierarchical structure of the data into account. In the current study, repeated momentary measurements (level 1) were nested in subjects (level 2) who were part of the same family (level 3). Data were analyzed using the XTMIXED or XTREG multilevel random regression routine in Stata 11.0 (StataCorp, 2009). Effect sizes from predictors in the multilevel model are expressed as *B*, representing the unstandardized fixed regression coefficient. Interactions were assessed by the Wald test. The size of the moderator effects was calculated by applying and testing the appropriate linear combinations using the Stata MARGIN command. Raw cortisol values were log transformed to reduce skewness of distribution, generating the variable lncort. The variable time was centered around the grand mean for all samples. To model the cortisol diurnal curve, the variable time was included as a predictor in all analyses with lncort as the dependent variable; addition of higher-order polynomial terms did not improve the model fit. Analyses were adjusted for the *a priori* selected confounders age, sex, intracranial volume and scan type. In the patient group, the effect of AP use on HV size was examined. Analyses were rerun including AP (Meador-Woodruff & Greden, 1988; Mondelli *et al*. 2010*a*), antidepressant medication and history of depression as covariates.

Group differences in HV, cortisol and stress reactivity

To test whether HV or mean cortisol level differed between groups, a multilevel regression was estimated with HV and lncort respectively as the dependent variable and the categorical variable group (0 = controls, 1 = siblings, 2 = patients; for cortisol, controls and siblings only) as the independent variable, taking into account that participants were nested within families.

To test whether stress reactivity differed by group, multilevel regression analyses were conducted with event stress and group, and also their interaction term, as independent variables and NA (and respectively cortisol for controls and siblings) as the dependent variable, again also controlling for familial clustering.

Interaction between group, stress reactivity and volume

To test whether HV was associated with emotional stress reactivity, and whether this was moderated by group, multilevel regression analyses were conducted with event stress, HV (continuous variable) and group (entered as a linear three-level variable of patients, siblings and controls = reference), and also their interaction terms, as independent variables and NA as the dependent variable:

$$\begin{aligned}\mathrm{NA} = {} & B_0 + B_1\,(\mathrm{group}) + B_2\,(\mathrm{stress}) + B_3\,(\mathrm{volume}) \\ & + B_4\,(\mathrm{group} \times \mathrm{stress}) + B_5\,(\mathrm{group} \times \mathrm{volume}) \\ & + B_6\,(\mathrm{stress} \times \mathrm{volume}) \\ & + B_7\,(\mathrm{group} \times \mathrm{stress} \times \mathrm{volume}).\end{aligned}$$

For visualization purposes, HV was entered as the dummy variable representing the distribution of volume calculated at the 50th percentiles of HV of the controls: where 1 represents $<$50th percentile (small HV) and 2 represents $>$50th percentile (large HV). To ensure that definitions for small and large HV were the same for all groups, patients and siblings were allocated to hippocampal group on the basis of the criteria for the control group (13 siblings and eight patients in the large total HV group; 14 siblings and six patients in the large left HV group; 12 siblings and six patients in the large right HV group).

To test the hypothesis that controls and siblings differed in their association between HV and cortisol stress reactivity, the same model as described above was applied to cortisol (lncort) as the dependent variable. Additional confounders for all cortisol analyses were: time of cortisol sample, estrogen exposure and recent consumption of food or tobacco.

Results

Descriptive analyses

Groups were well matched on most demographic variables (Table 1). Patients smoked more cigarettes and cannabis than siblings and controls and had more

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Table 1. *Sample characteristics*

	Controls ($n=32$)	Siblings ($n=37$)	Patients ($n=20$)	Test statistic + p value
Age (years), mean (S.D.)	31.7 (11.4)	28.3 (7.8)	29.1 (8.0)	$F=1.38$, $p=0.24$
Gender (male:female)	10:22	14:23	11:09	$\chi^2=2.97$, $p=0.23$
Completed education (primary:secondary:university)[a]	0:11:21	1:14:22	1:15:4	$\chi^2=12.0$, $p=0.02$
PANSS score, mean (S.D.)				
Positive scale	7.4 (1.3)	7.5 (1.1)	12.4 (5.1)	$F=28.89$, $p=0.00$
Negative scale	8.0 (0.2)	8.2 (1.0)	10.8 (3.3)	$F=25.04$, $p=0.00$
Disorganization scale	10.2 (0.4)	10.2 (0.5)	31.4 (4.1)	$F=23.55$, $p=0.00$
Excitement scale	8.3 (0.6)	8.4 (1.1)	9.9 (2.1)	$F=14.11$, $p=0.00$
Emotional distress scale	9.5 (2.5)	9.9 (2.3)	14.2 (5.0)	$F=20.57$, $p=0.00$
Alcohol use present state, mean (S.D.)	6.1 (8.7)	7.6 (9.2)	4.9 (6.6)	$F=0.11$, $p=0.74$
Cigarette use present state, mean (S.D.)	1.1 (3.9)	1.8 (4.6)	12.1 (11.9)	$F=23.50$, $p=0.00$
Cannabis use, frequency				
Past 12 months, mean (S.D.)	1.6 (8.8)	3.4 (12.6)	34.3 (99.8)	$F=4.79$, $p=0.03$
Lifetime, mean (S.D.)	16.8 (34.4)	19.6 (35.7)	54.2 (48.0)	$F=0.00$, $p=0.00$
Hard drug use, frequency				
Past 12 months, mean (S.D.)	1.6 (9.2)	0.0 (0.0)	5.0 (18.2)	$F=0.89$, $p=0.4$
Lifetime, mean (S.D.)	3.4 (13.0)	5.1 (15.4)	40.5 (73.05)	$F=8.66$, $p=0.01$
Antipsychotics				
Type of antipsychotic (typical: atypical)			2:16	
Haloperidol equivalent present state, mean (S.D.)			2.4 (1.9)	
Total antipsychotic use in haloperidol equivalents, mean (S.D.)			48.2 (47.1)	
Duration of illness (years), mean (S.D.)			6.2 (3.5)	
Lifetime estrogen exposure, mean (S.D.)	17 589 (31 700)	18 474 (29 410)	672 (2013)	$F=2.84$, $p=0.10$
Scan type (MDEFT *v.* MP-RAGE sequence)[b]	23:09	26:11	16:04	$\chi^2=0.7$, $p=0.72$
Hippocampal volume (mm^3), mean (S.D.)	3669 (340)	3618 (384)	3491 (319)	$F=10.25$, $p=0.003$
Cortisol (nmol/L), mean (S.D.)	2.65 (0.89)	3.63 (1.3)	N.A.	$F=11.95$, $p=0.001$
ESM observations, mean, n (S.D.)	44.19 (10.7)	40.68 (9.16)	42.05 (9.96)	$F=0.88$, $p=0.35$

PANSS, Positive and Negative Syndrome Scale; MDEFT, modified driven equilibrium Fourier transform; MP-RAGE, magnetization prepared rapid acquisition gradient echo; ESM, experience sampling method; S.D., standard deviation; N.A., not available.

F/χ^2 and p values refer to between-group differences.

[a] Educational level was defined as the highest accomplished level of education (0 = primary school, 1 = secondary education, 2 = university degree).

[b] Total proportion MP-RAGE scans balanced between the groups (around 1/3).

lifetime hard drug use than siblings and controls, with no significant differences between the latter two groups. With regard to handedness, 9.4% of the controls, 8.2% of the siblings and 20% of the patients were left-handed ($\chi^2_2=2.01$, $p=0.37$). All subjects were Caucasian. Eighteen patients received AP (atypical: $n=2$; typical: $n=16$). Furthermore, three patients used an antidepressant and one patient used a benzodiazepine. Six siblings and seven controls had a history of major depressive disorder, but none presented in a current depressive episode.

Two controls used an antidepressant and one control used a benzodiazepine. Patients reported higher total, positive and negative PANSS scores than controls and siblings, with no differences between the latter two groups (Table 1). The mean duration of illness in the patient group was 6.15 years (S.D. = 3.45). There was no overall difference in saliva collection times between the control and sibling group ($B=0.15$, 95% CI −0.27 to 0.56, $p=0.49$).

Group differences in HV, cortisol and stress reactivity

There was a significant association between group and HV. Patients ($B=-247.6$, 95% CI −415.1 to −80.01,

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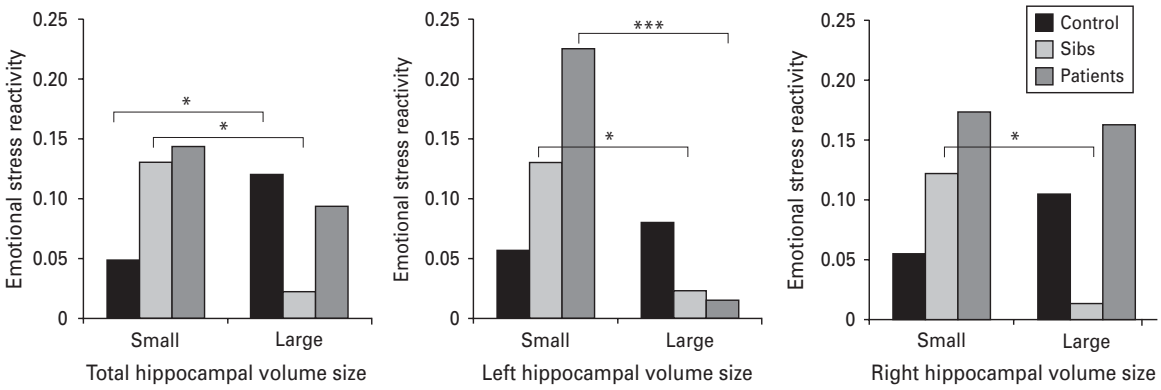

Fig. 1. Emotional stress reactivity stratified by hippocampal volume (HV), in control, sibling and patient groups: multilevel estimates of the effects of daily stress on momentary negative affect (NA). All interaction terms tested with the continuous HV variable were significant. Stratification by small and large HV for visualization purposes. The models control for age, gender, intracranial volume and scan type. Effects are unstandardized regression coefficients; range of all standard errors was 0.02–0.04 (not depicted) (*** $p<0.001$, * $p<0.05$).
$NA=\beta_0+\beta_1$ (group) $+\beta_2$ (stress) $+\beta_3$ (HV) $+\beta_4$ (group × stress) $+\beta_5$ (group × HV) $+\beta_6$ (stress × HV) $+\beta_7$ (group × stress × HV).

$p=0.01$) and siblings ($B=-148.6$, 95% CI −292.66 to −4.47, $p=0.04$) had smaller HV than controls. Patients and siblings did not differ ($B=99.0$, 95% CI −57.63 to 255.61, $p=0.22$).

Siblings had significantly higher cortisol levels than controls ($B=0.28$, 95% CI 0.11–0.45, $p=0.001$). However, no significant association between cortisol levels and total HV ($B=-186.2$, 95% CI −398.16 to 25.76, $p=0.085$), left HV ($B=-157.1$, 95% CI −393.72 to 79.62, $p=0.19$) or right HV ($B=-215.4$, 95% CI −452.63 to 21.94, $p=0.075$) was found in the combined group of siblings and controls and no significant interaction between cortisol and group (siblings and controls) was found for total HV ($\chi^2_1=0.00$, $p=0.99$), left HV ($\chi^2_1=0.03$, $p=0.85$) or right HV ($\chi^2_1=0.03$, $p=0.86$).

There was no significant group (patients, siblings, controls) × event stress interaction in the model of NA ($\chi^2_2=4.54$, $p=0.10$) or, for siblings and controls, in the model of cortisol ($\chi^2_1=0.03$, $p=0.87$).

Emotional stress reactivity contingent on HV and genetic risk

A significant group × event stress × total HV interaction was found in the model of NA ($\chi^2_2=6.54$, $p=0.04$). Differentiation by hemisphere revealed that the interaction with left HV ($\chi^2_2=7.90$, $p=0.02$) and right HV ($\chi^2_2=6.76$, $p=0.03$) was significant. Thus, the association between total, left and right HV and stress reactivity differed between groups (Fig. 1). Stratified analyses revealed increased emotional stress reactivity in controls with large HV in comparison to controls with small HV, being only significant for total HV (total: $\chi^2_1=3.93$, $p=0.048$; left: $\chi^2_1=3.13$, $p=0.077$; right: $\chi^2_1=1.95$, $p=0.16$). In siblings, small HV was consistently associated with significantly more stress reactivity than large HV (total: $\chi^2_1=6.89$, $p=0.009$; left: $\chi^2_1=6.20$, $p=0.013$; right: $\chi^2_1=5.73$, $p=0.017$). A similar pattern was found in patients: small left HV was associated with significantly more stress reactivity than large left HV (left: $\chi^2_1=18.53$, $p<0.0001$). No difference in stress reactivity was found for total and right HV (total: $\chi^2_1=1.20$, $p=0.27$; right: $\chi^2_1=0.06$, $p=0.81$).

Illness duration, AP use, antidepressant medication, depression and handedness

Lifetime AP use did not predict HV in the patient group (total: $B=0.42$, 95% CI −1.91 to 2.75, $p=0.70$; left: $B=1.69$, 95% CI −0.83 to 4.21, $p=0.17$; right: $B=-0.85$, 95% CI −3.18 to 1.48, $p=0.45$). Illness duration did not predict HV in the patient group (total: $B=-35.48$, 95% CI −75.98 to 5.01, $p=0.08$; left: $B=-40.92$, 95% CI −86.54 to 4.70, $p=0.08$; right: $B=-30.04$, 95% CI −72.16 to 2.08, $p=0.15$). Moreover, the results remained the same when handedness, AP use, antidepressant use or history of depression were entered as additional predictor to the analyses.

Cortisol stress reactivity contingent on HV and genetic risk

There was a significant group × event stress × total HV interaction in the model of cortisol ($\chi^2_1=5.74$, $p=0.017$). Differentiation by hemisphere revealed that the interaction was significant for left HV ($\chi^2_1=4.89$, $p=0.027$) and right HV ($\chi^2_1=3.89$, $p=0.049$), suggesting that the association between total, left and right HV and cortisol reactivity to stress differed between the control and sibling groups (Fig. 2). For the control group,

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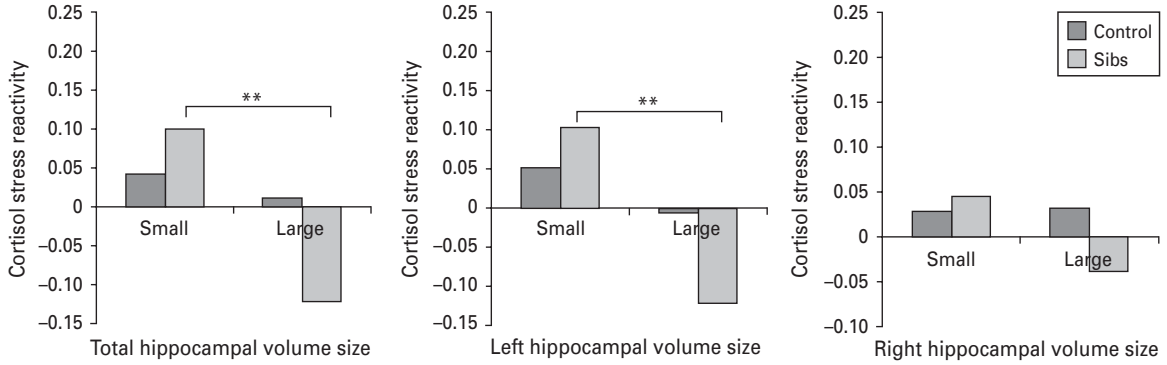

Fig. 2. Cortisol stress reactivity stratified by hippocampal volume (HV), in sibling and control groups: multilevel estimates of the effects of daily stress on cortisol. The dependent variable is log-transformed cortisol (lncort). All interaction terms tested with the continuous HV variable were significant. Stratification by small and large HV for visualization purposes. The models control for time, age, gender, oral estrogen exposure, recent food intake, recent smoking, intracranial volume and scan type. Effects are unstandardized regression coefficients; range of all standard errors was 0.04–0.07 (not depicted) (** $p<0.01$).
$\text{lncort} = \beta_0 + \beta_1\,(\text{group}) + \beta_2\,(\text{stress}) + \beta_3\,(\text{HV}) + \beta_4\,(\text{group} \times \text{stress}) + \beta_5\,(\text{group} \times \text{HV}) + \beta_6\,(\text{stress} \times \text{HV}) + \beta_7\,(\text{group} \times \text{stress} \times \text{HV})$.

stratified analyses revealed no significant differences in cortisol response to daily stress between the hippocampal groups (total: $\chi^2_1=0.19$, $p=0.66$; left: $\chi^2_1=0.71$, $p=0.40$; right: $\chi^2_1=0.00$, $p=0.95$). In the sibling group, however, small HV was associated with increased cortisol responses to stress for the total and left HV groups (total: $\chi^2_1=7.13$, $p=0.007$; left: $\chi^2_1=7.38$, $p=0.007$; right: $\chi^2_1=0.89$, $p=0.35$).

Discussion

To our knowledge, this is the first study to examine the association between stress sensitivity and HV in a sample with different levels of risk for psychosis. The results show that the immediate effect of daily stress on NA and cortisol was conditional not only on HV but also on risk for psychosis. Patients with a small left HV reported increased emotional stress reactivity compared to patients with a large left HV. In line with the results in patients, siblings with a small HV demonstrated increased emotional and cortisol reactivity to stress compared to those with a large HV. By contrast, controls with a large total HV were more emotionally stress reactive than controls with a small total HV, although this was not the case for cortisol reactivity.

HV and overall diurnal cortisol

In line with a substantial amount of (meta-analytic) evidence (Wright *et al*. 2000; Vita *et al*. 2006), HV in the patient group was smaller than that of the control participants. Similarly, decreased HV in the siblings of patients with a psychotic disorder was found, which corresponds with findings from a meta-analysis (Lawrie *et al*. 2008), as does the finding of absence of differences in HV between patients and their non-psychotic relatives (Seidman *et al*. 2002).

There was no association between overall diurnal cortisol levels and HV, which is in line with a previous study that found no association between HV and cortisol in first-episode psychosis (Gunduz-Bruce *et al*. 2007). Another study, however, that differentiated between left and right HV, found that baseline cortisol levels were associated with smaller left HV in first-episode psychosis, but not in controls (Mondelli *et al*. 2010*b*). Although we investigated left and right HV separately, no association between HV and overall cortisol level was found in siblings and controls. Nevertheless, there was a non-significant trend in the direction of a negative association between HV and overall diurnal cortisol levels, which is in line with the result of Mondelli *et al*. (2010*b*) in first-episode psychosis.

Stress reactivity and HV in patients with psychotic disorder

In patients with a psychotic disorder, smaller left HV was associated with increased emotional stress reactivity whereas larger left HV was associated with a diminished emotional response to stress. Thus, not only were patients with a psychotic disorder more likely to have a small hippocampus, but those with a decreased left HV were also more likely to experience augmented emotional stress reactivity. These findings extend earlier findings of the importance of the left hippocampus in the human stress response to the realm of daily life stress reactivity (Liu *et al*. 2012). Right HV, however, did not explain differences in stress reactivity.

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We found differences in stress reactivity within the group of patients with psychotic disorder that could be traced to differences in left HV; that is, patients with a smaller left HV were most responsive to the environment. This finding underscores the notion that there might be different pathways to psychotic disorder, the stress-related pathway being one of them (Myin-Germeys & van Os, 2007; Lataster *et al*. 2010). For example, patients with a smaller HV may have experienced childhood trauma, impacting on cumulative glucocorticoid exposure and HV. Childhood trauma has been associated with reductions in adult HV, particularly on the left side (Stein *et al*. 1997). Hereby, several hippocampal subfields are impacted by childhood trauma and adversities (Teicher *et al*. 2012). Another line of evidence underlines the importance of severe pregnancy and birth complications in making a significant contribution to hippocampal abnormalities in schizophrenia (Stefanis *et al*. 1999), particularly the left hippocampus, emphasizing the importance of non-genetic factors on HV reduction (Schulze *et al*. 2003). The HV, in turn, as shown in the current study, may regulate subtle everyday life stress responses. However, it is important to note that the direction of the association between HV and daily life stress reactivity is unresolved. The question of whether early acquired heightened cortisol reactivity may ultimately cause HV changes or whether alterations in HV, for instance acquired prenatally, are responsible for increased everyday stress reactivity should be answered in longitudinal studies.

Stress reactivity and HV in subjects at familial risk for psychotic disorder

Similar to the findings in patients, siblings with smaller HV exhibited increased emotional and cortisol stress reactivity whereas larger HV in the siblings was associated with decreased emotional and cortisol responses to stress. These findings suggest that the association between smaller HV and increased stress reactivity may be a trait marker for psychotic disorder. With respect to the related mechanisms, Buchanan *et al*. (2009) suggested that the hippocampus may be a crucial element of a network involved in producing an integrated response to psychosocial stress (indexed by behavior and HPA axis activity). Earlier ESM work suggests that an association between cortisol reactivity and negative emotions might be particularly present in those with an increased familial risk for psychotic disorders (Collip *et al*. 2011). In the current study, we found an increased emotional and cortisol response to stress in siblings with smaller HV and, in patients, a smaller left HV was also associated with increased emotional response to stress. It may be that these associations represent markers for reduced integration of the stress response in those with psychotic disorder or at familial risk for psychosis. In other words, the combination of a decreased stress response and larger HV in the siblings, in addition to the increased stress responses in those with smaller HV, may reflect suboptimal HPA axis functioning. This may be a sign of a suboptimal response to psychosocial stress, resulting in increased liability for psychosis. However, another possibility is that the blunted cortisol stress response in siblings with a larger HV represents a protective factor against illness expression, given increased background vulnerability.

Stress reactivity and HV in healthy controls

In controls, we found no association between left and right HV and stress reactivity. However, for total HV the reverse pattern was present, with smaller total HV associated with reduced emotional stress reactivity, and larger total HV associated with increased emotional stress reactivity. Cortisol reactivity to small daily hassles, however, did not differ as a function of HV in the control group.

These findings contradict another study in healthy adults that reported evidence for an association between stress level and smaller anterior HV (Szeszko *et al*. 2006). However, the stress measure used comprised retrospective summary information. By contrast, the current study measures emotional stress reactivity in daily life. Our findings at the emotional level do correspond with a study by Pruessner *et al*. (2007), who found that a larger HV in healthy young participants was associated with increased cortisol response to awakening (CAR) and to an experimental stressor. Pruessner *et al*. (2007) speculated that a larger hippocampus may require increased cortisol concentrations for optimal functioning. However, we found no association between HV and cortisol stress reactivity in the control group. Differences in cortisol measures between the current study and the study by Pruessner *et al*. (2007) may constitute one explanation for the discrepant findings. Cortisol responses to laboratory stress and to awakening may affect different aspects of HPA axis reactivity than the reactivity to everyday hassles, which are probably more subtle stimuli. Nevertheless, the control participants with larger HV reported elevated emotional stress reactivity to naturally occurring stressors compared to those with smaller HV, which corresponds to the cortisol reactivity findings reported by Pruessner *et al*. (2007) and indeed might reflect healthy functioning of the stress system.

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Strength and weaknesses

This study has several limitations. First, the use of ESM booklets instead of electronic devices means that the exact timing of participants' self-reports and saliva samples cannot be firmly established (Stone *et al*. 2002). However, the results of a study comparing self-reported and electronically monitored saliva collection times, with the same intensive, semi-random time-sampling protocol used in the current study, indicated that saliva was generally collected very close to the prescribed time and that self-reported collection times corresponded well with the electronic time-stamps (Jacobs *et al*. 2005). Another comparative study concluded that paper and electronic diaries yield similar results (Green *et al*. 2006).

Second, the current study used a daily life assessment technique in which participants had to comply with a paper-and-pencil diary protocol without the researcher being present, making it difficult to determine whether patients interpreted the ESM questions about, for instance, stress similarly to the other two groups. However, many ESM studies have shown meaningful associations also in groups of patients with psychotic disorders, suggesting that it is feasible for patients with psychotic disorders to participate in daily life research and to properly fill out questionnaires on a momentary basis (Oorschot *et al*. 2009). Third, cortisol stress reactivity was not examined in the patients, as no saliva samples were collected for the patient group (because of the study design and concern about illness and treatment effects on cortisol). Future studies should include cortisol measures in patients with a psychotic disorder, to explore associations between daily life cortisol stress reactivity and HV in patients. Fourth, no saliva samples were taken at the time of awakening, so that the current dataset does not allow examination of the CAR, a measure of HPA axis activity that seems to be blunted in first-episode psychosis (Mondelli *et al*. 2010*a*) and may be associated with HV (Pruessner *et al*. 2007). Another issues is the use of HV, as volume is not necessarily an indicator of hippocampal functioning. However, it should be underlined that this is the first study of its kind (combining brain imaging with momentary daily life measures). Future studies should examine these associations in more detail by including functional imaging.

The current study also has some specific strengths. In particular, the repeated sampling of salivary cortisol over 6 days takes into account the well-known but often ignored unreliability of cortisol measures obtained at infrequent intervals (Hruschka *et al*. 2005). Multiple cortisol measures per person were complemented by a relatively large number of participants. Use of multilevel modeling allowed assessment of within-person associations between cortisol and subjective experience in real time and real-life contexts, as moderated by the HV. Although cortisol measures were within the normal range, intensive sampling revealed different patterns of HPA axis activity with different HVs. Moreover, we combined measures of emotional and cortisol stress sensitivity with HV size, allowing a more comprehensive examination of HPA axis functioning.

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