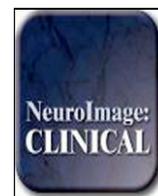




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Reduced hippocampal volume and hypothalamus–pituitary–adrenal axis function in first episode psychosis: Evidence for sex differences



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ABSTRACT

Background: Hippocampal volume (HV) decline is an important marker of psychosis and has been associated with hypothalamus–pituitary–adrenal (HPA) axis dysregulation in various disorders. Given recent findings of sex differences in HPA axis function in psychosis, the current study investigated differences in HV in male and female first episode psychosis (FEP) patients and controls and the interaction of HV with the cortisol awakening response (CAR) and symptoms.

Methods: Fifty-eight patients with a diagnosis of FEP (39 men, 19 women) and 27 healthy community controls (15 men, 12 women) underwent structural magnetic resonance imaging (MRI) on a 1.5 T scanner. Hippocampal volume was determined using previously established segmentation protocols. Saliva samples for cortisol assessment were collected at 0, 30 and 60 min after awakening. Psychotic symptoms were assessed with the Scale for Assessment of Positive Symptoms (SAPS), the Scale for Assessment of Negative Symptoms (SANS) and the Global Assessment of Functioning (GAF) scale.

Results: Male patients had significantly smaller left and right HVs compared to male controls, which appeared to be secondary to global brain volume differences. However, even when controlling for overall brain size, male patients showed smaller HV compared to female patients. The CAR was significantly lower in male patients compared to male controls and female patients. Only in male patients, smaller left HV was significantly associated with a blunted CAR, and smaller HV bilaterally was related to positive psychotic symptoms and lower levels of functioning.

Conclusions: We propose that reduced hippocampal volume and an attenuated cortisol awakening response are related markers of increased stress vulnerability in male psychosis patients and that both contribute to the unfavorable clinical picture in men.

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1. Introduction

Reduced hippocampal volume (HV) is a common finding in psychotic disorders (Adriano et al., 2012; Nelson et al., 1998; Pantelis et al., 2003; Steen et al., 2006; Velakoulis et al., 2006). It is apparent early in the course of psychosis, and further progression of structural abnormalities is observed as the illness evolves (Pantelis et al., 2003; Steen et al., 2006). Hippocampal volume reduction has been implicated in various aspects of the pathophysiology of psychosis including symptom severity (Bodnar et al., 2010; Watson et al., 2012), cognitive function and insight (Buchy et al., 2010; Harrison, 2004).

Smaller HV has been associated with abnormal regulation of the hypothalamus–pituitary–adrenal (HPA) axis in various neuropsychiatric conditions (Sapolsky, 2000). A dysregulation of HPA axis function is increasingly observed in psychosis, characterized by diurnal hyperactivity and a blunted cortisol response to awakening and to acute stress (Borges et al., 2013; Mondelli et al., 2010b; Pruessner et al., 2008; Pruessner et al., 2013; Ritsner et al., 2007; Ryan et al., 2004; van Venrooij et al., 2012). Still, very few researchers have investigated the relationship between HPA axis function and HV in psychosis. A recent study reported an association between higher diurnal cortisol levels and smaller HV in first episode psychosis (FEP) patients (Mondelli et al., 2010b), but a previous study had not found such a relationship (Gunduz-Bruce et al., 2007).

Research in patients with hippocampal damage suggests that reduced hippocampal integrity specifically compromises the cortisol awakening response (CAR), with diurnal cortisol secretion remaining intact (Buchanan et al., 2004; Wolf et al., 2005). Our research group has recently demonstrated a blunted CAR particularly in male FEP

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(Pruessner et al., 2008; Pruessner et al., 2013), and we had argued that this finding might be related to hippocampal and other gray matter abnormalities. Indeed, male psychosis patients show significantly greater structural brain abnormalities compared to female patients, such as larger ventricles (Nopoulos et al., 1997), smaller frontal lobes (Bora et al., 2012), smaller medial temporal lobe volumes (Gur et al., 2000) and reduced hippocampal volume (Adriano et al., 2012; Bogerts et al., 1990a; Bora et al., 2012; Bryant et al., 1999; Exner et al., 2008; Irlé et al., 2011).

The present study was designed to assess sex differences in hippocampal volume and their relationship with the cortisol awakening response and symptoms of psychosis. We hypothesized that reduced hippocampal volume will be associated with an attenuated cortisol awakening response and that both these measures will be related to symptom severity particularly in male patients.

2. Material and methods

2.1. Subjects

Fifty-eight patients with a first episode of psychosis (39 men, 19 women) were recruited from the Prevention and Early Intervention Program for Psychosis (PEPP) (Malla et al., 2003) at the Douglas Mental Health University Institute in Montreal. All patients were within the first 2 years of treatment and follow-up for a first episode of psychosis, had less than 30 days of exposure to antipsychotic medication prior to admission, and were recruited to the present study when they were deemed clinically stable to participate. Since patients usually stabilize within 3 months of admission, most were recruited within the first 6 months, assuring limited exposure to antipsychotic medications. Overlap of patients with our previous report (Pruessner et al., 2013) was 62%. Twenty-seven healthy community controls (15 men, 12 women) were recruited through advertisements in local free newspapers. Control subjects were screened with a telephone interview followed by a diagnostic interview with the Structured Clinical Interview for DSM IV, non-patient edition (SCID-NP) (First et al., 2002) to rule out a diagnosis of a mental disorder in the subjects themselves or in their first degree relatives, as well as use of psychotropic or other medication that could affect HPA axis functioning. All study procedures were approved by the McGill Institutional Review Board, and participants provided written informed consent prior to participation in the study.

2.2. Hippocampal volume assessment

All participants underwent structural high-resolution (isotropic 1 mm) MRI on a Siemens 1.5 T scanner. Hippocampal volume was determined using an appearance model-based automatic segmentation method with patch based local refinement (Hu et al., 2011) and was quality-controlled by a validated rater employing our manual segmentation protocol for this structure (Pruessner et al., 2000). As a measure of total brain volume differences, the individual scaling factor used to transform native into normalized brain volumes based on the MNI 152 template (Mazziotta et al., 1995) was employed.

2.3. The cortisol awakening response

All participants received oral and written instructions for saliva sampling with the Salivette® sampling device (Sarstedt, Quebec City, Canada) at 0, 30 and 60 min after awakening. Participants were instructed not to eat or drink before and during the sampling time and to refrain from brushing their teeth. Samples were stored in a -20°C freezer until analysis. Cortisol was analyzed using a time-resolved immunoassay with fluorescence detection (Dressendorfer et al., 1992). Intra- and inter-assay coefficients of variation were smaller than 10% and 12%, respectively.

2.4. Symptom assessment

Psychotic symptoms were assessed with the Scale for Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1983). Attention items were excluded for the SANS. Functioning was assessed with the Global Assessment of Functioning (GAF) scale (Luborsky, 1962), and depression was assessed with the Calgary Depression Scale (CDS) (Addington et al., 1990).

2.5. Statistical analyses

Differences in all demographic and biological measures were assessed first between the patient and control group as a whole, then in the male and female subgroups, and finally between male and female patients. Clinical and treatment related variables were compared in male and female patients. T-tests were employed for normally distributed data, Mann–Whitney U-tests for skewed data and Chi-Square tests for binary data. For biological variables, univariate ANOVAs were employed to assess group (patients, controls) differences stratified by sex in total brain and left and right hippocampal volume. Repeated measures (0, 30, 60 min) ANOVAs were used to determine group and sex differences in the CAR. These analyses were repeated with ANCOVAs controlling for potential confounders. Both native HV and HV adjusted for total brain size were employed as dependent variables to demonstrate actual volume differences and the impact of global brain volume. In order to assess sex differences in the patient and control groups, we conducted ANCOVAs with hippocampal volume corrected for total brain size as dependent variable, controlling for medication dose and other relevant confounders. Chlorpromazine equivalents (CPZEs) of individual medication dosages were calculated according to Bezchlibnik-Butler and Jeffries (2006). Paired t-tests were used to assess hemisphere differences in HV. In order to obtain a single value for correlational analyses including the CAR, we calculated the area under the curve with respect to ground (Pruessner et al., 2003). Spearman correlations were utilized to assess associations between HV, scaling factor, CAR, and symptoms. Demographic and treatment related variables were included as covariates in partial correlations where applicable.

3. Results

3.1. Demographic and clinical characteristics

Patients were younger than controls at trend level, reported higher rates of cannabis use and cigarette smoking and were more likely to be single. Table 1 provides details on demographic variables in male and female patients and controls. No significant differences between male and female patients were observed in the ratio of non-affective versus affective psychosis, duration of untreated psychosis, duration of untreated illness, positive and negative symptom severity, global functioning and treatment with antipsychotic medication. Table 2 provides details on these patient characteristics for men and women. Higher medication dose was significantly related to impairment in global functioning and more severe negative symptoms in male ($\rho = -.49$; $p = .006$ and $\rho = .59$; $p = .005$; respectively) but not female patients ($\rho = .49$; $p = .087$ and $p > .75$; respectively). In male patients, higher medication dose was also related to smaller right hippocampal volume ($\rho = -.38$; $p = .037$). No such relationship with medication dose was observed for left HV ($p > .12$), total brain volume ($p > .66$) or the CAR ($p > .75$). No association between biological variables and medication dose was observed in female patients (all $p > .55$). Age, cannabis use, cigarette smoking and relationship status were included as covariates in subsequent analyses comparing patients and controls where applicable. Medication dose was included as covariate when comparing male and female patients.

Table 1
Group and sex differences in socio-demographic variables and smoking.

Total group	Patients (N = 58)	Controls (N = 27)	Statistic	p-Value
Age, N (SD)	23.87 (3.71)	22.26 (3.61)	t = 1.88	.064
Sex, male, N (%)	39 (67.2)	15 (55.6)	$\chi^2 = 1.09$.297
Education > high school, N (%)	28 (48.3)	18 (66.7)	$\chi^2 = 2.51$.113
Ethnicity, white, N (%)	45 (77.6)	21 (77.8)	$\chi^2 = 0.00$.984
Relationship status, single, N (%)	54 (93.1)	19 (70.4)	$\chi^2 = 7.85$.005
Cannabis use past 3 months, N (%)	25 (43.1)	5 (18.5)	$\chi^2 = 4.88$.027
Tobacco smoking, >5 cigarettes/day, N (%)	32 (55.2)	5 (18.5)	$\chi^2 = 10.1$.002
Patients only	Men (N = 39)	Women (N = 19)	Statistic	p-Value
Age, N (SD)	23.79 (3.69)	24.04 (3.83)	t = -.24	.812
Education > high school, N (%)	17 (43.6)	11 (57.9)	$\chi^2 = 1.05$.306
Ethnicity, white, N (%)	30 (76.9)	15 (78.9)	$\chi^2 = .030$.862
Relationship status, single, N (%)	37 (94.9)	17 (89.5)	$\chi^2 = .580$.446
Cannabis use past 3 months, N (%)	18 (46.2)	7 (36.8)	$\chi^2 = .452$.502
Tobacco smoking, >5 cigarettes/day, N (%)	23 (59.0)	9 (47.4)	$\chi^2 = .696$.404
Men only	Patients (N = 39)	Controls (N = 15)	Statistic	p-Value
Age, N (SD)	23.79 (3.69)	21.60 (3.62)	t = 1.96	.055
Education > high school, N (%)	17 (43.6)	10 (66.7)	$\chi^2 = 2.31$.129
Ethnicity, white, N (%)	30 (76.9)	11 (73.3)	$\chi^2 = 0.08$.782
Relationship status, single, N (%)	37 (94.9)	13 (86.7)	$\chi^2 = 1.06$.302
Cannabis use past 3 months, N (%)	18 (46.2)	3 (20.0)	$\chi^2 = 3.12$.077
Tobacco smoking, >5 cigarettes/day, N (%)	23 (59.0)	3 (20.0)	$\chi^2 = 6.59$.010
Women only	Patients (N = 19)	Controls (N = 12)	Statistic	p-Value
Age, N (SD)	24.04 (3.83)	23.08 (3.58)	t = 0.69	.494
Education > high school, N (%)	11 (57.9)	8 (66.7)	$\chi^2 = 0.24$.625
Ethnicity, white, N (%)	15 (78.9)	10 (83.3)	$\chi^2 = 0.09$.763
Relationship status, single, N (%)	17 (89.5)	6 (50.0)	$\chi^2 = 5.98$.014
Cannabis use past 3 months, N (%)	7 (36.8)	2 (16.7)	$\chi^2 = 1.45$.228
Tobacco smoking, >5 cigarettes/day, N (%)	9 (47.4)	2 (16.7)	$\chi^2 = 3.03$.082

3.2. Group and sex differences in biological measures

Univariate ANOVAs revealed that left and right hippocampal volume were significantly smaller in patients compared to controls. When stratifying the groups by sex, the differences between patients and controls were only significant in men ($F(1) = 8.88$; $p = .004$ and $F(1) = 8.26$; $p = .006$, respectively; Fig. 1). Global brain volume was also smaller in male patients compared to male controls. Those group differences were still significant when ANCOVAs were conducted which included

age, cannabis use, cigarette smoking and relationship status as covariates (see Table 3 for details). When repeating these analyses with hippocampal volumes corrected for total brain size, differences between patients and controls were not significant anymore (all $p > .40$), suggesting that the observed volume differences in the hippocampus were secondary to global brain volume differences.

In order to compare the difference in hippocampal volume in male and female patients, we conducted ANCOVAs within the patient group with sex (male, female) as independent variable and hippocampal

Table 2
Patient characteristics: Diagnoses and treatment.

	Male (N = 39)	Female (N = 19)	Statistic	p-Value
Non-affective psychosis ^a , N (%)	29 (74.4)	13 (68.4)	$\chi^2 = 0.23$.635
Duration of untreated illness (DUI), weeks (median)	211.1	282.0	Z = -1.64	.101
Duration of untreated psychosis (DUP), weeks (median)	17.14	15.71	Z = -0.52	.603
Symptom ratings:				
Positive symptoms (SAPS), mean (SE)	11.48 (2.25)	7.94 (2.08)	T(56) = 1.00	.322
Negative symptoms (SANS), mean (SE)	22.69 (2.09)	18.56 (2.23)	T(56) = 1.34	.185
Global assessment of functioning (GAF), mean (SE)	48.69 (3.11)	56.32 (4.01)	T(56) = -1.45	.153
Depression (CDS), mean (SE)	3.72 (0.82)	4.94 (1.61)	T(55) = -0.75	.455
Time treated with antipsychotics, weeks (median)	16.71	17.26	Z = -0.42	.673
Dosage of antipsychotic medication (CPZE) ^b , mean (SD)	180.8 (159.6)	141.5 (112.1)	T(41) = 0.80	.427
Antipsychotic medication prescribed, N (%)				
Olanzapine	12 (30.8)	7 (35.9)		
Risperidone (oral)	10 (25.6)	4 (21.1)		
Risperidone (injectable) ^b	7 (18.0)	1 (5.3)		
Quetiapine	4 (10.3)	1 (5.3)		
Aripiprazole ^b	1 (2.6)	3 (15.8)		
Paliperidone ^b	1 (2.6)	2 (10.5)		
Clozapine	1 (2.6)	0 (0.0)		
Ziprasidone	1 (2.6)	0 (0.0)		
No antipsychotic medication	2 (5.1)	1 (5.3)		

^a According to the SCID, as apposed to affective psychosis.

^b Chlorpromazine equivalent doses; could not be calculated for patients treated with paliperidone, aripiprazole and long-acting injectable risperidone.

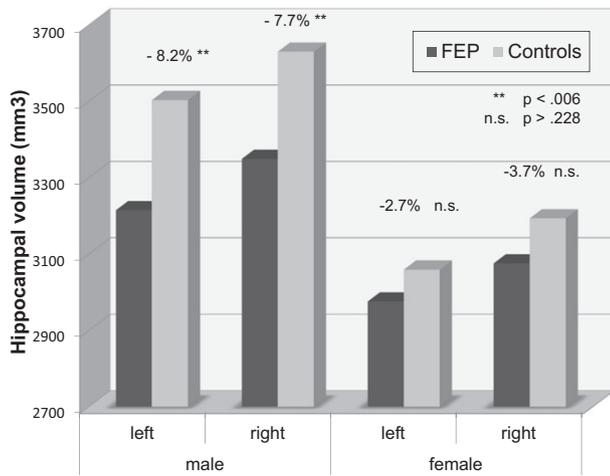


Fig. 1. Hippocampal volume in male and female FEP patients and controls.

volume corrected for total brain size as dependent variable while controlling for medication dose, age, cannabis use, smoking and relationship status. Male patients showed significantly smaller left and right hippocampal volumes compared to female patients ($F(1) = 19.14$; $p < .001$ and $F(1) = 16.84$; $p < .001$, respectively). In controls, relative left and right volume of the hippocampus was also smaller in men compared to women, but the difference was only significant for the right and not for the left hippocampus ($F(1) = 4.41$; $p = .048$ and $p = .34$, respectively). Paired sample *t*-tests revealed smaller left compared to right HV in both patients and controls ($t(57) = -5.96$; $p < .001$ and $t(26) = -4.02$; $p < .001$), and both men and women. The strongest difference between left and right HVs was observed in male patients ($t(38) = -5.74$; $p < .001$).

The CAR was significantly smaller in patients compared to controls ($F(1) = 8.03$; $p = .006$), but further analysis revealed that this difference was only significant in male but not female participants ($F(1) = 5.65$; $p = .021$ and $F(1) = 1.62$; $p = .214$, respectively; see Table 3 for details). The CAR was significantly smaller in men compared to women in both patients and controls ($F = 4.26$; $p = .044$ and $F = 4.96$; $p = .037$, respectively).

Table 3
Hippocampal volume and cortisol awakening response in male and female patients and controls.

Total group	FEP (N = 58)	Controls (N = 27)	ANOVA (F/p-value)	ANCOVA (F/p-value) ^e
Left HV, mean (SD) ^a	3136.5 (323.1)	3305.9 (343.9)	4.86/.030	3.99/.049
Right HV, mean (SD) ^a	3259.6 (343.9)	3435.9 (327.8)	4.98/.028	5.71/.019
Scaling factor (SD) ^b	1.249 (0.130)	1.202 (0.137)	2.30/.133	4.86/.030
CAR AUCg, mean (SD) ^c	693.0 (398.4)	932.6 (341.4)	8.03/.006	8.02/.006
Time of awakening, mean (SD) ^d	8:51 a.m. (1:53)	8:23 a.m. (1:31)	1.31/.255	1.26/.272
Men	FEP (N = 39)	Controls (N = 15)	ANOVA (F/p-value)	ANCOVA (F/p-value) ^e
Left HV, mean (SD) ^a	3214.7 (336.9)	3503.0 (261.6)	8.88/.004	4.09/.049
Right HV, mean (SD) ^a	3349.2 (351.5)	3629.9 (219.3)	8.26/.006	4.71/.035
Scaling factor ^b	1.194 (0.095)	1.109 (0.036)	10.23/.002	7.18/.010
CAR AUCg, mean (SD) ^c	620.1 (368.6)	861.3 (298.1)	5.65/.021	6.09/.021
Time of awakening, mean (SD) ^d	9:01 a.m. (2:01)	8:13 (1:33)	1.97/.166	2.31/.135
Women	FEP (N = 19)	Controls (N = 12)	ANOVA (F/p-value)	ANCOVA (F/p-value) ^e
Left HV, mean (SD) ^a	2975.9 (224.8)	3059.5 (270.7)	0.87/.359	1.87/.184
Right HV, mean (SD) ^a	3075.7 (246.6)	3193.3 (277.6)	1.52/.228	5.41/.028
Scaling factor ^b	1.363 (0.119)	1.319 (0.111)	1.03/.319	2.53/.124
CAR AUCg, mean (SD) ^c	842.7 (425.1)	1021.7 (383.2)	1.62/.214	1.67/.208
Time of awakening, mean (SD) ^d	8:31 a.m. (1:36)	8:36 (1:30)	0.02/.898	2.64/.612

^a Hippocampal volume, native space.

^b Transformation factor from native into standard space, indicates total brain volume differences.

^c Cortisol awakening response (area under the curve with respect to ground).

^d At the time of cortisol assessment.

^e Controlling for age, cigarette smoking, cannabis use and relationship status.

3.3. Associations between hippocampal volume and the CAR

In the total patient group, both left and right HVs (relative to total brain size) were related to the CAR at trend level ($\rho = .24$; $p = .073$ and $\rho = .25$; $p = .059$; respectively). No such association was observed in controls ($p > .222$). When separating the groups by sex, we observed a significant correlation between the CAR and left hippocampal volume only in male patients ($\rho = .37$; $p = .021$; see Fig. 2). This correlation was still significant when an outlier with cortisol levels more than three standard deviations above the group mean was excluded from the analysis ($\rho = .37$; $p = .024$). The correlation between right HV and the CAR in male patients was significant at trend level ($p = .10$). No significant association between left or right HV and the CAR was observed in female patients (both $p > .50$) and in male or female controls (all $p > .13$). When controlling for medication dose, cannabis use and cigarette smoking employing partial correlations in a subgroup of patients for which CPZE medication dose could be calculated (30 men, 13 women), the association between the CAR and left and right HV in male patients was still significant ($r(24) = .39$; $p = .011$ and $r(24) = .40$; $p = .034$; respectively). Again, no association was observed in female patients (all $p > .21$) and in male or female controls, controlling for cannabis use and smoking (all $p > .50$). No association was observed between the CAR and total brain volume in either group or sex (all $p > .14$).

3.4. Association between biological measures and symptoms

In the total patient group, smaller left and right HVs (adjusted for total brain size) were associated with lower global functioning ($\rho = .29$; $p = .026$ and $\rho = .32$; $p = .016$; respectively). Total brain volume differences were not related to symptoms in the total group ($p > .22$). When separated by sex, smaller left and right HVs in male patients were significantly associated with lower global functioning (both $\rho = .38$; $p = .017$) and more positive symptoms of psychosis ($\rho = -.39$; $p = .014$ and $\rho = -.37$; $p = .020$; respectively). No such associations with symptoms were observed in female patients (all $p > .18$) and for total brain volume ($p > .10$). Hippocampal and total brain volumes were not associated with negative symptoms and depression in either sex (all $p > .18$). Hippocampal volume was also not significantly related to DUP or DUI (all $p > .14$). Controlling for cannabis

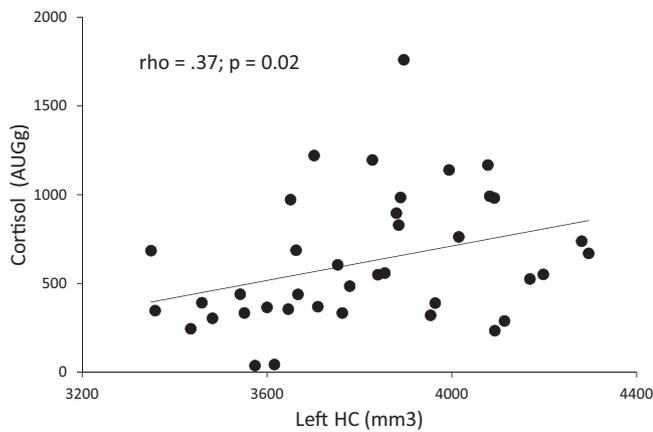


Fig. 2. Spearman correlation between left hippocampal volume and the cortisol awakening response in male first episode psychosis patients.

use and cigarette smoking in subgroups of patients using partial correlations confirmed the association between left and right HVs and positive symptoms in men ($r(36) = -.40$; $p = .012$ and $r(36) = -.36$; $p = .029$; respectively). However, when controlling for medication dose in a subgroup of patients, the previously observed associations between hippocampal volume and symptoms were not significant anymore (all $p > .11$). A more blunted CAR in patients was associated with a lower level of global functioning at trend level ($\rho = .24$; $p = .069$). The CAR was not related to any other symptoms in the total patient group or when separated by sex (all $p > .12$).

4. Discussion

The present study investigated sex differences in hippocampal volume and their association with the cortisol awakening response and symptoms in patients with a first episode of psychosis. As hypothesized, HV was significantly reduced in male patients both in comparison to male controls and to female patients. The observed HV differences between male patients and controls appeared to be secondary to whole brain volume differences and to be superimposed on HV differences between men and women, rendering male psychosis patients particularly vulnerable to HV loss. We furthermore observed a blunted CAR specifically in male patients and demonstrated an association between smaller HV and the lower CAR again only in male patients. Smaller left and right HVs were related to impaired global functioning and more positive symptoms in male patients only. To the best of our knowledge, the present study is the first to demonstrate a sex-specific relationship of smaller HV with both a blunted CAR and higher symptom severity in patients with a diagnosis of first-episode psychosis.

Our results confirm recent independent findings of sex differences in psychosis with regard to HV reduction (Adriano et al., 2012; Bogerts et al., 1990b; Bora et al., 2012; Exner et al., 2008; Irlle et al., 2011) and HPA axis regulation (Pruessner et al., 2008; Pruessner et al., 2013). The findings are also in line with several recent studies showing a relationship between reduced hippocampal volume and more severe positive symptoms (Bodnar et al., 2010; Brambilla et al., 2013; Ebdrup et al., 2011; Kuhn et al., 2012; Watson et al., 2012). Sex differences in these studies may have been masked by the consistently larger proportion of male patients.

The observed correlation between reduced HV and a dysregulated HPA axis resembles findings in various disorders such as depression (O'Brien et al., 1996), post-traumatic stress disorder (Yehuda, 2001), Cushing's syndrome (Starkman et al., 1992), aging (Lupien et al., 1998) and, more recently, FEP (Mondelli et al., 2010b). This association has been explained by the role of the hippocampus as a mediator of negative feedback in situations of elevated glucocorticoid levels (Jacobson

and Sapolsky, 1991; Pruessner et al., 2010). Chronically elevated cortisol levels have been shown to cause atrophy of dendrites in the hippocampal CA3 region and suppression of neurogenesis of dentate gyrus granule neurons (McEwen, 1999), which can result in overall volume reduction of the structure and further dysregulation of the HPA axis. On the other hand, hippocampal integrity can already be compromised due to genetic and neurodevelopmental abnormalities and early life adversity, constituting risk factors for the development of HPA dysregulation in response to subsequent traumatic or other chronic stress situations (Buss et al., 2007; Gilbertson et al., 2002; Smith et al., 2003).

The observed relationship between HV reduction and HPA axis dysregulation and the association of both with functional and symptom outcomes are in accordance with the neural-diathesis stress model of schizophrenia (Walker and Diforio, 1997) and support the notion that both biological factors together are implicated in the disease process of psychosis. In fact, our findings suggest that the neural-diathesis stress model might be particularly relevant for male patients. The here reported sex differences in neurobiological variables could furthermore be related to other disadvantages in male compared to female patients such as a higher rate of treated incidence of psychosis (Aleman et al., 2003; Anderson et al., 2012), an earlier age of onset (Angermeyer and Kuhn, 1988), and a poorer treatment response (Angermeyer et al., 1990).

In accordance with previous studies, the left hippocampus was generally smaller than the right in both patients and healthy controls (Adriano et al., 2012) and was particularly reduced in FEP patients (Buehlmann et al., 2010; Malchow et al., 2013; Velakoulis et al., 2006). Notably smaller left HV was related to a blunted CAR, which resembles another recent study in FEP patients reporting smaller left hippocampal volume in association with higher diurnal cortisol levels (Mondelli et al., 2010b). Studies reporting smaller left HV in adults diagnosed with PTSD or dissociative identity disorder (Bremner et al., 1997; Stein et al., 1997) and FEP patients (Hoy et al., 2012) who experienced childhood trauma, suggest that stress related mechanisms are implicated in left HV loss. Similarly, another recent study demonstrated an association of small left HV with increased emotional and cortisol reactivity to stress in schizophrenia patients and healthy siblings (Collip et al., 2011).

Compromised hippocampal integrity impairs episodic, relational and spatial memory processes (Bohbot et al., 1998; Cohen et al., 1999; Eichenbaum, 1999; Squire, 1992). Indeed, some research suggests that male schizophrenia patients may be more vulnerable to cognitive deficits (Goldstein et al., 1998) and show reduced volume in brain regions implicated in verbal memory circuitry (Abbs et al., 2011). It has been suggested that the CAR occurs in response to "activation of memory representations about the self and orientation in time and space upon awakening" (Fries et al., 2009). Pathological changes to the hippocampus might compromise these cognitive representations and the associated cortisol response, thus rendering male patients more vulnerable to stress.

It has been suggested that sex and gender differences in schizophrenia are a consequence of sex differences in brain development and a higher susceptibility of male fetuses to environmental insults (Goldstein et al., 2002; Seeman, 2008). A factor that not only is crucially involved in the sexual differentiation of the brain but also affects a variety of other neuronal and behavioral processes in development and adulthood is estrogen (Abel et al., 2010; Hafner, 2003; McEwen, 2002; Seeman, 1997). Estrogen receptors have been identified in many brain structures, importantly those comprising the HPA axis, including the hippocampus (McEwen, 2002), and gonadal steroids have effects on the HPA response to stress (Handa and Weiser, 2014; Kirschbaum et al., 1999). The putative neuroprotective effect of estrogen in women and its absence in men has been suggested as an explanation for the relatively greater hippocampal volume decline over time in men (Hu et al., 2013; Lord et al., 2008; Pruessner et al., 2001; Pruessner et al., 2010). Estrogen has furthermore been shown to improve hippocampus dependent learning and memory (McEwen, 2002). In psychosis, the 'estrogen hypothesis' is supported by the lower prevalence rate and more favorable course of schizophrenia

in women before menopause, higher rates of illness onset after menopause, and variability of psychotic symptoms over the menstrual cycle (Huber et al., 2004; Riecher-Rossler et al., 1994).

Another influential developmental factor is early life adversity, which can have important consequences for HPA axis regulation (Heim et al., 2008; Heim et al., 2009; Liu et al., 1997), hippocampal integrity (Buss et al., 2007; Driessen et al., 2000) and the development of psychosis (Fisher et al., 2013; Matheson et al., 2013; van Winkel et al., 2013; Varese et al., 2012) in adulthood. Some studies suggest that men might be particularly vulnerable to the effects of early life adversity on long-term mental health outcomes (Kivimaki et al., 2002; Pruessner et al., 2013; Shevlin et al., 2007). In support of this notion, we have recently reported an association between the blunted CAR in male FEP patients and poor self-reported parental bonding (Pruessner et al., 2013).

A limitation of the study is the cross sectional design, which prevents conclusive insights about cause and effect in the observed variables. Further limitations are the small sample size in the control group and the smaller number of female patients, which compromised the statistical power to detect significant associations in these subgroups. We have not considered several potential confounders of cortisol levels such as daylight exposure (Vreeburg et al., 2009), activity levels (Labsy et al., 2013) and oral contraceptive use (Bouma et al., 2009). The observed sex difference in HV might not be specific to psychosis, as it appears to begin in young adulthood even in a healthy population (Pruessner et al., 2001). It cannot be excluded that medication dose had an impact on hippocampal volume, although it is likely that the higher medication dose, seemingly explaining the relationship between hippocampal volume and symptoms, was a consequence of the relationship between symptom severity and medication dose in male patients. It could be considered another limitation that the CAR was the only measure of HPA axis regulation in the current study given that changes in the CAR do not necessarily correspond with diurnal measures of HPA function (Mondelli et al., 2010a).

In conclusion, our findings demonstrate sex specific reductions in hippocampal volume that are closely connected to HPA axis regulation and symptoms. We propose that these findings are likely a consequence of sex differences in neurodevelopment and a lack of the neuroprotective effects of estrogen, rendering men more vulnerable to the effects of stress and more prone to develop mental illness. Our results add to an increasing number of findings showing a disadvantage for male patients with psychosis. A better understanding of the associations between various pathophysiological mechanisms involved in the expression of sex differences in psychosis is expected to explain some of the heterogeneity in illness phenotypes, to reconcile inconsistent findings, and to open up new avenues for the development of effective interventions.

Authors' contributions

Ethical standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Conflict of interest

None of the authors declare any financial or other conflicts of interest.

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