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# Abnormal Volumetric Alterations in the Schizophrenic Brain

Original Paper

Different lines of evidence support a role for the cerebellum and the hippocampus in the pathology of schizophrenia. The involvement of the cerebellum might be represented in structural deficiencies in patients with schizophrenia. The current research investigates the possibility of volumetric differences between healthy controls and patients suffering from schizophrenia.

Volumetric measures were obtained from nineteen patients diagnosed with first episode psychosis, early psychosis or established schizophrenia and thirty healthy controls using a 1.5 Tesla magnetic resonance scanner. Results show a significant difference in the association patterns between groups in the structures of interest. This indicates possible structural abnormalities in the hippocampus and cerebellum, associated with the pathology of schizophrenia.

**Keywords**: Schizophrenia; MRI; Volumetrics; Hippocampus; Cerebellum

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## INTRODUCTION

Schizophrenia is a disorder that affects 1 - 2% of the population, and globally accounts for 1.1% of the disability adjusted life years. Because of this high level of incapacitating effect, schizophrenia is one of the most expensive pathologies in modern day health care (Picchioni & Murray, 2007). In recent years, schizophrenia has been conceptualized as a disorder caused by neurodevelopmental deficits (Insel, 2010), and neuroanatomical research has focused mainly on the higher cortical areas. Although schizophrenia is best known as a disease of cognition (Keefe, Eesley, & Poe, 2005) with no apparent pathology in motor function, the majority of patients (50-65%) show a variety of motor impairments (Bombin, Arango, & Buchanan, 2005;

Heinrichs & Buchanan, 1988). Recently it has been proposed that these deficits in motor coordination, combined with cognitive symptoms such as disinhibition and sensory integration, could imply a possible involvement of the cerebellum in the pathology of schizophrenia (Andreasen et al., 1996; Thomann et al., 2009).

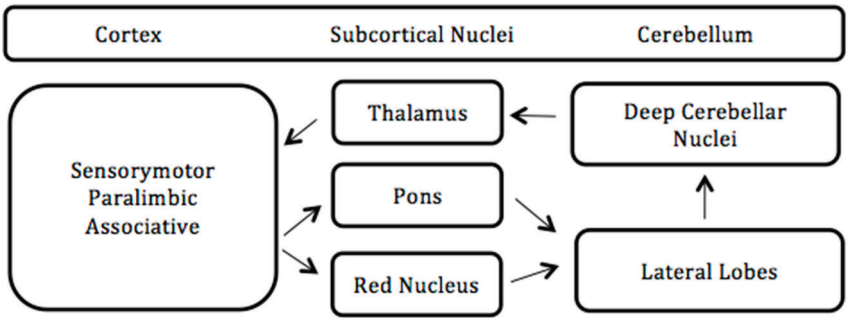


**Figure 1**. Sensorimotor and high-order information is carried from the cerebral cortex to the pons, after which fibbers carry the projections to the lateral lobes of the cerebellum. Additional projections from the cerebral cortex run through the red nucleus, where they synapse and subsequently give rise to the central tegmental tract that runs to the lateral cerebellar lobes. The deeper nuclei of the cerebellum project back to the cortex and close the loop (Andreasen et al., 1996).

Traditionally, the cerebellar structure is thought to be involved mainly in motor functioning, conditioning and coordination (Mottolese et al., 2013). Conversely, the use of modern paradigms combined with diffusion tensor imaging (DTI) tract-tracing methodologies, has lead researchers to believe that the cerebellum is also involved in higher cognitive functioning through multiple neural pathways involving subcortical structures such as the pons and the thalamus (Thach, 2007). Through these circuits, the cerebellum is able to project to sensorimotor, autonomic and multiple association cortices (Allen et al., 2005; Jissendi, Baudry, & Baleriaux, 2008).

One of the most evident pathways, the cortico-cerebellar-thalamic-cortical (CCTC) circuit, allows the higher order association areas to transfer information to the cerebellum through the basilar pons (Fig. 1). After processing the signal, the dentate nucleus of the cerebellum sends the information back to the frontal cortex and other related cerebral areas, making bidirectional information streaming possible (Andreasen et al., 1996; Middleton & Strick, 1994; Schmahmann & Pandya, 1997). These circuits are believed to allow the cerebellum to be involved in higher cognitive functions including reasoning and executive planning. Andreasen and Pierson (2008) proposed that the cerebellum operates as a regulatory mechanism within the CCTC circuit. During normal functioning, Purkinje cells decipher information that arrives at the cerebellum, and as a consequence, the input programs the cerebellar Purkinje cells by means of long-term depression. This programming allows the cerebellum to detect variations in the input signal and modulate the information in an inhibitory manner. Conversely, schizophrenic patients show symptoms

of cognitive dysmetria, which include difficulties in the coordination of mental processes. This disability could derive from a failing of the cerebellum to connect the information in the right order due to structural abnormalities. The information, directly relayed to the cortex, is then presented in a desynchronized manner, and the patient experiences a slowing of cognition (Andreasen & Pierson, 2008). The slowing of cognition combined with the wrong order of the input to the higher areas of the cortex could lead to symptoms relatively common in schizophrenia, including blurred thought and impaired speech, as well as hallucinations and loss of volition (Andreasen et al., 1999; Andreasen & Pierson, 2008; Mouchet-Mages et al., 2011).

Modern imaging techniques provide further evidence supporting the involvement of the cerebellum in schizophrenia (Crespo-Facorro et al., 2001; Paradiso et al., 2003). For example, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have shown a decreased blood flow in patients' cerebellum and other brain areas in response to tasks involving recognition memory and attention (Andreasen & Pierson, 2008; Crespo-Facorro et al., 1999). Structural volumetric studies have also shown abnormalities in cerebellar matter in schizophrenia. Using imaging modalities such as computed tomography (CT) (Heath, Franklin, & Shraberg, 1979; Weinberger, Torrey, & Wyatt, 1979) and magnetic resonance imaging (MRI) (Ichimiya, Okubo, Suhara, & Sudo, 2001; Loeber, Cintron, & Yurgelun-Todd, 2001; Okugawa, Nobuhara, Takase, & Kinoshita, 2007), research suggests that cerebellar matter was reduced in schizophrenic patients as compared to healthy controls. MRI studies have shown a particular reduction in the right vermal matter (Okugawa, Sedvall, & Agartz, 2003). Also, correlations between cognitive symptoms, clinically defined as neurological soft signs (NSS), and cerebellar volumes were found (Szeszko et al., 2003). Patients with smaller cerebral volumes scored higher on scales testing the severity of NSS; conversely, healthy controls scored lower than patients with schizophrenia (Heuser, Thomann, Essig, Bachmann, & Schroder, 2011; Janssen et al., 2009).

In addition to the cerebellum, Lodge and Grace (2007) suggest an involvement of the hippocampus in the pathology of schizophrenic patients. They propose that hippocampal irregularities might play a role in the dysregulation of subcortical dopamine system functioning, which could lead to positive symptoms such as hallucinations in patients suffering from psychosis or schizophrenia. Evidence seems to supports the possibility that the ventral portion of the hippocampus is involved in the activation of dopamine neurons in response to the environment. The ventral hippocampus projects to the nucleus accumbens, which in turn inhibits the activity of the ventral pallidum. Inhibition of the ventral pallidum is linked to the eliciting of higher amplitudes in the phasic dopamine signal, leading to an increase in dopamine (Floresco, Todd, & Grace, 2001). Lodge and Grace (2007) suggested that in schizophrenic patients, the function of ventrally located GABAergic interneurons in the hippocampus is impaired, rendering the hippocampus hyperactive when confronted with environmental stimulation. The inability to inhibit the hippocampus, due to structural abnormalities, could lead to elevated levels of limbic hippocampal activity, and result in higher dopamine levels (Grace, 2012). Kapur (2003) suggests that higher dopamine concentrations could in turn lead to positive symptoms, such as hallucinations and delusions, in patients

suffering from psychosis or schizophrenia. Dopamine is seen as a mediator in the assignment of salience to experienced events. If the phasic release of dopamine becomes greater, the patient is not able to discriminate and attribute the right level of salience to transient events, termed aberrant salience. This leads to an abnormal level of phenomenological attribution in the importance of a certain mundane aspect of the patients' life.

Although involvement of the hippocampus in schizophrenia remains controversial, evidence seems to support the notion of reduced hippocampal volumes in schizophrenia. A review by McCarley et al. (1999) suggests that the parahippocampal gyrus, the entorhinal cortex and the hippocampus show reduced volumes in 77% of the studies reviewed. Additionally, Sanfilipo et al. (2002) found correlations between reduced grey matter, but not white matter, volume in hippocampal regions and cognitive performance in patients, indicating an involvement of the hippocampus in schizophrenia.

Given these previous findings, the current research explores the possibility of volumetric differences in the hippocampal grey matter, and cerebellar white and grey matter. Using a 3-dimensional manual segmentation method, the structural volumes of schizophrenic patients and healthy controls were acquired and subsequently contrasted. Findings are expected to replicate previous findings; showing lower volumes of cerebellar and hippocampal matter in patients (Honea, Crow, Passingham, & Mackay, 2005; Loeber et al., 2001; Weinberger et al., 1979), as well as reduced white/grey matter ratios in the cerebellum.

## METHODS

### Participants

**Table 1**. Statistical parameters for group characteristics.

| | Schizophrenia ($n$ = 19) | Healthy controls ($n$ = 30) | Independent $t$ test | |
|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | $t$(df) | $p$ |
| Gender | 8 Male / 11 Female | 19 Male / 11 Female | - | - |
| Age (years) [a] | 26.5 (6.1) | 24.5 (3.4) | 1.48 (47) | 0.15 |
| BMI [b] | 27.9 (4.7) | 24.3 (3.3) | -2.92 (29) | 0.01* |
| Weight (kg) | 83.1 (17.7) | 73.0 (14.6) | -2.18 (47) | 0.04* |
| Height (cm) | 172.3 (8.6) | 172.8 (9.8) | 0.18 (47) | 0.86 |
| Chronicity (years) | 3.3 (3.8) | 0.0 (0.0) | - | - |
| Medication [c] | 14.0 | 0.0 | - | - |

[a] Age at time of scan. [b] Body Mass Index: mass (kg)/(height (m))$^2$. [c] Atypical antipsychotics.
* Significant group difference at $p < 0.05$.

Nineteen adults diagnosed with first episode psychosis (n=8), early phase psychosis (<5 years) (n=7) or established schizophrenia (>5 years) (n=4) were recruited from the Nova Scotia Early Psychosis Program (NSEPP), Halifax, Canada. Diagnosis was provided by the treating psychiatrist and was done using DSM-IV criteria. Demographic and clinical characteristics are summarized in Table 1. Thirty healthy controls were recruited through advertisements on posters and websites. Before admittance, healthy controls were screened for possible psychiatric history using

the Structured Clinical Interview for DSM-IV (SCID) (First, Gibbon, Spitzer, & Williams, 2002). Exclusion followed when participants were diagnosed with an axis I disorder, or if a first-degree relative was diagnosed with psychosis or bipolar disorder. Participants were also excluded if they had more than minimal experimentation with illicit drugs (less than 10 occasions of drug use during life time) or a pattern of alcohol misuse. Finally, all participants had to meet the MR safety criteria. Full ethics approval was obtained from the hospital ethics board, and a written consent was obtained after information about the study was provided.

**MR online acquisition protocol**

Brain images were acquired using a 1.5 Tesla GE scanner and a standard eight-channel head coil. The MR imaging acquisition protocol included the following parameters: a 3D SPGR T1-weighted sequence, time of echo (TE) = 4.2 ms, time of repetition (TR) = 11.3 ms, flip angle = 20 degrees, time of inversion (TI) = 500 ms, field of view (FOV) = 25.6 cm, matrix = 256 x 256 pixels, inter-slice gap = 0 mm and 170 axial slices with a 1 mm isotropic resolution.

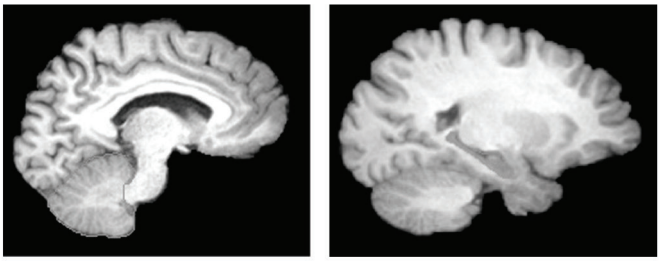

**Figure 2.** Sagittal plane illustrating the manual segmentation of the cerebellum (on the left) and the automatically segmented hippocampus (on the right).

**Offline volumetric measurements**

Using FSL software version 5.0.4 (FMRIB's Software Library), volumetric measures were acquired. During the delineation process, researchers were kept blind with regards to participants' group membership. First, brain matter was extracted using FSL's integrated BET procedure (Brain Extraction Tool, Bias Field & Neck Clean-up) (Smith, 2002). The output images were carefully examined for residual tissue, which was manually removed when present (special attention was given to eye, bone and neck areas, including the dura mater). Next, subcortical structures (including the hippocampus) were registered to the standard shape model, and subsequently segmented using the FIRST procedure (FMRIB's Integrated Registration & Segmentation Tool) (Patenaude, Smith, Kennedy, & Jenkinson, 2011) (Fig. 2). Finally, segmentation of grey matter, white matter and cerebrospinal fluid was performed using FSL's automated FAST procedure (FMRIB's Automated Segmentation Tool), a tool used to differentiate between different tissue types in 3D brain images (Zhang,

Brady, & Smith, 2001). FSLstats was used to calculate the final volumetric measures (voxel count, $mm^3$).

*Manual delineation of the cerebellum*

Using the automatically segmented images of the brain, fully manual segmentation of the cerebellum was performed. This experimenter-driven approach is the gold standard in volumetric studies (Tae, Kim, Lee, Nam, & Kim, 2008). Manual segmentation was based on images of the Human Brain Anatomy Atlas (Damasio, 2005) in order to ensure valid and consistent judgment across brains. First, the cerebellar hemispheres were separated using mainly the coronal view. The interhemispheric fissure was used as a central guideline in establishing a distinct border between the right and left half of the cerebellum. Second, the sagittal view was used to delineate the rest of the cerebellum. Starting from the most medial slice, the delineation process followed in the lateral direction demarcating voxels outlining the cerebellum. The small line of cerebrospinal fluid located superiorly to the cerebellum was used as the main landmark to separate the cerebellum from the cerebrum (Fig. 2).

*Manual delineation of the cerebrum*

The cerebrum was segmented, employing automated and manual methods similar to the procedure used in the delineation of the cerebellum. All brain structures located superiorly to the pons were included. The delineated cerebellar matter was excluded from the segmentation. Using the sagittal view, excessive cerebrospinal fluid was removed. The cerebrum was used as a covariant to assess whether the group differences in cerebellar and hippocampal volumes were not due to a general difference in brain size, but because of actual volumetric differences in the structures of interest. The cerebrum was chosen over the whole brain because it does not include the cerebellum structure itself, providing a more valid covariate.

## RESULTS

### Demographics & clinical characteristics

Independent sample t-tests were used to assess potential group differences in age, BMI, weight and height at time of scan (Table 1). No significant differences were found for age and height; however, the Body Mass Index (BMI) showed significant differences, which were driven by heavier weight in patients.

**Table 2.** Linear correlations between structures of interest and total cerebrum volume (voxel count).

| | Pearson (parametric) | | | | | | Spearman (non-parametric) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Schizophrenia ($n$ = 19) | | | Healthy controls ($n$ = 30) | | | Schizophrenia ($n$ = 19) | | | Healthy controls ($n$ = 30) | | |
| | $r$ | $r^2$ | $p$ | $r$ | $r^2$ | $p$ | $r$ | $r^2$ | $p$ | $r$ | $r^2$ | $p$ |
| Cerebellum | | | | | | | | | | | | |
| Total | 0.61 | 0.37 | 0.006 | 0.82* | 0.67 | 0.000 | 0.38 | 0.14 | 0.110 | 0.80* | 0.64 | 0.000 |
| Left | 0.67* | 0.45 | 0.002 | 0.78* | 0.61 | 0.000 | 0.51 | 0.26 | 0.026 | 0.79* | 0.62 | 0.000 |
| Right | 0.51 | 0.26 | 0.025 | 0.83* | 0.69 | 0.000 | 0.33 | 0.11 | 0.175 | 0.82* | 0.67 | 0.000 |
| Cerebellum GM | | | | | | | | | | | | |
| Total | 0.49 | 0.24 | 0.035 | 0.73* | 0.54 | 0.000 | 0.30 | 0.09 | 0.209 | 0.75* | 0.56 | 0.000 |
| Left | 0.53 | 0.28 | 0.020 | 0.71* | 0.50 | 0.000 | 0.31 | 0.10 | 0.204 | 0.73* | 0.53 | 0.000 |
| Right | 0.42 | 0.18 | 0.074 | 0.73* | 0.54 | 0.000 | 0.21 | 0.04 | 0.363 | 0.71* | 0.50 | 0.000 |
| Cerebellum WM | | | | | | | | | | | | |
| Total | 0.65* | 0.43 | 0.003 | 0.75* | 0.56 | 0.000 | 0.55 | 0.30 | 0.015 | 0.71* | 0.50 | 0.000 |
| Left | 0.65* | 0.43 | 0.003 | 0.75* | 0.56 | 0.000 | 0.51 | 0.26 | 0.027 | 0.68* | 0.46 | 0.000 |
| Right | 0.62 | 0.38 | 0.004 | 0.73* | 0.54 | 0.000 | 0.51 | 0.26 | 0.025 | 0.69* | 0.48 | 0.000 |
| Hippocampus | | | | | | | | | | | | |
| Total | 0.34 | 0.12 | 0.150 | 0.63* | 0.40 | 0.000 | 0.27 | 0.07 | 0.270 | 0.68* | 0.46 | 0.000 |
| Left | 0.31 | 0.10 | 0.204 | 0.54* | 0.29 | 0.002 | 0.35 | 0.12 | 0.141 | 0.62* | 0.38 | 0.000 |
| Right | 0.34 | 0.12 | 0.153 | 0.60* | 0.36 | 0.001 | 0.32 | 0.10 | 0.183 | 0.61* | 0.37 | 0.000 |

Note. GM, grey matter. WM, white matter. *A Bonferroni correction (12 comparisons) set the alpha value at < 0.004.

### *Associations between volumetric variables*

Pearson and Spearman correlations were computed within each group in order to search for associations between volumes (voxel count, $mm^3$). The total cerebrum volume was correlated with each of the following structures: total cerebellum matter volume, cerebellum grey and white matter volumes, left and right cerebellum volumes as well as corresponding grey and white matter volumes, hippocampus total matter volume, and right and left hippocampal grey matter volumes. A Bonferroni correction for multiple comparisons set the alpha value at $\alpha = 0.004$ (Table 2).

In healthy controls, parametric and non-parametric correlations yielded a similar pattern of associations, thus removing the possibility of leverage data points on the value of Pearson's correlations. As expected, healthy volunteers displayed moderate to strong linear associations between cerebrum total volume and a) total cerebellum matter volume, as well as grey and white matter volumes, b) total cerebellum left and right volumes, as well as corresponding gray and white matter volumes, and c) hippocampus grey matter volume, as well as right and left grey matter volumes (Table 2). Conversely, in patients, parametric and non-parametric correlations yielded a different pattern of associations. This indicates a likelihood of outliers in the patients' subgroup. We therefore opted for Spearman's correlations due to this possible monotonic relationship. The group of patients displayed none of the expected associations between the volumetric measures (Table 2).

### *Group difference in association patterns*

Excel was used to analyse the data using a Fisher's Z-transformation statistic. First, acquired correlations (Table 2) were standardized using the Fisher's Z transformation. Next, the standardized correlation coefficients were compared between groups for cerebrum total volume on the one hand and cerebellum total,

cerebellum GM, cerebellum WM or the total hippocampus for both the right and the left side on the other hand (Table 3). A significant group difference in association patterns were found for the cerebellum (Z = -2.21, p = 0.027), which was mainly observed in the right side (Z = -2.58, $p$ = 0.010). In addition, cerebellar differences in associations with the total cerebrum were mainly driven by grey matter tissue (Z = -2.10, $p$ = 0.036). A trend was observed for group differences in associations between the total hippocampus and cerebrum volume (Z = -1.75, $p$ = 0.080).

**Table 3**. Fisher's $Z$ transformation was used to standardize the $r$ values obtained with the Spearman correlation. In addition, a $Z$ test was used to asses the statistical significance of the difference in associations between patients suffering from schizophrenia and healthy controls.

| | $r_{patient}$ ($n$ = 19) | $r_{control}$ ($n$ = 30) | Z | $p$ |
|---|---|---|---|---|
| Cerebellum | | | | |
| Total | 0.38 | 0.80 | -2.21 | 0.027* |
| Left | 0.51 | 0.79 | -1.61 | 0.107 |
| Right | 0.33 | 0.82 | -2.58 | 0.010* |
| Cerebellum GM | | | | |
| Total | 0.30 | 0.75 | -2.10 | 0.036 |
| Left | 0.31 | 0.73 | -1.93 | 0.054 |
| Right | 0.21 | 0.71 | -2.14 | 0.032 |
| Cerebellum WM | | | | |
| Total | 0.55 | 0.71 | -0.85 | 0.395 |
| Left | 0.51 | 0.68 | -0.84 | 0.401 |
| Right | 0.51 | 0.69 | -0.90 | 0.368 |
| Hippocampus | | | | |
| Total | 0.27 | 0.68 | -1.75 | 0.080 |
| Left | 0.35 | 0.62 | -1.14 | 0.254 |
| Right | 0.32 | 0.61 | -1.20 | 0.230 |

Note. GM, grey matter. WM, white matter. * = Significant result after Bonferroni correction.

## Group differences in cerebellar volumes

Given the strong associations found in healthy controls between cerebrum and cerebellum volumes (Table 2), we opted for a covariance approach to assess group differences in cerebellum volumes. Therefore, a one-way analysis of covariance (ANCOVA) was computed including the following factors: two levels for the group factor (patient and healthy control), anatomical voxel count ($mm^3$) of manually segmented cerebellum as the dependent variable, and total cerebrum volume as the covariate factor. The Levene's test for equality of error variances between the two groups was not significant, $F(1, 47) = 0.56$, $p = .457$. The ANCOVA revealed no group difference, $F(1, 46) = 1.66$, $p = 0.204$. Second, a multivariate analysis of covariance (MANCOVA) was used to assess potential group differences in volumes of cerebellum grey and white matter, covaried for cerebrum total volume. The multivariate test showed no significant group differences, Wilks' $\Lambda = 0.954$, $F(2, 45) = 1.07$, $p = 0.348$. Descriptive parameters are presented in Table 4.

### *Group differences in right and left cerebellar volumes*

An analysis of group differences between right and left cerebellar volumes, covaried for cerebrum total volume, was conducted using a MANCOVA (Table 4). The

multivariate test revealed no group differences, Wilks' $\Lambda = 0.962$, $F(2, 45) = 0.90$, $p = 0.414$. Another MANCOVA was computed to assess potential group differences in right and left cerebellum volumes of grey or white matter, covaried for cerebrum total volume. The multivariate test showed no group differences, Wilks' $\Lambda = 0.950$, $F(4, 43) = 0.566$, $p = 0.688$ (Table 4).

### Group differences in hippocampal volumes

A significant association between cerebrum and hippocampal volumes was found (Table 2); therefore, a one-way analysis of covariance (ANCOVA) was conducted to assess group difference in hippocampal volumes (automatically segmented), covaried for cerebrum total volumes. The Levene's test for equality of error variances was not significant, $F(1, 47) = 0.22$, $p = .638$. The ANCOVA revealed no group differences, $F(1, 46) = 0.94$, $p = 0.338$. Descriptive parameters are presented in Table 4.

**Table 4**. Means (standard deviations) for cerebrum, cerebellum and hippocampus volumes (voxel count, $cm^3$).

| | Schizophrenia ($n$ = 19) | | | Healthy controls ($n$ = 30) | | |
|---|---|---|---|---|---|---|
| | Right | Left | Total | Right | Left | Total |
| Cerebrum | | | | | | |
| Total | - | - | 1257.9 (92.7) | - | - | 1271.4 (135.8) |
| GM | - | - | 553.2 (45.1) | - | - | 565.4 (59.3) |
| WM | - | - | 459.0 (37.1) | - | - | 462.2 (58.2) |
| Cerebellum | | | | | | |
| Total | 71.4 (5.6) | 71.9 (5.4) | 143.3 (10.7) | 73.8 (7.3) | 73.9 (7.5) | 147.7 (14.5) |
| GM | 32.8 (2.7) | 32.4 (2.5) | 65.2 (5.0) | 34.0 (3.7) | 33.7 (3.6) | 67.8 (7.3) |
| WM | 26.3 (2.0) | 26.8 (2.4) | 53.1 (4.3) | 27.0 (3.4) | 27.4 (3.4) | 54.3 (6.7) |
| Hippocampus | | | | | | |
| Total | 3.8 (0.5) | 3.7 (0.4) | 7.4 (0.9) | 3.9 (0.5) | 3.8 (0.5) | 7.7 (0.8) |

Note. GM, grey matter. WM, white matter.

#### *Group differences in right and left hippocampal volumes*

The effect of group on left and right hippocampal volumes, covaried for cerebrum total volume, was tested using a MANCOVA (Table 4). The multivariate test showed no group difference, Wilks' $\Lambda = 0.980$, $F(2, 45) = 0.47$, $p = 0.631$.

## DISCUSSION

The current study investigated whether there is a difference in structural volume between schizophrenic patients and healthy controls. In order to find volumetric differences in cerebellar and hippocampal volumes we first gathered T1-weighted MR images in a sample of patients suffering from first episode psychosis, early phase psychosis or established schizophrenia and healthy controls. Subsequently, to determine whether structural differences were present, cerebellar and hippocampal

volumes were contrasted between groups. By using the cerebrum total volume as a covariant, we were able to control for the random variability in human brain size due to height and mass differences in participants. Furthermore, we computed the correlations between the acquired cerebrum volume (voxel count) and the hippocampal and cerebellar delineated volumes. In addition, we determined whether there was a group difference between acquired association patterns.

Findings revealed no significant volumetric differences in relative voxel count ($mm^3$) between healthy controls and schizophrenic patients, in the cerebellum, cerebellar grey and white matter, or the hippocampus. However, the associations between total cerebrum volumes and cerebellum or hippocampus volumes showed opposite results between groups. As proposed *a priori*, parametric and non-parametric tests showed a moderate to strong linear association in healthy controls (Table 2). Conversely, in the patients group, parametric and non-parametric tests showed a different pattern of associations. We therefore decided to use a non-parametric approach to adjust for the possible leverage points. Contrasting healthy controls, the data from patients showed no significant correlations between the cerebrum volume, and hippocampal and cerebellar volumes in schizophrenic patients. This could indicate abnormalities in the proportions of the hippocampus and cerebellum relative to the total cerebrum, existing only in patients but not healthy controls. Especially cerebellar grey matter seemed to be affected in schizophrenic patients (Table 2). Furthermore, the data shows the group difference in associations to be significant for the hippocampal and cerebellar matter relative to the total cerebrum. The group differences in cerebellar association with cerebrum volume seemed to be driven by grey matter, and were mostly apparent on the right cerebellar side (Table 3). A significant group difference in correlations adds to the possibility of a contrast in the ratio between the volume of the cerebrum and the investigated structures in patients relative to healthy controls, denoting a possibility for volumetric abnormalities in patients.

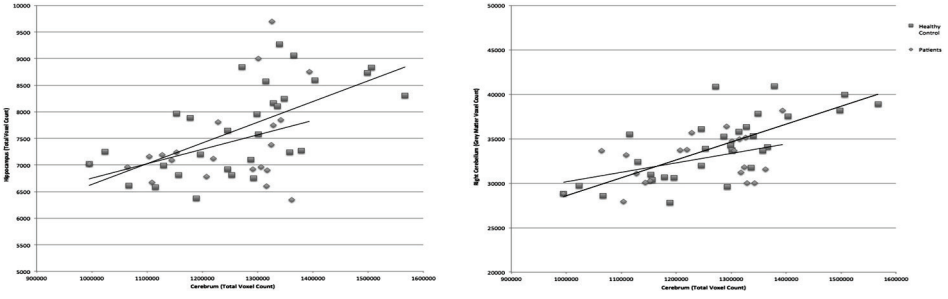


**Figure 3.** Spearman and Pearson correlations were calculated to determine whether hippocampal and cerebellar structures were significantly associated in patients and healthy controls. Both correlations between Hippocampal GM and Cerebrum Total as well as Right Cerebellum GM and Cerebrum Total were significant for the healthy control group. No significant correlations were found for the patient group. A significant difference was found in correlations between both groups, indicating possible structural abnormalities in the hippocampal and cerebellar volumes of patients suffering from schizophrenia.

Results seem to support a lack of association between the structures of interest and the cerebrum in patients, implying possible structural abnormalities in the hippocampal and cerebellar volumes (Table 3). The difference in the cerebellum was especially apparent on the right side, and was mainly driven by grey matter differences (Fig. 3). The finding of abnormalities in the structural volume of cerebellar and hippocampal matter is consistent with a large body of evidence (Ichimiya et al., 2001; Keller et al., 2003; Lee et al., 2007; Loeber et al., 2001; Lungu et al., 2013). Research indicates an asymmetry in the cerebellum, with lower volumes on the right as compared to the left (Levitt et al., 1999). Different lines of research show a parallel between the increase of cognitive symptoms and a decrease in cerebellar volumes in schizophrenia (Andreasen & Pierson, 2008). For example, Szeszko et al. (2003) showed that neuropsychological functions, including visuospatial awareness, executive functioning, and memory, were impaired in patients but not in healthy controls. Additionally, the decline in neurological functioning was associated with a decline in cerebellar volume. Again, increases in NSS were most apparent when the right side of the cerebellum showed reduced volumes (Bottmer et al., 2005).

A large body of research, focussing on the volumetric properties of the cerebellum in schizophrenia, has shown that the cerebellar vermis is mainly compromised in patients (Loeber et al., 2001; Okugawa et al., 2007). This reduction in cerebellar vermis volume has been linked to affective as well as cognitive deficits, although impaired cognition is mainly observed when other parts of the cerebellum have also been affected (Schmahmann, 2004; Schmahmann & Pandya, 1997; Tavano et al., 2007). Vermal abnormalities are also evident in congenital neurodevelopmental disorders such as Dandy Walker malformation (Klein, Pierre-Kahn, Boddaert, Parisot, & Brunelle, 2003) and Joubert syndrome (Saraiva & Baraitser, 1992). Currently, evidence is accumulating rapidly, implying an important role of the cerebellar vermis in schizophrenia (Lawyer, Nesvag, Varnas, Okugawa, & Agartz, 2009; Okugawa et al., 2003). Interestingly, a higher prevalence of excessive white mater seems to manifest itself in male patients, as opposed to female patients (Lee et al., 2007; Okugawa et al., 2002).

The ability to learn new information, as well as retrieval of episodic and semantic memory, is also impaired in schizophrenic patients (Holthausen et al., 2003). Research by Egeland et al. (2003) showed that these abnormalities are the result of problems in encoding processes. This is different in depressed patients, who mainly show difficulties in the retrieval process (Veiel, 1997). Problems in memory, especially with regards to encoding processes, have been linked to structural differences located in the medial temporal lobe (Boyer, Phillips, Rousseau, & Ilivitsky, 2007). In schizophrenia, research shows that especially the hippocampal structure is impaired. A meta-study by Nelson, Saykin, Flashman, and Riordan (1998), in which 18 studies were compiled, showed a bilateral decrease of 4% in hippocampal volume. In addition, a more recent meta-study involving 300 patients and 287 healthy controls showed an 8% decrease in both left and right hippocampal volume (Steen, Mull, McClure, Hamer, & Lieberman, 2006).

In conclusion, our results seem to confirm a trend towards an abnormal volumetric pattern in both the cerebellum and the hippocampus. These findings, combined with earlier volumetric and functional research in schizophrenia seem to indicate these structures in schizophrenic pathology.

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