NeuroImage 53 (2010) 1175–1180

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Cerebellar grey matter deficits in first-episode schizophrenia mapped using cortical pattern matching

Paul E. Rasser [a,b,c,*], Ulrich Schall [a,b,c], Greg Peck [b], Martin Cohen [a,b,c], Patrick Johnston [d], Kathleen Khoo [b], Vaughan J. Carr [a,e], Philip B. Ward [e], Paul M. Thompson [f]

[a] Schizophrenia Research Institute, Sydney, Australia
[b] Priority Centre for Brain & Mental Health Research, The University of Newcastle, New South Wales, Australia
[c] Hunter Medical Research Institute, Newcastle, Australia
[d] Swinburn University of Technology, Melbourne, Australia
[e] School of Psychiatry, University of New South Wales, Sydney, Australia
[f] Laboratory of Neuro Imaging, University of California, Los Angeles, CA, USA

ARTICLE INFO

Article history:
Received 26 May 2010
Accepted 7 July 2010
Available online 12 July 2010

Keywords:
Psychosis
Magnetic resonance imaging
Parametric mapping
Cerebellum
Grey matter
White matter
Cerebellar lobules
Superior vermis
Flocculus
Pedunculus
Cognitive dysmetria

ABSTRACT

Cerebellar dysfunction has been proposed to lead to "cognitive dysmetria" in schizophrenia via the cortico-cerebellar-thalamic-cortical circuit, contributing to a range of cognitive and clinical symptoms of the disorder. Here we investigated total cerebellar grey and white matter volumes and cerebellar regional grey matter abnormalities in 13 remitted first-episode schizophrenia patients with less than 2 years' duration of illness. Patient data were compared to 13 pair-wise age, gender, and handedness-matched healthy volunteers using cortical pattern averaging on high-resolution magnetic resonance images. Total cerebellar volume and total grey matter volumes in first-episode schizophrenia patients did not differ from healthy control subjects, but total cerebellar white matter was increased and total grey to white matter ratios were reduced in patients. Four clusters of cerebellar grey matter reduction were identified: (i) in superior vermis; (ii) in the left lobuli VI; (iii) in right-inferior lobule IX, extending into left lobule IX; and (iv) bilaterally in the areas of lobuli III, peduncle and left flocculus. Grey matter deficits were particularly prominent in right lobuli III and IX, left flocculus and bilateral pedunculi. These cerebellar areas have been implicated in attention control, emotional regulation, social functioning, initiation of smooth pursuit eye movements, eye-blink conditioning, language processing, verbal memory, executive function and the processing of spatial and emotional information. Consistent with common clinical, cognitive, and pathophysiological signs of established illness, our findings demonstrate cerebellar pathology as early as in first-episode schizophrenia.

Introduction

Cerebellar dysfunction in schizophrenia has gained substantial attention in recent years (e.g., Andreasen and Pierson, 2008; Picard et al., 2008, for a review) and led to the notion of "cognitive dysmetria"—a syndrome characterised by neurological soft signs, impaired coordination, abnormal posture and proprioception, impaired eye-blink conditioning, vestibulo-ocular dysadaptation, and poor performance on procedural learning tasks. Post mortem micro- and macroscopic investigations identified the vermis region as most affected in schizophrenia. In their early studies, Weinberger and colleagues (1980) reported anterior vermal atrophy accompanied by Purkinje and granule cell loss, thus resulting in thinning of the granular and molecular layers (Martin and Albers, 1995, for review). These early post mortem findings are consistent with reports derived from *in vivo* brain imaging research confirming vermal atrophy by computerised tomography (e.g., Weinberger et al., 1979; Heath et al., 1979; Lippmann et al., 1982; Dewan et al., 1983) and magnetic resonance imaging (MRI; e.g., Rossi et al., 1993; Nopoulos et al., 1999; Volz et al., 2000; Ichimiya et al., 2001; Loeber et al., 2001; Joyal et al., 2004; Okugawa et al., 2002, 2003, 2007). More recent reports also suggest an altered proportional relationship of vermal grey to white matter in schizophrenia (e.g., Lawyer et al., 2009).

Meta-analysis of voxel-based morphometry data by Honea and colleagues (2005) conducted on 15 studies with a total of 390 patients and 364 healthy volunteers confirmed predominantly left-hemispheric cerebellar atrophy in schizophrenia. However, two studies did not include the cerebellum and only four studies independently reported significant cerebellar atrophy. Posterior cerebellar atrophy and increased grey matter in the medial cerebellum and culmen was detected in a sample of 169 patients from the National Institute of Mental Health Genetic Study of Schizophrenia when comparing patient MRI data with data from 212 healthy volunteers by optimised voxel-based morphometry (Honea et al., 2008). Left cerebellar atrophy was also reported for 213 unaffected siblings, although this finding was not confirmed by intra-class correlation analysis conducted on 116 sibling pairs.

* Corresponding author. Priority Centre for Brain & Mental Health Research, The University of Newcastle, Mater Hospital, McAuley Centre, Waratah, New South Wales 2298, Australia.
E-mail address: Paul.Rasser@newcastle.edu.au (P.E. Rasser).

1053-8119/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2010.07.018

MRI studies have also investigated structural/functional relationships and, for instance, have shown that cerebellar atrophy is linked to impaired motor sequencing (Venkatasubramanian et al., 2008). Other research has linked cerebellar dysfunction to neurological soft signs, abnormal posture and gait in schizophrenia (Andreasen and Pierson, 2008, for review). Moreover, functional brain imaging research has also provided some evidence for a cerebellar contribution to neurocognitive impairment in schizophrenia (see Picard et al., 2008, for review).

Clinical lesion studies (Schmahmann et al., 2008) suggest that abnormal vermal-fastigial function can contribute to delusion symptoms, impaired control of attention and affect, and social dysfunction (including autistic spectrum symptoms and impaired Theory of Mind performance) via interactions with the anterior thalamic nuclei, hippocampus, septum, amygdala, ventral tegmental area, periaqueductal grey and mamillary bodies relevant for memory and emotion. This spectrum of putatively cerebellar psychopathology is largely consistent with some of the defining symptoms of schizophrenia, such as psychosis, inattention, flat affect, and social withdrawal.

When investigating associations of neurocognitive function with cerebral structure, Segarra and colleagues (2008) reported a correlation of vermal grey matter atrophy with working memory deficits. By contrast, increased vermal white matter volumes have been linked to poor verbal fluency performance in schizophrenia (Lee et al., 2007). Smaller volumes of the posterior and superior vermis were also found to correlate with impaired cognition in drug-naïve first-episode schizophrenia patients (Okugawa et al., 2007) while positive symptom ratings were reported to correlate with vermal white matter volumes in early-onset schizophrenia (Yoshihara et al., 2008). Moreover, cerebellar atrophy has also been detected in individuals followed longitudinally from the prodromal phase of the illness (Pantelis et al., 2003; Borgwardt et al., 2008). However, in contrast to general cerebral atrophy, progression of vermal atrophy has not been confirmed by repeated MRI in childhood-onset schizophrenia patients (Keller et al., 2003). Together, these findings support the notion of clinically relevant cerebellar neuropathology in schizophrenia that is already present in the emerging phase of illness and, to some extent, also appears to be present in unaffected biological relatives (Honea et al., 2008).

We investigated regional cerebellar grey matter in well-remitted first-episode schizophrenia outpatients with less than 2 years' duration of illness by applying a novel MRI brain imaging analysing technique. This method has been widely used for mapping abnormalities of the cerebral cortex (Thompson et al., 2004) and is applied here to the cerebellum for the first time.

The analysis methods preserve the three-dimensional lobular information of the cerebellum when generating statistical maps for group comparisons. In other words, data from the same lobules are averaged together across subjects when generating the average maps. Surface-based anatomical landmarks are used to enforce more accurate co-registration of individual lobule anatomy and more precise mapping of group-averaged surface anatomy. This is of particular importance when investigating potential regional grey matter differences in clinical populations where brain pathology can render more common co-registration algorithms less accurate, and where anatomical variance may be greater than in controls (Narr et al., 2001, Thompson et al., 1998).

We predicted that there would be cerebellar grey matter deficits in first-episode schizophrenia that would also affect grey to white matter ratios (Lawyer et al., 2009), with the most pronounced regional grey matter deficit in the vermis area in this early phase of illness (Okugawa et al., 2007).

Methods

Ethics approval for this study was granted by the human research ethics committees of the University of Newcastle and Hunter New England Health. Participants gave written informed consent.

Subjects

Thirteen first-episode schizophrenia outpatients with less than 2 years' duration of illness since meeting DSM-IV criteria (Structured Clinical Interview for DSM-IV Axis I Disorders; First et al., 1997) participated in the study. Patients had to be 16–28 years old, in symptom remission following no more than one hospital admission and on maintenance atypical antipsychotic monotherapy (i.e., risperidone, olanzapine, aripiprazole, or quetiapine) at the time of recruitment into the study.

Patients were pair-wise matched to 13 healthy control subjects by age (mean: 21.6 ± S.D. 2.8 years; patients: 20.7 ± S.D. 3.6 years) and sex (12 males and 1 female) and are – with the exception of one subject – a subset of the 18 control subjects (mean age: 21.7 ± S.D. 2.3, 15 males and 3 females) who formed the standard average cerebellar reference atlas for this study. All subjects were right-handed (Edinburgh Handedness Scale; Oldfield, 1971).

Exclusion criteria for all participants included substance abuse or addiction (DSM-IV criteria), a history of significant head injury, relevant neurological (e.g., epilepsy) or medical (e.g., endocrine) conditions, ferromagnetic implants, claustrophobia or other anxiety disorders, a failure to complete at least 3 years of secondary school, or National Adult Reading Test (NART; Nelson and Willison, 1991) IQ estimates of less than 70.

Magnetic resonance data acquisition and processing

MRI data were acquired using a Siemens Magnetom Vision 1.5 T MRI scanner (John Hunter Hospital, Newcastle). For each subject, high-resolution structural MR data was collected with approximate dimensions of 164 × 256 × 256 with each voxel being 1 × 1 × 1 mm using a 3D MPRAGE protocol with TR = 9.7 ms, TE = 4 ms, and flip angle = 12°.

Subjects MRIs were transformed to ICBM (Mazziotta et al., 2001) space using the software program register available at http://www.bic.mni.mcgill.ca/software/register/register.html. Following radio frequency bias correction (Sled et al., 1998), the cerebellum was manually traced blind to diagnosis and isolated to extract a model of the cerebellar cortex (MacDonald et al., 1994)

Fig. 1. (a) Masked cerebellum in an MRI coronal section. (b) Extracted cerebellum coronal section (surrounding tissue removed). (c) Grey and white matter tissue classification by thresholding procedure (Atkins and Mackiewich, 1998). Red circle illustrates spherical kernel of 15 mm radius (adjusted by individual total cerebellar volume) to calculate the proportion of grey matter within the kernel sphere for each cerebellar surface vertex.

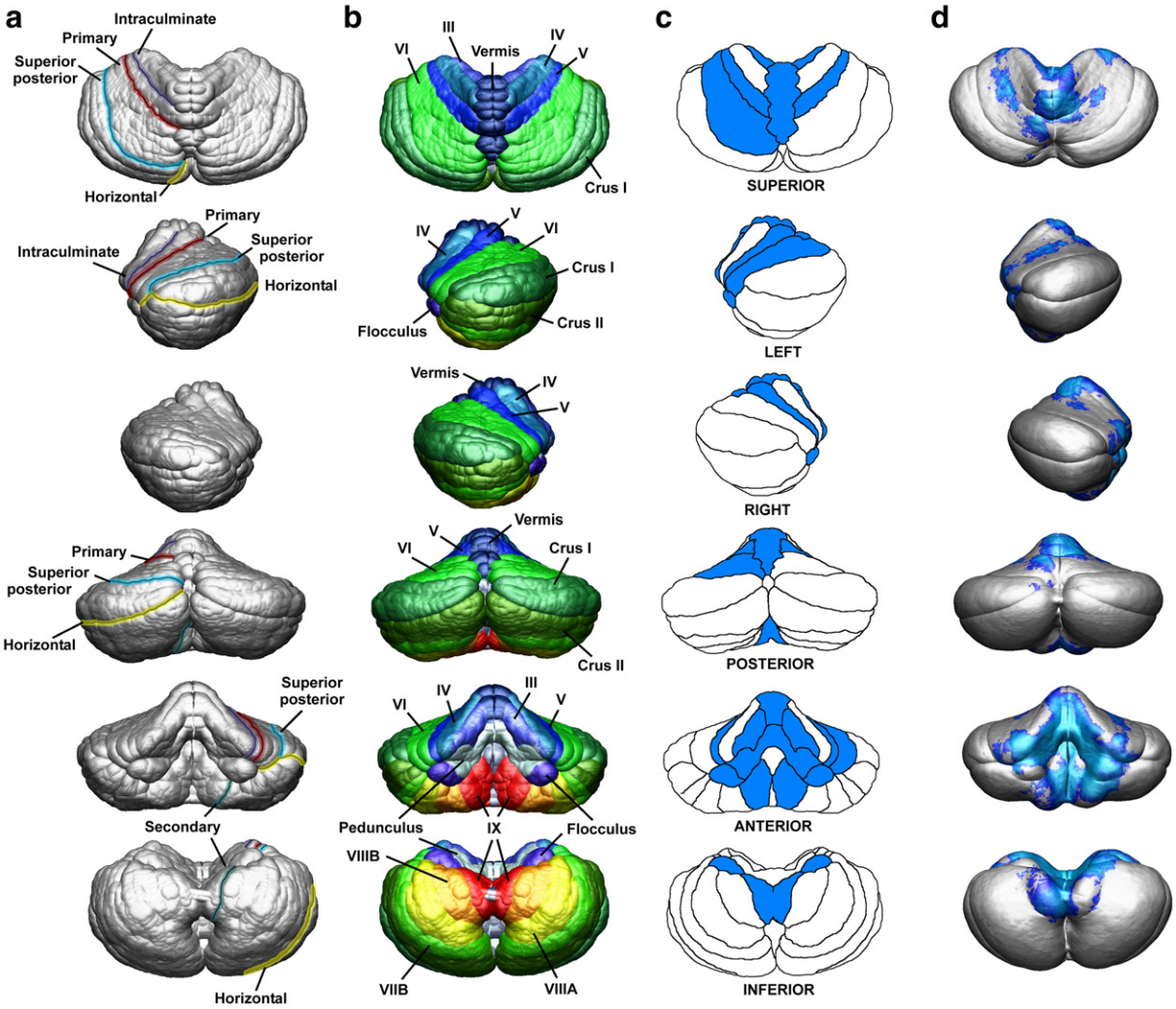

Fig. 2. From top to bottom, superior, left, right, posterior, anterior, and inferior views of cerebellum. (a) Traced fissure lines (intra-culminate, primary, superior posterior, horizontal, and secondary) for cortex model transformation. (b) Deformable lobule labels, enabling lobule-wise grey matter measures for each subject. (c) Cerebellar lobules with significant grey matter reduction (blue) in first-episode schizophrenia. Left hemisphere: vermis, lobuli III, V, VI, IX, pedunculus, and flocculus. Right hemisphere: vermis, lobuli III, V, and IX, pedunculus, and flocculus. (d) Statistical maps of regional cerebellar grey matter deficits ($P<0.05$) in the superior vermis, the left lobuli VI, in right-inferior lobule IX, extending into left lobule IX, bilaterally in the areas of lobuli III, peduncle and in left flocculus.

(Fig. 1a and b). This model was used together with the subject's MRI to identify and trace the intra-culminate, primary, superior posterior, horizontal and secondary fissures (Fig. 2a). A cortical pattern matching technique (Thompson et al., 2004; Rasser et al., 2005) was then employed to create a geometric average target set of fissures to which each subject's cerebellar cortex model was deformed.

In native space, a secondary correction of radio frequency bias was applied on the subject's MRI that included using a dilated version of their native space cerebellar mask. This was done to improve the homogeneity of the intensities within each tissue class across the cerebellum. The cerebellum was then isolated using the cerebellar mask, followed by intensity normalization, and calculation of the total cerebellar volume for each subject.

Grey and white matter tissue was classified using a thresholding procedure (Atkins and Mackiewich, 1998) that employed a single Gaussian model for each subject (Fig. 1c). This threshold, standardised across all subjects, was based on a constant offset from the mean of each subject's fitted Gaussian curve. Volumetric measurements of total cerebellar grey and white matter were then calculated from these tissue-classified volumes.

In native space, the proportion of cerebellar voxels labelled as grey matter was determined within volume-dependent spherical kernels with centres that correspond to the vertices of the subject's deformed cerebellar cortex model (Fig. 1c). This is a standard approach in voxel-based morphometry studies and allows the regional assessment of grey matter volumes. The size of the spherical kernel for each subject was varied dependent on their total cerebellar volume, with the volume of the sphere kernel of radius 15 mm adjusted by the ratio of the individual to the average cerebellar volume determined from the reference sample of 18 control subjects.

A deformable cerebellar atlas was applied to label the cerebellar lobules of the average model, enabling lobule-wise averaging of the grey matter measure for each subject (Fig. 2b).

The deformable atlas was generated from a three-dimensional model of the cerebellar cortex extracted (MacDonald et al., 1994) from a symmetrical version of the Montreal Neurological Institute intensity-averaged single-subject MRI (Holmes et al., 1998) The symmetry was deliberately ensured by mirroring the right-hand side across the central sagittal plane.

The cerebellar fissures, as described in (Schmahmann et al., 2000) were used to describe the lobule and feature boundaries on the

Table 1
Comparisons of total cerebellar volumes, total grey and white matter volumes, and grey to total cerebellar volume ratios (standard deviations are shown in parentheses).

	Control subjects ($n=13$)	First-episode schizophrenia patients ($n=13$)	t-statistic ($df=24$)	P (2-sided)
Total cerebellar volume (cc)	145.9 (11.7)	149.5 (10.5)	−0.82	0.42
Total grey matter volume (cc)	104.9 (8.5)	105.0 (7.3)	−0.04	0.96
Total white matter volume (cc)	41.0 (3.7)	44.4 (4.3)	−2.17	0.04
Total grey to total cerebellar volume ratio	0.72 (0.01)	0.70 (0.02)	2.91	0.008

cerebellar cortical surface model. The cerebellar model was then deformed using cortical pattern matching to the average target atlas followed by tabulation of each subject's average proportion of grey matter for each lobule.

Statistical analyses

Total cerebellar volume, total grey and white matter volumes and total grey to white matter ratios were t-tested at $P<0.05$ (two-tailed). Parametric statistical maps of cerebellar grey matter measures by group were calculated and permutation-tested (Thompson et al., 2003) at $P<0.05$ for each hemisphere. Permutation testing ascribes an overall corrected P-value to a whole map of statistics, based on estimating the chance that the overall surface area of suprathreshold statistics could have been obtained by chance in null data, simulated by randomly assigning patients and controls to two groups. Lobule-level group differences of grey matter were t-tested at $P<0.05$ (two-sided) and Bonferroni-corrected for multiple tests for each hemisphere.

Results

Total cerebellar volume and total grey matter volume of first-episode schizophrenia patients did not differ from healthy control subjects (Table 1). By contrast, first-episode schizophrenia was associated with increased total white matter volume ($t=-2.17$; $P<0.05$) and smaller total grey to white matter ratios ($t=2.91$; $P<0.01$).

Grey matter deficits in first-episode schizophrenia patients were confirmed by permutation testing at $P<0.005$ for the left and at $P<0.003$ for the right hemisphere of the cerebellum (Fig. 2d). Four clusters of cerebellar grey matter reduction were identified: (i) in superior vermis; (ii) in the left lobuli VI; (iii) in right-inferior lobule IX, extending into left lobule IX; and (iv) bilaterally in the areas of lobuli III, peduncle and left flocculus (Fig. 2d).

This topographic pattern of grey matter reduction in first-episode schizophrenia was also confirmed at $P<0.05$ at the lobule level (Fig. 2c). In the left cerebellar hemisphere, reduced grey matter was present in vermis, lobuli III, V, VI, IX, pedunculus, and flocculus (Table 2). Right hemispheric grey matter reductions were found in vermis, lobuli III, V, and IX, pedunculus, and flocculus (Table 3). When applying Bonferroni correction for multiple comparisons, grey matter reductions in patients were confirmed at $P<0.004$ for right lobuli III and IX, left flocculus and pedunculi in both hemispheres.

Discussion

In terms of overall volume, the cerebellum was not atrophic in first-episode schizophrenia, but patients exhibited increased total white matter volumes, resulting in smaller global grey to white matter ratios. Regional grey matter deficiencies were also detected. These findings suggest that grey matter loss contributing eventually to global cerebellar atrophy may be partly compensated initially by increased volumes of global white matter and, furthermore, that grey matter deficits are regionally circumscribed to areas of the cerebellum linked to symptoms and cognitive deficits expressed in established schizophrenia. Our findings further demonstrate that cerebellar pathology has already emerged in the early first-episode stage of the condition.

Consistent with previous findings (Okugawa et al., 2007), our data confirm cerebellar grey matter reduction in the superior vermal region. The vermis is mainly involved in spinocerebellar processing of axial muscle coordination. According to Schmahmann et al. (2008) neuropathology in vermis has also been linked to impaired attention control, dysregulation of affect, social dysfunction and delusions. This spectrum of psychopathology is consistent with some of the positive (e.g., delusions and inattention) and negative symptoms (e.g., flat affect and social withdrawal) of schizophrenia. Other reports found correlations of reduced vermal volume with the depression and paranoia sub scores of the Brief Psychiatric Rating Scale (Ichimiya et al., 2001) and greater vermis white matter volumes with severity of positive symptoms, thought disorder and impaired verbal logical memory in patients with schizophrenia (Levitt et al., 1999).

Table 2
Comparison of grey matter proportion by lobule (standard deviations are in parentheses) in the left cerebellar hemisphere.

Lobules (left hemisphere)	Control subjects ($n=13$)	First-episode schizophrenia patients ($n=13$)	t-statistic ($df=24$)	P (2-sided)
III	0.73 (0.03)	0.69 (0.04)	3.09	0.005
IV	0.78 (0.04)	0.75 (0.04)	1.60	0.12
V	0.75 (0.03)	0.72 (0.03)	2.18	0.04
VI	0.75 (0.02)	0.73 (0.02)	2.50	0.02
Pedunculus	0.65 (0.03)	0.60 (0.02)	4.78	<0.001*
Crus I	0.79 (0.02)	0.78 (0.03)	0.86	0.40
Crus II	0.76 (0.02)	0.76 (0.02)	0.63	0.54
VIIB	0.76 (0.02)	0.75 (0.03)	0.33	0.74
VIIIA	0.76 (0.02)	0.75 (0.04)	0.75	0.46
VIIIB	0.77 (0.02)	0.75 (0.04)	1.16	0.11
IX	0.78 (0.01)	0.75 (0.03)	3.10	0.005
Vermis	0.80 (0.03)	0.76 (0.03)	3.10	0.005
Flocculus	0.78 (0.01)	0.75 (0.02)	4.13	<0.001*

* Significant following Bonferroni correction ($P<0.004$).

Table 3
Comparison of grey matter proportion by lobule (standard deviations are in parentheses) in the right cerebellar hemisphere.

Lobules (right hemisphere)	Control subjects ($n=13$)	First-episode schizophrenia patients ($n=13$)	t-statistic ($df=24$)	P (2-sided)
III	0.74 (0.03)	0.69 (0.03)	3.82	0.001*
IV	0.78 (0.03)	0.76 (0.03)	1.88	0.07
V	0.75 (0.03)	0.72 (0.02)	2.40	0.02
VI	0.75 (0.03)	0.73 (0.02)	1.81	0.08
Pedunculus	0.65 (0.03)	0.61 (0.02)	4.77	<0.001*
Crus I	0.79 (0.02)	0.79 (0.03)	0.06	0.95
Crus II	0.77 (0.02)	0.77 (0.02)	0.11	0.91
VIIB	0.76 (0.02)	0.75 (0.03)	0.70	0.49
VIIIA	0.77 (0.03)	0.76 (0.04)	1.07	0.29
VIIIB	0.78 (0.03)	0.76 (0.03)	1.91	0.07
IX	0.81 (0.02)	0.78 (0.03)	3.19	0.004*
Vermis	0.80 (0.03)	0.77 (0.03)	2.97	0.007
Flocculus	0.64 (0.03)	0.61 (0.02)	3.12	0.005

* Significant following Bonferroni correction ($P<0.004$).

However, our study lacks the power to detect any potential association of symptom expression with morphological data, particularly since our first-episode cohort displayed very little ongoing psychopathology when investigated following recovery from their first psychotic episode. Notwithstanding, the regions with cerebellar grey matter deficits in this early phase of confirmed schizophrenia are nevertheless consistent with functional deficits described in established and more chronic forms of illness.

For instance, our data indicate pronounced grey matter deficits in the flocculus bilaterally. The flocculus and paraflocculus, together with anterior vermis, are involved in the execution of smooth pursuit eye movements, preventing blurring of the retinal image of moving objects. This process integrates retinal image motion signals with ongoing eye and head movements in frontal and supplementary eye fields, medial superior temporal and ventral intraparietal cortex. The flocculus and paraflocculus receive cortical input via the pontine nuclei for processing visual and vestibulo-ocular information and to the vermis for pursuit initiation (Ilg and Thier, 2008).

Impaired smooth pursuit eye movements are well documented in schizophrenia (see O'Driscoll and Callahan, 2008 for review), including in first-episode patients (e.g., Bagary et al., 2004; Keedy et al., 2006). Reduced grey matter in the flocculus region suggests local cerebellar neuropathology consistent with a pursuit deficit.

Moreover, our data also suggest grey matter deficits in this early phase of illness in cerebellar pedunculi. Functionally, the pedunculi are involved in associative learning, such as the formation of memory traces for the conditioned eye-blink response (Thompson et al., 1997). A previous report described lower rates of eye-blink conditioning, particularly less adaptively timed conditioned response latencies (Bolbecker et al., 2009) in schizophrenia. Our finding of reduced grey matter in pedunculi further suggests cerebellar pathology that is already emerging in this area following the first episode of illness.

However, our data suggest even more widespread cerebellar neuropathology in this early phase of schizophrenia affecting lobuli III, V, VI, and IX. Some of these cerebellar regions are involved in somatosensory, language, verbal working memory, spatial, and executive cognitive functions and the processing of emotional information (Stoodley and Schmahmann, 2009). When reviewing functional brain imaging data however, function/structure associations are less well-defined and depend on task type and cognitive domain. Most studies have not used methods capable of precisely mapping subtle regional morphological differences. Cortical pattern averaging overcomes some of these limitations, allowing a more accurate mapping of grey matter abnormalities in relatively small patient cohorts. This suggests the promise of investigating function/structure associations in more detail. Such research should also include corresponding morphological measures from the cerebrum in order to investigate the contribution of individual cortico-cerebellar circuits to functional deficits and clinical features of the disorder.

Another inherent problem with studies on schizophrenia patients is their treatment history. While vermal volume reduction has been found in neuroleptic-naïve schizophrenia patients (Ichimiya et al., 2001; Okugawa et al., 2007), antipsychotic medication is a potential confound associated with cerebral grey matter reduction (Thompson et al., 2009). This finding must be considered when interpreting structural brain imaging data in schizophrenia patients. Even so, the patients in this study were treated for a relatively short period of time, using atypical antipsychotics that are thought to have less pronounced effects on grey matter changes (McClure et al., 2008).

In summary, cortical pattern matching overcomes some limitations of other morphometric methods by accurately aligning group-averaged cortical MRI data in relatively small cohorts. The findings confirm cerebellar grey and white matter pathology in schizophrenia (Andreasen and Pierson, 2008; Picard et al., 2008); these deficits are already detectable in the first-episode phase of the illness, following remission from acute psychosis. These findings are consistent with the notion that the cerebellum contributes to the clinical, cognitive, and pathophysiological signs of the disorder. However, further research is required to confirm the association of functional deficits with morphological differences in the cerebrum and cerebellum. Future studies should also target potentially confounding medication effects as well as longitudinal morphological changes with progression of illness.

Acknowledgments

The study was supported by project grants of the National Health & Medical Research Council of Australia (300734), Pfizer Neuroscience, the Hunter Medical Research Institute, and the University of Newcastle. We gratefully acknowledge infrastructure support from the Hunter Medical Research Institute, the Schizophrenia Research Institute, and New South Wales Health and valuable assistance by V. Case, G. Cooper, D. Draganic, R. Fulham, S. Hudson, G. O'Connor. Algorithm development for this study was also funded by agencies of the U.S. National Institutes of Health: NIBIB (R01 EB007813, R01 EB008281, R01 EB008432), NICHD (R01 HD050735), and NIA (R01 AG020098).

References

Andreasen, N.C., Pierson, R., 2008. The role of the cerebellum in schizophrenia. Biological Psychiatry 64 (2), 81–88.
Atkins, M., Mackiewich, B., 1998. Fully automatic segmentation of the brain in MRI. Medical Imaging, IEEE Transactions on 17 (1), 98–107.
Bagary, M.S., et al., 2004. Structural neural networks subserving oculomotor function in first-episode schizophrenia. Biological Psychiatry 56 (9), 620–627.
Bolbecker, A.R., et al., 2009. Eye-blink conditioning deficits indicate temporal processing abnormalities in schizophrenia. Schizophrenia Research 111 (1–3), 182–191.
Borgwardt, S.J., et al., 2008. Reductions in frontal, temporal and parietal volume associated with the onset of psychosis. Schizophrenia Research 106 (2–3), 108–114.
Dewan, M.J., et al., 1983. Cerebellar morphology in chronic schizophrenic patients: a controlled computed tomography study. Psychiatry Research 10 (2), 97–103.
First, M.B., et al., 1997. *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)*. American Psychiatric Publishing, Inc., Clinician Version.
Heath, R.G., Franklin, D.E., Shraberg, D., 1979. Gross pathology of the cerebellum in patients diagnosed and treated as functional psychiatric disorders. The Journal of Nervous and Mental Disease 167 (10), 585–592.
Holmes, C.J., et al., 1998. Enhancement of MR images using registration for signal averaging. Journal of Computer Assisted Tomography 22 (2), 324–333.
Honea, R., et al., 2005. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. The American Journal of Psychiatry 162 (12), 2233–2245.
Honea, R.A., et al., 2008. Is gray matter volume an intermediate phenotype for schizophrenia? A voxel-based morphometry study of patients with schizophrenia and their healthy siblings. Biological Psychiatry 63 (5), 465–474.
Ichimiya, T., et al., 2001. Reduced volume of the cerebellar vermis in neuroleptic naïve schizophrenia. Biological Psychiatry 49 (1), 20–27.
Ilg, U.J., Thier, P., 2008. The neural basis of smooth pursuit eye movements in the rhesus monkey brain. Brain and Cognition 68 (3), 229–240.
Joyal, C.C., et al., 2004. MRI volumetry of the vermis and the cerebellar hemispheres in men with schizophrenia. Psychiatry Research 131 (2), 115–124.
Keedy, S.K., et al., 2006. Functional magnetic resonance imaging studies of eye movements in first episode schizophrenia: smooth pursuit, visually guided saccades and the oculomotor delayed response task. Psychiatry Research 146 (3), 199–211.
Keller, A., et al., 2003. Progressive loss of cerebellar volume in childhood-onset schizophrenia. The American Journal of Psychiatry 160 (1), 128–133.
Lawyer, G., et al., 2009. Grey and white matter proportional relationships in the cerebellar vermis altered in schizophrenia. Cerebellum 8 (1), 52–60.
Lee, K., et al., 2007. Increased cerebellar vermis white-matter volume in men with schizophrenia. Journal of Psychiatric Research 41 (8), 645–651.
Levitt, J.J., et al., 1999. Quantitative volumetric MRI study of the cerebellum and vermis in schizophrenia: clinical and cognitive correlates. The American Journal of Psychiatry 156 (7), 1105–1107.
Lippmann, S., et al., 1982. Cerebellar vermis dimensions on computerized tomographic scans of schizophrenic and bipolar patients. The American Journal of Psychiatry 139 (5), 667–668.
Loeber, R.T., et al., 2001. Morphometry of individual cerebellar lobules in schizophrenia. The American Journal of Psychiatry 158 (6), 952–954.
MacDonald, D., Avis, D., Evans, A., 1994. Multiple surfaceidentification and matching in magnetic resonance images. Proceedings of SPIE 2359, 160–169.
Martin, P., Albers, M., 1995. Cerebellum and schizophrenia: a selective review. Schizophrenia Bulletin 21 (2), 241–250.

Mazziotta, J., et al., 2001. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 356(1412), 1293-1322.
McClure, R.K., et al., 2008. Absence of regional brain volume change in schizophrenia associated with short-term atypical antipsychotic treatment. Schizophrenia Research 98 (1–3), 29–39.
Narr, K., et al., 2001. Three-dimensional mapping of gyral shape and cortical surface asymmetries in schizophrenia: gender effects. The American Journal of Psychiatry 158 (2), 244–255.
Nelson, H.E., Willison, J.R., 1991. The revised national adult reading test—test manual. NFER-Nelson, Windsor, UK.
Nopoulos, P.C., et al., 1999. An MRI study of cerebellar vermis morphology in patients with schizophrenia: evidence in support of the cognitive dysmetria concept. Biological Psychiatry 46 (5), 703–711.
O'Driscoll, G.A., Callahan, B.L., 2008. Smooth pursuit in schizophrenia: a meta-analytic review of research since 1993. Brain and Cognition 68 (3), 359–370.
Okugawa, G., et al., 2002. Selective reduction of the posterior superior vermis in men with chronic schizophrenia. Schizophrenia Research 55 (1–2), 61–67.
Okugawa, G., Sedvall, G.C., Agartz, I., 2003. Smaller cerebellar vermis but not hemisphere volumes in patients with chronic schizophrenia. The American Journal of Psychiatry 160 (9), 1614–1617.
Okugawa, G., et al., 2007. Cerebellar posterior superior vermis and cognitive cluster scores in drug-naive patients with first-episode schizophrenia. Neuropsychobiology 56 (4), 216–219.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9 (1), 97–113.
Pantelis, C., et al., 2003. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet 361 (9354), 281–288.
Picard, H., et al., 2008. The role of the cerebellum in schizophrenia: an update of clinical, cognitive, and functional evidences. Schizophrenia Bulletin 34 (1), 155–172.
Rasser, P.E., et al., 2005. Functional MRI BOLD response to Tower of London performance of first-episode schizophrenia patients using cortical pattern matching. Neuroimage 26 (3), 941–951.
Rossi, A., et al., 1993. Cerebellar vermal size in schizophrenia: a male effect. Biological Psychiatry 33 (5), 354–357.
Schmahmann, J.D., et al., 2008. Cerebral white matter: neuroanatomy, clinical neurology, and neurobehavioral correlates. Annals of the New York Academy of Sciences 1142, 266–309.
Schmahmann, J.D., et al., 2000. MRI atlas of the human cerebellum, Academic Press. San Diego, California 92101–4495, USA.
Segarra, N., et al., 2008. Cerebellar deficits in schizophrenia are associated with executive dysfunction. Neuroreport 19 (15), 1513–1517.
Sled, J.G., Zijdenbos, A.P., Evans, A.C., 1998. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Transactions on Medical Imaging 17 (1), 87–97.
Stoodley, C.J., Schmahmann, J.D., 2009. The cerebellum and language: evidence from patients with cerebellar degeneration. Brain and Language 110 (3), 149–153.
Thompson, P.M., et al., 1998. Cortical variability and asymmetry in normal aging and Alzheimer's disease. Cerebral Cortex 8 (6), 492–509.
Thompson, P.M., et al., 2003. Dynamics of gray matter loss in Alzheimer's disease. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 23 (3), 994–1005.
Thompson, P.M., et al., 2004. Mapping cortical change in Alzheimer's disease, brain development, and schizophrenia. NeuroImage 23 (Suppl 1), S2–18.
Thompson, P.M., et al., 2009. Time-lapse mapping of cortical changes in schizophrenia with different treatments. Cerebral Cortex 19 (5), 1107–1123.
Thompson, R.F., et al., 1997. Associative learning. International Review of Neurobiology 41, 151–189.
Venkatasubramanian, G., et al., 2008. Neuroanatomical correlates of neurological soft signs in antipsychotic-naive schizophrenia. Psychiatry Research 164 (3), 215–222.
Volz, H., Gaser, C., Sauer, H., 2000. Supporting evidence for the model of cognitive dysmetria in schizophrenia—a structural magnetic resonance imaging study using deformation-based morphometry. Schizophrenia Research 46 (1), 45–56.
Weinberger, D., Torrey, E.F., Wyatt, R., 1979. Cerebellar atrophy in chronic schizophrenia. The Lancet 313 (8118), 718–719.
Weinberger, D.R., et al., 1980. Cerebellar pathology in schizophrenia: a controlled postmortem study. The American Journal of Psychiatry 137 (3), 359–361.
Yoshihara, Y., et al., 2008. Voxel-based structural magnetic resonance imaging (MRI) study of patients with early onset schizophrenia. Annals of General Psychiatry 7, 25.