Psychiatry Research: Neuroimaging 173 (2009) 83–87

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Cerebellar substructures and neurological soft signs in first-episode schizophrenia

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ARTICLE INFO

Article history:
Received 31 July 2007
Received in revised form 7 June 2008
Accepted 9 July 2008

Keywords:
Schizophrenia
First episode
Neurological soft signs
Cerebellum
Magnetic resonance imaging

ABSTRACT

A subtle impairment of motor coordination and sensory integration functions is frequently found in schizophrenia. Clinically these deficits present as neurological soft signs (NSS). Because of its crucial role in motor function, control of muscle tone and equilibrium, the cerebellum is likely to be involved in the appearance of NSS. Magnetic resonance imaging (MRI) was performed in 30 patients with first-episode schizophrenia – all treated with atypical neuroleptics – and 21 healthy controls. NSS were rated on the Heidelberg Scale. By manual tracing, the cerebellum was divided into the following subregions bilaterally: anterior lobe, superior posterior lobe, inferior posterior lobe, and corpus medullare, respectively. Volumetric measures were compared between the two groups and related to NSS scores. NSS scores were significantly higher in patients than in controls. Cerebella of patients were significantly smaller with atrophy pronounced in the corpus medullare bilaterally. In the patients' group, higher NSS scores were found to be related to reduced volumes of the posterior lobes of the cerebellum. In contrast, no significant associations between NSS scores and cerebellar subregions in healthy subjects arose. Our findings support the hypothesis of cerebellar involvement in schizophrenia and indicate that alterations in distinct cerebellar regions are related to NSS.

1. Introduction

The term 'neurological soft signs' (NSS) refers to subtle neurological abnormalities in motor and sensory performance which are frequently found in patients with schizophrenia (Heinrichs and Buchanan, 1988). Previous studies indicated that NSS are not only restricted to clinically manifest psychosis but are also more prevalent in high-risk subjects than in healthy controls (Ismail et al., 1998; Lawrie et al., 2001; Niethammer et al., 2000). Although neuroleptic agents may have a discrete influence on the severity of NSS (Flashman et al., 1996; King et al., 1991), findings of increased NSS in antipsychotic-naïve patients suggest them to be a fundamental characteristic of schizophrenia (Browne et al., 2000; Keshavan et al., 2003).

Since the cerebellum is crucial for motor function, control of muscle tone and equilibrium, it is likely to be involved in the appearance of NSS. Putative structural alterations of the cerebellum have been addressed in a number of computed tomography (CT) and magnetic resonance imaging (MRI) studies (for review see Bottmer et al., 2005). These studies yielded inconsistent findings, a fact probably attributable to methodological aspects like image acquisition, image analysis procedures, and sample selection. For example, the vast majority of these studies did not concentrate on first-episode patients and, hence, their results have to be carefully interpreted as both chronicity (DeLisi et al., 1997) and constant neuroleptic treatment (for review see Scherk and Falkai, 2006) may alter brain morphology themselves.

In a recent MRI study conducted by our group (Bottmer et al., 2005), we found significant cerebellar atrophy in patients with first-episode schizophrenia spectrum psychosis compared with healthy controls. Moreover, in the patient group increased scores of NSS – rated on the Heidelberg Scale (Schröder et al., 1992) – were found to be associated with a reduced volume of the right cerebellar hemisphere. Based on these findings, we conducted the present study, which has been extended by means of delineating subdivisions of the cerebellum and relating them to NSS in both patients with schizophrenia and healthy controls in order to

(i) determine whether there is a general deficit to the cerebellum or whether cerebellar subregions are selectively affected and related to NSS and
(ii) investigate whether associations between cerebellar morphology and presence of NSS also apply to healthy controls or are restricted to patients with schizophrenia and thus might relate to different pathogenetic processes.

2. Materials and methods

2.1. Subjects

Thirty subjects with first-episode schizophrenia and 21 healthy controls matched for age, gender, education and handedness were enrolled. Subjects'

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doi:10.1016/j.pscychresns.2008.07.006

Table 1
Demographic data of patients and healthy controls.

	Patients	Controls	*t*	*df*	*P*
Sex	15 F/15 M	12 F/9 M			n.sig.[a]
Age, years	27.73 ± 6.62	27.48 ± 4.86	−0.15	49	0.88
Education, years	12.23 ± 1.43	11.81 ± 1.47	−1.03	49	0.31

Means ± S.D.; *df* = degrees of freedom; n.sig. = not significant.
[a] = χ^2-test.

demographics are reported in Table 1. The patients, who had been consecutively admitted to the inpatient unit of the Department of Psychiatry (University of Heidelberg, Germany), were diagnosed as suffering from schizophrenia or schizophrenia spectrum psychosis according to DSM-IV criteria (Wittchen et al., 1997). All patients were treated with atypical antipsychotics according to their psychiatrist's choice (mean dose of 555.83 ± 170.79 mg in chlorpromazine equivalents) (Woods, 2003). The mean duration of neuroleptic treatment was 33.97 ± 9.59 days. Twenty-one healthy comparison subjects were recruited from the general population through advertisements after screening for and exclusion of major psychiatric disorders. The clinical evaluation of all subjects included ascertainment of personal and family history as well as thorough physical and neurological examination. None of the participants had a lifetime history of neurological or systemic illness, head injury or substance abuse. All subjects were dominantly right-handed (Oldfield, 1971).

The investigations were approved by the local ethics committee and informed consent was obtained from all participants after the procedures of the study had been fully explained.

NSS were examined on the Heidelberg Scale (Schröder et al., 1992) after remission of the patients' florid symptoms. The scale consists of five items assessing "motor coordination" (Ozeretzki's test, diadochokinesia, pronation/supination, finger-to-thumb opposition, speech articulation), three items assessing "integrative functions" (station and gait, tandem walking, two-point discrimination), two items assessing "complex motor tasks" (finger-to-nose test, fist-edge–palm test), four items assessing "right/left and spatial orientation" (right/left orientation, graphesthesia, face–hand test, stereognosis), and two items assessing "hard signs" (arm holding test, mirror movements). Ratings are given on a 0 (no prevalence) to 3 (marked prevalence) point scale. A sufficient internal reliability (Cronbach's alpha = 0.85/0.89 for patients with schizophrenia/healthy subjects), interrater reliability (0.88, $P<0.005$) and test–retest reliability (r_{tt} = 0.80, $P<0.001$) were established in the evaluation of the Heidelberg Scale (Schröder et al., 1992; Bachmann et al., 2005).

The German version of the Structured Clinical Interview for DSM-IV (Wittchen et al., 1997) was used to establish diagnoses and to exclude further major psychiatric disorders. Psychopathological symptoms were rated on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), and predictors of outcome were rated on the Strauss–Carpenter Scale (Strauss and Carpenter, 1974). Potential extrapyramidal side effects were assessed with the scales of Simpson and Angus (1970), Barnes (1989), and the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976), respectively. Handedness was ascertained with the Edinburgh Inventory (Oldfield, 1971).

2.2. MRI acquisition

MRI data were obtained at the German Cancer Research Center with a 1.5-T Magnetom Vision MR scanner (Siemens Medical Solutions, Erlangen, Germany) by using a T1-weighted 3D magnetization prepared rapid gradient echo sequence (MP-RAGE, 126 coronal slices, image matrix = 256 × 256, voxel size = 0.98 mm × 0.98 mm × 1.8 mm, TR = 10 ms, TE = 4 ms, flip angle = 12°).

2.3. Parcellation of the cerebellum

Cerebellar tracing was performed using the manual segmentation function implemented in BRAINS2 software (Magnotta et al., 2002). Ascertainment of cerebellar structures followed an established protocol that has been described in detail elsewhere (Pierson et al., 2002). Briefly, the cerebellum was parcellated into right and left anterior lobes, superior posterior lobes, inferior posterior lobes, and corpus medullare, respectively.

According to the nomenclature of Larsell and Jansen (1972), the traced cerebellar structures comprised the following regions: anterior lobes — I, II, III, IV, V; superior posterior lobes — VI, Crus I of VIIA; inferior posterior lobes — Crus II of VIIA, VIIB, VIII, IX, X; Corpus medullare — central white matter and output nuclei. In the present study, no distinction was made between the vermis and the hemispheres. The output nuclei and central white matter were designated as the corpus medullare, which was traced as a structure separate from the lobes. White matter branching off the corpus medullare into the folia was defined to be included in the lobes. The cerebellar peduncles were excluded at the point where they extended past the cerebellar grey matter.

Guide traces marking fissures and borders in several planes were used to maintain consistency and accuracy during parcellation. All measured subregions of the cerebellum were traced in the sagittal plane (Fig. 1). The raters (P.A.T., M.R.) were blinded to the diagnoses. To achieve a measure of interrater and intrarater reliability, 10 randomly selected scans were retraced by the same as well as by the other rater. Intraclass correlation coefficients ranged from 0.86 to 0.91 for intraobserver, and from 0.85 to 0.91 for interobserver variation.

2.4. Statistical analysis

The SPSS for Windows version 14 was used for statistical analysis; *P*-values less than 0.05 were considered significant. To account for inter-individual differences in head size, the cerebellar volumes were corrected by dividing them by each subject's intracranial volume. The latter was estimated by the sum of grey matter, white matter and cerebrospinal fluid after segmentation of the T1-weighted scans by applying the iterative a priori knowledge-based algorithm implemented in SPM2 software (http://www.fil.ion.ucl.ac.uk/spm).

Student's two-tailed *t*-test procedure was used to evaluate significant differences between patients and controls. The gender distribution was analyzed by the χ^2-test. The relationship between cerebellar volumes and clinical variables was assessed by using Pearson's correlation coefficient.

3. Results

3.1. Clinical data

As shown in Table 1, patients and healthy controls did not differ significantly with respect to age, gender and educational level. DSM-IV assessment revealed a diagnosis of schizophrenia in 21 patients and a diagnosis of schizophreniform disorder in 9 patients. Patients' total NSS scores and single item scores on the Heidelberg Scale were significantly higher than those of controls (Table 2). Extrapyramidal side effects were low according to the

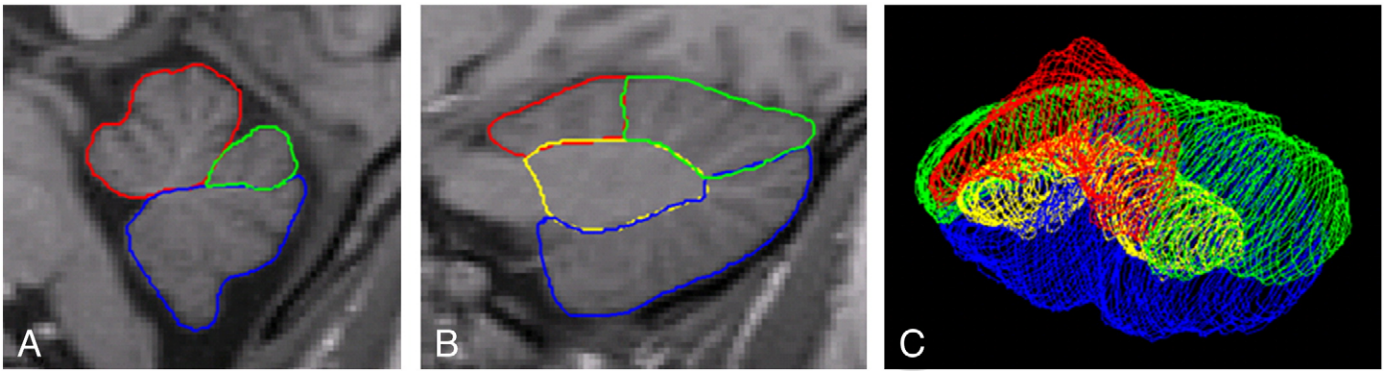

Fig. 1. Region of interest traces performed in sagittal orientation: (A) middle of the cerebellum, (B) lateral portion of the cerebellum, (C) 3-dimensional illustration of a completely traced cerebellum; red: anterior lobe, green: superior posterior lobe, blue: inferior posterior lobe; yellow: corpus medullare.

Table 2
Neurological soft sign levels in patients and healthy controls.

Heidelberg Scale score	Patients ($n=30$)	Controls ($n=21$)	t	df	P
Total	15.17 ± 6.61	3.43 ± 2.20	−7.82	49	<0.001
Motor coordination	6.23 ± 3.64	0.81 ± 1.08	−6.62	49	<0.001
Sensory integration	1.23 ± 1.14	0.29 ± 0.56	−3.53	49	<0.001
Complex motor tasks	3.17 ± 1.74	0.90 ± 0.89	−5.46	49	<0.001
Right/left and spatial orientation	1.60 ± 1.65	0.62 ± 0.81	−2.51	49	0.02
Hard signs	2.90 ± 1.95	0.81 ± 0.87	−4.58	49	<0.001

Means ± S.D.; df = degrees of freedom.

Simpson and Angus Rating Scale (11.93 ± 1.89), the Barnes Scale (1.00 ± 1.72), and the AIMS (0.83 ± 2.10), respectively. Mean scores were 52.03 ± 9.50 on the PANSS and 58.10 ± 7.50 on the Strauss–Carpenter Scale.

3.2. Volumes of cerebellar regions

A comparison of the volumetric measures is displayed in Table 3. According to statistical analysis, the intracranial volume did not differ significantly between the groups. Total cerebellar volume was significantly reduced in patients compared with controls. Cerebellar atrophy was found to be most prominent in the corpus medullare bilaterally, followed by the left and right superior posterior lobe. Comparison of cerebellar hemispheric volumes revealed solely the right hemisphere as being significantly smaller in patients.

3.3. Correlation of NSS with cerebellar volumes

In patients with schizophrenia, total NSS scores were found to be significantly associated with the volume of the right cerebellar hemisphere according to Pearson's product-moment correlation ($r=-0.46$, $P=0.01$). Total NSS scores were also inversely correlated with the volume of the right and left superior posterior lobe ($r=-0.41$, $P=0.03$, and $r=-0.38$, $P=0.04$, respectively). Overall, associations between NSS and cerebellar volumes were found to be most significant for the item "motor coordination" and the posterior superior lobes (right: $r=-0.58$, $P=0.001$; left: $r=-0.55$, $P=0.002$). Furthermore, significant correlations emerged between the items "hard signs" and the superior posterior lobes (right: $r=-0.48$, $P=0.007$; left: $r=-0.46$, $P=0.01$), "right/left and spatial orientation" and the anterior lobes (right: $r=-0.45$, $P=0.01$; left: $r=-0.42$, $P=0.02$), and between "right/left and spatial orientation" and the left corpus medullare ($r=-0.41$, $P=0.03$). The results of the correlation analyses are summarized in Table 4.

In healthy comparison subjects, no significant associations between NSS and cerebellar volumes arose. There was also no significant correlation of volumetric measurements with PANSS or Strauss-Carpenter Scale scores, neuroleptic dose, duration of treatment, age, gender, or educational level.

4. Discussion

The present MRI study ascertained volumes of cerebellar subdivisions in both schizophrenia patients and healthy controls, and related the morphometric measures to levels of NSS rated on the Heidelberg Scale (Schröder et al., 1992). There were the following three major findings: (i) first-episode patients with schizophrenia have significantly reduced cerebellar volumes with atrophy pronounced in the corpus medullare bilaterally, (ii) increased NSS scores are related to decreased volumes predominantly in anterior and superior posterior cerebellar regions, and (iii) this association only applies to patients with schizophrenia but not to healthy controls.

There is an increasing body of literature providing evidence for cerebellar dysfunction in schizophrenia. With regard to structural imaging, findings of cerebellar alteration in schizophrenia have been rather inconclusive. Both decreased as well as enlarged volumes, mainly in the vermian region, have been reported, while others revealed no significant differences in schizophrenia patients when compared with healthy controls (for review, see Bottmer et al., 2005). This discrepancy might be explained by aspects of sample selection, namely with respect to age, stage and course of the disease. The single study investigating patients with childhood-onset schizophrenia (Jacobsen et al., 1997) found significant cerebellar atrophy in patients compared with controls, underlining that these structural differences may occur before age-related volumetric changes.

Studies examining the effect of neuroleptic treatment on brain structure (for review, see Scherk and Falkai, 2006) detected the basal ganglia, mainly with regard to typical antipsychotics, to be particularly sensitive to morphological changes. However, an influence of medication in our study is unlikely as every patient was treated with atypical neuroleptics and duration of treatment was relatively short. The finding of significantly smaller cerebellar volumes in neuroleptic-naïve patients with schizophrenia (Ichimiya et al., 2001) furthermore suggests that cerebellar atrophy may be related to the disease rather than being psychotropic-associated. Moreover, the observation of reduced cerebellar volumes in unaffected first-degree relatives of patients with schizophrenia (Seidman et al., 1999) emphasizes cerebellar alteration as a hereditary trait phenomenon in this disorder.

In a first study on NSS and brain structure, we compared MRI-derived cerebellar measures (total tissue and hemispheric volumes) in 37 first-episode schizophrenia patients and 18 healthy controls, and found both hemispheres to be significantly smaller in the former group (Bottmer et al., 2005). In first-episode patients, NSS were inversely correlated with right hemispheric tissue volume, a finding consistent with the results of the present study, where NSS-related structural changes were pronounced in the right cerebellar hemisphere. Potential cerebellar involvement with NSS was also addressed in an MRI study by Keshavan et al. (2003), who observed a significant inverse correlation between cerebellar volume and repetitive motor tasks, and cognitively demanding and perceptual tasks, respectively. An involvement of the cerebellum in the pathogenesis of NSS is furthermore emphasized by findings of Ho et al. (2004), who investigated a large sample of neuroleptic-naïve patients with schizophrenia ($n=155$) and compared MRI-derived brain volumes

Table 3
Cerebellar measures (normalized to the intracranial volume) in patients and healthy controls.

Variable	Patients	Controls	t	df	P
ICV	1.33 ± 0.10	1.31 ± 0.08	−0.48	49	0.63
alr	5.03 ± 0.99	5.07 ± 0.69	0.18	49	0.86
all	5.42 ± 1.01	5.25 ± 0.70	−0.66	49	0.51
splr	16.33 ± 2.39	17.64 ± 1.53	2.21	49	0.03
spll	16.04 ± 2.33	17.62 ± 1.33	2.81	49	0.01
iplr	19.99 ± 2.90	20.93 ± 2.03	1.28	49	0.21
ipll	20.22 ± 2.89	21.00 ± 2.44	1.01	49	0.32
cmr	4.96 ± 0.64	5.51 ± 0.51	3.25	49	0.002
cml	5.01 ± 0.67	5.49 ± 0.48	2.83	49	0.01
hemr	46.31 ± 5.23	49.16 ± 3.71	2.14	49	0.04
heml	46.69 ± 5.37	49.37 ± 3.85	1.91	49	0.06
ctotal	93.00 ± 10.41	98.52 ± 7.26	2.10	49	0.04

Means ± S.D.; df = degrees of freedom; ICV = intracranial volume; alr/l = anterior lobe right/left; splr/l = superior posterior lobe right/left; iplr/l = inferior posterior lobe right/left; cmr/l = corpus medullare right/left; hemr/l = hemisphere right/left.

Table 4
Relationship between neurological soft sign levels and cerebellar volumes in patients (assessed by using Pearson's correlation coefficient).

Variable	alr	all	splr	spll	iplr	ipll	cmr	cml	hemr	heml
	r; *P*	*r*; *P*	*r*; *P*	*r*; *P*	*r*; *P*	*r*; *P*	*r*; *P*	*r*; *P*	*r*; *P*	*r*; *P*
Total NSS	−0.05; 0.78	−0.23; 0.23	**−0.41; 0.03**	**−0.38; 0.04**	−0.07; 0.72	−0.09; 0.65	−0.10; 0.59	−0.17; 0.37	**−0.46; 0.01**	−0.33; 0.07
Motor coordination	−0.12; 0.53	−0.12; 0.54	**−0.58; 0.001**	**−0.55; 0.002**	−0.06; 0.76	−0.09; 0.65	−0.03; 0.86	−0.19; 0.33	−0.32; 0.08	−0.33; 0.08
Sensory integration	−0.32; 0.09	−0.06; 0.76	0.03; 0.87	0.01; 0.96	−0.12; 0.53	0.06; 0.77	0.09; 0.65	0.11; 0.57	−0.10; 0.59	0.04; 0.85
Complex motor tasks	−0.08; 0.69	−0.12; 0.52	−0.22; 0.24	−0.25; 0.18	−0.15; 0.43	−0.11; 0.58	−0.11; 0.56	−0.13; 0.49	−0.21; 0.26	−0.21; 0.28
Right/left and spatial orientation	**−0.45; 0.01**	**−0.42; 0.02**	−0.27; 0.15	−0.26; 0.18	−0.33; 0.07	−0.26; 0.16	−0.33; 0.08	**−0.41; 0.03**	−0.12; 0.45	0.36; 0.05
Hard signs	0.02; 0.90	0.07; 0.71	**−0.48; 0.007**	**−0.46; 0.01**	−1.18; 0.36	−0.25; 0.19	0.03; 0.88	−0.03; 0.88	−0.31; 0.10	0.32; 0.08

alr/l = anterior lobe right/left; splr/l = superior posterior lobe right/left; iplr/l = inferior posterior lobe right/left; cmr/l = corpus medullare right/left; hemr/l = hemisphere right/left; statistically significant results in bold.

(i.e. total cerebral tissue, lateral ventricles, frontal, temporal and parietal lobes, and total cerebellar tissue, respectively) between patients with and without cerebellar neurological signs; in this study, significant atrophy in patients presenting with neurological abnormalities was restricted to the cerebellum, a finding supporting the hypothesis of its important role in the pathogenesis of NSS in schizophrenia. More recently, two studies using voxel-based morphometry corroborated the discussed findings in that higher NSS levels were significantly correlated with a regional loss of cerebellar gray and white matter density (Mouchet-Mages et al., 2007; Thomann et al., 2009).

In contrast to the above-cited studies, which solely investigated the relation between NSS and cerebral morphology in patients with schizophrenia, the present study also addressed putative associations in healthy comparison subjects. As expected, NSS levels in healthy individuals were rather low compared with levels in first-episode patients. Statistical analysis revealed no significant correlation between NSS and cerebellar volumes in the control group, indicating that NSS in patients and controls may relate to different pathogenetic factors. Putatively, NSS in healthy subjects rather refer to peristatic factors such as less developed skills, factors occurring at random in each individual and hence not corresponding to a specific pattern of brain structural alteration. The hypothesis that NSS in healthy controls and patients with schizophrenia are based on a different pathogenesis is supported by the North Finland 1966 general population birth cohort study, where ratings for infant motor development at age 1 year were related to cerebral changes assessed by MRI at age 33–35 years (Ridler et al., 2006). Ridler and colleagues found delay of infant motor development to be associated with cerebral changes in healthy individuals, but not in the patients' group. According to this dissociation, NSS in schizophrenia only partly depend on delays of infant motor development. The corresponding assumption that brain structural changes underlying NSS are not entirely preformatted or static but may also increase as psychosis develops is substantiated by a longitudinal study indicating progressive alteration of the cerebellum (Pantelis et al., 2003).

According to previous structural and functional neuroimaging studies, further brain regions have been shown to be associated with NSS in patients with schizophrenia, predominantly consisting of subcortical structures (basal ganglia and thalamus), the sensorimotor cortex, and the supplementary motor area, respectively (Dazzan et al., 2004; Keshavan et al., 2003; Schröder et al., 1992, 1995, 1999; Thomann et al., 2009). Taken together with the evidence for cerebellar involvement in NSS, these findings strongly support the hypothesis that NSS may be related to a disrupted cortico-cerebellar-thalamic-cortical circuit as conceptualized in the model of "cognitive dysmetria" (Andreasen et al., 1998).

Acknowledgments

The present study was supported by the Stanley Medical Research Institute. The authors are grateful to Mrs. A. Schneider for her assistance in the preparation and proof-reading of the manuscript.

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