The structural brain correlates of neurological soft signs in AESOP first-episode psychoses study

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Summary
Patients with schizophrenia and related psychoses have an excess of minor neurological abnormalities (neurological soft signs, NSS) of unclear neuropathological origin. These include poor motor coordination, sensory perceptual difficulties and difficulties in sequencing complex motor tasks. Neurological soft signs seem not to reflect primary tract or nuclear pathology. It still has to be established whether neurological soft signs result from specific or diffuse brain structural abnormalities. Studying their anatomical correlates can provide not only a better understanding of the aetiopathogenesis of soft signs, but also of the pathophysiology of schizophrenia. Surprisingly few studies have investigated the brain correlates of neurological soft signs. In the present study, we investigated the relationship between brain structure and neurological soft signs in an epidemiologically based sample of 77 first-episode psychosis patients.

We used the Neurological Evaluation Scale for neurological assessment and high-resolution MRI and voxel-based methods of image analysis to investigate brain structure. Higher rates of soft neurological signs (both motor and sensory) were associated with a reduction of grey matter volume of subcortical structures (putamen, globus pallidus and thalamus). Signs of sensory integration deficits were additionally associated with volume reduction in the cerebral cortex, including the precentral, superior and middle temporal, and lingual gyri. Neurological soft signs and their associated brain changes were independent of antipsychotic exposure. We conclude that neurological soft signs are associated with regional grey matter volume changes and that they may represent a clinical sign of the perturbed cortical–subcortical connectivity that putatively underlies psychotic disorders.

Keywords: neurological soft signs; first-episode psychosis; magnetic resonance imaging; voxel-based morphometry; basal ganglia

Abbreviations: EPS = extrapyramidal symptoms; NART = National Adult Reading Test; NES = Neurological Evaluation Scale; NSS = neurological soft signs

Introduction
Patients with schizophrenia and related psychoses have an excess of minor neurological abnormalities (neurological soft signs, NSS) of unclear neuropathological origin (Woods et al., 1986; Buchanan and Heinrichs, 1989). NSS include poor motor coordination, sensory perceptual difficulties and difficulties in sequencing complex motor tasks. NSS do not reflect primary tract or nuclear pathology. It still has to be established whether they result from specific or diffuse brain structural abnormalities.

NSS probably predate the onset of psychosis and are at least in part related to the pathogenic process underlying this illness. Thus, impairments of coordination, motor dysfunction and sensory integration have been observed in pre-schizophrenic children, in non-psychotic individuals at
increased genetic risk, and in patients at the first onset of psychosis (Kinney et al., 1986; Crow et al., 1995; Griffiths et al., 1998; Browne et al., 2000; Niethammer et al., 2000; Lawrie et al., 2001a). Furthermore, the presence of NSS in neuroleptic-naïve subjects suggests that, although antipsychotics may have some influence on NSS (King et al., 1991; Flashman et al., 1996), these signs are not simply a side-effect of antipsychotic medication. Further support is given by evidence that brain areas normally involved in motor coordination and in the integration of sensory and motor information, like subcortical regions and the frontal and temporal lobes, have been frequently reported as abnormal in schizophrenia (Buchsbaum, 1990).

To date, there is no agreement on what underlies NSS. It has been suggested that they reflect a failure in integration within or between sensory and motor systems (Griffiths et al., 1998), while others advocate deficits at subcortical level (basal ganglia, brainstem or limbic system) (Kennard, 1960; Mosher et al., 1971). It is possible that soft signs reflect an impairment of the normal corticocortical and corticosubcortical interneuronal anatomical connections, which have been proposed as one of the fundamental pathophysiological substrates of schizophrenia (Friston and Frith, 1995). Surprisingly few studies have investigated the anatomical substrate(s) of NSS (Dazzan and Murray, 2002). The results to date have been inconsistent, perhaps reflecting the use of CT scanning, as opposed to MRI, the study of heterogeneous groups of patients with chronic schizophrenia, and the examination of selected brain structures, such as the whole brain, and ventricular volume (Weinberger and Wyatt, 1982; Kolakowska et al., 1985; King et al., 1991). Studying the anatomical correlates of NSS can provide a better understanding not only of their aetiopathogenesis but also of the pathophysiology of schizophrenia.

In the present study, we investigated the relationship between brain structure and NSS in an epidemiologically based sample of first-episode psychosis patients. Investigating patients at the onset of illness may clarify whether NSS and brain abnormalities reflect a neurodysfunction that underlies psychosis rather than being the consequence of degenerative processes. Using an epidemiological sample avoids the potential bias of recruiting subjects selected for their neurological dysfunction, while studying patients at the onset of illness minimizes the confounding effects of long-term pharmacological treatment. We used a validated instrument for neurological assessment, and high-resolution MRI and voxel-based methods of image analysis. Voxel-based analysis of magnetic resonance images allows the evaluation of the entire brain rather than a few preselected regions. We predicted: (i) that the presence of an excess of NSS would be accompanied by abnormalities of cortical and subcortical brain structures involved in motor coordination and integration of sensory perceptions; and (ii) that the presence of NSS and the accompanying brain structural abnormalities would not be attributable to antipsychotic treatment.

### Methods

#### Study population

Subjects were recruited as part of a large epidemiological study (ÁSOP; Aetiology and Ethnicity in Schizophrenia and Other Psychoses) carried out in South London (UK), which investigated the higher rates of schizophrenia in the African–Caribbean population in the UK. As part of this study, we approached subjects aged 16–65 years who consecutively presented for the first time to the local psychiatric services for a functional psychotic illness (ICD-10 F10–19, excluding coding F1x.0 for acute intoxication; F20–29 and F30–39, psychotic codings) (World Health Organization, 1992) over a 3-year period. Exclusion criteria were: (i) a history of head trauma resulting in loss of consciousness for >1 h; (ii) the presence of a disease of the CNS; (iii) moderate or severe learning disabilities (IQ <50) as defined by ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th Revision, World Health Organization, 1992); (iv) poor fluency in the English language; and (v) transient psychotic symptoms resulting from acute intoxication, as defined by ICD-10 (World Health Organization, 1992), following the administration of alcohol or other psychoactive substance. A total of 281 patients met the inclusion criteria and were invited to participate; 90 of these refused to take part in the investigation. Of the 191 who participated in the study, 97 disengaged before completing the NSS assessment, and a total of 94 subjects underwent both an NSS evaluation and an MRI scan. These 94 subjects were younger (mean age 27.9 ± 8.7 years versus 32.6 ± 11.1 years; t test, P = 0.002), but were otherwise comparable to the total sample in terms of gender, ethnicity, years of education, diagnosis and duration of illness. From this final sample,
we excluded 17 MRI scans (15 due to subject motion, one because of the presence of congenital hydrocephalus, and one for the presence of a subarachnoid cyst). Demographic and clinical characteristics of the final sample (77 patients) are shown in Table 1. Ethical approval for the study was granted by the Ethical Committee of the Institute of Psychiatry, and the participants gave written informed consent.

Clinical and neurological assessments
We interviewed patients with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (World Health Organization, 1994). We made a diagnosis according to ICD-10 criteria (World Health Organization, 1992) by consensus in meetings with senior clinicians (Robin.M.M. or J.L.) from the Institute of Psychiatry, in which all clinical information was presented. The premorbid IQ was estimated with the National Adult Reading Test (NART) (Nelson and Willison, 1991). From clinical notes we calculated the duration of antipsychotic exposure in weeks and the daily antipsychotic dose at the time of NSS assessment, converted into chlorpromazine equivalents (Bazire, 1998; Taylor et al., 1999; Bezchlibnyk-Butler and Jeffries, 2000).

We assessed neurological function as soon as possible after initial presentation, with an expanded, previously validated version of the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989; Griffiths et al., 1998) (Appendix). This expanded version consists of four subscales reflecting different functional areas and showing good construct validity (Buchanan and Heinrichs, 1989; Sanders et al., 2000). (i) ‘Primary neurological dysfunction’ reflects a dysfunction that can be identified by a standard neurological examination, and includes the cranial nerves, eye movement, laterализing limb pyramidal signs and frontal release signs. (ii) ‘Sensory integration dysfunction’ reflects a dysfunction in the integration of sensory information and includes signs such as right/ left confusion, asterognosia, agraphaesthesia and audiovisual integration. (iii) ‘Motor coordination dysfunction’ reflects signs of motor incoordination, and includes tests such as tandem walk, dysdiadochokinesis and the finger-to-nose test. (iv) ‘Motor sequencing dysfunction’ reflects the ability to perform complex motor sequences and includes such tests as the fist-ring and the fist-edge-palm. We administered the schedule in a standardized manner as specified for each item, and according to a fixed order. The scores for the items present in the original NES (those included in the three subscales sensory integration, motor coordination and motor sequencing) (Buchanan and Heinrichs, 1989) were left unchanged (items scored on a three-point scale, from 0 = no abnormality to 2 = marked impairment, except for the snout and suck reflexes, which are scored either as 0 or 2). For the remaining items (included in the primary signs subscale), we used the scores as in Griffiths and colleagues (Griffiths et al., 1998): a three-point scale: 0 = no abnormality; 1 = intermediate criterion; 2 = a score at or above a reference criterion regarded as clearly abnormal/marked impairment. Assessment of NSS was always performed by a physician who was blind to diagnosis. The inter-rater reliability was evaluated with multiple examiners rating the same subjects on a videotape (agreement rates for the four subscales were: primary, \( r = 0.94 \); motor coordination, \( r = 0.96 \); sensory integrative, \( r = 0.87 \); motor sequencing, \( r = 0.92 \)). We analysed each subscale score separately, as this is thought to better represent the diversity of neurological dysfunction compared with the evaluation of the global score (Sanders et al., 2000).

We compared the brain structure of patients with more marked neurological signs (‘high’ NSS) with that of patients with no or few neurological signs (‘low’ NSS). In the MRI analysis, this division would permit optimal identification of the brain structural changes associated with the presence of a neurological dysfunction. As attempts to identify a clear cut-off score to distinguish subjects high and low for NSS have shown only a moderate discriminant value (Cuesta et al., 2002), we used the value of the median for each subscale of the NES to divide patients into high NSS and low NSS, a method previously described by Ismail and colleagues (Ismail et al., 1998). We evaluated the presence of extrapyramidal symptoms (EPS) with the Simpson–Angus scale (Simpson and Angus, 1970), akathisia with the Barnes rating scale (Barnes, 1989), and tardive dyskinesia with the Abnormal Involuntary Movement in Schizophrenia (AIMS) scale (National Institute of Mental Health, 1976). Hand preference was assessed according to the Annett Hand Preference Questionnaire (Annett, 1970).

Structural MRI acquisition
Scans were acquired with a General Electric Signa 1.5-T system (GE Medical Systems, Milwaukee, WI, USA) at the Maudsley Hospital, London. Contiguous, interleaved proton density- and T2-weighted images, each 3 mm thick, were acquired in the coronal plane to provide whole-brain coverage. A repetition time (TR) of 4000 ms and effective echo times (TE) of 20 and 85 ms were used with an eight-echo train length. The matrix size was 256 × 192, collected from a rectangular field of view of 22 × 16.5 cm, giving an in-plane resolution of 0.859 mm. The total acquisition time was 10 min 12 s.

Structural MRI processing
The methods used for segmentation and registration of each fast spin-echo data set have been described in detail elsewhere (Bullmore et al., 1999; Suckling et al., 1999a,b). Briefly, extracerebral tissues were initially removed, using an automated algorithm. Manual editing of the skull-stripped images was necessary only to remove brainstem and cerebellum from the cerebral hemispheres and diencephalon. The probability of each intracerebral voxel belonging to each of four possible tissue classes (grey matter, white matter, CSF or dura/vasculature) was then estimated with a modified fuzzy clustering algorithm (Suckling et al., 1999b). This type of segmentation assigns to each voxel a value in the range 0–1 indicating the fraction of the voxel constituted by each tissue type (for example, a grey matter value of 0.7 means that 70% of the tissue represented by that voxel is grey matter). Images were then mapped into standard space using a nine-parameter affine registration. This registration aligns all the images together and scales them to the same gross dimensions.

A template image in the standard space of Talairach and Tournoux (Talairach and Tournoux, 1988) was constructed using the AFNI (Analysis of Functional Neuro Images) program from six proton density images acquired from six healthy subjects and then averaging these images. Maps of tissue distribution were then calculated into standard space using a nine-parameter affine registration aligning all the images together and scaling them to the standard space using a nine-parameter affine registration. This registration aligns all the images together and scales them to the same gross dimensions.

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Permutation testing was used to assess statistical significance, and regional relationships were tested at the level of voxel clusters (Bullmore et al., 1999; Sigmundsson et al., 2001). Given that structural brain changes are likely to extend over a number of contiguous voxels, test statistics which incorporate spatial information, such as 3D cluster mass (the sum of suprathreshold voxel statistics), are generally more powerful than other possible test statistics, which are informed only by data at a single voxel. We set the statistical threshold for cluster significance in all analyses so that the expected number of false-positive clusters (P value times number of tests) was <1 false positive. We conducted additional analyses, correlating the size of the resulting grey matter or white matter clusters with the total NSS score using the Pearson correlation coefficient. This clarifies whether there is a relationship between the volume of cluster and increased severity of neurological signs.

Results
The sociodemographic and clinical characteristics of the sample are shown in Table 1.

Group scores for NSS
The total NSS score is shown in Table 1. The value of the median for each subscale and the differences between patients with high and low NSS for sociodemographic (gender, age, years of education) and clinical characteristics (premorbid IQ, diagnosis, duration of illness, number of subjects currently taking antipsychotics, duration of antipsychotic exposure, current antipsychotic dose, antipsychotic side-effects, global grey and white matter and CSF) at each subscale are shown in Table 2. Eighteen subjects were above the median of all four subscales, while 16 were below the median of all subscales. In all subscales, the high-NSS subjects had a significantly lower IQ (Table 2). Twenty-two subjects were not on any antipsychotics at the time of assessment. These 22 drug-free patients were evenly distributed between the two groups of high and low NSS in all but the primary signs subscale, in which 76% of the drug-free subjects were in the group of low NSS. Subjects high in primary signs also had more EPS on the Simpson–Angus scale. There was no difference in duration of antipsychotic exposure or current antipsychotic dose between patients high and low for NSS at any of the four subscales.

Relationship between NSS and brain structure

Total tissue volumes
There were no significant differences in total grey or white matter volume between subjects high and low for NSS on any of the NSS subscales.

Primary signs
The high score group showed one cluster of grey matter deficit focused on the left putamen (P < 0.002), which extended medially to include the globus pallidus and laterally to include the insula (Table 3, Fig. 1A). There were no white matter differences between the high and low score groups. For the primary signs, there was a negative correlation between score on these signs and size of the putamen cluster (Pearson r = −0.4; P < 0.001), thus confirming that the higher the primary NSS score, the smaller the volume of the putamen.

Motor coordination signs
The high score group showed one cluster of grey matter deficit focused on the left putamen (P < 0.002), which extended medially into the globus pallidus (P < 0.002) (Table 3, Fig. 1B, upper panel); moreover, we also found an adjacent cluster of white matter excess of the left internal capsule, which included the external and extreme capsules across a few slices (Table 3; Fig. 1B, lower panel). The score for motor coordination was

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Table 2 Neurological performance of the sample and differences in sociodemographic1 and clinical2 characteristics of subjects with high and low NSS

<table>
<thead>
<tr>
<th></th>
<th>Median (25th, 75th percentiles)</th>
<th>Subjects above/below the median (n)</th>
<th>Significant differences in subjects with high NSS compared with those with low NSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>4 (2, 6)</td>
<td>34/39</td>
<td>Lower IQ (P = 0.02)1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Higher Simpson–Angus score (P = 0.008)3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>More subjects receiving antipsychotic treatment (P = 0.001)4</td>
</tr>
<tr>
<td>Motor coordination</td>
<td>1 (0, 2)</td>
<td>31/46</td>
<td>Lower IQ (P = 0.02)1</td>
</tr>
<tr>
<td>Sensory integration</td>
<td>1 (0, 2)</td>
<td>37/40</td>
<td>Lower IQ (P &lt; 0.001)3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Higher CSF volume (P = 0.001)3</td>
</tr>
<tr>
<td>Motor sequencing</td>
<td>1 (0, 3)</td>
<td>36/41</td>
<td>Lower IQ (P = 0.008)1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>More males (P = 0.04)4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>More subjects with schizophrenia (P = 0.01)4</td>
</tr>
</tbody>
</table>

1Sociodemographic characteristics: gender, age, years of education; 2clinical characteristics: premorbid IQ, diagnosis, duration of illness, number of subjects currently taking antipsychotics, duration of antipsychotic exposure, current antipsychotic dose, antipsychotic side-effects, global grey and white matter and CSF; 3t test; 4χ2 test.
negatively correlated with the putamen size (Pearson $r = -0.27; P = 0.009$) and positively correlated with the size of the internal capsule cluster (Pearson $r = 0.26; P = 0.01$), again confirming that subjects with more problems in motor coordination had a smaller volume of the left putamen and a larger volume of the internal capsule.

**Sensory integration signs**

The high score group showed a reduction of grey matter volume in several regions ($P < 0.002$) (Table 3; Fig. 1C, upper panel). Most of these differences were bilateral, and included the lenticular nucleus, thalamus, pulvinar, insula, middle temporal and lingual gyrus. There was also a smaller grey matter volume in the right precentral gyrus and adjacent inferior frontal gyrus, and in the left superior temporal gyrus.

In the white matter, subjects with high sensory integration scores showed an excess of volume of the left internal capsule, which in some slices also extended to the external and extreme capsules (Table 3; Fig. 1C, lower picture). This excess was adjacent to the grey matter deficit focused on the left lenticular nucleus. There was a negative correlation between score on sensory integrative signs and volume of all the grey matter clusters (Pearson $r$, range $-0.29$ to $-0.57; P < 0.005$) and a positive correlation with the white matter cluster (Pearson $r = 0.44; P < 0.001$).

**Motor sequencing signs**

At a statistical threshold for cluster significance set at $<1$ false-positive cluster, we found no association between scores on the motor sequencing subscale and grey or white matter volume changes. However, at a slightly less stringent $P$ value (with $<2$ false-positive clusters), the subjects with a high motor sequencing score showed a cluster of grey matter reduction at the level of the left putamen.

**Role of antipsychotic medication**

There was no correlation between the size of any of the clusters identified above and either duration of antipsychotic exposure or current dose of antipsychotic medications.

**Discussion**

We have evaluated NSS and brain structure in a large epidemiological sample of first-episode psychosis patients. We have shown that higher rates of soft neurological signs (both motor and sensory) are associated with a reduction of grey matter volume of subcortical structures (putamen, globus pallidus and thalamus). Furthermore, we have shown that higher rates of sensory integration signs are additionally associated with distributed volume reduction in the cerebral cortex, including the precentral, superior temporal and lingual gyri.

Our main finding was that of smaller basal ganglia volume in subjects with more neurological signs in each of the domains of (i) primary, (ii) motor coordination and (iii) sensory integration signs. A similar association between motor coordination abnormalities and reduced basal ganglia and thalamus volume (as indirectly suggested by the ratio of the frontal horn to caudate head) has been reported by Schroder and colleagues in patients with schizophrenia or schizophreniform disorder (Schroder et al., 1991). The basal ganglia include five subcortical nuclei: the caudate and putamen (which together constitute the striatum), the globus pallidus, the subthalamic nucleus and the substantia nigra. They are an essential integrative centre: the entire cerebral

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Table 3 *Regional differences in grey and white matter in subjects with high versus subjects with low NSS*

<table>
<thead>
<tr>
<th>Anatomical area</th>
<th>Number of voxels in cluster</th>
<th>Location of cluster centre $(x, y, z)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less grey matter in subjects high for primary signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left putamen</td>
<td>323</td>
<td>$-26.1, 6.5, 4.7$</td>
</tr>
<tr>
<td>Less grey matter in subjects high for motor coordination signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left putamen</td>
<td>336</td>
<td>$-20.4, -1.5, 4.6$</td>
</tr>
<tr>
<td>More white matter in subjects high for motor coordination signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left internal capsule</td>
<td>303</td>
<td>$-14.2, 9, 1.3$</td>
</tr>
<tr>
<td>Less grey matter in subjects high for sensory integration signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lenticular nucleus, extending into the insula</td>
<td>746</td>
<td>$-26.1, 2.2, 9.0$</td>
</tr>
<tr>
<td>Right lenticular nucleus, extending into the insula</td>
<td>1153</td>
<td>$30.2, -0.9, 8.1$</td>
</tr>
<tr>
<td>Right precentral gyrus (BA 6, 4), extending into the inferior frontal gyrus</td>
<td>269</td>
<td>$51.3, 3.8, 26.5$</td>
</tr>
<tr>
<td>Left middle temporal gyrus (BA 21), extending into the superior temporal gyrus</td>
<td>345</td>
<td>$-56.3, -8.8, -5.6$</td>
</tr>
<tr>
<td>Left and right thalamus and pulvinar</td>
<td>603</td>
<td>$7.6, -23.1, 6.3$</td>
</tr>
<tr>
<td>Right middle temporal gyrus (BA 21)</td>
<td>264</td>
<td>$60.3, -43.7, 7.7$</td>
</tr>
<tr>
<td>Left and right lingual gyrus (BA 18)</td>
<td>536</td>
<td>$4.5, -75.5, -4.9$</td>
</tr>
<tr>
<td>More white matter in subjects high for sensory integration signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left internal capsule</td>
<td>533</td>
<td>$-20.6, 15, 7.7$</td>
</tr>
</tbody>
</table>

BA = Brodmann area.
cortex (sensory, motor, association and limbic areas) projects topographically to the nuclei of the striatum, which not only have extensive interconnections but also send their outputs back to the prefrontal, premotor and motor cortices, via the thalamus. These nuclei, therefore, have parallel but different functions: the caudate has a role in the control of eye movements and in cognitive functions; the putamen is involved in motor control; and the ventral striatum is involved in limbic functions (DeLong, 2000).

Our results showing reduced basal ganglia volumes in patients with psychosis and marked NSS further confirm the involvement of the basal ganglia in schizophrenia, as suggested by neuropathological and neuropsychological studies (Bilder et al., 1993; Heckers, 1997). Although imaging studies have described an enlargement of these ganglia in subjects on antipsychotic treatment, studies on neuroleptic-naive patients or never-treated subjects at high risk have shown a reduced size and activity of these structures relative to healthy controls (DeLisi et al., 1991; Chakos et al., 1994; Lieberman et al., 1997; Keshavan et al., 1998; Shihabuddin et al., 1998; Corson et al., 1999; Lawrie et al., 2001b). It is possible that excessive synaptic pruning of cortical–subcortical neurons reduces their trophic effect, leading to reduced synaptic neuropil and thereby to smaller size of the basal ganglia (Keshavan et al., 1994). It is conceivable that these basal ganglia defects may be manifest in neurological abnormalities of functions regulated by these structures, such as motor coordination, and our finding of a putamen reduction supports this.

An excess of sensory integration signs (audiovisual integration, stereognosis, graphaesthesia, extinction, right/ left confusion) was associated with distributed cortical abnormalities. The performance of these tests requires the individual’s capacity to use information arriving through different sensory modalities coherently and interchangeably (Calvert, 2001). We found that difficulties in sensory integration were associated with a grey matter reduction in the right precentral gyrus [primary motor cortex Brodmann area (BA) 4 and premotor area BA 6]. The pyramidal neurons in these areas project to subcortical structures and control somatic movements and integrate complex sensory and motor information (DeLong, 2000). Sensory integration deficits were also associated with deficits in middle and superior temporal volume. These regions are involved in auditory and language processes, visual information, visual recognition and audiovisual integration (Calvert, 2001). Further grey matter reductions were evident in the insula and claustrum, areas important for the transfer of sensory information arriving through different sensory modalities, and particularly for the processing of somatosensory shape representation (Hadjikhani and Roland, 1998; Calvert, 2001). These findings are consistent with reports of a failure in processes that require integration of audiovisual integration in patients with schizophrenia, which could be particularly related to a deficit in movement perception (de Gelder et al., 2002). Finally, a grey matter deficit of the lingual gyrus (BA 17) was associated with more sensory integration abnormalities. This gyrus is the site of the secondary visual cortex (BA 18) and is involved with the integration of primary visual stimuli and sensory information. Connections are sent from the lingual gyrus to the pulvinar (also smaller in these patients), which is thought to be important for visual attention. The lingual gyrus has been reported previously as abnormal in schizophrenia in neuroimaging studies (Gaser et al., 1999; Shapleske et al., 2002). Moreover, previous studies have found that patients with schizophrenia have impaired processing of higher-level visual information, such as object recognition and identification, a deficit that resembles the visual associative agnosia described in neurological patients (Gabrovská et al., 2003).

We observed an increase of the white matter of the internal capsule, which accompanied the volume reduction in the putamen. This increased white matter volume, coexisting with areas of grey matter deficits, is consistent with MRI data from studies of patients with schizophrenia (Shapleske et al., 2002). The internal capsule contains cortical–subcortical projections and this increase in volume might represent a compensatory response to the reduction in striatal volume (Lawrie and Abukmeil, 1998; Gaser et al., 1999). Alternatively, a regional excess could reflect a disorganization of fibre structure, corresponding functionally to a neurological abnormality. Finally, we cannot exclude the possibility that some of the adjacent areas of grey and white matter abnormalities could be due to an artefact of the registration of the images into standard (Talairach) space.

Our results add strength to the notion that NSS reflect the pathophysiology of schizophrenia rather than being an effect of antipsychotic treatment. First, there was no difference in the duration of antipsychotic exposure or in antipsychotic dose between subjects with high and low NSS in each subscale. Secondly, the large number of subjects who were not taking antipsychotic medication at assessment was evenly distributed among the high and the low NSS groups for all subscales except the primary sign subscale. This scale includes focal signs but also EPS that could be the result of drug treatment (such as tremor or glabellar reflex). It is

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**Fig. 1** Brain changes in subjects with ‘high’ neurological soft signs compared with subjects with ‘low’ NSS. Regions of tissue deficit in patients with high soft signs are shown in blue; regions of tissue excess in patients with high soft signs are shown in red. Results are displayed on an averaged grey- and white-matter map. The left side of the image corresponds to the right side of the brain. Numbers refer to the approximate y coordinates in the standard space of Talairach and Tournoux. (A) Primary signs. Regions of grey matter deficits (blue) in subjects high for primary signs. (B) Motor coordination signs. Regions of grey matter deficit (upper, blue) and white matter excess (lower, red) in subjects high for motor coordination signs. (C) Sensory integration signs. Regions of grey matter deficit (blue) in subjects high for sensory integration signs. Regions of white matter excess (red) in subjects high for Sensory integration signs.
possible that subjects on medication, who are more likely to show EPS, fell in the group with high primary scores. Indeed, these subjects also had a higher score on the Simpson–Angus scale for EPS. However, if subjects had more primary signs (or more NSS in general) because of antipsychotics, they should have had larger, not smaller, basal ganglia (DeLisi et al., 1991; Chakos et al., 1994; Lieberman et al., 1997). In fact, we conducted a separate MRI analysis in this sample, comparing the drug-free subjects with subjects on antipsychotics, and we found that subjects on antipsychotics had a larger left putamen than drug-free subjects (P.Dazzan and K.D.Morgan, unpublished data). Therefore, smaller basal ganglia in subjects with more signs (primary and others), even if on antipsychotics, are more likely to reflect a neurological dysfunction than to be a consequence of antipsychotic drugs. Our findings are in accordance with a number of studies that failed to find any association between NSS and either daily antipsychotic dosage or length of exposure to antipsychotics (Wegner et al., 1985; Cuesta et al., 1996; Mohr et al., 1996; Ismail et al., 1998; Flyckt et al., 1999; Browne et al., 2000; Lawrie et al., 2001a). Indeed, even when an association between NSS and duration of neuroleptic treatment has been reported (King et al., 1991), NSS appear more marked among cases with early onset or more severe psychopathology.

NSS have been associated with a more severe clinical course of psychosis, worse psychosocial performance, and cognitive dysfunction (Mosher et al., 1971; Quitkin et al., 1976; Tucker and Silberfarb, 1978; Kolakowska et al., 1985; Wong et al., 1997), suggesting that they may characterize a subgroup of patients sharing a more severe pathophysiological process. Consistently with this literature, we found that subjects with more NSS had a lower IQ than those with fewer NSS (Kennard, 1960; Mosher et al., 1971; Manschreck and Ames, 1984). Therefore, we considered the possibility that the brain structural changes that we have observed could in fact be related to the severity of the illness rather than to the presence of NSS. Within the limits of the data available, we investigated this possibility further. We compared factors that could be indicative of a more severe illness (duration of illness, number of subjects on antipsychotic treatment and current antipsychotic dose, percentage of subjects with a diagnosis of schizophrenia, and years of education as a measure of premorbid achievement) in subjects high and low for NSS. We found no differences between the groups for these factors, with the exception of a more frequent diagnosis of schizophrenia only among subjects with more motor sequencing signs. On this basis, we feel that the brain structural changes that we have observed reflect an association with neurological dysfunction rather than with other clinical factors.

The comparison of NSS rates in patients with psychosis across different studies is made difficult by the fact that they are evaluated with a variety of instruments and not always with a published, validated scale. The percentage of subjects with abnormal scores for motor coordination, motor sequencing and sensory integration in our study was 67%, which is similar to that found by Griffiths and colleagues (Griffiths et al., 1998) (range 37.2–61.1%). The percentage of subjects scored as abnormal for the primary scale in our study (78%) was higher than that reported by Griffiths and colleagues (range 39–57%). As the primary scale also includes signs that can represent an antipsychotic side-effect, we cannot exclude the possibility that our higher primary rates reflect the presence of worse extrapyramidal symptoms in our sample. Still, as also found by Griffiths and colleagues (Griffiths et al., 1998), the rates of NSS observed in our sample of first-episode psychosis patients were lower than those of other studies that have used the NES (Buchanan and Heinrichs, 1989; Mohr et al., 1996; Smith et al., 1996; Arango et al., 1999; Yazici et al., 2002). Interestingly, like Griffiths and colleagues (Griffiths et al., 1998) we used a conservative approach to scoring and always scored equivocal signs as the lower value. It is possible that other studies have used a less conservative approach, hence their higher values (Cox and Ludwig, 1979).

Our lower scores could also reflect the fact that we included subjects with non-schizophrenic psychoses, who have been described in the literature as having less NSS than subjects with schizophrenia (Boks et al., 2000). Finally, it is possible that subjects at their first psychotic episode show less NSS than subjects at more advanced stages of the illness (Madsen et al., 1999), who, in contrast, may have a worse neurological dysfunction related to the progression of the disease.

Previous studies of the anatomical correlates of NSS have focused on gross measures of brain abnormality, such as whole-brain or ventricle : brain ratio. The results have been inconsistent. Some have described an association of NSS with enlargement of the cerebral ventricles (Weinberger and Wyatt, 1982; Schroder et al., 1991; Mohr et al., 1996) and with smaller frontal brain areas and volumes (DeMyer et al., 1988; Rubin et al., 1994), but others have reported no correlation between NSS and ventricular size (King et al., 1991) or the ventricle : brain ratio (Kolakowska et al., 1985). These apparently conflicting results may reflect the use of different instruments to evaluate NSS, the use of CT rather than high-resolution MRI, and the inclusion of patients at various stages of illness. We sought to avoid these potential confounds by studying patients in their first episode of psychosis who had been ill and on treatment for a relatively short period of time, using high-resolution MRIs analysed with a voxel-based method that evaluates the entire brain as opposed to a few preselected regions. Voxel-based morphometry (VBM) offers several advantages over the region-of-interest approach, and the methods have been well validated (Wright et al., 1995, 1999). Although there has been some debate on the methodology (Bookstein, 2001), studies using this approach have produced relatively consistent results in studies of patients with psychosis and the methods have been extensively validated (Wright et al., 1999; Sigmundsson et al., 2001; Shapleske et al., 2002; Watkins et al., 2002; Panetlis et al., 2003).
A potential limitation of our study is the lack of comparison with a group of healthy controls. Comparing patients with and without NSS and healthy controls might tell us whether patients with more NSS have more brain structural abnormalities than the normal population, and also where these abnormalities would be located. However, comparing patients and controls would also introduce a main confounder: the fact that patients suffer from psychosis while the controls do not. This would make it difficult to distinguish what is related to NSS and what is related to psychosis. Furthermore, when investigating brain changes potentially located at subcortical level, the comparison with healthy controls would be difficult to interpret, as patients would be treated with antipsychotics (which are likely to affect these structures), while controls would not. For these reasons we believe that comparing two patient groups different only in their NSS levels is more informative of the brain differences that characterize a subgroup of patients with more neurological abnormalities. This approach has been used in a number of similar studies that have looked at NSS correlates, including neuroanatomical ones (Cuesta et al., 1996; Flashman et al., 1996; Ismail et al., 1998; Browne et al., 2000; Keshavan et al., 2003). Furthermore, a recent study on the neuroanatomical correlates of NSS in first-episode psychosis patients and in healthy controls has shown no association between NSS and brain regions in healthy controls (Keshavan et al., 2003). Instead it showed that, in schizophrenia patients, motor abnormalities were associated with a reduction of the basal ganglia, while sensory processing abnormalities were associated with a reduction of the heteromodal cortex. These results suggest that the relation between neurological and neuroanatomical abnormalities is specific to schizophrenia.

Conclusion

To our knowledge, ours is the first study evaluating the entire brain and showing an association between NSS and regional grey matter volume changes. Our findings suggest that NSS are associated with a smaller volume of the subcortical and cortical structures involved in sensory–motor integration, independent of psychopharmacological treatment. NSS may represent a clinical sign of the perturbed cortical–subcortical connectivity that putatively underlies psychotic disorders.

As pointed out by Heinrichs and Buchanan (1988), the fact that ‘their [NSS] meaning in schizophrenia is uncertain reflects not the unreality of findings but limitations in our knowledge’. We have shown that this knowledge can be advanced using validated instruments and high-resolution images.

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Appendix

Table 1A Tests included in each subscale

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<tr>
<th>Primary signs</th>
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<tr>
<td>Cranial nerve palsy (right and left)</td>
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<td>Smooth pursuit</td>
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<td>Saccade to target</td>
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<td>Saccade to command</td>
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<td>Synkinesis</td>
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<td>Gaze impersistence</td>
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<td>Convergence</td>
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<td>Tone increase (right and left)</td>
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<td>Limb hyporeflexia (right and left)</td>
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<td>Plantar (right and left)</td>
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<td>Romberg</td>
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<td>Chorea (right and left)</td>
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<td>Tremor (right and left)</td>
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<td>Mirror movements (right and left)</td>
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<td>Glabellar reflex</td>
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<td>Snout reflex</td>
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<td>Grasp reflex (right and left)</td>
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<td>Suck reflex</td>
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<th>Sensory integration signs</th>
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<tr>
<td>Audiovisual integration</td>
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<tr>
<td>Stereognosis (right and left)</td>
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<tr>
<td>Graphaesthesia (right and left)</td>
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<tr>
<td>Extinction</td>
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<td>Right/left confusion</td>
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<th>Motor coordination signs</th>
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<tr>
<td>Tandem walk</td>
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<td>Rapid alternating movements (right and left)</td>
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<tr>
<td>Finger–thumb opposition (right and left)</td>
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<td>Finger–nose test (right and left)</td>
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<th>Motor sequencing signs</th>
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<tr>
<td>Fist-ring test (right and left)</td>
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<td>Fist-edge-palm test (right and left)</td>
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<td>Ozeretski test</td>
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