Neurological soft signs in obsessive–compulsive disorder: The effect of co-morbid psychosis and evidence for familiality

Zi-wen Peng, Ting Xu, Guo-dong Miao, Qing-huan He, Qing Zhao, Paola Dazzan, Raymond C.K. Chan

Abstract

Patients with obsessive–compulsive disorder (OCD) have increased rates of neurological soft signs (NSS) when compared to healthy controls. However, previous findings have been confounded by the presence of co-morbidity with disorders themselves associated with increased NSS, such as schizophrenia. Moreover, it remains unclear whether NSS in OCD reflect a vulnerability to this disorder. This study aimed to examine: 1) the severity of NSS in patients with OCD alone, in patients with OCD and co-morbid psychosis (schizophrenia or bipolar disorders), and in healthy controls; and b) whether unaffected first-degree relatives of patients with OCD also demonstrate a higher prevalence rate of NSS than healthy controls. NSS were assessed with the Cambridge Neurological Inventory (CNI) in 100 patients with OCD, 38 patients with OCD and psychosis (22 with bipolar disorders and 16 with schizophrenia), and 101 healthy controls. Forty-seven unaffected first-degree relatives of patients with OCD only were also administered the CNI. Patients with OCD showed significantly higher scores in motor coordination and total NSS than controls, and patients with OCD co-morbid with psychosis also showed significantly higher scores in motor coordination and total NSS than controls. Although there were no differences in NSS between patients with OCD only and OCD and psychosis as a whole, patients with OCD co-morbid with schizophrenia showed significantly higher scores in motor coordination than patients with OCD, patients with OCD and bipolar disorder, and healthy controls. Unaffected first-degree relatives only showed a higher prevalence rate than healthy controls in specific motor coordination signs, such as Opposition and Extinction. These findings suggest that patients with OCD exhibit more NSS than healthy controls, and that motor coordination signs may be even more extensive when OCD is co-morbid with psychosis. Some of these abnormalities may be indicative of a vulnerability to these disorders, as indicated by their presence in un-affected first-degree relatives.

1. Introduction

Obsessive–compulsive disorder (OCD) and schizophrenia are disorders of neurodevelopmental origin, and are highly co-morbid (Fabisch et al., 2001). These disorders share many similarities in clinical and neurological manifestations (Thomas and Tharyan, 2011), neurocognitive deficits (Mataix-Cols et al., 2003), and underlying neural circuitry alterations (Gold et al., 1997; Saxena and Rauch, 2000). Evidence to suggest their neurodevelopmental origin comes from findings of increased rates of neurological soft signs (NSS) in both OCD and schizophrenia (Bolton et al., 1998; Poyurovsky et al., 2007; Sevincok et al., 2006; Thomas and Tharyan, 2011). NSS include subtle abnormalities in sensory and motor functions, which seem to be already present at the time of the first schizophrenia episode, and which may reflect a vulnerability to this illness (Dazzan et al., 2008; Thomas and Tharyan, 2011). Interestingly, supporting the notion that schizophrenia lies with the other psychoses along a continuum of vulnerability, higher NSS rates have been reported also in psychoses of the affective spectrum, such as bipolar disorder (Dazzan et al., 2008). It remains unclear if NSS occur at even higher rates in individuals who have a co-morbidity for OCD and either schizophrenia or bipolar disorder, as it might be expected if a broader

Abbreviations: BD, bipolar disorder; BDI, Beck depression inventory; CNI, Cambridge neurological inventory; DIA, diadochokinesia; Dis, disinhibition; EXTINT, extinction; FEP, fist-edge-palm; FG_AG, finger agnosia; FG_OP, finger-thumb opposition; GRAP, graphesthesia; GO_NG, go no-go; LR_ORN, left–right orientation; MC, motor coordination; MIR, mirror; NSS, neurological soft signs; OCD, obsessive–compulsive disorder; OCI-R, obsessive–compulsive inventory-revised; OSE, Oseretsky; SBLK, saccade blink; SCHEAD, saccade head; SCC, schizophrenia; SL, sensory integration; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRIs, selective serotonin reuptake inhibitors; STAI, state–trait anxiety inventory; STER, stereognosia; TAP, finger tapping; Y-BOCS, Yale–Brown obsessive–compulsive scale.

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neurodevelopmental hit underlies the pathophysiology of both OCD and these disorders. Interestingly, the origin of NSS seems to be, at least in part, genetic. In fact, studies of relatives of patients with schizophrenia also suggest that NSS are, to some extent, heritable, and as such represent a potential endophenotype for schizophrenia (Chan and Gottesman, 2008). For example, a recent meta-analysis has shown that the prevalence rates of NSS in unaffected first-degree relatives of patients with schizophrenia are intermediate between those of their psychotic probands and those of healthy controls (Chan et al., 2010c). Unfortunately, there is no study that has specifically examined the prevalence of NSS in unaffected first-degree relatives of patients with OCD. It is therefore theoretically and clinically important to examine the prevalence of NSS in patients with co-morbid OCD and psychosis, and also in unaffected first-degree relatives of OCD patients to understand their role in the etiopathogenesis of this disorder. This is the first study that has investigated the prevalence rates of NSS in patients with OCD alone, and OCD and co-morbid psychosis in comparison to healthy controls. Furthermore, the study also examined whether unaffected first-degree relatives of OCD probands have a higher prevalence rate of NSS than healthy controls.

2. Materials and methods

2.1. Participants

A sample of 100 patients with OCD (29 females) (paired with 47 of their unaffected first-degree relatives), and 38 patients (16 females) with OCD and co-morbid psychosis (22 with bipolar disorder and 16 with schizophrenia) were recruited from Guangzhou Psychiatry Hospital, China. They all fulfilled the Diagnostic and Statistical Manual of Mental Disorder-fourth edition (DSM-IV) (APA, 1994) criteria for OCD, and/or bipolar disorder, or schizophrenia. The diagnosis was ascertained in clinical interviews by two qualified psychiatrists (ZWP and GDM), and supplemented by information from medical records. Exclusion criteria included: (1) the presence of major depression (DSM-IV), (2) life-time history of substance abuse (DSM-IV), (3) history of electroconvulsive therapy in the previous six months, (2) life-time history of substance abuse (DSM-IV), (3) history of electroconvulsive therapy in the previous six months, (4) history of neurological disorder, (5) a history of head injury with loss of consciousness for more than 30 min, and (6) mental retardation. All patients received treatment for the obsessive symptoms, with the majority receiving selective serotonin reuptake inhibitors (SSRIs: citalopram, escitalopram, fluoxetine, paroxetine; daily dose ranging from 20 mg to 60 mg), and the others receiving a serotonin–norepinephrine reuptake inhibitor (SNRIs; venlafaxine; daily dose ranging from 75 mg to 225 mg), sertraline (daily doses ranging from 100 mg to 200 mg), fluvoxamine (daily doses ranging from 100 mg to 250 mg) or clomipramine (daily doses ranging from 100 mg to 200 mg). (Details please refer to the Appendix A.) The 22 patients with OCD and co-morbid bipolar disorder were receiving a combination of SSRIs (twelve) or SNRIs (two) and lithium carbonate (daily dose: 0.75 g–1.5 g), and the other eight patients were treated with combination of SSRIs (seven) or SNRIs (one) and sodium valproate (daily dose: 0.6 g–2.0 g). The 16 patients with OCD and co-morbid schizophrenia were receiving a combination of SSRIs and second-generation antipsychotics (daily dose ranging from 25 mg to 100 mg chlorpromazine equivalent). Twenty-six patients were receiving anticholinergic medication (benzhexol; daily dose ranging from 2 mg to 6 mg). Fifty-four patients had received short-acting low-dose benzodiazepines (lorazepam; daily dose ranging from 0.5 mg to 2 mg) at least 12 h prior to the NSS assessment.

We also included 47 unaffected first-degree relatives (22 females) of the patients with OCD only. All of them were interviewed by a psychiatrist (ZWP). Exclusion criteria were identical to those of the patients. One hundred and one healthy controls (32 females) were recruited from the community in Guangzhou. The healthy controls also received an interview conducted by an experienced psychiatrist and were excluded if they had a lifetime history of a psychotic disorder or a positive family history of psychosis. All participants were explained the aims of the study and included after signing a written informed consent. The study was approved by the Ethics Committees of the Institute of Psychology, Chinese Academy of Sciences, and the Guangzhou Psychiatry Hospital.

2.2. Measures

2.2.1. Neurological soft signs

NSS were assessed by the principal researcher who is also a qualified psychiatrist using the NSS subscales of the Cambridge Neurological Inventory (CNI) (Chen et al., 1995). The CNI consists of three subscales capturing motor coordination (e.g., finger/thumb tapping, finger/thumb opposition, fist-edge-palm), sensory integration (e.g., finger agnosia, stereognosia, left-right orientation), and disinhibition (e.g., saccade blink, go no-go disinhibition, mirror movement of finger/thumb opposition). Item scores were dichotomized as “present” (1) or “absent” (0) (Chan and Chen, 2007). The CNI has been found to be sensitive to neurodevelopmental disorders and sub-clinical samples in Chinese settings (Chan and Chen, 2007; Chan et al., 2009, 2010a, 2010b).

2.2.2. Clinical symptoms

OCD symptoms were assessed with the Yale–Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989a, 1989b) and patients were included if they had a total Y-BOCS score > 16. The Obsessive–Compulsive Inventory-Revised (OCI-R) was used to characterize OCD sub-clinical symptoms as obsessive thoughts, washing, checking, neutralizing, ordering, and hoarding (Foa et al., 2002; Peng et al., 2011). Depressive symptoms were evaluated with the Beck Depression Inventory (BDI) (Beck and Steer, 1984), and anxiety symptoms were evaluated with the 40-item State–Trait Anxiety Inventory (STAI) (Spielberger, 1983).

2.2.3. IQ estimate

IQ was estimated by the short form of the Chinese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), including four subscales: information, arithmetic, similarity and digit span (Gong, 1992).

2.3. Statistical analysis

First, we compared NSS scores in patients with OCD only, OCD co-morbid with psychosis and healthy controls, using an ANCOVA analysis, controlling for age, education and IQ as these factors have been consistently associated with NSS performance. Then, we examined if there was any difference in NSS scores in patients with OCD co-morbid with schizophrenia (OCD + SCZ) and bipolar disorder (OCD + BD). Third, we examined the NSS scores in patients with OCD, their unaffected first-degree relatives, and healthy controls, using an ANCOVA analysis, again controlling for age, education and IQ. Finally, we estimated item-by-item prevalence rates by using Fisher’s exact test across these three groups. All analyses were performed using the SPSS version 15.0. We set the significant threshold at p < 0.05.

3. Results

The demographic characteristics of the samples (patients with OCD, their first-degree relatives, patients with OCD and psychosis, and healthy controls) are summarized in Table 1. No significant differences were found in age and years of education.
3.1. NSS in patients with OCD and patients with OCD co-morbid with psychosis.

Table 2 shows the results of the three group comparison. Patients with OCD showed significantly higher scores in Motor Coordination and total NSS than healthy controls (p ranging from 0.004, F(2, 233) = 7.2 to 0.001, F(2, 233) = 7.6). This was also the case for patients with OCD co-morbid with psychosis, who showed significantly higher scores in Motor Coordination and total NSS than controls (p ranging from 0.004 to 0.001), and only at trend level higher Disinhibition scores. However, there were no significant differences between patients with OCD only and those with OCD co-morbid with psychosis.

Table 3 shows that, when we divided the OCD and psychosis group into those with co-morbid schizophrenia (OCD+SCZ) and those with co-morbid bipolar disorder (OCD+BD), patients with OCD+SCZ showed significantly higher scores in Motor Coordination than patients with OCD only, patients with OCD+BD, and healthy controls (p ranging 0.016 and 0.001). They also showed higher total NSS than controls (p = 0.001, F(3, 232) = 5.43). Patients with OCD+BD showed higher scores in total NSS compared with healthy controls (p = 0.02), but no differences with OCD only patients.

3.2. NSS in OCD, first-degree relatives, and healthy controls.

The NSS total and subscale scores of these three groups are presented in Table 4. Compared to healthy controls, patients with OCD had significantly higher Motor Coordination (p = 0.003; Cohen’s d = 0.60), and total NSS (p = 0.008) scores. However, there were no differences in NSS scores between relatives and either patients with OCD and healthy controls.

Table 5 shows the items prevalence rates for the three groups. Five items of the Motor Coordination subscale (Finger–Thumb Opposition Left and Right, Finger Tapping Left, and Diadokokinesis Left and Right), and one item from the Sensory Integration subscale (Extinction) were significantly different among patients with OCD, unaffected first-degree relatives, and healthy controls (p ranging from 0.048 to 0.001). Patients with OCD showed higher prevalence rates than healthy controls in Opposition Left and Right Hands, Diadokokinesis Left and Right Hands, Extinction, and Finger Agnosia Right Hands (p ranging from 0.047 to 0.002). Unaffected first-degree relatives also showed a higher prevalence rate than healthy controls in Opposition Left and Right Hands (p ranging from 0.014 to 0.016) and Extinction (p = 0.033).

4. Discussion.

The first major finding of this study is that of a significant difference in the prevalence of NSS among patients with OCD, patients with OCD co-morbid psychosis, and healthy controls. This seems to be particularly the case for the Motor Coordination signs. Our findings also show that such an increase is particularly associated with a comorbidity with schizophrenia (Poyurovsky et al., 2007; Sevinçok et al., 2004, 2006). Interestingly, Sevinçok et al. (2004, 2006) showed that patients with schizo-obsessive symptoms had significantly more NSS than patients with schizophrenia without OCD symptoms. Poyurovsky et al. (2007) also showed an elevation of NSS total scores.
in patients with schizophrenia co-morbid with OCD symptoms than in patients without OCD symptoms and in healthy controls. It is of note that worse motor coordination has been found to be specifically impaired in psychoses, independently of IQ, and it has been suggested that an impaired motor function reflects a dysfunctions of brain areas specifically affected by psychosis, being associated for example with volume reductions in the basal ganglia (Dazzan et al., 2008). This evidence is consistent with our finding of significantly higher motor coordination scores in patients with OCD and co-morbid psychosis. Interestingly, we found that there were no differences in sensory integrative signs across patient groups and healthy controls. This is in contrast with findings from some studies in patients with or without co-morbidity (Poyurovsky et al., 2007; Sevincok et al., 2004; Thomas and Tharyan, 2011). Nevertheless, similarly to our findings, Thomas and Tharyan (2011) did not find a significant difference in total NSS signs between patients with schizophrenia with and without co-morbidity (Poyurovsky et al., 2007; Sevincok et al., 2004; Thomas and Tharyan, 2011). The lack of difference in rates of sensory integration signs we found might also be due to differences in sample recruitment, as other studies may have included OCD patients with shorter illness duration or medication naïve, or used a different measure to evaluate NSS (Poyurovsky et al., 2007; Sevincok et al., 2004). Interestingly, most previous studies on NSS and OCD evaluated patients on different medications although medications have been found to have little or no effect on NSS (Bersani et al., 2005; Boks et al., 2003), making it difficult to ascertain whether the presence of NSS was due to the potential medication effect or the disease process itself.

The second major finding of the our study is that unaffected first-degree relatives seem to have motor coordination and total NSS rates intermediate between those of healthy controls and patients with OCD. The current study is, to the best of our knowledge, the first study to examine the prevalence rate of NSS in unaffected first-degree relatives of OCD patients. These findings provide partial support for the fact that NSS may be familial and heritable in OCD, as in other disorders considered to have a neurodevelopmental component, such as schizophrenia (Chan and Gottesman, 2008). In fact, a meta-analysis of NSS in schizophrenia suggests that there are large to very large effect sizes of NSS abnormalities in schizophrenia, as well as small to moderate effect size in unaffected probands, with the first-degree relatives having NSS rates intermediate between those of patients and healthy controls (Chan et al., 2010c, 2010d). Our findings are the first to suggest that a similar pattern might be present in another neurodevelopmental disorder like OCD, providing the first report on this issue.

However, it should be noted that the majority of the patients with OCD recruited for the current study have been receiving medication. It was particularly important for those patients comorbid with psychosis because the prevalence of NSS might have been associated with the impact of antipsychotic medication. Second, the sample size for the sub-groups of patients comorbid with schizophrenia and bipolar disorders was relatively small. The insignificant differences of sensory integration and disinhibition signs found among the sub-groups might have been due to the small sample size. Future study should adopt a more rigorous approach to recruit a larger sample size of each sub-group of patients to further cross-validate the current findings.

### 5. Conclusion

In conclusion, OCD is associated with higher NSS rates, particularly in motor coordination signs, and these rates seem to be higher when the OCD is co-morbid with psychosis. However, the higher rates of

### Table 3

NSS scores in OCD, OCD co-morbid with bipolar disorder, OCD comorbid with schizophrenia, and healthy controls (controlling for age, years of education, IQ).

<table>
<thead>
<tr>
<th></th>
<th>OCD (N = 100)</th>
<th>OCD + BD (N = 22)</th>
<th>OCD + SCZ (N = 16)</th>
<th>HC (N = 101)</th>
<th>ANCOVA F (p-value)</th>
<th>Pairwise (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± s.d.</td>
<td>Mean ± s.d.</td>
<td>Mean ± s.d.</td>
<td>Mean ± s.d.</td>
<td>Group</td>
<td></td>
</tr>
<tr>
<td>SI</td>
<td>1.97 ± 1.74</td>
<td>2.05 ± 1.52</td>
<td>1.77 ± 1.56</td>
<td>1.89 ± 1.72</td>
<td>1.50 (p = 0.19)</td>
<td>0.13</td>
</tr>
<tr>
<td>MC</td>
<td>2.00 ± 1.97</td>
<td>2.17 ± 1.91</td>
<td>2.05 ± 1.12</td>
<td>2.13 ± 1.36</td>
<td>1.00</td>
<td>0.01</td>
</tr>
<tr>
<td>Dis</td>
<td>0.50 ± 0.57</td>
<td>0.64 ± 0.68</td>
<td>0.71 ± 0.79</td>
<td>0.51 ± 0.80</td>
<td>1.00</td>
<td>0.01</td>
</tr>
<tr>
<td>NSS</td>
<td>3.44 ± 2.58</td>
<td>4.00 ± 2.89</td>
<td>3.50 ± 2.29</td>
<td>2.09 ± 1.92</td>
<td>0.004</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**OCD + BD = Obsessive Compulsive Disorder with Bipolar Disorder.**

**OCD + SCZ = Obsessive Compulsive Disorder with Schizophrenia.**

**MC = Motor Coordination.**

**SI = Sensory Integration.**

**Dis = Disinhibition.**

**NSS = Total NSS score.**

**a** Education effect is significant (p = 0.03).

**b** IQ effect is significant (SI: p < 0.001, NSS: p < 0.001).

### Table 4

NSS scores in OCD, unaffected first-degree relatives, and controls (controlling for age, years of education, IQ).

<table>
<thead>
<tr>
<th></th>
<th>OCD (N = 100)</th>
<th>Relatives (N = 47)</th>
<th>HC (N = 101)</th>
<th>ANCOVA F (p-value)</th>
<th>Pairwise (p-value; Cohen’s d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± s.d.</td>
<td>Mean ± s.d.</td>
<td>Mean ± s.d.</td>
<td>Group</td>
<td>OCD vs HC</td>
</tr>
<tr>
<td>SI</td>
<td>1.97 ± 1.74</td>
<td>2.05 ± 1.52</td>
<td>1.89 ± 1.72</td>
<td>1.50 (p = 0.19)</td>
<td>0.004; 0.6</td>
</tr>
<tr>
<td>MC</td>
<td>2.00 ± 1.97</td>
<td>2.17 ± 1.91</td>
<td>2.13 ± 1.36</td>
<td>1.00</td>
<td>0.01; 0.6</td>
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<td>0.64 ± 0.68</td>
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<td>1.00</td>
<td>0.01; 0.6</td>
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<td>0.004</td>
<td>0.01; 0.6</td>
</tr>
</tbody>
</table>

**MC = Motor Coordination.**

**SI = Sensory Integration.**

**Dis = Disinhibition.**

**NSS = Total NSS score.**

**a** Education effect is significant (p = 0.03).

**b** IQ covariance effect is significant (SI: p < 0.001, NSS: p < 0.001).
these signs in the relatives of OCD patients additionally suggest the contribution of a genetic vulnerability to these signs.

Acknowledgments

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Appendix A. Treatment details of OCD patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of case</th>
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<tbody>
<tr>
<td>Clomipramine</td>
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</tr>
<tr>
<td>Citipramol</td>
<td>4</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>6</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>2</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>3</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>12</td>
</tr>
<tr>
<td>Sertraline</td>
<td>6</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>6</td>
</tr>
<tr>
<td>Citalopram + quetiapine</td>
<td>4</td>
</tr>
<tr>
<td>Fluvoxamine + risperidone</td>
<td>4</td>
</tr>
<tr>
<td>Paroxetine + clomipramine</td>
<td>4</td>
</tr>
<tr>
<td>Paroxetine + olanzapine</td>
<td>5</td>
</tr>
<tr>
<td>Paroxetine + sodium valproate</td>
<td>6</td>
</tr>
<tr>
<td>Paroxetine + risperidone</td>
<td>6</td>
</tr>
<tr>
<td>Venlafaxine + olanzapine</td>
<td>5</td>
</tr>
<tr>
<td>Venlafaxine + risperidone</td>
<td>6</td>
</tr>
<tr>
<td>Paroxetine + risperidone + sodium valproate</td>
<td>3</td>
</tr>
</tbody>
</table>

References


