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Which neurological abnormalities and neuropsychological impairments share the same substrate in psychosis?

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Approximately 60% of subjects with schizophrenia present minor neurological signs (neurological soft signs, NSS), which include abnormalities in sensory and motor performance indicative of a non-specific cerebral dysfunction. These are also present in healthy individuals and relatives of patients with psychosis, at significantly lower rates. The excess of NSS in psychosis may be a potential endophenotype for this disorder, and reflect the same neurodevelopmental brain dysfunction that also underlies the cognitive deficits consistently reported in psychosis. To establish whether neurological and cognitive dysfunction meet the essential criterion required for a refined endophenotype for psychosis, the association with the illness, we explored evidence that certain neurological and cognitive deficits co-occur in affected individuals. This evidence suggests that signs of motor dysfunctions may be specific to patients with psychosis, in whom they are associated with dysfunction in cognitive tasks requiring motor skills. Thus, they may form a promising candidate endophenotype for psychosis.

schizophrenia, neurological soft signs, motor dysfunction, basal ganglia, cognition

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There is consistent evidence that abnormalities in both cognitive function and brain structure are already present at the time of onset of the psychotic illness [1]. Over the last 20 years, further support for the presence of an underlying brain disorder in schizophrenia [2] has derived from the observation that approximately 60% of subjects with schizophrenia present with minor neurological signs [3]. These are sometimes termed "soft" signs, and include abnormalities in sensory and motor performance, which are indicative of non-specific cerebral dysfunction and are also present in healthy individuals and relatives of patients with psychosis, though at significantly lower rates [4].

The term "soft" was originally used, as opposed to "hard", to reflect the absence of any obvious localised pathological lesion underlying these signs [5,6]. This term has been employed, more recently, to indicate signs which do not reflect primary tract or nuclear pathology [7], but more an impaired integration within and between the sensory and motor systems (integrative signs). However, the categorisation of neurological signs as "hard" or "soft" (or primary and integrative) is not always straightforward. For example, signs such as the fist-edge-palm, or the fist-ring, require integration of the sensory and motor system (integrative signs), but are also present in frontal lobe damage (primary signs). The same can be said for tandem walk or finger-nose tests that can reflect impaired sensory-motor integration, but also focal cerebellar damage.

1 Neurological soft signs in psychosis

The term "soft" has often caused doubts about whether these signs can be defined with rigour, are reliable, have neurological meaning, and are reproducible. However, numerous

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systematic and controlled studies have described neurological dysfunction in schizophrenia, and the doubts on its meaning "reflects not the unreality of findings but limitations in our knowledge" [8]. Studies using standardised and validated schedules, investigating both primary signs (including the evaluation of cranial nerves and reflexes) and integrative signs, and specifying which signs were tested, can in fact be helpful in overcoming some of the problems described above [9].

Neurological abnormalities in adult patients with schizophrenia seem to be localised to three main neurological domains: (1) integrative sensory function, (2) motor coordination, and (3) motor sequencing [3]. Deficits in integrative sensory function (possibly resulting from a parietal dysfunction), are reflected in higher rates of bilateral extinction, impaired audio-visual integration, agraphaesthesia and astereognosis [3,9]. Deficits in motor coordination have been reported through tests of general coordination, intention tremor, finger-thumb opposition, balance and gait. Finally, poor performance in complex motor tasks (possibly resulting from a dysfunction of the frontal-basal ganglial circuitry) has been reported in tests that involve repetitive alternating hand positions, such as the fist-edge-palm, the fist-ring and the Ozeretski tests. A fourth group of signs includes those reflecting a "primary neurological dysfunction", signs that reflect a dysfunction that can be identified by a standard neurological examination. These signs include abnormal function of cranial nerves, abnormal eye movement, lateralising limb pyramidal signs and frontal release signs.

A large number of studies now suggest that these signs are already present at the time of the first psychotic episode [4,10–13], although the mean scores may be even higher in subjects at more advanced stages of the illness [14], where worse neurological dysfunction could be a consequence of the progression of the disease. Although significantly lower than those of patients, NSS are also present in healthy individuals from the general population, with rates varying from 5% [15,16] to more than 50% [17,18], the proportion reported being mainly a function of the measure used. Interestingly, in healthy individuals, the scores of sensory integration signs are often higher than the scores of primary, motor coordination, and motor sequencing signs [10,19,20]. This is an aspect that should be considered when evaluating the relationship between these signs and cognitive function.

2 The substrate of NSS

A mounting body of evidence suggests that the excess of NSS signs in psychosis reflects a vulnerability to this illness and may be a potential endophenotype for this disorder [21]. More specifically, it has been suggested that the presence of neurological signs may reflect the same neurodevelopmental brain dysfunction that also underlies the cognitive deficits consistently reported in individuals with psychosis [10]. Indeed, Chan et al. [22] have proposed that neurological abnormalities predict the neuropsychological deficits frequently found in schizophrenia and psychosis in general, such as executive and memory functions. However, cognitive and neurological deficits share only up to 10% of their variance, suggesting that although associated, some of these deficits represent distinct aspects of the pathophysiology of the disorder.

To establish whether neurological and cognitive dysfunction meet the essential criterion required for a refined endophenotype for psychosis, the association with the illness, it is therefore important to explore whether certain neurological and cognitive deficits specifically co-occur in affected individuals.

3 NSS and general cognitive function

A number of papers, including work from our groups, suggest that neurological abnormalities are associated with poorer general intellectual function, evaluated as IQ, even in first episode psychosis patients [12,18] and in individuals with proneness to psychosis [23]. For instance, problems in sensory integration and in the execution of complex motor sequences seem associated with worse general cognitive ability, and this is the case both in patients with psychosis and in healthy individuals [22,24]. Therefore, it is possible that existing reports of higher sensory integrative and motor sequencing scores in patients with psychosis in comparison to healthy controls were related to the presence of a lower IQ in patients than in healthy controls [11,20,25,26]. In fact, our study comparing NSS in patients and healthy controls matched for IQ found no differences between these two groups in the rates of these signs [18]. Consistently with this result, Arango et al. [10] found no differences in motor sequencing signs when they compared only patients with high IQ with controls. Taken together, these findings suggest that sensory integrative and motor sequencing signs in psychosis may share the same pathophysiological substrate that also underlies lower general cognitive ability. Therefore, the presence of these signs in patients with psychosis would not be purely a consequence of the psychotic illness, but the reflection of a more general brain dysfunction that also affects general intellectual performance.

In contrast with sensory integrative and sequencing signs, other signs, like motor incoordination, abnormal eye movements, disinhibition, appear to be present in excess in patients with psychosis even when differences in cognitive ability are considered [18]. This suggests that while some neurological and cognitive deficits co-occur in affected individuals and in the general population, other neurological signs may be specific to the pathophysiology of psychosis.

It has been suggested that the concomitant presence of

NSS and cognitive deficits in schizophrenia could reflect a diffuse, generalised brain disorder [27–29]. However, the line between some NSS and selected neuropsychological tests is often difficult to draw, and evaluating both could provide comprehensive information on a range of regional neurological dysfunctions. Clarifying which neurological and cognitive deficits share the same regional functional association, and whether this association is specific to patients with psychosis, would help establishing if these deficits, and which deficits, are a good candidate endophenotype for psychosis.

4 NSS and specific cognitive deficits

Studies that have evaluated the association between NSS and specific cognitive domains in psychosis have found that a poorer performance on sensory integrative tests is associated with more cognitive measures that any other NSS subset [10,30]. Sensory integrative tasks test the ability to interpret information from different sensory modalities coherently and interchangeably [31]. It is interesting that these signs seem to be associated with a poorer performance in tests that more specifically involve memory, attention, executive function and visual perceptual domains, which all require the processing and integration of multiple sensory stimuli [22,30]. This evidence further suggests that they may share the same underlying biological basis. In fact, neuroimaging data from our and other groups have found that more sensory integrative signs are associated with distributed reductions of cortical parietal, frontal, and temporal association areas [30,32,33]. These areas are important in supporting complex, widely distributed cognitive functions, and are also involved in these neurological functions, supporting the idea of a common biological substrate for these deficits.

In patients with psychosis, motor function has been frequently associated with deficits in specific cognitive domains. For example, motor sequencing signs have been associated with poorer performance in executive functions [11,34] possibly reflecting a common underlying dysfunction at prefrontal level. The presence of motor coordination signs has been associated with worse performance in cognitive tasks requiring motor speed and coordination [27,35]. It is interesting that, from an anatomical point of view, more motor coordination signs have been found in association with reduced grey matter volume in subcortical structures (putamen, globus pallidus and thalamus) [30,32,36]. Basal ganglia send information via the thalamus to the prefrontal and premotor areas of the cortex. This may help explaining why motor coordination signs may be associated with deficits in tasks that require motor skills be completed. In view of evidence that motor coordination dysfunction may be specific to psychosis, rather than the reflection of a worse intellectual function in these patients, it is possible that motor coordination signs reflect the basal ganglia dysfunction that has been proposed as one of the fundamental pathophysiological mechanisms of psychosis.

In terms of primary signs, such as cranial nerves, abnormal eye movements, lateralising limb pyramidal signs and frontal release signs, there appear to be less evidence that their presence is associated with a dysfunction of specific cognitive domains [18]. While some studies have found that frontal release signs are associated with reasoning and problem solving, visual-spatial memory, visuo-spatial processing, and visuo-constructive tasks, others have not found these associations [10,24]. Interestingly, Arango et al. [10] found frontal release and eye movement signs to be present in excess even in patients with a high IQ. On one side, this inconsistency may reflect the heterogeneity of these neurological signs, which are often lumped together in one global score, although it cannot be excluded that they simply do not share the same substrate of general or specific cognitive deficits.

5 A possible interpretation

It is possible that certain neurological signs (reflecting problems in integrative functions) are associated with a generalised neurocognitive dysfunction, and possibly reflect a diffused deficit of the same brain regions. This could be the case in both patients with psychosis and healthy individuals, as suggested by evidence that sensory integrative deficits share the same neuroanatomical correlates in both psychotic patients and controls, that is, frontal and temporal lobe reductions [32,37]. In contrast, signs that can be considered “harder” and signs of motor dysfunctions may represent distinct entities, with a different pathophysiological substrate. Specifically, motor coordination deficits appear associated with a reduction of the basal ganglia, but only in patients [30,37], suggesting that motor coordination deficits may be indeed specifically associated with the pathogenesis and vulnerability for this illness.

As such, among neurological and cognitive deficits, motor dysfunction may, with neurocognitive deficits in tests requiring motor skills, form a promising candidate endophenotype for psychosis, satisfying the first essential criterion that it should be associated with the illness, an association that appears to be not a pure reflection of a worse general intellectual performance in psychosis patients. Evidence that these deficits have some heritability [38], show familial association [39] and may be state independent [40] suggests that future studies of neurological and neurocognitive tests involving motor skills could establish whether these deficits meet all the requirements needed by a good endophenotype. If this is the case, a short targeted assessment of these specific domains would be easier to implement in the research and clinical setting than a full neurological and neurocognitive evaluation.

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