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Sex and laterality differences in parkinsonian impairment and transcranial ultrasound in never-treated schizophrenics and their first degree relatives in an Andean population

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ABSTRACT

We tested the hypothesis that loss of substantia nigra neurons in subjects at risk of schizophrenia (1), as reflected by midbrain hyperechogenicity (2) and parkinsonian motor impairment (3), is asymmetric and influenced by sex. We evaluated 62 subjects with never-treated chronic schizophrenia, 80 of their adult, unaffected first degree relatives and 62 healthy controls (matched by sex and age to the cases), part of an Andean population of Northern Argentina. Parkinsonism was scored blindly using UPDRS-3 (Unified Parkinson's Disease Rating Scale) on videotaped exams by 2 independent raters. Transcranial ultrasound was performed by an expert sonographist blind to subject condition with a 2.5 MHz transducer through a temporal bone window. Quantification of echogenic area was carried out on saved images by a different evaluator. We found a significant difference in parkinsonian motor impairment between patients, their relatives as well as controls. All three groups showed worse parkinsonism on the left side than the right, corresponding with increased echogenicity on the right substantia nigra compared with the left. Females had significantly more right echogenicity than males, and patients and unaffected relatives were significantly more echogenic than controls on that side. On the left, only female patients had significant echogenicity. Our data supports the notion that unaffected relatives of schizophrenic subjects have increased parkinsonism and concomitant brainstem abnormalities which may represent a vulnerability to the disease. Both motor and brainstem abnormalities are asymmetric and influenced by sex.

1. Introduction

Schizophrenia is a devastating condition that is normally diagnosed upon the onset of psychosis and leads to a functional deterioration in early adult life. It affects nearly 50 million people worldwide. Its global economic burden is estimated between 1.5 and 3% of total health expenditures (Knapp et al., 2004) and has increased by 50% over the past ten years (Murray et al., 2012). Available medications reduce the hallucinations and delusions commonly seen in schizophrenia, but result in very limited functional outcomes.

The prevalence of parkinsonism in schizophrenia has been well documented. All clinically effective antipsychotic medications mediate their therapeutic actions, at least partially, through inhibition of dopaminergic neurotransmission (Yilmaz et al., 2012), often leading to occurrence of parkinsonian features (Leucht et al., 2013). On the other hand, parkinsonism has been found repeatedly in first-episode untreated patients (Chakos et al., 1992; Caligiuri et al., 1993; Chatterjee et al., 1995; Honer et al., 2005; McCreadie et al., 2005), and in at-risk offspring of schizophrenics (Marcus et al., 1985a,b). In each of these cases parkinsonism predated exposure to antipsychotic medications. Indeed, dysregulation of brain dopamine function has been shown to correlate with genetic risk of schizophrenia (Egan et al., 2001). Based on these findings we proposed that risk of schizophrenia may correlate with severity of parkinsonian impairment, such that motor disturbances would reflect a mechanism of genetic liability to the disease, expressed as prenatal injury to a subpopulation of dopaminergic neurons projecting from the midbrain to the prefrontal cortex (Weinberger and Berman, 1988; Finlay, 2001; Masciotra et al., 2005). Over time these deficits would lead to an inadequate compensatory response that ultimately manifest as psychotic phenomena. This model is supported by imaging studies in patients with schizophrenia showing that impairment in executive function and working memory correlates

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with lower dopamine availability in the prefrontal cortex (Egan et al., 2001), whereas the acute psychotic symptoms correlate with excessive release of endogenous dopamine in the basal ganglia (Breier et al., 1997).

Structural abnormalities in schizophrenia brains have been replicated to variable degrees and are influenced by gender, laterality, exposure to medications, and duration of illness (Chiapponi et al., 2013). Men, compared to women, have higher incidence, earlier age at onset, greater expression of negative symptoms and neurologic deficits, worse premorbid history and course of illness, and differential treatment outcomes, and sex-specific brain abnormalities (Abel et al., 2010).

Gestational risk factors for schizophrenia occurring during sexual differentiation of the brain may result in sex-specific abnormalities in the brain in schizophrenia (Abel, 2004). In fact, nigrostriatal, mesolimbic, and mesocortical projection neurons have an early role in the development of sexual dimorphism in the brain (Reisert et al., 1990; Harrison and Tunbridge, 2008). Specifically, there are more dopaminergic neurons in the mesocortical projection in females than in males, and dopaminergic neurons are more resistant to toxic insults in females than in males (Johnson et al., 2010). Thus, if the development of psychosis is a failed compensatory attempt by the mesolimbic projection neurons for the prenatal or perinatal loss of mesocortical projection neurons as mentioned, the relative excess of mesocortical neurons and their greater resistance in females could protect them from environmental insults and explain some gender differences in the course of illness. We therefore hypothesized that the dopaminergic neurons giving rise to the nigrostriatal projections are more affected in males than in females with (or at risk for) schizophrenia.

Transcranial ultrasound (TUS) studies have shown a direct relationship between the degree of echogenicity and motor and functional impairment in patients with Parkinson disease (Berg, 2011a; Bouwmans et al., 2013). In schizophrenia, substantia nigra hyperechogenicity predicts susceptibility to drug-induced parkinsonism (Berg et al., 2001), but no previous studies have investigated unaffected first-degree relatives. Given the considerable genetic predisposition to the disease, substantia nigra hyperechogenicity and parkinsonism, if present in unaffected relatives, could serve as an intermediate phenotype and predictor of psychotic derangement in at-risk individuals.

We studied echogenicity and motor function in subjects with chronic schizophrenia never exposed to antipsychotic medications, their unaffected siblings, and healthy controls from a population of the Central Andes in Argentina. Due to its geographical isolation, patients were unlikely to receive antipsychotic treatment and allowed us to ideally address this question at the clinical and imaging level before offering them treatment. In addition, this sample contains approximately equal number of female and male patients, thus allowing for direct comparisons. Here, we tested the hypotheses that parkinsonism:

1 is a manifestation of risk of schizophrenia as reflected by its presence in at-risk unaffected relatives of patients with schizophrenia and,
2 is asymmetric and influenced by sex.

2. Experimental/materials and methods

2.1. Sample and ascertainment

We evaluated 62 subjects with never-treated chronic schizophrenia, 80 of their adult, unaffected first degree relatives and 62 healthy controls (matched by sex, age and educational level to the cases) of the same Andean population of Northern Argentina. Therefore, all subjects (including controls) come from the same population and from the same ethnic background as the patients and their relatives. Average duration of untreated illness was 68.9 ± 97.5 months. Table 1 shows the demographic characteristics of the sample. Educational level represents completed elementary (1), completed high school (2), or additional education at trade school or college level (3). Diagnostic ascertainment was carried out with the Schedules of Clinical Assessment in Neuropsychiatry scored blindly by 2 independent raters (EP, GG, MC, BMR, GdE, SCAN 2.1, World Health Organization, Geneva). SCAN is a set of instruments and manuals aimed at assessing, measuring and classifying psychopathology and behavior associated with the major psychiatric disorders in adult life. It can be used for clinical, research- and training purposes and was developed within the framework of the World Health Organization (http://whoscan.org). SCAN has a bottom-up approach where no diagnosis-driven frames are applied in grouping the symptoms. Each symptom is assessed in its own right. It has a proven stability and robustness to differentially assess psychotic states. Interview data are entered into the program and fed into algorithms for ICD-10 and DSM-IV diagnoses. These algorithms produce a diagnostic classification for both systems. To meet selection criteria all subjects met the criteria for DSM-IV schizophrenia when scored by two independent raters. Treatment was offered to all participants and provided free of charge by the local government. All procedures and human protections were approved by the local government Bioethics Committee and by the University of South Florida Internal Review Board.

Table 1
Demographic and clinical characteristics of the sample.

Risk status	Age	Educational level	% male	UPDRS-3
Schizophrenia	28.9 ± 11.7	1.9 ± 0.7	65	17.7 ± 4.6
Unaffected relatives	34.7 ± 15.2	2.1 ± 1.1	50	8.3 ± 5.5
Healthy controls	31.3 ± 8.9	2.7 ± 1.0	65	2.8 ± 0.4

2.2. Motor assessment

Parkinsonism was scored blindly using UPDRS-3 (Unified Parkinson's Disease Rating Scale) on videotaped exams by 2 independent raters certified on its use (GdE and GG). Thus, the diagnosis of parkinsonism was not based on the UK Brain Bank criteria but on an arbitrary cut-off of UPDRS-3. Rigidity could not be directly assessed on the videotapes and was not scored (thus, the maximum possible score is 88 instead of 108). Video examples of movement impairment are provided as Supplementary material. The Asymmetry Index was calculated as the absolute difference between the sides divided by the sum of their scores (L − R / [L + R]) (Espay et al., 2006). A larger Asymmetry Index indicates greater difference in disease burden between sides and therefore more asymmetry.

2.3. Transcranial ultrasound

For transcranial ultrasound examination, we employed a color-coded, phased array ultrasound system, equipped with a 2.5 MHz transducer (Micromaxx, Sonosite Inc., Bothell, Washington). Examinations were performed through a preauricular acoustic bone window (penetration depth = 16 cm, dynamic range = 45 dB) by an expert sonographist (NF) with more than 20 years experience on the technique blind to subject condition. Less than 3% of cases were non-insonnable because of skull thickness (a much lower % of that reported in the Parkinson disease population, most likely because our patients were much younger). The substantia nigra was identified within the butterfly-shaped structure of the brainstem, scanning from each temporal bone window. Since the signal brightness (echogenicity) is not quantifiable by ultrasound, the area of hyperechogenic signals in the substantia nigra (SN) region was measured (in square cm) from each ipsilateral side separately by a highly trained radiologist with >15 years experience on the procedure (NF). Unbiased quantification of echogenic area was carried out post hoc on saved images by two