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Multivariate neuroanatomical classification of cognitive subtypes in schizophrenia: A support vector machine learning approach

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ABSTRACT

Heterogeneity in the structural brain abnormalities associated with schizophrenia has made identification of reliable neuroanatomical markers of the disease difficult. The use of more homogenous clinical phenotypes may improve the accuracy of predicting psychotic disorder/s on the basis of observable brain disturbances. Here we investigate the utility of cognitive subtypes of schizophrenia – 'cognitive deficit' and 'cognitively spared' – in determining whether multivariate patterns of volumetric brain differences can accurately discriminate these clinical subtypes from healthy controls, and from each other. We applied support vector machine classification to grey- and white-matter volume data from 126 schizophrenia patients previously allocated to the cognitive spared subtype, 74 cognitive deficit schizophrenia patients, and 134 healthy controls. Using this method, cognitive subtypes were distinguished from healthy controls with up to 72% accuracy. Cross-validation analyses between subtypes achieved an accuracy of 71%, suggesting that some common neuroanatomical patterns distinguish both subtypes from healthy controls. Notably, cognitive subtypes were best distinguished from one another when the sample was stratified by sex prior to classification analysis: cognitive subtype classification accuracy was relatively low (<60%) without stratification, and increased to 83% for females with sex stratification. Distinct neuroanatomical patterns predicted cognitive subtype status in each sex: sex-specific multivariate patterns did not predict cognitive subtype status in the other sex above chance, and weight map analyses demonstrated negative correlations between the spatial patterns of weights underlying classification for each sex. These results suggest that in typical mixed-sex samples of schizophrenia patients, the volumetric brain differences between cognitive subtypes are relatively minor in contrast to the large common disease-associated changes. Volumetric differences that distinguish between cognitive subtypes on a case-by-case basis appear to occur in a sex-specific manner that is consistent with previous evidence of disrupted relationships between brain structure and cognition in male, but not female, schizophrenia patients. Consideration of sex-specific differences in brain organization is thus likely to assist future attempts to distinguish subgroups of schizophrenia patients on the basis of neuroanatomical features.

1. Introduction

Cognitive deficits are a core feature of schizophrenia and are closely linked with disability and treatment outcomes (Brekke et al., 2007; Green, 2006; Heinrichs, 2005; Jablensky, 2006; Keefe and Harvey, 2012; Ammari et al., 2010). While severe cognitive deficits are observed in many patients, the magnitude of cognitive dysfunction may vary between individuals. Attempts to reduce such phenotypic heterogeneity have seen the delineation of two subtypes of schizophrenia in large cohort studies – 'cognitive deficit' (CD) and 'cognitively spared' (CS) – based on cognitive performance across multiple domains (Green et al., 2013; Hallmayer et al., 2005; Jablensky, 2006). These subtypes of schizophrenia thus show distinct cognitive profiles, in the context of other differential illness characteristics: CD patients tend to be impaired across all cognitive domains, are more likely to be male, have earlier illness onset, and a greater severity of functional disability (Green et al., 2013); in contrast, CS cases show a cognitive profile that remains somewhat impaired relative to healthy controls (HCs), but is significantly

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better than CD cases, and is associated with greater complexity of delusional systems (Morar et al., 2011). Preliminary genetic investigation of these subtypes has revealed an association of CD case status with the MIR137 microRNA locus and negative symptoms (Green et al., 2013), and genetic linkage to chromosome 6p24 (Hallmayer et al., 2005). In contrast, CS cases show relatively stronger genetic association with Neuregulin 3 (Morar et al., 2011). These cognitive subtypes may thus represent more phenotypically homogenous patient groups with at least partially distinct neuropathological processes, about which clues may be evident in differential brain structure.

Considerable neuroanatomical evidence shows that schizophrenia is associated with substantial, diffuse brain volume loss, though the exact location of changes is not well-replicated across studies, likely reflecting the phenotypic heterogeneity among cases and samples (Shepherd et al., 2012). Recent attempts to delineate a neuroanatomical signature of schizophrenia have employed multivariate classification techniques to distinguish patients from controls on the basis of neuroanatomical feature sets (Nieuwenhuis et al., 2012; Davatzikos et al., 2005; Fan et al., 2007; Klöppel et al., 2012; Koutsouleris et al., 2009). While these studies demonstrate the capacity to successfully predict schizophrenia 'case-ness' on the basis of multivariate neuroanatomical patterns, classification accuracy in large cohort studies is typically around 70% — less than 50% above chance — leaving considerable room for improvement (Nieuwenhuis et al., 2012). Investigation of putative subtypes of schizophrenia that appear to represent more homogenous phenotypes, such as those delineated via cognitive profiling (Koutsouleris et al., 2012; Ammari et al., 2010; Green et al., 2013; Jablensky, 2006), may improve the accuracy with which schizophrenia case-ness can be predicted on the basis of brain structure.

Neuroanatomical features associated with cognitive deficits in schizophrenia include reduced whole-brain grey matter volume and cortical thickness, localized reductions in prefrontal, temporal and parietal grey matter volume, basal ganglia and thalamic volume reductions (Cobia et al., 2011; Rais et al., 2012; Rüsch et al., 2007; Crespo-Facorro et al., 2007), and alterations in the integrity of white matter pathways (Nazeri et al., 2013; Wexler et al., 2009). Disruptions of the normal associations between cognitive performance measures and global and regional brain volumes have also been reported (Antonova et al., 2004; Ehrlich et al., 2012; Hartberg et al., 2010; Wexler et al., 2009; Nazeri et al., 2013; Cocchi et al., 2009; Killgore et al., 2009; Antonova et al., 2005; Salgado-Pineda et al., 2003; Sanfilipo et al., 2002). However, the utility of multivariate neuroanatomical profiles in discriminating between cognitive subtypes on a case-by-case basis remains unclear.

Several studies have additionally demonstrated that schizophrenia-associated disruptions to the normal relationships between cognition and brain volumes occur in a sex-related manner. For example, normal structure–cognition relationships in the cerebellum may be attenuated or absent for male patients as compared with female patients and HCs (Antonova et al., 2004; Flaum et al., 1994; Picard et al., 2008). Disruption of normal neuroanatomical sexual dimorphisms in schizophrenia patients' brains has also been reported (Abbs et al., 2011; Crow, 2013; Goldstein et al., 2002; Narr et al., 2004; Gur et al., 2004). As sexually dimorphic neuroanatomical differences arise during brain development through interaction of hormonal, genetic and epigenetic factors, their characterization in sexually asymmetric psychiatric conditions may provide insights into neurodevelopmental processes relevant to disease aetiology, and stratifying samples by sex may further assist efforts to reduce within-sample heterogeneity (Goldstein et al., 2013; Lombardo et al., 2012; Ruigrok et al., 2014; Paus et al., 2008). However, the relevance of sex-specific neuroanatomical patterns to the classification of schizophrenia and its subtypes has not yet been determined.

Here, we set out to characterize multivariate patterns of grey- and white-matter volumes that discriminate between CD patients, CS patients and HCs. We hypothesized that the cognitive and genetic differences associated with cognitive subtypes would manifest in neuroanatomical changes distinguishing each group from HCs, and from each other. We specifically predicted that CS and CD subtypes would be distinguished by changes in brain regions associated with cognition in schizophrenia, such as frontal and temporal cortices (Shepherd et al., 2012) and distributed white matter networks (Wexler et al., 2009). As schizophrenia patients show sexual asymmetries in phenotypic features including cognitive deficits, age of onset and symptom severity (Green et al., 2013; Hallmayer et al., 2005; Jablensky, 2006; Han et al., 2012), and schizophrenia is associated with disruption of sexual dimorphisms in brain structure and structure–function relationships (Antonova et al., 2004; Goldstein et al., 2002; Picard et al., 2008), we further hypothesized that neuroanatomical features distinguishing cognitive subtypes (from healthy controls, and from each other) would differ between males and females. Specifically, we predicted that classification accuracy would be higher when performed on a sex-stratified sample, as compared to when performed on a mixed-sex sample.

2. Methods

2.1. Participants

Structural MRI scans were available for 427 participants (249 cases, 179 male; 163 controls, 76 male). These comprise a subset of 629 scans obtained from the Australian Schizophrenia Research Bank (ASRB); we excluded 25 participants who met ICD-10 criteria for bipolar disorder, major depression with psychotic features, or psychosis not otherwise specified, and an additional 177 scans failing stringent exclusion criteria for excess motion or other T1 image artefacts. Scan quality control was performed by a trained investigator who was blind to participants' clinical and cognitive status. All included cases met ICD-10 criteria for schizophrenia ($N = 208$) or schizoaffective disorder ($N = 41$) with diagnoses confirmed using the OPCRIT algorithm (McGuffin and Farmer, 1991) applied to interviewer ratings on the diagnostic interview for psychosis (DIP) (Castle et al., 2006).

Detailed information regarding sampling, recruitment strategies, and consent procedures are published elsewhere (Loughland et al., 2010). Participants were aged 18–65 years and spoke fluent English. Exclusion criteria included the presence of an organic brain disorder, brain injury with post-traumatic amnesia, mental retardation, movement disorders, and recent (within 6 months) substance dependence or electroconvulsive therapy. HCs were screened for the absence of personal or family history of psychosis or bipolar-I disorder.

2.2. Cognitive and clinical characterization

Cognitive subtypes of patients were previously determined (Green et al., 2013) by applying multi-dimensional Grade of Membership (GoM) analysis to cognitive performance data from a broader sample of ASRB schizophrenia patients ($N = 617$). In brief, nine cognitive performance measures contributed to the GoM: the Wechler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001), Letter Number Sequencing (Wechsler, 1997), Controlled Oral Word Association Test (Spreen and Strauss, 1998), and five subscales from the Repeatable Battery for Assessment of Neuropsychological Status (Randolph, 1998). The GoM analysis identified two latent subtypes (CD and CS) within the sample of schizophrenia cases (Green et al., 2013). Within the subset of patients for whom MRI scans were available, 74 patients (57 male) were classified into the CD subtype and 126 patients (74 male) were classified into the CS subtype.

The DIP (Castle et al., 2006) was used to establish a lifetime diagnosis of a psychotic disorder, according to ICD-10 criteria (McGuffin and Farmer, 1991). In addition, the DIP provides data on socio-demographic data, family and medical history, and drug and alcohol assessment. As per methods outlined by Green et al. (2013), lifetime data for 11 DIP items assessing hallucinations and delusions were summed to provide an index of positive symptom severity; a negative symptom severity