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Neurocognitive performance in family-based and case-control studies of schizophrenia

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ABSTRACT

Background: Neurocognitive deficits in schizophrenia (SZ) are established and the Consortium on the Genetics of Schizophrenia (COGS) investigated such measures as endophenotypes in family-based (COGS-1) and case-control (COGS-2) studies. By requiring family participation, family-based sampling may result in samples that vary demographically and perform better on neurocognitive measures.
Methods: The Penn computerized neurocognitive battery (CNB) evaluates accuracy and speed of performance for several domains and was administered across sites in COGS-1 and COGS-2. Most tests were included in both studies. COGS-1 included 328 patients with SZ and 497 healthy comparison subjects (HCS) and COGS-2 included 1195 patients and 1009 HCS.
Results: Demographically, COGS-1 participants were younger, more educated, with more educated parents and higher estimated IQ compared to COGS-2 participants. After controlling for demographics, the two samples produced very similar performance profiles compared to their respective controls. As expected, performance was better and with smaller effect sizes compared to controls in COGS-1 relative to COGS-2. Better performance was most pronounced for spatial processing while emotion identification had large effect sizes for both accuracy and speed in both samples. Performance was positively correlated with functioning and negatively with negative and positive symptoms in both samples, but correlations were attenuated in COGS-2, especially with positive symptoms.
Conclusions: Patients ascertained through family-based design have more favorable demographics and better performance on some neurocognitive domains. Thus, studies that use case-control ascertainment may tap into populations with more severe forms of illness that are exposed to less favorable factors compared to those ascertained with family-based designs.

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1. Introduction

Methods of ascertainment are pivotal across biomedical research and are an important consideration in the research design. In genetic

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studies, the utility and statistical approach of family-based and unrelated case-controls studies has been discussed (e. g. Hiekkalinna et al., 2012). The incorporation of endophenotypes to genetic investigations of schizophrenia (SZ) has grown significantly with neurocognitive measures (Gur et al., 2007a, 2007b; Lee et al., 2015–in this issue; Nuechterlein et al., 2015–in this issue; Stone et al., 2015–in this issue) and neurophysiological measures (Swerdlow et al., 2014; Light et al. 2015–in this issue; Turetsky et al. 2015–in this issue) playing key roles. Family-based designs enable testing the endophenotype criteria (Braff et al., 2007; Braff, 2015–in this issue; Gottesman and Gould, 2003) and, when sufficiently powered, allow for the examination of heritability, association with the disease phenotype and co-segregation within families (Glahn et al., 2014; Greenwood et al., 2007, 2011, 2013).

Several meta-analyses have reported that adult relatives of probands with SZ show intermediate deficits in neurocognitive measures including executive functions, such as working memory and attention, verbal fluency and sensori-motor speed (Faraone et al., 2001; Kremen and Hoff, 2004; Sitskoorn et al., 2004; Snitz et al., 2006). Similar deficits have also been observed in younger relatives (Niemi et al., 2003; Seidman et al., 2006; Keshavan et al., 2010; Agnew-Blais and Siedman, 2013). The neurocognitive domains implicated in family-based studies are similar to deficits observed in case-control studies (Gur et al., 2001b). Yet, direct evaluation of these complementary ascertainment strategies applying the same measures has not been conducted. The Penn computerized neurocognitive battery (CNB) used in the Consortium on the Genetics of Schizophrenia (COGS) provides a unique opportunity to evaluate effects of ascertainment methods—family-based (COGS-1) vs. case control (COGS-2)—with the same neurocognitive battery across the participating sites.

The CNB, developed in concert with functional neuroimaging studies (Gur et al., 2010), has been validated in healthy participants and people with SZ (Gur et al., 2001a,b) and is sensitive to the effects of age and sex (Gur et al., 2012; Irani et al., 2012). The battery, which provides measures of performance accuracy and response time, was applied in three independent large-scale family-based genetic studies. The Multiplex Multigenerational Investigation of Schizophrenia (MGI; Gur et al., 2007a) reported that probands demonstrated greatest impairment relative to healthy controls, with intermediate performance of family members. Liability for SZ affected the speed–accuracy tradeoff differently for specific neurocognitive domains. Significant heritability estimates were obtained for accuracy of verbal, facial, and spatial memory and spatial and emotion processing. For speed, estimates of heritability were significant for abstraction and mental flexibility, attention, face memory, and spatial and sensorimotor processing. The results of the Project among African-Americans to Explore Risks for Schizophrenia (PAARTNERS) revealed that patients with SZ exhibited less accuracy and speed in most neurocognitive domains than their relatives, who were impaired relative to HCS in most domains. Significant heritabilities were observed for most neurocognitive domains, with the highest for accuracy of abstraction and mental flexibility, verbal memory, face memory, spatial processing, and emotion processing and for speed of attention (Calkins et al., 2010).

In COGS-1 all of the measures applied from the Penn CNB (Abstraction and Mental Flexibility, Face Memory, Spatial Memory, Spatial Processing, Sensorimotor Dexterity, and Emotion Recognition) were significantly heritable with heritability estimates ranging from 24% for Spatial Memory to 55% for Spatial Processing (Greenwood et al., 2007). These heritabilities are in the same range as the heritability of SZ itself in the COGS-1 families (Light et al., in press). Furthermore, we noted sex differences in familiality effects with male probands' performance predictive of performance of their unaffected relatives (Calkins et al., 2013). The subsequent application of the CNB in the case-control design of COGS-2 enabled evaluation of the pattern of performance of individuals with SZ, compared to HCS, ascertained in family-based and case-control designs. We noted that in some endophenotypic measures in COGS-1 probands were less impaired than observed in other samples of patients with SZ (Greenwood et al., 2007). The major ascertainment difference between the samples is that patients recruited for COGS-1 required the availability of parents and siblings while COGS-2 permitted participation of patients regardless of family availability (Swerdlow et al., 2015–in this issue). This difference likely affects multiple demographic characteristics related to age, education, socioeconomic status as well as severity of illness, favoring COGS-1. We hypothesized that while the profile of impairment would be similar, probands in the COGS-1 family-based ascertainment would perform better than those ascertained as cases in COGS-2.

2. Materials and methods

2.1. Participants

Details on the COGS-1 and COGS-2 samples' ascertainment, inclusion and exclusion criteria and clinical assessment are provided elsewhere in this issue (Braff et al.; Swerdlow et al.). Briefly, COGS-1, a family-based design, and COG-2, a case-control design, included probands 18–65 years old who met DSM-IV criteria for schizophrenia based on established diagnostic procedures. COGS-1 required that both biological parents were available for genotyping, and that at least one full sibling, unaffected with schizophrenia, was available for endophenotyping and genotyping. Probands with one available parent but two or more available siblings, with at least one unaffected by schizophrenia, were also included, as were probands with no available parents but three or more available siblings (≥ 1 unaffected by schizophrenia). COGS-2 had the same diagnostic requirements for probands and controls as COGS-1, but the availability of family members was not required. Here we focus on COG-1 and COGS-2 patients and controls who completed the CNB testing. COGS-1 included 328 patients and 497 controls and COGS-2 included 1195 patients and 1009 controls. Demographic information is presented at the top portion of Table 1. As can be seen, COGS-1 patients did not differ from their controls in age, or parental education, but had lower education and lower reading level with moderate effect sizes. COGS-2 patients were significantly older than their controls as well as less educated with lower parental education and Wide Range Achievement Test (WRAT4, Wilkinson and Robertson, 2006) scores, with effect sizes ranging from moderate to large. COGS-1 controls were younger, attained higher educational level, had higher paternal education and higher WRAT scores compared to COGS-2 controls, but all these effect sizes were small (<2 SD). COGS-1 patients were younger and had higher educational attainment, higher parental education and higher WRAT compared to COGS-2 patients and these effect sizes were moderate to large. Notably, the variances did not differ between the samples on most measures (Satterthwaite's correction was used for these p values).

2.2. The computerized neurocognitive battery (CNB)

The Penn CNB (Gur et al., 2001a,b) was administered in the COGS along with other candidate endophenotypes. It was abbreviated to reduce redundancy with other core endophenotypes. COGS-1 and COGS-2 CNB differed in three ways. First, for COGS-1 Degraded Stimulus CPT and CPT, identical pairs were used to cover the attention domain (Nuechterlein et al., 2015–in this issue), while in COGS-2 the Penn CPT data were also added to allow the full CNB to be represented. Second, for measuring working memory, different forms of the letter n-back test were used in COGS-1 and COGS-2. Third, many participants from COGS-1 did not receive the delayed recognition tests because the CNB was administered last and time limitations and fatigue attenuated the test sessions.

The CNB was administered on Macintosh computers (Apple Inc., Cupertino, California) in a fixed order and included brief standardized rest periods, for a total administration time of about 60 min. The

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