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Neurocognitive and Social Cognitive Impairments in Early-Onset Psychosis and At-Risk Youth: Implications for Intervention Strategies

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Neurocognitive and Social Cognitive Impairments in Early-Onset Psychosis and At-Risk Youth: Implications for Intervention Strategies

A dissertation submitted in partial satisfaction

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Doctor of Philosophy in Psychology

by

Ariel Jenys Eckfeld

2017

ABSTRACT OF THE DISSERTATION

Neurocognitive and Social Cognitive Impairments in Early-Onset Psychosis and At-Risk Youth: Implications for Intervention Strategies

by

Ariel Jenys Eckfeld

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2017

Professor Carrie Bearden, Co-Chair

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Early-onset psychosis (EOP), or onset of overt psychosis prior to age 18, is associated with particularly severe neurocognitive and social impairment, and poor prognosis (Frangou, 2010; Vyas & Gogtay, 2012). While significant impairments have been documented in specific cognitive domains (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Heinrichs & Zakzanis, 1998), working memory (WM) in particular is an area that has been theorized to represent a reliable cognitive endophenotype of schizophrenia. However, the majority of literature to date has focused on adult-onset schizophrenia, in which relevant developmental processes have already unfolded. Adolescence provides a privileged opportunity to understand how psychosis-related abnormalities in the structure and function of neural networks affect the relationships

between social cognition, neurocognition and functioning, as well as an opportunity to define biomarkers for development of treatments to improve functional outcomes.

As such, the first study examined the relationship between individual WM capacity and task-based neural activation and functional connectivity. Results indicated that, relative to typically developing controls, patients with EOP have poorer WM performance, lower overall WM capacity, reduced neural activity in WM-associated brain regions, and reduced coupling of WM-associated regions. Additionally, EOP patients evidenced greater neural activation and connectivity with increasing age, suggesting an atypical developmental trajectory along with general inefficiency of WM circuitry.

Additional insight into the neurodevelopmental processes relevant to psychosis can come from examining genetically defined high-risk cohorts, such as 22q11.2 deletion syndrome (22q11DS). The second study evaluated the phenotypic overlap between EOP and 22q11DS by investigating the profile of neurocognitive and social cognitive impairment in individuals with EOP relative to 22q11DS patients and healthy controls. Despite greater overall cognitive impairment in the 22q11DS group (with the exception of verbal fluency, for which EOP patients evidenced greater impairment), patients with EOP and 22q11DS had comparable deficits in processing speed. 22q11DS and EOP patients also evidenced similar patterns of relationships between cognitive measures and psychotic symptoms. However, neurocognition and social cognition largely did not predict future functioning among the groups.

The third and final study examined plasticity-based cognitive training (CT) as a potential intervention for such cognitive impairments in EOP. Results from the feasibility study indicated that slightly over half of participants were able to complete at least 10 hours of CT; dropout was

primarily due to finding training boring. However, patients completing training showed higher post- versus pre-CT social functioning, and pre- to post-CT reductions in general and anxiety symptoms. This investigation into neurocognitive and social cognitive dysfunction in EOP, which incorporates perspectives from an fMRI paradigm and a comparison to a genetic high-risk cohort, has the potential to generate knowledge on a clinically significant and understudied area, and potentially produce new treatment targets for EOP.

The dissertation of Ariel Jenys Eckfeld is approved.

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DEDICATION

I would like to thank my advisor, Dr. Carrie Bearden, for all of her support and guidance throughout graduate school. Her dedication to mentorship and her love of science have been inspirational. I am also thankful to Drs. Cindy Yee-Bradbury, Sophia Vinogradov, and Adriana Galvan for the learning opportunities they have provided. I am particularly appreciative of the love, laughs, and adventures that I have been privileged to experience with my cohort of six years; it is an understatement to say that graduate school would have been impossible without you, friends. To my parents, your intelligence, strength, love, and endless encouragement of my ambitions have made me who I am; I am doubly blessed to have amazing in-laws who have made California my home away from home. Thank you for all that you have done and continue to do for me. Lastly, thank you to my husband David, whose constant affection, support, wit, and shared animal enthusiasm have guided me through many challenging times. I am deeply grateful to you all.

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GENERAL BACKGROUND

Although the precise etiology of schizophrenia (SZ) remains unclear, several lines of evidence point to a neurodevelopmental model in which early brain insults interact with, and are exacerbated by, normal or abnormal neural maturation and biochemical processes during adolescence to result in the emergence of psychotic symptoms and impairment (Fatemi & Folsom, 2009; Lewis & Levitt, 2002; McGrath, Féron, Burne, Mackay-Sim, & Eyles, 2003; Pantelis, Yücel, Wood, McGorry, & Velakoulis, 2003). Despite indications that multiple liability markers for SZ emerge during early brain development (Fatemi & Folsom, 2009; Lewis & Levitt, 2002; McGrath et al., 2003; Rapoport, Giedd, & Gogtay, 2012), formal diagnostic symptoms and signs of the disorder do not typically manifest until the late adolescent period. Indeed, there is a remarkable consistency in age-at-onset distributions for SZ in diverse cultures around the world, implicating the late adolescent/early adult period as the peak period of risk for onset (Giedd, Keshavan, & Paus, 2008; Gogtay, Vyas, Testa, Wood, & Pantelis, 2011).

Adolescent Developmental Changes and Psychosis Onset

In general, adolescence represents a period of active brain development and several inter-related changes: increased salience of and stress associated with social stimuli; increased intensity of and capacity to regulate emotions and behaviors; improved cognitive control, reasoning skills, and executive function; and in parallel, integration and optimization of neural networks supporting efficient social cognition, neurocognition and behavior (Casey et al., 2010; Luna, Padmanabhan, & O'Hearn, 2010; Spear, 2000; Steinberg, 2005). Increased neuronal efficiency during adolescence is believed to correspond to a reduction (i.e., pruning) of excess synapses and increasing myelination of axonal connections in regions critical for higher order cognition, particularly within the prefrontal cortex (Paus, 2005; Petanjek et al., 2011). These

transitions are necessary to navigate the social and cognitive demands of adulthood. Thus, psychotic disorders such as SZ, which tend to emerge around adolescence/young adulthood, appear to represent a dramatic deviation from this developmental trajectory.

Correspondingly, onset of illness *during* adolescence, also referred to as early-onset psychosis (EOP; onset of overt psychosis prior to age 18), is associated with particularly severe social and neurocognitive impairment and poor prognosis for later functioning (Frangou, 2010; Vyas & Gogtay, 2012). As indicated above, according to numerous prominent models of psychosis, the neural, social and cognitive changes that typically occur during adolescence may precipitate symptom emergence (see Figure 1) (Fatemi & Folsom, 2009; Rapoport et al., 2012; Reichenberg et al., 2010; Schvarcz & Bearden, 2015). The development of symptoms and deterioration of functioning during this period is proposed to result from several potential causal mechanisms working either independently or collaboratively, such as brain inflammation, stressful psychosocial events, and pubertal hormones triggering expression of faulty genes further affecting neural structures and cortical connections/networks (e.g., excessive synaptic pruning, altered neurotransmitter systems) (Fatemi & Folsom, 2009; Lewis & Levitt, 2002; Rapoport et al., 2012; Uhlhaas & Singer, 2011). However, studies directly examining the interaction between psychosis onset and adolescent development are scarce. As a period of rapid development of social and cognitive competence and of increased plasticity in underlying neural networks, adolescence provides a privileged opportunity to understand how psychosis-related abnormalities in the structure and function of neural networks affect the relationship between social cognition, neurocognition and functioning, as well as an opportunity to define biomarkers for development of treatments to improve long-term social and role functioning.

The development of appropriate treatments for EOP is a major unmet need; EOP chronically and consistently impacts the lives of both patients and their families, and absorbs a disproportionate share of personal and public resources (e.g., high rates of service utilization, homelessness, and suicide, and low rates of employment and supportive relationships) (Mueser & McGurk, 2004). Furthermore, early and targeted intervention for EOP is crucial as such youth reportedly experience greater delays in receiving treatment as compared to adult-onset patients (Ballageer, Malla, Manchanda, Takhar, & Haricharan, 2005; Díaz-Caneja et al., 2015), which has been associated with subsequent declines in cognition and functioning (Amminger, Edwards, Brewer, Harrigan, & McGorry, 2002). However, no empirically supported psychosocial intervention for EOP patients currently exists (Hollis & Rapoport, 2011), despite increasing evidence highlighting the need for early psychosis treatment even in premorbid phases (Seidman & Nordentoft, 2015). In fact, even basic questions such as why earlier onset of psychosis predicts poorer outcome remain unanswered.

In part, this may be due to an incomplete understanding of the pathophysiologic mechanisms underlying development of cognitive and social-affective impairment in EOP; most research in this area is conducted in adults, whose brain development and neurocognitive/social-affective development are mostly complete. Nevertheless, we know that aberrant maturational processes during adolescent neurodevelopment likely play a significant role (e.g., Cannon et al., 2015; Haut, Schvarcz, Cannon, & Bearden, 2016; Insel, 2010; Karlsgodt et al., 2009). Of note, in a longitudinal study of subjects ages 12-35 at clinical high-risk for psychosis, 40% of conversions to a diagnosable psychotic disorder occurred prior to age 18 (Cannon et al., 2008). However, most first-episode psychosis research programs enroll participants age 18 or older,

meaning that individuals with early onset may be studied in the prodromal phase but not in the earliest stage of the manifest illness.

Genetic Risk Models

Additional insight into the neurodevelopmental processes relevant to SZ can come from examining genetically defined HR cohorts, which provide an opportunity to investigate disease mechanisms long before onset of overt illness. One particularly compelling example is the 22q11.2 deletion syndrome (Velocardiofacial Syndrome; 22q11DS), a recurrent copy number variant (CNV) involving a hemizygous microdeletion of 1.5 – 3 megabases in the 22q11.2 chromosomal region that affects 1 in every 2000-4000 live births (Botto et al., 2003; Grati et al., 2015; Kobrynski & Sullivan, 2007; Robin & Shprintzen, 2005). Multiple genes within the 22q11 locus are highly expressed in the brain, and involved in early neuronal migration and brain development (Bassett & Chow, 2008; Drew et al., 2011; Schreiner, Lazaro, Jalbrzikowski, & Bearden, 2013). 22q11DS results in variable phenotypic expression, including congenital heart defects, facial dysmorphology, cognitive impairment, and developmental delays, and confers dramatically increased risk for psychosis (CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium, 2017; Drew et al., 2011; Schneider et al., 2014; Schreiner et al., 2013). Specifically, 22q11DS adolescents and young adults have an increased risk for SZ of 25-30 times that of the general population (Drew et al., 2011); conversely, 22q11DS is believed to account for ~1% of cases of SZ in the general population (Bassett & Chow, 2008). 22q11DS has therefore been established as a reliable genetic high-risk group that may be particularly informative in comparisons to EOP, which has been shown via family studies to have greater genetic loading than adult-onset SZ (Frangou, 2010; Nicolson et al., 2003).

Furthermore, as the deletion can be detected very early in development, even *in utero*, 22q11DS provides a unique opportunity to study the molecular pathogenesis of psychosis, while mitigating the challenges posed by the genetic heterogeneity of this highly complex illness. However, in order to establish the relevance of 22q11DS as a model for idiopathic psychosis it is necessary to first establish overlap at an intermediate phenotype level, i.e., at the level of neurocognitive and social cognitive indices. These may represent biomarkers that predict functional outcome, thereby elucidating possible targets for intervention. However, to our knowledge, only one study has conducted a direct comparison of these two cohorts, although it had several significant limitations, as discussed in more detail below. Thus, more comprehensive and larger-scale investigations are needed to assess whether there is shared etiology at the neurocognitive and social cognitive level between 22q11DS and EOP.

Cognitive Deficits as a Hallmark of SZ

In general, SZ is associated with enduring cognitive deficits (Frazier et al., 2012; Keefe et al., 2012a). Specifically, adults with SZ typically demonstrate a degree of global cognitive impairment (~1 SD below population norms), accompanied by additional, differential impairments in specific cognitive domains (i.e., long-term memory, working memory, attention, and processing speed) (Dickinson, Ramsey, & Gold, 2007; Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Heinrichs & Zakzanis, 1998; Knowles, David, & Reichenberg, 2010).

Deficits in working memory (WM), or the ability to hold and manipulate information in one's mind, have been found to be a particular core feature of SZ (Forbes, Carrick, McIntosh, & Lawrie, 2009; Lee & Park, 2005; Park & Gooding, 2014, 2014; Piskulic, Olver, Norman, & Maruff, 2007; Silver, Feldman, Bilker, & Gur, 2003), leading to a large number of investigations into the underlying neural abnormalities in associated brain regions (e.g., prefrontal cortex

(PFC), parietal cortex) (Constantinidis & Wang, 2004; Curtis & D'Esposito, 2003; D'Esposito, Postle, & Rypma, 2000; Jonides et al., 1998; Pasternak & Greenlee, 2005; Petrides, 2000). Deficits in social cognition have also been well-documented in adults with SZ, particularly in the area of Theory of Mind (i.e.,, the ability to take the perspective of another) (Bora & Pantelis, 2013; Brüne, 2005; Martin, Robinson, Dzafic, Reutens, & Mowry, 2014; Penn, Sanna, & Roberts, 2008; Savla, Vella, Armstrong, Penn, & Twamley, 2012).

The existing neurocognitive research on EOP has noted persistent deficits in similar domains, particularly in the areas of WM, verbal declarative memory, and psychomotor processing speed, which tend to be more severe than those of adult-onset patients (Basso, Nasrallah, Olson, & Bornstein, 1997; Frangou, 2010). Less is known about impairment in EOP in the domain of social cognition, though early evidence suggests that EOP patients exhibit difficulties that are similar to those of adults with SZ in the domains of emotion recognition and emotional intelligence (Barkl et al., 2014; Linke et al., 2015). Earlier age of psychosis onset (APO) also appears to be associated with increasing disruption of typical developmental trajectories, as individuals with EOP fail to demonstrate age-appropriate increases in cognitive processing speed as compared to typically developing adolescents (Bachman et al., 2012).

Impairments in social cognition, verbal/language and memory skills, and executive function in patients with SZ have been associated with poorer subsequent functional outcome (Allott, Liu, Proffitt, & Killackey, 2011; Bachman et al., 2012; Couture, Penn, & Roberts, 2006; Fett et al., 2011). However, the literature to-date has largely focused on adults, for which certain operationalized definitions of "functional outcome" (e.g., workplace functioning) may not apply to the EOP population. This is particularly relevant given that the relationship between cognition and outcome has been shown to vary widely as a function of examined constructs (Couture et al.,

2006; Fett et al., 2011). For example, results appear dependent upon factors such as which social cognitive or neurocognitive domain is examined, which tests were used to assess a particular skill and how sensitive they are, what definition or measure of outcome was used, and/or whether moderator variables such as symptom severity were considered. As such, further research is necessary to evaluate the extent to which cognitive deficits may relate to everyday functioning among adolescents with EOP, as well as among high-risk groups such as 22q11DS. In turn, this research may inform potential treatments to improve outcomes in these youth.

The profile of neurocognitive deficits observed in EOP patients is nevertheless consistent with the observation that brain functions that typically develop during adolescence are relatively more impaired among EOP patients. For example, WM, a skill that develops throughout adolescence and peaks at age 20, has been found to be more compromised among adolescents and young adults with SZ as compared to set-shifting, a cognitive function that purportedly matures earlier in development (Pantelis et al., 2003). Impaired WM among patients with SZ has been consistently reported, regardless of study method or task utilized, with deficits in visuospatial WM appearing more robust than those in verbal WM (Lee & Park, 2005; Park & Gooding, 2014). These deficits are significantly heritable (Knowles et al., 2014), and are present in a dose-dependent manner among individuals with increased genetic risk for SZ (i.e., from largest to smallest impairment: patients, non-affected dizygotic twins, non-affected monozygotic twins, unrelated healthy twin controls) (Glahn et al., 2003). Moreover, WM impairment among adolescents at genetic (Choi et al., 2012) and clinical (Smith, Park, & Cornblatt, 2006; Wood et al., 2003) high-risk for SZ appears to confer increased risk for later developing overt psychosis (Brewer et al., 2006; Pukrop et al., 2007). Spatial WM has thus been identified as a cognitive

endophenotype of SZ, which may be amenable to interventions through targeting underlying abnormal cognitive processes.

WM-Associated Neural Abnormalities in SZ

Several brain changes have been identified as occurring around the time of illness onset, including structural (e.g., reduced gray matter volume and white matter integrity) and neural changes (e.g., decreased brain activation, decreased neuronal density) particularly within the prefrontal cortex (PFC) (Bois, Whalley, McIntosh, & Lawrie, 2014; Fornito, Zalesky, Pantelis, & Bullmore, 2012; Friston, 1998; Fusar-Poli et al., 2011; Hohenberg et al., 2013; Koutsouleris et al., 2014; Smieskova et al., 2010; White & Gottesman, 2012). Therefore, neuroimaging investigations may be informative for evaluating neural changes during adolescence that underlie such WM and other cognitive impairments. Among adults with SZ, neuroimaging work has highlighted that PFC activity during WM tasks varies depending on task load demands and range of performance ability; increased WM demand is associated with increased activity within the PFC and related regions (Curtis & D'Esposito, 2003; Finn, Sheridan, Kam, Hinshaw, & D'Esposito, 2010; Klingberg, Forssberg, & Westerberg, 2002), but PFC activity declines when WM load exceeds an individual's own capacity (Callicott, Mattay, et al., 2003; Manoach, 2003; Van Snellenberg et al., 2015). In addition to regional neural activity, researchers have noted substantial SZ-associated abnormalities in functional connectivity, or the working relationship between anatomically separate brain regions (i.e., regions that are temporally correlated during a given condition). For example, reduced connectivity between fronto-parietal and fronto-hippocampal regions during WM performance among adult patients with SZ relative to controls has been found, which has in turn been shown to correlate with psychotic symptom severity and

WM task accuracy (Henseler, Falkai, & Gruber, 2010). Collectively, these findings suggest that abnormalities in WM circuitry substantially contribute to the clinical and cognitive profile of SZ.

Even in the context of typical development, functional magnetic resonance imaging (fMRI) studies have revealed maturational changes in WM-associated neural activity in the PFC (Bunge & Wright, 2007; Luna et al., 2010), involving primarily increased neural activity with age through adolescence, as well as differences in the regions recruited over time. Specifically, this involves a shift to more specialized network circuitry including parietal and frontal regions. These neural maturational changes coincide with the major neural reorganization that occurs during the adolescent developmental period (Insel, 2010; Paus, 2005; Petanjek et al., 2011; Stiles & Jernigan, 2010). Given this literature, investigations into the neural dysfunction associated with adolescent-onset psychosis may be informative regarding disrupted maturational trajectories in this time period. Yet, very few fMRI studies of early onset psychosis have been conducted to date. Existing fMRI studies of WM in EOP implicate abnormal patterns of neural activity in various WM-associated brain regions (e.g., frontal cortex, anterior cingulate cortex), as well as disrupted functional connectivity between prefrontal/limbic and visual processing networks (e.g., occipital lobe) relative to healthy controls, similar to findings in adults with SZ (Bittner et al., 2014; Kyriakopoulos et al., 2012; Sugranyes et al., 2012; Thormodsen et al., 2011; Tonya White, Hongwanishkul, & Schmidt, 2011; Tonya White, Schmidt, Kim, & Calhoun, 2011).. Among these six EOP studies that have been published to date, only one has focused on individual WM capacity (Bittner et al., 2014), despite literature suggesting the importance of individual capacity in moderating neural response (Callicott et al., 2003; Manoach, 2003; Van Snellenberg et al., 2015). Thus, further examination into the effects of individual WM capacity on task-based activation and functional connectivity in EOP is warranted.

Development of Interventions for Cognitive Deficits in Schizophrenia

Given the marked cognitive deficits and atypical neurodevelopment associated with EOP, and the relevance of such deficits to functional outcome that has been observed in adults with SZ, one potential intervention under investigation is cognitive training (CT). CT relies upon the principles of neural plasticity, which can be induced by just minutes of exposure to an experience or stimulus (Kolb & Gibb, 2011). Although there are various forms of CT for SZ, one neuroplasticity-based program seems particularly efficacious. This program was developed to specifically target the early perceptual processing deficits in SZ that may underlie impairment in higher-order cognitive processes. Its success in improving cognitive function among adult patients has been documented (e.g., (Fisher, Holland, Merzenich, & Vinogradov, 2009; Fisher, Holland, Subramaniam, & Vinogradov, 2010; Hooker et al., 2012, 2013; Keshavan, Vinogradov, Rumsey, Sherrill, & Wagner, 2014; Nahum et al., 2014; Sacks et al., 2013; Subramaniam et al., 2012, 2014; Vinogradov, Fisher, & de Villers-Sidani, 2012; Vinogradov, Fisher, & Nagarajan, 2013).

Furthermore, cognitive improvements have been associated with increased functioning (quality of life) at 6-month follow-ups following CT completion among adults with SZ (Adcock et al., 2009; Fisher et al., 2010; Genevsky, Garrett, Alexander, & Vinogradov, 2010). As adolescence is a time of ongoing neural development and increased neural plasticity (Blakemore, 2012; Kolb & Gibb, 2011; Spear, 2000), CT may promote increased cognitive gains among EOP patients. Therefore, CT is of particular interest for this population due to the inability of other existing treatments to sufficiently address the observed cognitive deficits (Frazier et al., 2012; Keefe et al., 2012b) and subsequent functional impairment.

Dissertation Aims

Following from this literature, the first aim of this dissertation project is to investigate the neural substrates of spatial working memory in EOP as compared to healthy controls (HC) using an fMRI approach. Specifically, we examined the relationship between individual WM capacity, calculated via a parametric manipulation of WM load, and task-based neural activation. Additionally, given prior findings of reduced connectivity between the dorsolateral PFC and regions implicated in WM performance, we also sought to determine whether abnormal patterns of functional connectivity between key components of working memory circuitry were present among individuals with EOP relative to HCs. We then investigated age-related changes in working memory function in EOP. Lastly, we explored the relationship between WM-related neural dysfunction and neurocognitive performance on out-of-scanner tasks.

The second aim of this dissertation project is to evaluate the phenotypic overlap between EOP and 22q11DS, a genetic high risk model for psychosis, by investigating the profile of neurocognitive and social cognitive impairment in individuals with EOP relative to 22q11DS patients and HC. In order to evaluate the relevance of these cognitive deficits to psychotic symptoms, we also evaluated the relationship between neurocognitive deficits and psychotic symptom severity in both groups. We further investigated the role of neurocognition and social cognition in the prediction of social and role functioning at follow-up, and examined the effects of age on both group differences at initial assessment and the prediction of future functioning. Lastly, given that decreased premorbid global cognitive ability (IQ) and cognitive decline over time, particularly in the verbal domain, may predict psychosis emergence among high-risk patients (Debbané, Glaser, David, Feinstein, & Eliez, 2006; Gothelf et al., 2013; Green et al., 2009; Vorstman et al., 2015), and that IQ tends to be at least modestly correlated with other cognition (Mohn, Sundet, & Rund, 2014), we investigated the relationship of IQ to

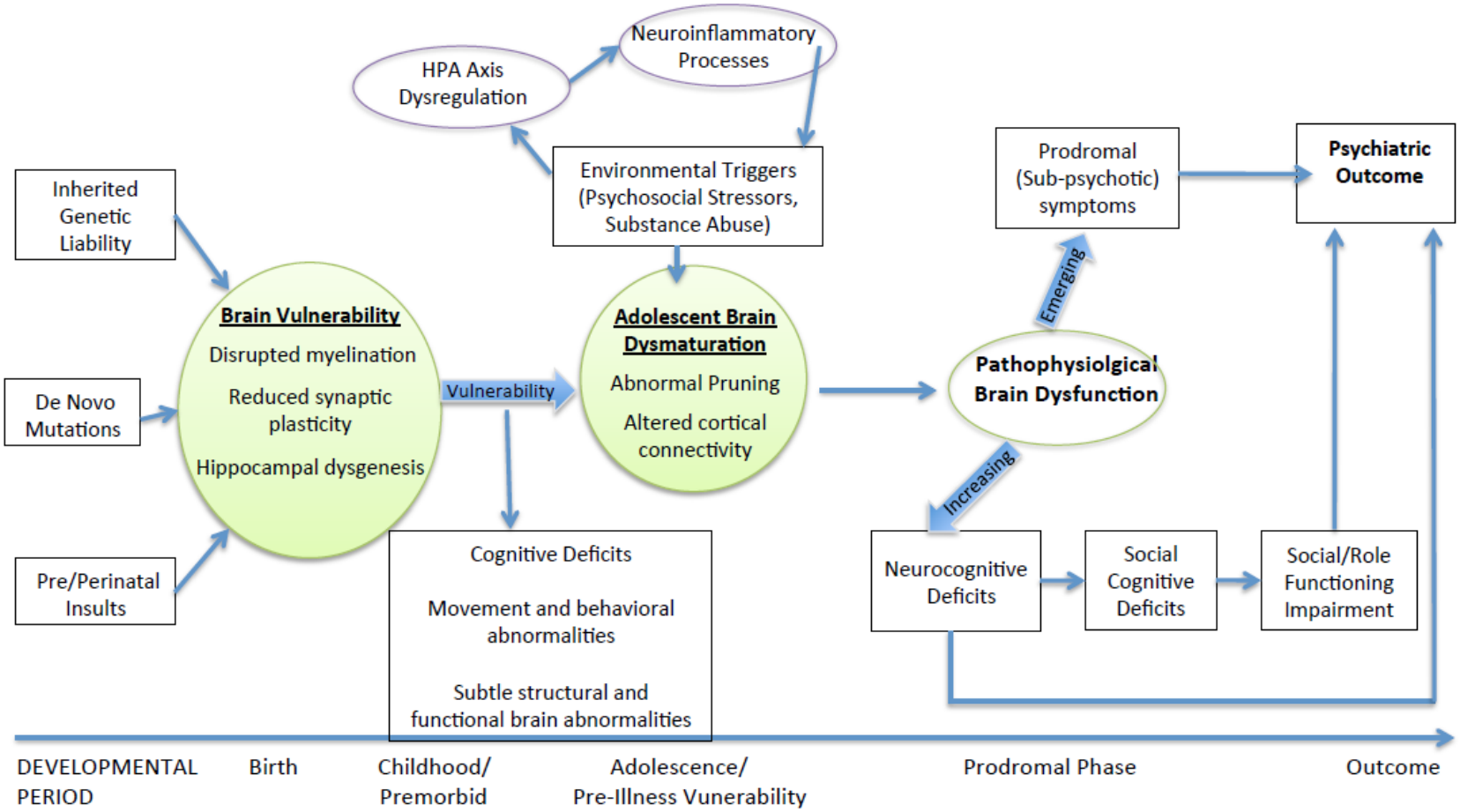
neurocognitive and social cognitive domains across groups. These findings will provide a window into how a major risk factor like a 22q11.2 deletion may disrupt the brain and ultimately contribute to disease pathogenesis and related impairments.

These findings may also prove beneficial for identifying intervention targets for psychosis. As highlighted previously, treatment delays among patients with psychotic illness have been associated with poorer performance on cognitive tasks and greater positive and negative symptom severity, which is in turn associated with reduced overall functioning and poorer longer term outcome (Amminger et al., 2002; Boonstra et al., 2012; Marshall et al., 2005; Penttilä, Jääskeläinen, Hirvonen, Isohanni, & Miettunen, 2014; Perkins, Gu, Boteva, & Lieberman, 2005). The final aim of this dissertation is therefore to examine plasticity-based cognitive training (CT) as a potential intervention for such cognitive impairments within EOP. Findings will help clarify the feasibility of at-home and/or clinic-based training for improving cognitive and functioning skills among EOP youth.

In summary, the substantial and widespread functional, cognitive, and social morbidity among EOP patients – when measured at the group level – belies tremendous variability in clinical presentation and functional outcome. Thus, our investigation into neurocognitive and social cognitive dysfunction in EOP, which incorporates perspectives from an fMRI paradigm and a comparison to a genetic high-risk cohort, has the potential to generate knowledge on a clinically significant and understudied area. Furthermore, given our evaluation of the association between cognition and functional impairment, this research may produce new treatment targets for enhancing global functioning and quality of life in a wide spectrum of help-seeking individuals over the course of their lives.

Figure 1. *Early and Late Neurodevelopmental Abnormalities in Schizophrenia.*

Conceptual model of the hypothesized relationship of vulnerability-related and progressive neuroanatomic abnormalities to the development of neurocognitive and functional impairment in the early phases of psychosis.



STUDY 1: DISRUPTED WORKING MEMORY CIRCUITRY IN EARLY-ONSET PSYCHOSIS

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Abstract

Individuals with schizophrenia (SZ) consistently show deficits in spatial working memory (WM), and associated atypical patterns of neural activity within key WM regions, including the dorsolateral prefrontal (dlPFC) and parietal cortices. However, little research has focused on early-onset psychosis (EOP) and potential age-associated disruptions of WM circuitry that may occur in youth with this severe form of illness. Here we utilized each subject's individual spatial WM capacity to investigate task-based neural dysfunction in 17 patients with EOP (16.58±2.60 years old) as compared to 17 typically developing, demographically comparable adolescents (18.07±3.26 years old). EOP patients showed lower behavioral performance at higher WM loads and lower overall WM capacity compared to healthy controls. Whole-brain activation analyses revealed greater bilateral precentral and right postcentral activity in controls relative to EOP patients, when controlling for individual WM capacity. Seed-based psychophysiological interaction (PPI) analyses revealed significantly greater co-activation between the left dlPFC and left frontal pole in controls relative to EOP patients. Significant group-by-age interactions were observed in both whole-brain and PPI analyses, with EOP patients showing atypically greater neural activity and stronger coupling between WM task activated brain regions as a function of increasing age. Additionally, EOP patients demonstrated positive relationships between right dlPFC neural activity and task performance, but unlike healthy controls, failed to show associations between neural activity and out-of-scanner neurocognitive performance. Collectively, these findings are consistent with atypical WM-related functioning and disrupted developmental processes in youth with early-onset psychosis.

Keywords: schizophrenia, connectivity, development, adolescence, working memory capacity

Introduction

Schizophrenia (SZ) is considered a neurodevelopmental disorder of brain connectivity (Fatemi & Folsom, 2009; Fitzsimmons, Kubicki, & Shenton, 2013; Fornito, Zalesky, Pantelis, & Bullmore, 2012; Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011; Stephan, Baldeweg, & Friston, 2006; Stephan, Friston, & Frith, 2009) but few functional magnetic resonance imaging (fMRI) studies have examined brain connectivity during the putatively critical developmental period of adolescence. To date, the focus has been on connectivity abnormalities in adults with SZ by examining neural activity during cognitively demanding tasks, such as working memory (WM). Deficits in WM, particularly visuospatial, are a well-documented and robust core feature of SZ (Forbes, Carrick, McIntosh, & Lawrie, 2009; Lee & Park, 2005; Park & Gooding, 2014, 2014; Piskulic, Olver, Norman, & Maruff, 2007; Silver, Feldman, Bilker, & Gur, 2003). Furthermore, WM impairment is considered a reliable cognitive endophenotype of SZ given the presence of WM deficits and related neural dysfunction in clinically unaffected relatives (Callicott, Egan, et al., 2003; Knowles et al., 2014; Saperstein et al., 2006) and individuals with elevated genetic and clinical risk (Choi et al., 2012; Fusar-Poli et al., 2010; Glahn et al., 2003; Smith, Park, & Cornblatt, 2006; Wood et al., 2003). Deficits in WM have also been shown to predict future development of overt psychosis (Brewer et al., 2006; Pukrop et al., 2007).

Although visual short term capacity has been estimated at approximately 4 separate items among healthy individuals (Cowan, 2010; Todd & Marois, 2004), individual variability (Barrett, Tugade, & Engle, 2004; Cowan, 2001, 2010; Gold, Wilk, McMahon, Buchanan, & Luck, 2003; Unsworth & Engle, 2007) has led to the estimation of subjects' individual short-term WM

capacity from behavioral data (Cowan, 2001). Individual capacity has been used to assess neural circuitry abnormalities in SZ, with patients demonstrating decreased individual visual WM capacity compared to healthy controls across a range of tasks; this has been posited to result from difficulties encoding the information (Gold et al., 2010; Gold et al., 2003; Jansma, Ramsey, van der Wee, & Kahn, 2004) and/or impaired attentional control (Leonard et al., 2012; Mayer, Fukuda, Vogel, & Park, 2012). Spatial WM capacity among adults with SZ also correlates with overall cognitive abilities (e.g., IQ) (Johnson et al., 2013).

Neuroimaging studies to date have largely focused on the dorsolateral PFC (dlPFC) and parietal cortex, key regions involved in WM processing (e.g., Constantinidis & Wang, 2004; Curtis & D'Esposito, 2003; D'Esposito, Postle, & Rypma, 2000; Jonides et al., 1998; Pasternak & Greenlee, 2005; Petrides, 2000), though a larger network of WM-related dysfunction including the anterior cingulate cortex (ACC) and left frontal pole has also been proposed (Glahn et al., 2005). Specifically, dlPFC activity among SZ patients varies depending on task load demands and range of capacity/performance ability (Jansma et al., 2004; Karlsgodt et al., 2009; Manoach, 2003), suggesting generalized dlPFC 'inefficiency' during WM (Potkin et al., 2009). Notably, these studies did not directly utilize capacity load estimates in group comparisons of neural activity during WM performance, focusing primarily on post-hoc correlations and regressions. However, the proposed 'neural inefficiency' in patients with SZ mimics the inverted-U pattern described among healthy individuals; while increased WM demand is associated with increased activity within the dlPFC and other regions (e.g., superior frontal cortex, intraparietal cortex) (Curtis & D'Esposito, 2003; Finn, Sheridan, Kam, Hinshaw, & D'Esposito, 2010; Klingberg, Forssberg, & Westerberg, 2002), dlPFC activation decreases once

WM load exceeds individual capacity (Callicott, Mattay, et al., 2003; Manoach, 2003; Van Snellenberg et al., 2015). Additionally, reduced connectivity between fronto-parietal and fronto-hippocampal regions during WM performance among patients with SZ has been associated with severity of positive symptoms and reduced task accuracy in a cross-sectional analysis, in line with neural dysfunction underlying the clinical and cognitive phenotype (Henseler, Falkai, & Gruber, 2010).

However, the focus on WM dysfunction among adults with SZ disregards the major neural reorganization that occurs in adolescence (Insel, 2010; Paus, 2005; Petanjek et al., 2011; Stiles & Jernigan, 2010). This is striking, as age-related increases in neural activity have been found within core fronto-parietal WM circuitry during visual WM tasks in healthy adolescents (Andre, Picchioni, Zhang, & Toulopoulou, 2016). Moreover, significant associations between WM capacity and neural activity have been found in the same regions, suggesting that WM capacity may also increase with age (Klingberg et al., 2002). Yet the literature remains inconsistent, as increasing age has also correlated with decreasing activation in the superior frontal, limbic cingulate gyrus (Andre et al., 2016), and superior parietal regions (Schweinsburg, Nagel, & Tapert, 2005). Regardless, differences in the role of the PFC during WM performance can be distinguished within the adolescent period. For example, while the PFC is recruited during WM tasks throughout adolescence, neural activity correlates with behavior (i.e., task accuracy) only in late adolescence (Finn et al., 2010), suggesting further refinement of WM-related circuitry and PFC maturation with increasing age (Casey, Galvan, & Hare, 2005; Paus, 2005; Petanjek et al., 2011).

Given this role of age on neural and cognitive development, an investigation of WM deficits and underlying neural dysfunction among individuals who develop overt psychosis during adolescence may be particularly enlightening. Early-onset psychosis (EOP; overt psychosis emergence prior to age 18) is a particularly virulent and chronic form of psychotic disorder that is associated with poor prognosis (Vyas & Gogtay, 2012). EOP is also typically associated with more severe cognitive deficits relative to the adult-onset form of illness, particularly in the domain of WM (Frangou, 2010; Zabala et al., 2010). This model therefore may provide greater insight into the neural and neurocognitive abnormalities associated with the disorder, while simultaneously allowing for investigations of effects of earlier onset age on brain development.

Existing functional imaging studies of WM in EOP have revealed both abnormal patterns of neural activity across brain regions critical for higher-order cognitive activity (e.g., frontal regions, anterior cingulate cortex) and disrupted functional connectivity within prefrontal/limbic and visual processing networks (e.g., occipital lobe) relative to healthy controls (Bittner et al., 2014; Kyriakopoulos et al., 2012; Sugranyes et al., 2012; Thormodsen et al., 2011; White, Hongwanishkul, & Schmidt, 2011; White, Schmidt, Kim, & Calhoun, 2011). EOP patients also evidence reduced coupling of the dorsolateral prefrontal cortex (dlPFC) with other key regions implicated in WM (e.g., anterior cingulate cortex; ACC) as compared to healthy adolescents when individual capacity is not factored in (Kyriakopoulos et al., 2012). Interestingly, an investigation of age-associated changes revealed decreases in dlPFC activity and increases in dlPFC-ACC coupling among EOP patients as compared to controls, suggesting growing inefficiency of neural networks with increasing age (Kyriakopoulos et al., 2012). However, to

our knowledge, only one prior study of EOP to date has considered individual capacity, finding that relative to healthy controls, EOP patients evidence reduced capacity at each WM load and a negative correlation between neural activity and capacity during a late maintenance phase (Bittner et al., 2014). Correspondingly, the literature addressing functional dysconnectivity during WM performance in EOP is still in its infancy, particularly with respects to the effects of manipulating memory demand and accounting for individual WM capacity on task-based activation and functional connectivity.

The present study therefore investigated behavioral correlates of neural activity and connectivity during WM engagement in adolescents with EOP relative to typically developing controls. As a novel extension of prior work, we examined the relationship between individual WM capacity, calculated via a parametric manipulation of WM load, and task-based neural activation, and further assessed the association with development. In particular, we examined whether the fine-tuning of functional networks during adolescence is disrupted in EOP, which may result in an absence of typical age-associated increases in focal activation as well as abnormal patterns of functional connectivity, particularly in the prefrontal and parietal regions. Lastly, we examined the relationship between WM-related neural dysfunction and out-of-scanner neurocognitive performance. We thus hypothesized the following:

1. Individuals with EOP will evidence WM impairment compared to controls, as indexed by lower overall WM capacity and decreased task accuracy at higher spatial WM loads.
2. Controlling for individual WM capacity, EOP patients will show an abnormal pattern of neural activity within WM-relevant neural circuitry (i.e., prefrontal and parietal

cortices) during task performance relative to controls. Specifically, based on prior studies in adult patients with SZ, we expect youth with EOP to evidence reduced neural activity in dlPFC and parietal regions, but increased activity in less task-relevant regions, such as the frontal pole, anterior cingulate, and occipital cortex.

3. Relative to controls, EOP patients will demonstrate reduced efficiency of WM-related neural circuitry as evidenced by a decoupling of typically interactive regions (e.g., fronto-parietal connections).
4. Given that patients with EOP are hypothesized to differentially and/or inefficiently recruit relevant brain regions during WM performance as a function of increasing age, we anticipate that, relative to controls, EOP patients will show an altered pattern of age-associated changes in WM circuitry. Specifically, patients will fail to show the expected positive association between age and increased neural activity within frontal and parietal regions during task performance.
5. Decreased neural activity during spatial WM task administration will be associated with poorer behavioral performance and poorer performance on neurocognitive tasks completed outside the scanner.

Methods

Participants

Twenty-one healthy volunteers (18.07±3.26 years old) and 23 EOP patients (16.58±2.60 years old) were recruited as part of a larger, ongoing study (UCLA Adolescent Brain–Behavior Research Clinic; ABBRC). Demographic variables (age, IQ, participant and parental education

level) did not differ between the groups, nor did gender, handedness, and race/ethnicity distributions (see Table 1 for demographic and diagnostic information). EOP patients with past substance abuse diagnoses were permitted to participate if they were free of substance abuse for the preceding six months; patients with substance dependence diagnoses were excluded. Inclusion criteria for EOP patients included the following diagnoses: schizophrenia, psychotic disorder not otherwise specified (NOS), schizophreniform disorder, and schizoaffective disorder. All control participants were free of Axis I disorders and of schizophrenia-spectrum disorders among first-degree relatives. This study was carried out in accordance with the recommendations of UCLA's Institutional Review Board with written informed consent from all subjects, and from their parents for participants under the age of 18. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the UCLA's Institutional Review Board.

Behavioral Assessments

All diagnostic and neuropsychological assessment measures used have been previously described (Bachman et al., 2012). Diagnoses for all participants were determined using the Structured Clinical Interview for DSM-IV Axis I diagnoses (SCID; First, Spitzer, Gibbon, & Williams, 1998) and by review of medical records; final diagnoses required consensus among supervising clinical psychologists. Current level of symptomatology (within the current month of the clinical assessment) was determined via the Structured Interview for Prodromal Syndromes (SIPS; Thomas H. McGlashan, Miller, Woods, Hoffman, & Davidson, 2001). Participants were also administered a neurocognitive battery, including measures of intelligence (Wechsler Abbreviated Scale of Intelligence – Full-scale IQ, T-score) and working memory (Wechsler

Memory Scales-3 – Spatial Span, total scaled score; Wechsler Adult Intelligence Scale-III – Digit Span, total scaled score). Control subjects were screened for Axis I disorders with the SCID and for history of schizophrenia-spectrum disorders among first-degree relatives using the Family Interview for Genetic Studies (FIGS; Maxwell, 1992). All assessments were administered by clinicians trained to a standard reliability criterion (Ventura, Liberman, Green, Shaner, & Mintz, 1998). Medication information was obtained via participant and parent/guardian report and medical record review.

fMRI Acquisition and SCAP Task

Following behavioral assessments, participants were scanned on a 3.0 Tesla (3T) Siemens Allegra scanner. The fMRI sequence consisted of 180 echoplanar images for a total scan time of nine minutes (TR/TE 3000/45ms, 90° flip angle, 33 3mm slices). While in the scanner, participants were administered a spatial WM task assessing spatial capacity (SCAP), which has been shown to be sensitive to spatial WM deficits in individuals with SZ (Cannon, Glahn, Kim, & et al, 2005; Glahn et al., 2003).The SCAP task involved showing participants a target array of 1, 3, 5, or 7 yellow circles per trial (2-second presentation) after a 1-second fixation period. Following a fixed delay of three seconds, subjects were shown a probe of a single green circle for three seconds. They were then asked whether the probe dot's location corresponded to a location of one of the yellow target dots in the most recently presented set. There were 12 trials of each load (48 trials in total) presented in two acquisition sessions. Each load was presented in pseudorandom order in sets of two trials (3 per session), and data were analyzed in those blocks (correct trials only). To better isolate effects due to WM activity only, the fixation period was excluded from analysis. Participants with more than 3mm of average

translational motion were also excluded from subsequent analyses (n=6 patients, 4 controls) for a final sample of 17 patients and 17 controls. Timepoints corresponding to motion outliers were added to the model as nuisance regressors using framewise displacement as determined by FSL motion outliers (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLMotionOutliers). Analyses of overall neural activation utilized a whole-brain approach.

Statistical Analysis

Analysis I: Behavioral Performance. Behavioral data from the SCAP task were analyzed in SPSS (v20) using repeated measures ANOVA with group (EOP patients or controls) as the between subjects factor, load as the within subjects factor, and percent correct at each load as the dependent variable (as described in Karlsgodt et al., 2009; Shilyansky et al., 2010). Additionally, we covaried for age. Between-group differences in reaction time were also examined.

Analysis II: WM Capacity-associated Neural Activity and Age-associated Effects. In order to examine group differences in neural activity during SCAP task performance, each subject's WM capacity was first calculated at each load. The formula $k=n*(H+CR-1)$ was used, where k=capacity, n=load #, H=hit rate, and CR=correct rejection rate (Cowan, 2001). Final capacity was identified by the highest value calculated; the load corresponding to each subject's highest capacity was entered into group analyses. Overall group differences in WM capacity (via selected load) were compared using SPSS (v20). Group analyses related to neural activity were then performed using FSL FEAT (Local Analysis of Mixed Effects; FLAME), which has been shown to be less vulnerable than other methodologies to inflation of familywise Type-1 error rates (Eklund, Nichols, & Knutsson, 2016), with age, gender, and handedness as covariates.

Overall behavioral performance (% correct) was also included as a covariate to control for differences in ability related to clinical status and to ensure group differences in magnitude of activation were not due to non-specific effects (e.g., effort or strategy) (Meda, Stevens, Folley, Calhoun, & Pearlson, 2009; Satterthwaite et al., 2013; Wadehra, Pruitt, Murphy, & Diwadkar, 2013; White, Hongwanishkul, et al., 2011). Main effects of group and age were modeled, as well as a group-by-age interaction, in order to investigate differential effects of age between groups. Threshold for cluster statistical significance was set at $Z>2.3$, $p<0.05$, with multiple comparison correction implemented in FSL FEAT (Forman et al., 1995; Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994; Jenkinson & Smith, 2001).

Analysis III: Psychophysiological Interaction (PPI) Analysis and Age-associated Effects on Functional Connectivity. To test whether patients show a de-coupling of regions that typically are functionally connected during WM demands (e.g., dlPFC with parietal regions), a psychophysiological interaction (PPI) analysis (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012) was conducted. Structural regions of interest (ROIs) including the dlPFC and parietal cortex in each hemisphere were identified using a probabilistic cluster atlas (Harvard-Oxford, 2mm). Next, functional ROIs were defined in the study-specific average brain space. Activation clusters were identified using the FSL cluster option from the all-participants, all-loads omnibus contrast. Those that overlapped with the above anatomical ROIs were masked. Final masks were created from the voxels common to both the functional and anatomical ROIs, resulting in four final regions of interest in the right and left dlPFC and parietal lobes (Figure 1). Mean activation for each ROI was then extracted following registration to each participant's preprocessed data.

First-level PPI analyses modeled the interaction between mean activation within each ROI and load condition, with loads determined by each subject's WM capacity as previously defined; other load conditions were controlled for. Group analyses were then modeled identically as described above, including main effects and group-by-age interaction.

Analysis IV: Association between Neural Activity and Task Performance/Neurocognitive Measures. Partial correlations were calculated examining the relationship between neural activity within WM task-related regions (% signal change (%SC) within each bilateral dlPFC and parietal ROI) and task performance (% correct), controlling for the effects of age and gender. Similar partial correlations were performed for neural activity and each of 3 neurocognitive measures completed outside of the scanner (IQ, digit span, spatial span). IQ was particularly examined given previous findings that spatial WM capacity is associated with IQ among adults with SZ (Johnson et al., 2013). Due to the inherent group differences in task performance and neurocognition, correlations were run separately for EOP patients and controls, with a total of 16 comparisons per group. Given the exploratory nature of these analyses, comparisons for multiple corrections were not performed. In order to determine %SC, the Featquery (fmrib.ox.ac.uk/fsl/feat5/featquery.html) program applied the inverse of the initial transformation matrix from individual to the average brain to transform the ROIs back into each participant's individual space. The motion corrected, smoothed, and filtered data across each entire ROI were probed for %SC (i.e., individual loads as compared to resting baseline) for use in correlation analyses.

Results

Analysis I: Behavioral Performance. Age was significantly correlated with task performance (percent correct; r=0.336, $p<0.001$), and was thus included as a covariate in subsequent behavioral analyses. Because gender and task performance were not significantly correlated (r=-0.140, $p=0.429$), gender was not included in final models. A repeated measures ANOVA showed a significant age-by-load interaction ($F(3,96)=7.07$, $p<0.001$) along with a significant group-by-load interaction ($F(3,96)=2.72$, $p<0.05$). Decomposed effects revealed that age was significantly positively correlated with increased task performance at load 3 only ($r=0.581$, $p<.001$), and while controls performed nominally better than EOP patients at each load, group differences in performance were significant at the highest load (Load 7) only ($t(32)=-3.051$, $p<0.01$; Figure 2). Reaction time did not significantly differ between groups ($t(32)=-0.08$, $p=0.94$).

Analysis IIa: WM Capacity-associated Neural Activity. EOP patients evidenced lower overall WM capacity as compared to controls ($t(26)=2.508$, $p<0.05$). Whole-brain analyses based on individual subject capacity revealed a significant main effect of group, with greater bilateral precentral and right postcentral gyrus and precuneus activity in healthy controls relative to patients (Figure 3). EOP patients did not exhibit greater neural activity in any regions relative to controls.

Analysis IIb: Age-associated Effects on Neural Activity during Spatial Working Memory. fMRI contrasts based on individual capacity also revealed a significant group-by-age interaction, with differentially greater activation in the bilateral middle frontal, right superior frontal gyrus,

left inferior frontal gyrus, left insula, left lingual gyrus, left precentral gyrus, and left occipital pole as a function of increasing age in EOP patients relative to controls (Figure 4A); controls exhibited concomitant decreased activation in these areas (Figure 4B). Additionally, significant main effects of age indicated that, overall, older subjects exhibited greater activity in the left superior parietal lobule, precuneus, postcentral gyrus, and lateral occipital cortex.

Analysis IIIa: PPI Analysis. PPI analyses based on individual capacity revealed that, relative to youth with EOP, controls exhibited greater connectivity between the left dlPFC and left frontal pole. No significant group differences were observed for any other ROI, and EOP patients did not evidence greater co-activation between any regions as compared to healthy controls.

Analysis IIIb: Age-associated Effects on Connectivity. PPI contrasts revealed a significant group-by-age interaction for the left dlPFC ROI (Figure 5). Increased WM-associated coupling between the left dlPFC and right cerebellum, right lateral occipital cortex and right occipital fusiform gyrus was observed among older as compared to younger EOP patients; this pattern was not observed among healthy controls. All other age main effect and interaction contrasts were not significant.

Analysis IVa: Association of Neural Activity with Task Performance. Partial correlations controlling for the effects of age and gender revealed a significant relationship between right dlPFC activity and overall % correct among EOP patients ($r=0.628$, $p<0.05$; see Figure 6A) but not among healthy controls ($r=0.146$, $p=0.605$). Correlations between task accuracy and %SC in all other ROIs were nonsignificant across both participant groups.

Analysis IVb: Association of Neural Activity with Neurocognitive Measures. Controlling for the effects of age and gender, controls demonstrated a significant association between %SC in the left dlPFC and IQ (r=0.534, $p<0.05$; see Figure 6B), which was not observed in EOP patients (r=-0.258, $p=0.373$). Partial correlations also revealed a significant relationship between %SC in the left parietal cortex and IQ in controls (r=0.648, $p<0.05$; see Figure 6C), but not in EOP patients (r=-0.356, $p=0.212$). All other correlations between neuropsychological measures and %SC were not significant.

Conclusion

This study investigated the nature and magnitude of spatial WM-related neural circuitry disruption as well as age-associated changes in WM circuitry in EOP patients as compared to healthy adolescents. It further examined whether alterations in neural activity were related to neurocognitive functioning. To our knowledge, this is the first study to investigate both individual differences in WM capacity in early-onset psychosis and their relationship to development. The study yielded several main findings: 1) EOP patients, relative to healthy controls, exhibited lower neural activity within bilateral precentral and right postcentral/precuneus areas during spatial WM performance when controlling for individual capacity, which is consistent with previous findings that did not incorporate capacity estimations (White, Hongwanishkul, et al., 2011); 2) Similarly, relative to typically developing controls, EOP patients showed reduced coupling between the left dlPFC and frontal pole during WM task engagement relative to controls, which is distinct from a prior study suggesting reduced connectivity between the dlPFC and ACC, inferior parietal lobule, and middle occipital gyrus

among EOP patients (Kyriakopoulos et al., 2012); 3) Differential effects of age on neural activity and functional connectivity, respectively, suggest preliminary (cross-sectional) evidence for altered developmental trajectories in working memory circuitry in EOP; and 4) EOP patients evidenced distinct relationships between neural activity and both SCAP task performance and global cognition as compared to controls, in that only patients showed an association between task accuracy and % signal change in the right dlPFC, whereas only controls demonstrated a significant association between IQ and % signal change in the left dlPFC and left parietal cortex.

Consistent with our hypotheses and with previous literature that both did (e.g., Bittner et al., 2014) and did not take individual capacity into account (White, Hongwanishkul, et al., 2011), EOP patients in the current study evidenced lower whole-brain activation in specific frontal and parietal regions relative to healthy adolescents during a WM task. However, we identified fewer regions of significant group differences in neural activity as compared to other reports that did not factor in individual capacity differences (Kyriakopoulos et al., 2012). We did not find evidence of hyperactivation in prefrontal and temporal regions in EOP patients relative to controls, which has been reported in some prior studies of youth with EOP that did not include capacity and utilized either an n-back (Sugranyes et al., 2012; Thormodsen et al., 2011) or Sternberg paradigm (White, Hongwanishkul, et al., 2011). Some of these distinctions may be accounted for by paradigm differences, particularly those that primarily utilized verbal WM tasks versus our spatial WM design (e.g., Kyriakopoulos et al., 2012; Sugranyes et al., 2012). As previously suggested, recent work points to a generalized inefficiency of WM circuitry that varies by WM load (Potkin et al., 2009). Thus, discrepancies in prior neural findings may be

reflective of how well the capacity of each participant mapped on to the various task demands, which has not been well considered to date.

Controlling for individual capacity may have also led to distinct patterns of functional connectivity, indicating greater co-activation between the left dlPFC and left frontal pole among controls, relative to EOP patients. This suggests that at their own maximum WM level, controls are better able to sustain the prefrontal network to process visual information as compared to patients. This is consistent with previous PPI work among healthy adults showing that increased connectivity between bilateral frontoparietal areas, as a function of increasing WM load, predicted better n-back task performance (Cassidy et al., 2016). Although the PPI approach has not been widely applied to the SZ WM literature, previous findings in an EOP sample similarly noted reductions in dlPFC coupling, albeit with other brain regions (anterior cingulate cortex, occipital gyrus, and inferior parietal lobule) (Kyriakopoulos et al., 2012). However, in addition to not accounting for capacity, Kyriakopoulos et al. (2012) utilized a letter-based 2-back task that did not parametrically vary WM demand, perhaps also accounting for the lack of performance deficit in the SZ group that we and others have found.

This study additionally found a positive association between age and frontal and occipital activation at WM capacity in individuals with EOP. In contrast, among healthy controls, WM-related brain activity in some of these regions (e.g., right superior frontal gyrus) has instead been shown to negatively correlate with age (Andre et al., 2016). Previous work has identified a progression of increasing network specialization from childhood to adulthood, in that children are more likely to recruit regions such as the lateral cerebellum and thalamus, while adolescents rely on premotor and inferior parietal regions, and adults primarily recruit the dlPFC and

ventromedial PFC (Geier, Garver, Terwilliger, & Luna, 2009; Klingberg et al., 2002; Scherf, Sweeney, & Luna, 2006). Cerebellar recruitment during visuospatial working memory tasks has been uniquely found among children, and has been associated with unskilled performance related to error detection and corrections (Scherf et al., 2006). Here, EOP patients also demonstrated increased coupling between prefrontal and occipital/cerebellar regions with increasing age, suggesting more pronounced network inefficiency over time. Thus, EOP patients evidence atypical development of WM-related regions, consistent with our hypotheses. Results are also in line with previous findings suggesting differential recruitment of cerebellar regions among patients with schizophrenia as compared to healthy controls during working memory tasks (Meyer-Lindenberg et al., 2001).

These functional findings are corroborated by behavioral and WM capacity group differences. Patients performed with decreased task accuracy as compared to controls, significantly so at the highest working memory demand, which is in agreement with our hypotheses and previous literature (Bittner et al., 2014; Lee & Park, 2005; Piskulic et al., 2007; White, Hongwanishkul, et al., 2011). Correspondingly, patients evidenced reduced overall WM capacity compared to controls, thus leading to expectations that their performance would degrade accordingly above that lowered threshold. Task accuracy also correlated with neural activity in the right dlPFC among patients only, suggesting atypical recruitment of frontal regions while attempting to sustain performance. Of note, dlPFC activity has been shown to increase parametrically with WM demand until load exceeds the individual's capacity, though WM capacity for those with schizophrenia is reduced relative to controls (Manoach, 2003). Given our study's selection of each individual's optimal load/capacity, it is possible that findings reflect

patient's experience of a more challenging task relative to controls, thus requiring increased dlPFC recruitment to sustain better task accuracy.

Higher neural activity in both the left dlPFC and left parietal regions was associated with higher overall intelligence among healthy controls only. This suggests that neural activity during higher-order cognitive tasks is less predictive of global cognition in EOP patients relative to healthy controls. While prior research among adults with SZ has demonstrated positive correlations between cognitive functioning and WM/capacity (Gold et al., 2010; Johnson et al., 2013; Piskulic et al., 2007), the relationship may be attenuated as compared to healthy individuals (Gold et al., 2010). Prior work has suggested that the neural mechanisms leading to reduced WM capacity in SZ are not identical to those producing variations among healthy controls (Gold et al., 2006; Leonard et al., 2012; Vogel & Machizawa, 2004); for EOP patients who are undergoing atypical neural development of WM-related networks, these correlations may be even more diminished when compared to typical adolescents.

It is important to note that the regression analyses examining relationships between neural activity, task performance, and neurocognitive measures were exploratory and would not survive corrections for multiple comparisons. This is likely due in large part to the limitations of our sample size and the heterogeneity of the patient sample, including the wide age range of participants. Future, larger-scale studies may benefit from conducting analyses with subjects stratified by age clusters. Moreover, we were unable to investigate effects of age of illness onset on neural and behavioral WM measures; however, earlier onset may yield more significant impairment across multiple cognitive domains as compared to adult-onset patients (Basso, Nasrallah, Olson, & Bornstein, 1997; Collinson et al., 2003; Frangou, 2010; Rajji, Ismail, &

Mulsant, 2009). Furthermore, given the extensive history of psychotropic medication use in several patients, studies with medication-naïve EOP individuals would be necessary to confirm that observed differences were independent of medication effects.

Through emphasizing early indicators of neural dysfunction, this work has the potential to better elucidate endophenotypes of schizophrenia (Glahn et al., 2003; Wood et al., 2003). The abnormal developmental trajectories of WM-associated neural activity that we observed in youth with EOP also suggest a window of opportunity for early intervention. Visual WM capacity in both healthy adults and adult patients with schizophrenia is strongly correlated with overall cognitive abilities (Johnson et al., 2013; Kyllonen & Christal, 1990; Luck & Vogel, 2013). Replication of this work in EOP samples is critical to determine if reduced capacity can lead to decreased intellectual functioning over time (Luck & Vogel, 2013). Studies have demonstrated that early detection and treatment of schizophrenia is associated with improved long-term outcomes (Larsen et al., 2011). These findings suggest reduced WM capacity may be a key area for potential cognitive remediation studies. Finally, this work further highlights the need for longitudinal studies, which are essential to determine when in the course of development abnormal patterns of WM-associated neural activity emerge.

Table 1

Demographic Information Characterizing Study Sample[1]

	Controls (*N*=17)	EOP Patients (*N*=17)	*p* value
Mean age, years (± SD)	18.07(3.26)	16.58(2.60)	0.15
Number female (%)	8(47.1)	6(35.3)	0.49
Number left-hand dominant (%)	0(0)	1(5.9)	0.31
Mean participant education, years (± SD)	11.53(2.62)	10.41(2.29)	0.20
Mean parental education, years (± SD)	15.97(2.67)	14.59(2.45)	0.64
Race/Ethnicity (%)			0.61
Caucasian, Non-Hispanic	10(58.82)	9(52.94)	
Caucasian, Hispanic	2(11.76)	5(29.41)	
African-American	2(11.76)	1(5.88)	
Asian-American/Pacific Islander	2(11.76)	2(11.76)	
Other	1(5.88)	0(0)	
Diagnoses (%)			
Schizophrenia	0(0)	6(35.29)	
Psychotic Disorder NOS	0(0)	5(29.41)	
Schizophreniform disorder	0(0)	3(17.65)	
Schizoaffective disorder	0(0)	3(17.65)	

Medication (%)[2]			
Atypical antipsychotic	0(0)	10(58.82)	
Typical antipsychotic	0(0)	1(5.88)	
SSRI	0(0)	6*(35.29)	
Mood stabilizer	0(0)	2§(11.76)	
Antidepressant	0(0)	3§(17.65)	
Anxiolytic	0(0)	3§(17.65)	
Sedative	0(0)	1§(5.88)	
Anticonvulsant	0(0)	2(11.76)	
Mean SIPS: total Positive Symptoms score (±SD)[3]	1.38(1.96)	16.40(7.20)	<0.001
Mean neurocognitive score (±SD)[4]			
WASI IQ	111.56(11.34)	103.00(14.92)	0.08
WMS Spatial Span	11.63(3.46)	9.50(3.25)	0.08
WAIS-III Digit Span	11.88(2.63)	9.50(3.46)	0.04
Mean load corresponding to highest capacity	3.76(0.44)	3.24(0.75)	0.02

[1]Mean values for each continuous variable were tested for group differences at the univariate level. Gender, handedness, and race/ethnicity distributions were tested with *Chi*-squared analyses; no significant group differences were detected for any comparisons except on clinical and neurocognitive measures (all $p>0.05$).

[2]Patients reported a mean of 94.15 (*SE* = 27.85) days on antipsychotic medication and a mean of 130.48 (*SE* = 41.04) days on other psychoactive medications at the time of assessment. Mean days on medication was missing for one patient. Medication history was missing for one EOP participant and one control participant

[3]SIPS=Structured Interview for Prodromal Syndromes. Higher scores denote better levels of functioning. SIPS data was missing for one control participant and seven EOP participants.

[4]WASI=Wechsler Abbreviated Scale of Intelligence; WMS=Wechsler Memory Scales-3; WAIS-III=Wechsler Adult Intelligence Scale-III. Neurocognitive data was missing for one control and one EOP patient.

*Taken concurrently with antipsychotic medication for all but one patient

§Taken concurrently with antipsychotic medication

Figure 1. *Anatomical-Functional Regions of Interest (Bilateral dlPFC and Parietal Cortex).*

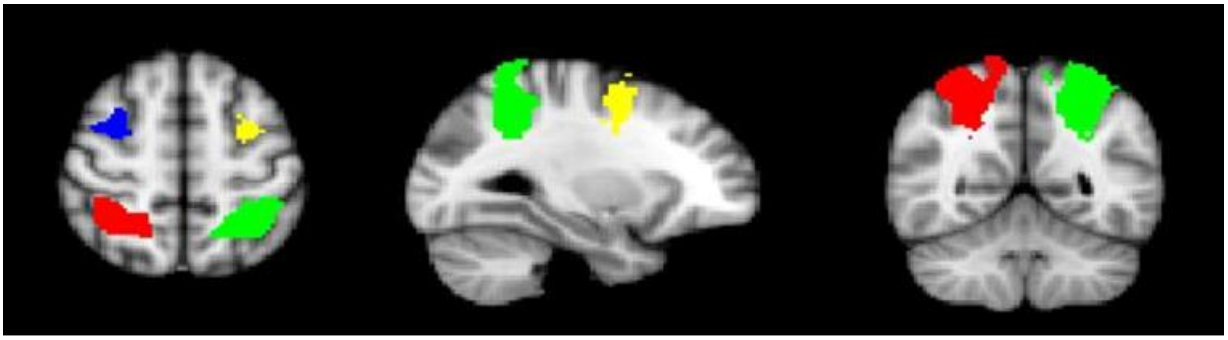


Figure 2. *Group Differences in WM-Task Accuracy.*

As depicted, when adjusting for age, group differences in performance were significant at load 7 only ($t(32)=-3.051$, $p<0.01$), although controls performed nominally better than EOP patients at each WM load.

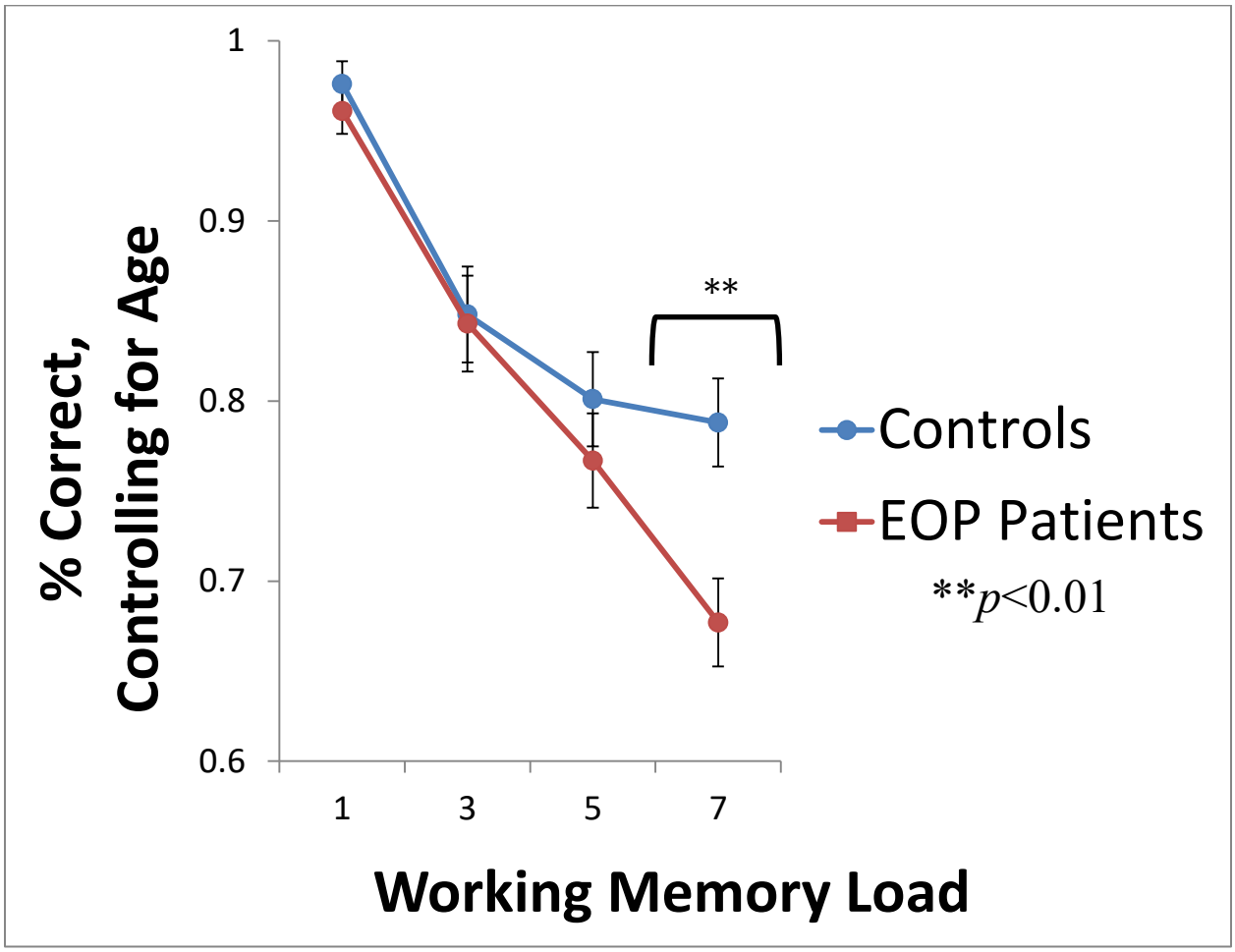


Figure 3. *Main Effect of Group in Whole-Brain WM Capacity Analysis.*

Healthy controls displayed greater bilateral precentral and right postcentral/precuneus activity relative to EOP patients.

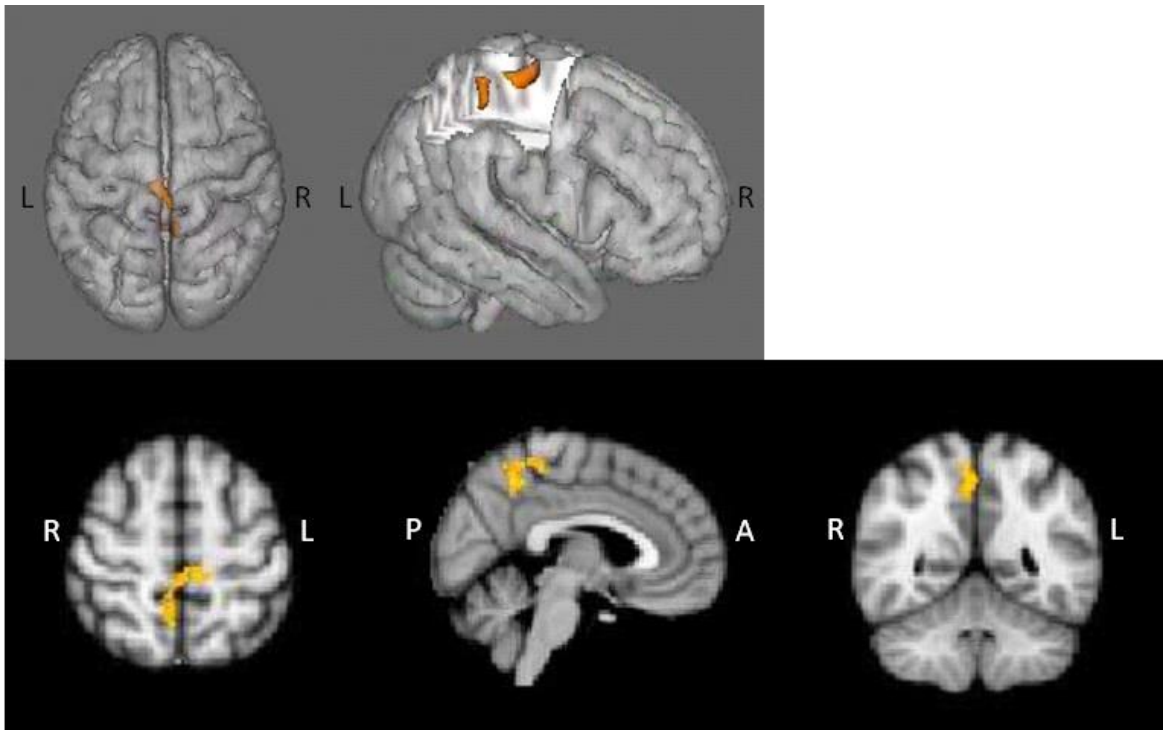
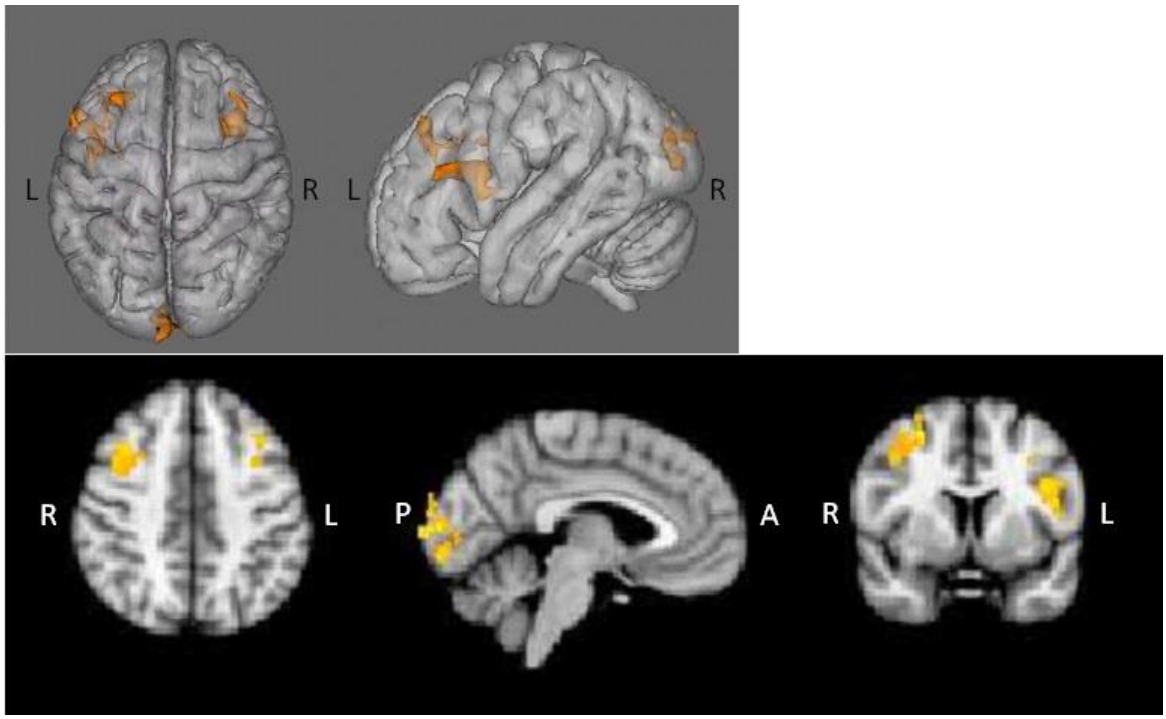


Figure 4. *SCAP Group-by-Age Interaction.*

Top panels (A) depict group differences in neural activity as a function of age, based on individual capacity. As shown, increasing age in the EOP patients was associated with greater activity in bilateral middle frontal gyrus, right superior frontal gyrus, left inferior frontal gyrus, left insula, left lingual gyrus, left precentral gyrus, and left occipital pole activation during task performance, which was not observed in healthy controls. The bottom panel (B) depicts the direction of effect based on percent signal change from the most significant cluster. While increased age was associated with increased task-based neural activity among EOP patients, the opposite effect was observed among controls.

(A)



(B)

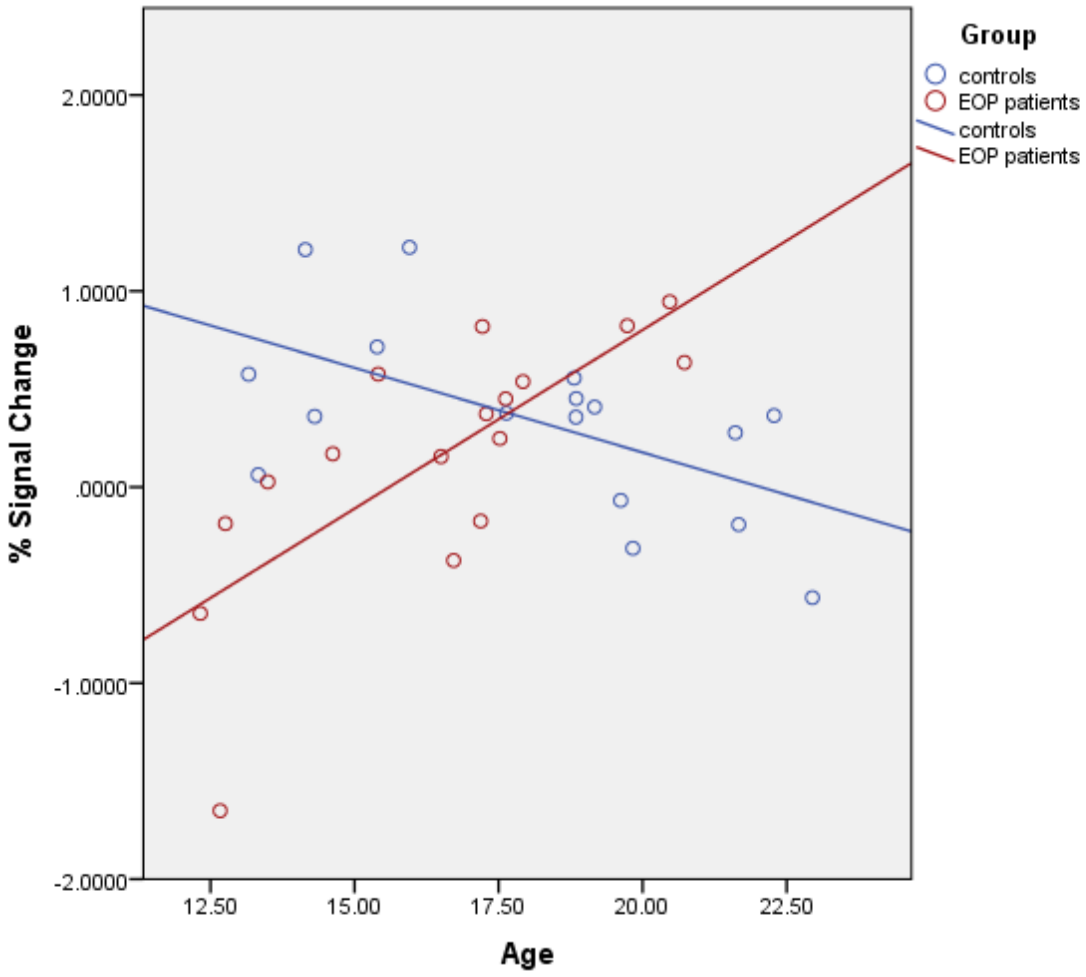
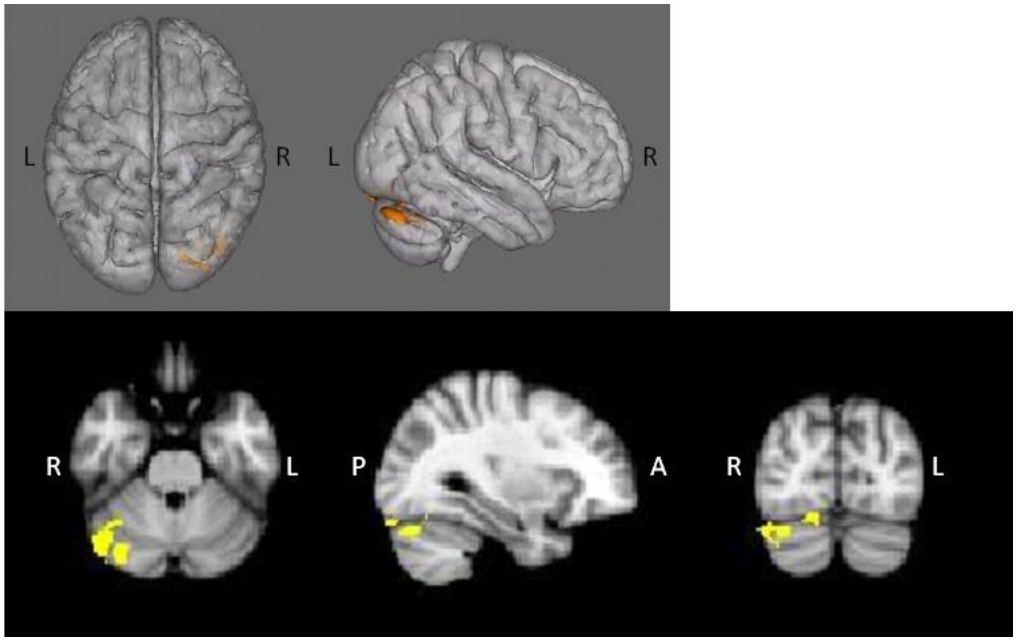

Group
controls
EOP patients
controls
EOP patients
% Signal Change
2.0000
1.0000
.0000
-1.0000
-2.0000
12.50
15.00
17.50
20.00
22.50
Age

Figure 5. *PPI Group-by-Age Interaction for the Left dlPFC.*

Top panels (A) depict that as compared to healthy controls, increased age among EOP patients was associated with increased coupling between the left dlPFC and the right cerebellum, right lateral occipital cortex and right occipital fusiform gyrus. The bottom panel (B) depicts the direction of effect based on percent signal change from the single significant contrast cluster. While task-based neural activity did not vary with age among controls, increased age among EOP patients was associated with an increase in activity.

(A)



(B)

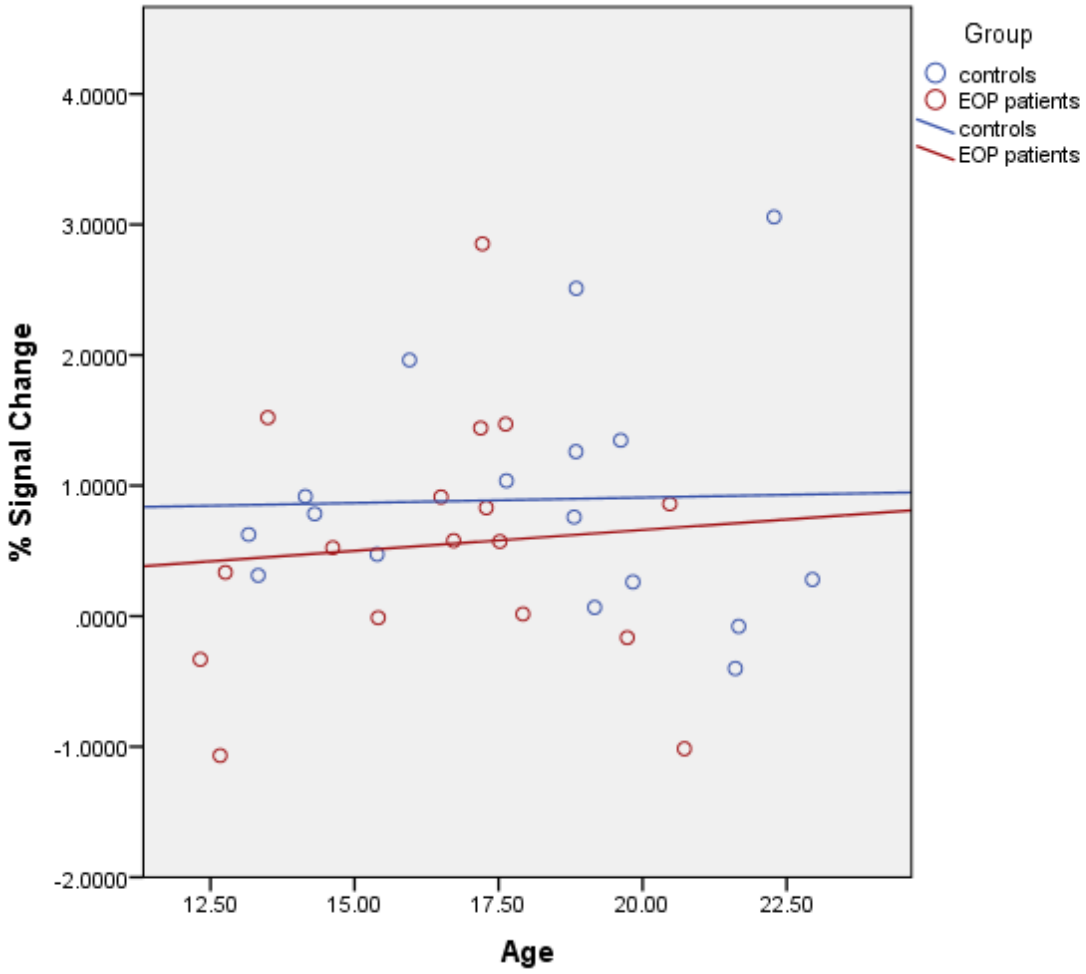
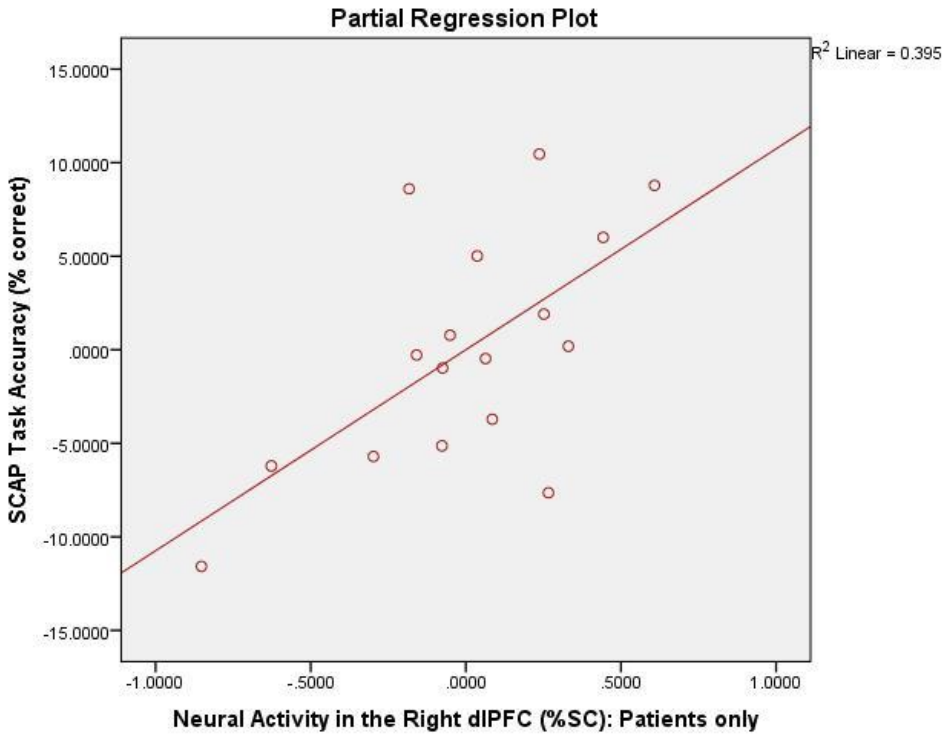

Group
controls
EOP patients
controls
EOP patients
% Signal Change
4.0000
3.0000
2.0000
1.0000
.0000
-1.0000
-2.0000
12.50
15.00
17.50
20.00
22.50
Age

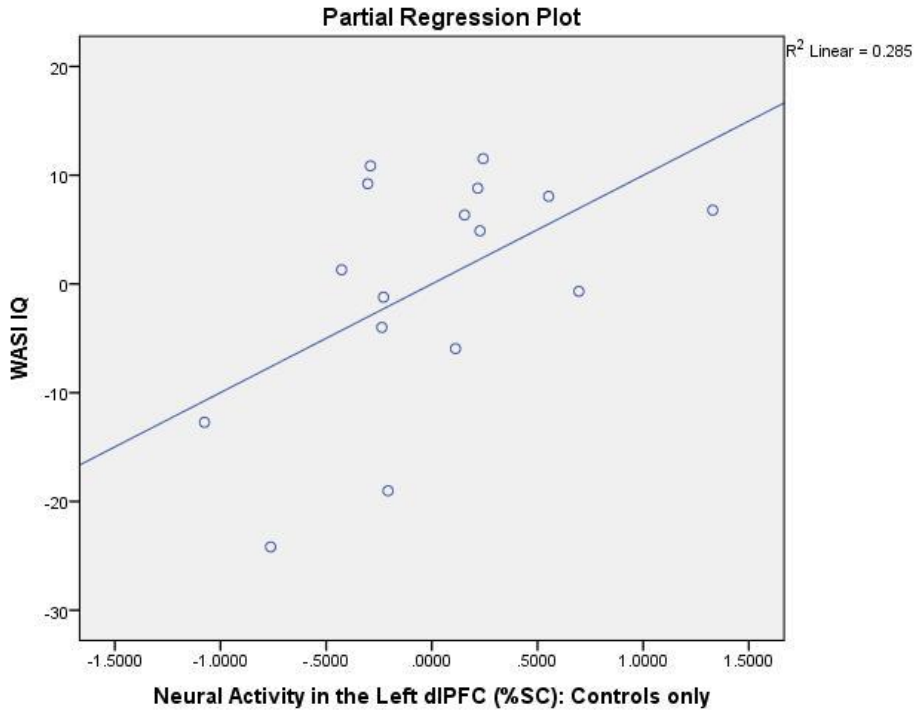
Figure 6. *Correlation Plots between Neural Activity and Task Performance/Neurocognitive Measures.*

Graphs depict (A) significant association between %SC in the right dlPFC and SCAP task accuracy among patients only (r=0.628, $p<0.05$); (B) significant association between %SC in the left dlPFC and IQ in control group only (r=0.534, $p<0.05$); and (C) significant association between %SC in the left parietal cortex and IQ among controls only (r=0.648, $p<0.05$).

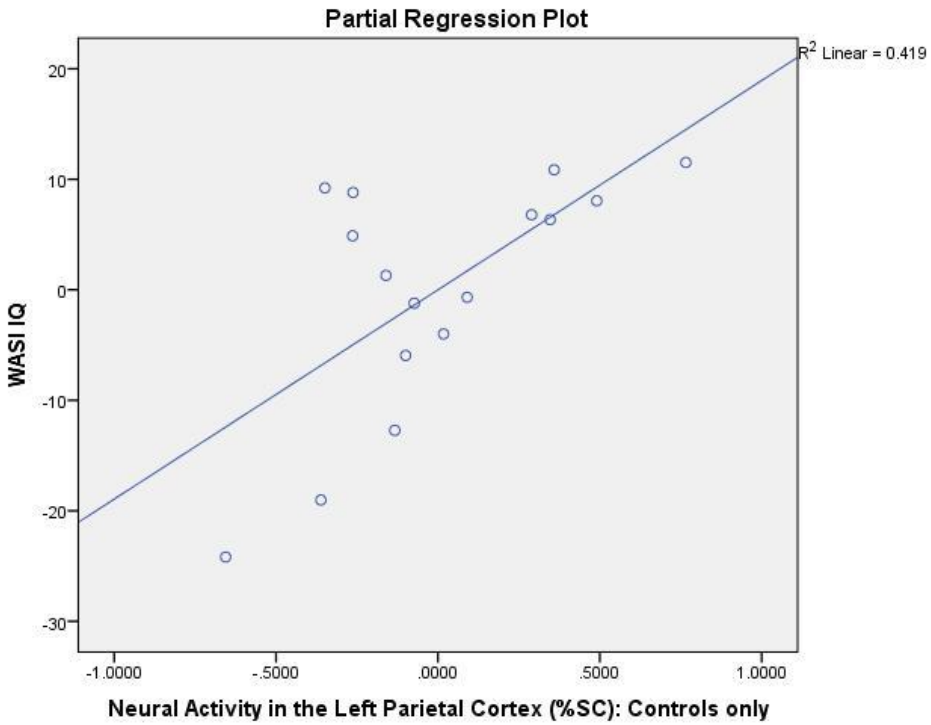
(A)



(B)


Partial Regression Plot
R^2 Linear = 0.285
WASI IQ
20
10
0
-10
-20
-30
-1.5000
-1.0000
-.5000
.0000
.5000
1.0000
1.5000
Neural Activity in the Left dlPFC (%SC): Controls only

(C)


Partial Regression Plot
R2 Linear = 0.419
WASI IQ
20
10
0
-10
-20
-30
-1.0000
-.5000
.0000
.5000
1.0000
Neural Activity in the Left Parietal Cortex (%SC): Controls only

STUDY 2: NEUROCOGNITIVE AND SOCIAL COGNITIVE PROFILES OF EARLY-ONSET PSYCHOSIS AND 22Q11.2 DELETION SYNDROME: RELATIONSHIP TO FUNCTIONAL OUTCOME

Abstract

Genetic models of psychotic symptoms and related impairments may provide insight into the pathophysiology of SZ, provided that intermediate phenotypes can first be established. 22q11.2 Deletion Syndrome (22q11DS) provides a particularly compelling example, as a genetic disorder that is one the greatest known risk factors for psychosis. It is thought to be a useful model for forms of SZ thought to have greater genetic loading, such as early-onset psychosis (EOP), which is defined by overt psychosis emergence prior to age 18. While 22q11DS and EOP are both associated with cognitive impairment, only one study to date has investigated whether 22q11DS and EOP have phenotypic overlap at the cognitive level. We compared clinical symptomatology, functioning, and cognitive profiles of 22q11DS patients and EOP patients relative to healthy controls at initial assessment, and examined whether cognitive performance at initial assessment predicted social and role functioning at follow-up.

A significant main effect of group (all $p<0.001$), when controlling for the effects of age and gender, was found for each clinical, neurocognitive, and social cognitive measure at initial assessment, with effects mostly in the large range. Specifically, EOP patients evidenced greater deficits than 22q11DS patients and healthy controls on all clinical measures; however, both patient groups showed comparable impairment in the areas of social and role functioning. In the neurocognitive and social cognitive domains, healthy controls performed significantly better than both patient groups ($p<0.01$ or smaller, for post-hoc pairwise comparisons) on the majority of cognitive measures. Patients with EOP performed significantly better than 22q11DS patients on the majority of cognitive measures; however, clinical groups did not differ from each other on measures of verbal fluency and processing speed. Among EOP patients, greater positive psychotic symptom severity was associated with reduced performance on measures of processing

speed, vocabulary, IQ, and theory of mind; 22q11DS patients evidenced an association between positive symptom severity and reduced performance on measures of vocabulary, IQ, verbal fluency, working memory, emotion recognition, and emotion discrimination. Comparison between measures that were significantly correlated with positive symptoms in both patient groups (i.e., vocabulary, IQ) found no significant difference in correlations between groups, suggesting similar patterns of cognition-symptom relationships across groups. Lastly, better initial neurocognitive performance was associated with better role functioning at follow-up, although neurocognitive and/or social cognitive task performance at initial assessment was not predictive of global or social functioning at follow-up. Nevertheless, this study offers a unique first look into a broad comparison of deficits in EOP and 22q11DS samples relative to healthy controls, and the utility of initial cognitive deficits in predicting future outcome in these clinical populations.

Keywords: schizophrenia, adolescence, 22q11DS, neurocognition, functioning

Introduction

Despite an abundance of research, the etiology of schizophrenia (SZ) remains poorly understood. This is perhaps not surprising, as the disorder is thought to reflect a constellation of symptoms potentially arising from multiple aberrant neurodevelopmental pathways (Hollis & Rapoport, 2011). While the disorder is substantially heritable (Flint & Munafò, 2014; Gejman, Sanders, & Duan, 2010; Gottesman & Shields, 1972; Sullivan, Kendler, & Neale, 2003; Weissman, Merikangas, Pauls, Leckman, & Gammon, 1983), until recently we had a very poor understanding of its genetic architecture. Notably, major recent advances in psychiatric genetics have revealed that both common and rare genetic variants appear to play a role in disease etiology. In particular, while over 100 common risk loci have now been identified via genome-wide association studies (GWAS) (Ripke et al., 2013; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), SZ patients also exhibit significantly higher rates of rare structural genomic variation (copy number variants; CNVs) as compared to the general population (Sebat, Levy, & McCarthy, 2009; Stefansson et al., 2008, 2009; Walsh et al., 2008). Therefore, genetic models of psychotic symptoms and related impairments may provide additional insight into the pathophysiology of SZ, as such models that take advantage of a known, homogeneous genetic etiology, and allow for investigation into neurodevelopmental processes that take place prior to overt symptom onset. In particular, deletions at chromosome 22q11.2 confer the strongest known association of any CNV (CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium, 2017), suggesting that investigation of this genetic cause may offer a particularly useful, high penetrance model of the illness.

However, in order to determine the utility of genetic high-risk models, convergence between genetic conditions and clinically-defined SZ first needs to be established at the level of

an intermediate phenotype. For example, neurocognitive deficits are a fundamental aspect of SZ (Frazier et al., 2012; Keefe et al., 2012), but it is not yet clear whether the cognitive profile of SZ resembles that of identified genetic high-risk groups. Determining convergence across neurocognitive deficit profiles can help to elucidate potential early biomarkers of psychosis risk, in the context of a highly penetrant disease model.

22q11.2 Deletion Syndrome (22q11DS; also known as Velocardiofacial or DiGeorge Syndrome; 22q11DS), results from a hemizygous deletion at chromosome 22q11.2, which includes about 46 known protein-coding genes, many of which are involved in brain development (Maynard et al., 2003; McDonald-McGinn et al., 2015; McDonald-McGinn & Sullivan, 2011). 22q11DS is associated with variable phenotypic expression, including congenital heart defects, facial dysmorphology, cognitive impairment, and developmental delays (Bassett & Chow, 2008; Drew et al., 2011; Jonas, Montojo, & Bearden, 2014; Schneider et al., 2014; Schreiner, Lazaro, Jalbrzikowski, & Bearden, 2013). In the cognitive domain, individuals with 22q11DS evidence discrepancies between general cognitive abilities (well below average range) and academic achievement (low average to average ranges, with particular difficulties in mathematics), as well as stronger verbal IQ than performance IQ abilities (e.g., poor visuospatial, motor, and numerical skills). Deficits in auditory attention, executive functioning, spatial reasoning, and memory have been additionally noted in both youths and adults with 22q11DS (Antshel, Fremont, & Kates, 2008; Baker & Vorstman, 2012; Ousley, Rockers, Dell, Coleman, & Cubells, 2009). Additionally, individuals with 22q11DS show impaired social cognitive skills such as social-emotional face processing (Amelsvoort et al., 2006; Baker & Vorstman, 2012; Campbell et al., 2011), social competence (Campbell et al., 2011; Ousley et al., 2009), and social comprehension (Antshel et al., 2008; Ho et al., 2012; Jalbrzikowski et al., 2012).

22q11DS also confers dramatically increased risk for psychosis (Bassett & Chow, 2008; Drew et al., 2011; Jonas et al., 2014); up to 30% of 22q11DS patients develop SZ-spectrum disorders in adolescence/young adulthood (Murphy, 2002; Schneider et al., 2014), and rates of subthreshold psychotic-like symptoms (e.g., positive symptoms, poor social functioning) are significantly elevated relative to healthy controls (Antshel et al., 2010; Jalbrzikowski et al., 2012; Murphy, 2002; Shapiro, Cubells, Ousley, Rockers, & Walker, 2011; Stoddard, Niendam, Hendren, Carter, & Simon, 2010; Tang et al., 2014; Weisman et al., 2017). Conversely, this deletion is thought to account for approximately 1% of schizophrenia cases in the general population (Philip & Bassett, 2011). As such, 22q11DS may be a particularly useful model for forms of SZ thought to have greater genetic loading, such as early-onset psychosis (EOP), which is defined by overt psychosis emergence prior to age 18 (Vyas & Gogtay, 2012); EOP has been associated with increased rates of familial SZ-spectrum disorders as compared to the adult-onset form of illness (Frangou, 2010; Nicolson et al., 2003; Nicolson & Rapoport, 1999). Correspondingly, early evidence suggests that the rate of 22q11DS may even be higher among EOP individuals as compared to adult-onset SZ (Schneider et al., 2014; Usiskin et al., 1999). Therefore, 22q11DS is a potentially informative model of a more homogenous and developmental form of psychosis, which can increase current understanding of EOP and SZ broadly. However, there is a paucity of existing studies directly comparing these cohorts, which has hindered efforts to establish overlap at an intermediate phenotypic level, such as in the domain of shared cognitive impairment.

EOP is considered to represent a more insidious form of SZ relative to the more typical adult onset form, with greater disorganization, more negative symptoms, poorer prognosis, and more severe cognitive deficits (Hollis & Rapoport, 2011). Specifically, non-deleted individuals

with EOP demonstrate a wide range of specific neurocognitive deficits against a background of generalized cognitive impairment compared to healthy adolescents, particularly in learning, attention, executive function, and memory, all with medium to large effect sizes (Frangou, 2010, 2013; Nieto & Castellanos, 2011; Rajji, Ismail, & Mulsant, 2009). Earlier age of psychosis onset (APO) is also associated with increasing disruption of typical developmental trajectories, as individuals with EOP fail to demonstrate age-appropriate increases in cognitive processing speed as compared to typically developing adolescents (Bachman et al., 2012).

In the social cognitive domain, impairments have been well-established among adult-onset SZ patients, particularly in the area of Theory of Mind (ToM); that is, the ability to infer mental states, including taking the perspective of others (for reviews, see: Bora & Pantelis, 2013; Brüne, 2005; Martin, Robinson, Dzafic, Reutens, & Mowry, 2014; Savla, Vella, Armstrong, Penn, & Twamley, 2012). While there is limited research examining social cognition within EOP cohorts, preliminary evidence suggests impaired emotion recognition and emotional intelligence, relative to typically developing controls (Barkl et al., 2014; Linke et al., 2015).

Moreover, the relationship between social cognitive or neurocognitive domains and psychotic (positive) symptoms in both adult-onset SZ and EOP is tenuous. The adult SZ literature is inconsistent, with some studies suggesting the absence of such associations (Binder et al., 1998; Gold, Arndt, Nopoulos, O'Leary, & Andreasen, 1999; Milev, Ho, Arndt, & Andreasen, 2005) and others finding correlations between positive symptom severity and impairment in domains such as auditory processing (Strauss, 1993), verbal memory (M. Green & Walker, 1985, 1986), and motor speed (Rund et al., 2004). A meta-analysis of 73 studies suggested that while positive symptoms did not correlate with neurocognition (a composite score representing the 6 domains of processing speed, attention/vigilance, working memory, verbal

learning, visual learning, and problem solving), negative symptoms did (Ventura, Hellemann, Thames, Koellner, & Nuechterlein, 2009). To our knowledge, only one EOP study to date has directly assessed this relationship, indicating some associations between clinical symptomatology and areas such as verbal memory, spatial memory, concentration, and motor speed (Hoff et al., 1996). Specifically, greater positive symptoms were strongly associated with poorer performance on measures of executive function, verbal memory, spatial memory, concentration, and motor speed, with the strongest correlation being with verbal memory performance. Notably, and in contrast to many findings in adult-onset SZ, negative symptoms did not correlate with any neurocognitive variables.

Distinct cognitive deficits associated with SZ diagnosis have also been identified among 22q11DS patients. Decreased verbal and overall cognitive ability (IQ) have been identified among 22q11DS individuals with comorbid psychotic symptoms as compared to those without such symptoms (Debbané, Glaser, David, Feinstein, & Eliez, 2006). Cognitive differences are observed even among adults with 22q11DS who evidence similar demographic and academic profiles, including comparable IQ; those with SZ had significantly poorer performance on measures of verbal learning, verbal recognition, social cognition, and motor skills, as compared to 22q11DS patients without psychosis (Chow, Watson, Young, & Bassett, 2006). In another 22q11DS cohort, a diagnosis of SZ was associated with poorer performance on measures of spatial working memory, visual recognition, attention, and abstract verbal reasoning, but not with verbal learning/recognition performance or general cognitive ability (van Amelsvoort et al., 2004).

Although the above findings are largely consistent with the idiopathic SZ literature, these cross-sectional studies could not clarify whether such deficits emerge prior to or following overt

psychosis onset. Longitudinal studies have identified lower IQ, particularly decreased verbal IQ at study entry (T. Green et al., 2009) and a decline in verbal IQ over time (Gothelf et al., 2013), as predictors of psychosis emergence among samples of 125 and 172 22q11DS patients, respectively, across a wide age range (ages 5-54 years). The largest longitudinal study to date included 411 individuals with 22q11DS ages 8-24 years, drawing from a collaborative database across 22 research locations (Vorstman et al., 2015). Premorbid general cognitive ability (full-scale IQ) was shown to be lower in the 55 patients (13.4%) who subsequently met criteria for a psychotic disorder as compared to patients who did not develop psychosis over follow up, particularly within the verbal domain; furthermore, individuals who ultimately developed psychosis showed a steeper decline in verbal IQ over time. This deviation from the overall 22q11DS verbal cognitive trajectory was distinguishable starting at age 11, highlighting cognitive decline as an early biomarker for psychosis. Performance on social cognitive tasks, such as ToM, has additionally been shown (cross-sectionally) to correlate with positive symptoms of psychosis among youth with 22q11DS (19% of whom met criteria for overt psychotic disorder), highlighting the potential association of social cognition to psychotic symptomatology (Jalbrzikowski et al., 2012). These results are consistent with literature suggesting impaired verbal skills (Becker et al., 2010) and social cognition (Kim et al., 2011) are predictive of future psychosis among non-deleted individuals at risk for SZ.

Importantly, these deficits in neurocognitive and social cognitive domains are also predictive of later functional outcome following psychosis emergence in idiopathic adult-onset SZ, as well as EOP (Allott, Liu, Proffitt, & Killackey, 2011; Bachman et al., 2012; Couture, Penn, & Roberts, 2006; Fett et al., 2011a), reiterating the importance of identifying early developmental biomarkers that may inform treatments. A recent review of 22 SZ studies that

have examined the relationship between neurocognitive deficits and long-term functioning (e.g., working/studying vs. unemployed; self-rated or clinician-rated social, role, and community functioning) suggested that 73% of these studies found significant associations (Allott et al., 2011). Those that didn't were more likely to have less sophisticated methodology, and/or looked at very few cognitive domains. Of note, however, when each cognitive domain was analyzed individually, more null than positive relationships emerged, suggesting additional factors may be involved in the prediction of functioning. Additionally, among an EOP sample, poor baseline processing speed was associated with decreased social functioning approximately one year later (Bachman et al., 2012). Impaired social cognition, including ToM skills, are also associated with poorer outcomes in domains such as community functioning, social behavior at work, and social problem-solving among adults with SZ (Couture et al., 2006; Fett et al., 2011b; Hoe, Nakagami, Green, & Brekke, 2012; Horan et al., 2011). However, inconsistencies in methodologies, such as differences in the number and type of cognitive domains examined, length of follow-up period, and definition of future outcome, make it challenging to establish a definitive relationship between cognition and the prediction of future functioning, and highlight the need for standardized methodologies for ongoing research (Allott et al., 2011).

Following from this literature, there appears to be overlapping cognitive impairment between 22q11DS and EOP, with verbal and social cognitive (e.g., ToM) skills seeming to have a particularly strong association with psychosis in both groups. However, to our knowledge, only one study has directly investigated whether 22q11DS and EOP have phenotypic overlap at the cognitive level. Specifically, the neurocognitive profile of EOP patients was contrasted with that of a 22q11DS cohort (Kravariti et al., 2010), focusing solely on measures of verbal/visual memory and attention. Fifteen EOP patients ages 14-21 years were group-matched on global

cognitive ability to 29 22q11DS patients ages 7-14 years, the latter of whom were free of psychiatric diagnoses but were recruited for academic under-achievement. Results revealed significantly greater impairment in verbal memory and attention/concentration among patients with EOP relative to those with 22q11DS, but no group differences in visual memory, suggesting that relative impairment in verbal memory may be a differentiating feature of psychosis. However, this study has several limitations, including the small sample size, particularly of EOP patients, its focus on a limited set of neurocognitive domains, contrasting memory skills in groups that varied significantly in age, and oversampling for a non-representative, non-psychiatric 22q11DS sample. A more comprehensive and rigorous examination, addressing the above issues, may more clearly establish shared etiology by identifying the overlap between 22q11DS and EOP at an intermediate trait level (i.e., neurocognitive profile), thereby suggesting possible target sites for early intervention.

The present study therefore sought to compare deficits in neurocognition and social cognition among individuals with EOP and 22q11DS relative to the performance of healthy controls (HC). To better understand developmental effects, we also sought to evaluate whether the two clinical groups demonstrated differential developmental patterns on assessment measures by examining the effects of age on variables of interest. We further investigated the effect of global cognitive ability (IQ) on neurocognitive and social cognitive domains across all groups, as well as the role of APO on measures within the EOP group and among participants with 22q11DS who also met criteria for a psychosis-spectrum diagnosis. Next, in order to investigate the phenotypic overlap between 22q11DS and EOP, we evaluated the relationship between neurocognitive deficits and psychotic symptoms in both groups. Specifically, we first examined whether areas of relative cognitive impairment within the EOP group were associated with

psychotic symptom severity, and then determined if similar patterns were observed among individuals with 22q11DS. Lastly, we examined whether performance on neurocognitive and social cognitive measures correlated with subsequent functioning across global, role, and social domains, using social and role functioning measures specifically designed for adolescents (Cornblatt et al., 2007). We thus hypothesized the following:

1. Due to having a CNV that is deleterious for cognitive function, 22q11DS patients will evidence greater impairment at initial assessment across all cognitive domains as compared to EOP patients, with the exception of verbal memory and processing speed, given evidence that these deficits appear particularly relevant to psychosis (Bachman et al., 2012) and/or more severe among individuals with EOP (Kravariti et al., 2010). We also expect patients with EOP to evidence more severe clinical symptomatology and poorer functioning as compared to HCs and to 22q11DS patients, who have variable phenotypic expression. We further predict that earlier age at onset (APO) will correlate with greater impairment across neurocognitive domains within the EOP cohort, and within the subset of 22q11DS patients with a psychosis diagnosis. Our examination of APO as a continuous variable within an early-onset cohort represents a relatively novel approach, as only one previous study has done so (Hoff et al., 1996).
2. Given previous findings indicating that the domains of working and declarative memory, verbal fluency, processing speed, and ToM are most affected by psychotic symptomatology, cognitive function in these domains is predicted to be associated with psychotic symptoms among EOP patients, with 22q11DS patients showing a similar pattern of effects.

3. Lastly, we hypothesize that that poorer performance in neurocognitive and social cognitive domains at initial assessment will predict decreased global, social, and role functioning across groups, over a 5-25 month follow-up period.

Methods

Participants

Subjects were drawn from multiple studies conducted by the same research group, based on having complete measures in all of the domains of interest (clinical, neurocognitive, and social cognitive). Specifically, patients with psychosis-spectrum disorders were recruited as part of an ongoing study for adolescents (ages 12-18) with psychotic illness (University of California, Los Angeles Adolescent Brain–Behavior Research Clinic; ABBRC). Individuals (ages 10-28 years) with molecularly confirmed 22q11.2 deletions were recruited from an ongoing longitudinal study at UCLA. Healthy controls (ages 10-28 years) were recruited from within the community as part of the 22q11DS study and another longitudinal study of youth ongoing at UCLA. Controls for both protocols were recruited using the same procedures, including flyers and web-based advertisements. The total combined sample therefore consisted of 238 participants (n=51 EOP, 61 22q11DS, 126 HC; see Table 1 for participant demographics), for whom relevant data were available at initial assessment. All study participants with past substance abuse diagnoses were permitted to participate if they were free of substance abuse for the preceding six months; patients with substance dependence diagnoses were excluded. Additional exclusion criteria for all participants consisted of evidence of known neurological conditions (e.g., epilepsy), significant head injuries, and/or insufficient fluency in English. EOP patients and healthy controls were additionally excluded for intellectual disability (estimated premorbid IQ <70). Healthy controls additionally did not meet criteria for any major psychiatric

disorder, with the exception of anxiety disorders, depressive disorders, and Attention-Deficit/Hyperactivity Disorder, as described in prior publications (e.g., Bachman et al., 2012; Jalbrzikowski et al., 2012). Informed consent was provided by all participants, and by their parents for participants under the age of 18, using procedures approved by UCLA's Institutional Review Board. Participants were reimbursed for all assessments.

The studies included initial evaluations for all participants, which were conducted upon initial presentation to the relevant research study and involved assessments for current symptomatology and functioning as well as a neuropsychological assessment consisting of neurocognitive and social cognitive measures, described below. A subset of participants was then re-assessed on clinical and cognitive measures approximately 12 months later. (n=131; n=25 EOP, 35 22q11DS, 71 HC). In some instances, however, the timeline of longitudinal follow-up assessments varied, ranging from 4.9 to 36.87 months post-initial assessment. Individuals for whom follow-up assessments occurred more than 800 days (26.67 months) after the initial assessment were removed from longitudinal analyses (n=6; n=1 EOP, 2 22q11DS, 3 HC). Remaining participants (n= 125; n=24 EOP, 33 22q11DS, 68 HC) had follow-up assessments that were conducted on average within 393 days (range: 147-767 days) following the initial assessment.

No significant group differences were observed between participants that had follow-up data and those who did not, across all demographic variables of interest (i.e., all $p>0.05$ for age, gender, handedness, IQ, parent education, patient education, positive symptoms, global functioning, social functioning, and role functioning), although a trend emerged for race, such that Caucasian participants tended to be more likely to have follow-up data compared to other ethnic groups ($p=0.051$).

Materials and Procedures

Clinical Assessment

Diagnoses for all participants were determined at initial assessment using the Structured Clinical Interview for DSM-IV Axis I diagnoses (SCID-IV; First, Spitzer, Gibbon, & Williams, 1997) and by review of medical records when available. All assessments were administered by masters- or doctoral-level clinicians trained to a standard reliability criterion (Ventura, Liberman, Green, Shaner, & Mintz, 1998). Final diagnoses required consensus among supervising clinical psychologists. Current level of symptomatology for all participants (within the current month of the clinical assessment) was determined via the Structured Interview for Prodromal Syndromes (SIPS; Thomas H. McGlashan, Miller, Woods, Hoffman, & Davidson, 2001) and the Extended Brief Psychiatric Rating Scale (BPRS; Lukoff, Liberman, & Nuechterlein, 1986). The SIPS evaluates positive, negative, disorganized, and general symptoms on a scale from 0-6, with zero representing an absence of symptoms and six referring to a severe and psychotic level of symptoms. The SIPS also encompasses a range of symptom severity with 0-2 representing a healthy adult, 3-5 representing subthreshold (prodromal) symptoms, and 6 suggesting a psychotic level. The BPRS assesses symptom severity across multiple domains (ratings from 1-7, with one representing the absence of a symptom and seven representing an extremely severe symptom). All participants were rated on the Global Assessment of Functioning Scale (GAF; Miller et al., 2002b), the Global Functioning: Role Scale (GF:R), and the Global Functioning: Social Scale (GF:S), the latter two of which measure functioning on a scale from 1 (extreme dysfunction) to 10 (superior functioning) (Cornblatt et al., 2007).

Neuropsychological Assessment

All participants completed a standard research neuropsychological battery, which included measures of general cognitive abilities (Wechsler Abbreviated Scale of Intelligence (WASI) – Vocabulary (Vocab) and Matrix Reasoning (MR) subtests, and Full Scale IQ), visuomotor sequencing and set-shifting speed (Trails A and B), sustained attention (Continuous Performance Task – Identical Pairs (CPT); averaged across 3 trials), verbal fluency (semantic: D-KEFS Category Fluency Test – Animal Naming (ANT); phonemic: D-KEFS Letter Fluency (FAS)), processing speed (Brief Assessment of Cognition in Schizophrenia (BACS) – Symbol-Coding subtest, Wechsler Intelligence Scale for Children (WISC) – Coding subtest, or Wechsler Adult Intelligence Scale – Coding subtest), declarative memory (verbal episodic: California Verbal Learning Test (CVLT) or Hopkins Verbal Learning Test (HVLT)) and working memory (WISC-IV Letter Number Span (LNS) or University of Maryland LNS). As 22q11DS and EOP participants were part of two separate, parallel studies, there were differences in the specific test used for some domains (e.g., within processing speed, verbal learning, and working memory; see Table 2 for the specific tests administered for each group at initial assessment); these tests were subsequently combined in analyses, as previously described (Seidman et al., 2010).

Social Cognition Assessment

Social cognition was assessed via Part 3 of The Awareness of Social Inferences Test (TASIT; McDonald, Flanagan, Rollins, & Kinch, 2003), the Penn Emotion Recognition Test (ER40; Kohler, Bilker, Hagendoorn, Gur, & Gur, 2000), and the Penn Emotion Differentiation Task (EMODIFF (ED); Erwin et al., 1992). All participants in the current study were administered all three social cognitive measures (TASIT, ER40, ED).

The TASIT is a computerized task consisting of 16 vignettes believed to assess one's ability to comprehend the intentions of others, particularly how one comprehends white lies or

sarcasm. An overall score (total correct) was calculated (maximum=64). The TASIT has shown adequate reliability and validity with brain-injured patients (McDonald et al., 2006), and has been used with adolescents at clinical high-risk for psychosis, along with first-episode and chronic patients with schizophrenia (M. F. Green et al., 2011).

The Penn ER40 is a computerized emotion identification task in which 40 color photographs of adult faces, varying in race and gender, are randomly presented. Participants were asked to identify the emotion of each face (happy, sad, angry, afraid, or no emotion) and were given as long as needed to respond (total maximum score=40, each emotion presented 8 times). The Penn EMODIFF (ED) is a computerized emotion differentiation task in which individuals are presented with two black and white faces of the same person and are asked to choose which of the two faces displayed expresses an emotion more intensely (e.g., more happy, more sad), or decide that the two faces are equally happy or sad (total maximum score=40). Both measures have shown adequate construct validity and test-retest reliability (Carter et al., 2009; Rojahn, Gerhards, Matlock, & Kroeger, 2000), and have been widely used in studies with schizophrenia patients (e.g., Butler et al., 2009; Sachs, Steger-Wuchse, Kryspin-Exner, Gur, & Katschnig, 2004; Silver, Shlomo, Turner, & Gur, 2002), as well as in adolescents with mental illness (Roddy et al., 2012; Schenkel, Pavuluri, Herbener, Harral, & Sweeney, 2007).

Statistical Analyses

Analysis I:

a) Initial Assessment of Group Differences. All statistical analyses were performed using SPSS software v. 20 (Chicago, Illinois). For clinical measures, the sum of symptom scores within each SIPS dimension (positive, negative, general, and disorganized) was calculated and analyzed separately. On the BPRS, the items assessing symptoms of depression (BPRSdep) and

anxiety (BPRSanx) were entered into regression analyses; these particular symptom domains were included due to their relation to EOP and 22q11DS symptomatology (Achim et al., 2011; Baker & Vorstman, 2012; Buckley, Miller, Lehrer, & Castle, 2009; Jolin, Weller, & Weller, 2012; Philip & Bassett, 2011; Siris, 2000), and because they are not specifically assessed by the SIPS. Neurocognitive variables displaying substantially skewed distributions were first log-transformed (Trails A, Trails B) or reverse log-transformed (TASIT). Additionally, given variability in standardized norms for the age range of participants within this study, raw scores were utilized for all measures across neurocognitive/social cognitive domains except IQ. Percent correct was utilized when versions of specific measures were not identical across studies (symbol coding (SC), verbal learning (VLT), and LNS). The Full Scale IQ from the WASI (T-score derived from Vocabulary and Matrix Reasoning tests) was used for an estimate of overall IQ.

Group differences were assessed for 23 neurocognitive, social cognitive, and clinical measures at initial assessment using linear regressions adjusting for age and gender. In addition to main effects, group-by-age interactions were examined to determine whether groups demonstrated differential developmental patterns on assessment measures. Effect sizes for overall group differences were quantified using the *partial* η^2 (η_p^2) statistic. Next, pairwise comparisons between groups were conducted.

We then created a normative model using the control sample to generate means and standard deviations for each clinical, neurocognitive, and social cognitive measure at initial assessment. This normative data was then used to generate standardized scores (z-scores) for each subject across each measure, in order to facilitate comparisons across domains.

b) Secondary Analyses – Effects of IQ and Age at Psychosis Onset. In order to examine whether IQ may partly explain group differences at initial assessment, the above linear

regressions were re-run adding global cognitive ability (IQ) as a covariate. This approach was taken rather than controlling for IQ in the primary analyses, as intellectual deficits are an inherent feature of 22q11DS and covarying for IQ may, in effect, adjust out part of the group effect we were attempting to measure.

Secondly, within the EOP group, a correlation analysis controlling for age and gender was performed to examine the possible effect of APO on outcome measures. While existing literature suggests that earlier onset is associated with greater impairment (Basso, Nasrallah, Olson, & Bornstein, 1997; Frangou, 2010; Hoff et al., 1996; Rajji et al., 2009), only one study to date has directly examined APO as a continuous variable within an early-onset cohort (Hoff et al., 1996). The same correlational analysis was then conducted among the subset of 22q11DS patients concurrently meeting criteria for a psychotic-spectrum disorder (n=8).

Analysis II: Prediction of Psychotic Symptoms. To examine whether similar cognitive deficits are relevant to dimensionally measured psychotic symptoms in both idiopathic EOP and in 22q11DS, we evaluated whether the measures demonstrating impairment in both patient groups relative to healthy controls as determined in Analysis I correlated with concurrently assessed psychotic symptom severity. Specifically, we examined the association of performance on each of the neurocognitive/social cognitive measures with positive symptom severity (total SIPS positive symptoms) at initial assessment among the EOP sample, and then separately, within the 22q11DS cohort. Differences in correlations between the patient groups were then examined using the Fisher r-to-z transformation, in order to determine whether the groups differed in the relationship between neurocognitive performance and psychotic symptoms.

Analysis III: Prediction of Functional Outcome. To examine the role of neurocognition at initial assessment in predicting functional outcome, the aforementioned z-scores for measures

within the neurocognitive and social cognitive domains, respectively, were averaged for each subject to create composite domain scores to minimize number of comparisons and maximize statistical power in subsequent analyses (see Table 3 for correlations between measures within the neurocognition and social cognition composite domains). The composite z-scores were used to predict functional outcome at follow-up in the global, social, and role domains (GAF, GF:S, and GF:R, respectively). Specifically, regression models were fit for each of the functioning measures at follow-up based on the following predictors: functioning score at initial assessment, composite neurocognitive or social cognitive z-score at initial assessment, age, and gender. Given variability in the amount of time between initial and follow-up assessments among participants, the time interval was also included as a predictor, along with selected two-way interactions (group-by-age, group-by-initial functioning, group-by-time, initial functioning score-by-time). These interactions were chosen among the larger set of possible interactions based on the primary variables and primary relationships of interest in the analyses, while also being mindful of controlling Type I error. In total, 6 models were run, predicting each of the 3 functioning measures based on either the neurocognitive or social cognitive composite score.

Results

Analysis I: a) Group Differences at Initial Assessment. A significant main effect of group (all $p<0.001$), when controlling for the effects of age and gender, was found for each clinical, neurocognitive, and social cognitive measure (except ED, as described below), with effects mostly in the large range (see Table 4 for full regression results and effect sizes).

A significant group-by-age interaction was observed only for the ED measure ($F(2, 174)=3.75$, $p<0.05$). As expected, healthy controls demonstrated higher ED values relative to

patient groups at all ages, with an upward developmental trajectory. While 22q11DS and EOP patients evidenced lower ED values compared to HC, performance of individuals with EOP rapidly improved over the examined age range; patients with 22q11DS showed a slower rate of change with age. Figure 1 depicts the group-by-age interaction for this measure. Group-by-age interactions were non-significant for all other variables.

Figures 2 and 3 depict the group z-score means for clinical and cognitive measures, respectively. In the clinical domain, patients with EOP evidenced significantly greater deficits compared to 22q11DS patients and HCs on all measures except social and role functioning, for which both patient groups evidenced similar levels of impairment. Healthy controls significantly differed from both clinical groups on all measures (all $p<0.001$), except on a clinician-rated measure of depression severity (BPRSdep), in which there was no difference between controls and 22q11DS patients.

In the neurocognitive and social cognitive domains, healthy controls performed significantly better than both patient groups ($p<0.01$ or smaller, for post-hoc pairwise comparisons) on the majority of cognitive measures: specifically, FSIQ, Vocab, LNS, VLT, FAS, Trails A, Trails B, SC, CPT, and TASIT. EOP patients and controls did not significantly differ in performance on MR, ER40, and ED tasks, but 22q11DS patients performed worse than the other two groups. For the ANT measure, EOP patients performed worse than controls and 22q11DS, who did not differ from one another. Patients with EOP performed significantly better than 22q11DS patients on all but three measures: verbal fluency (ANT), as mentioned above, as well as processing speed tasks (Trails A and B).

b) Secondary Analyses. As shown in Table 5, with the addition of IQ as a covariate in the linear regressions, significant overall main effects continued to be found for all measures except

LNS and ER40. However, the strength of the effects for Vocab, VLT, FAS, CPT, and TASIT was attenuated. Additionally, a significant main effect of IQ was found for all measures except SIPS general symptoms, BPRS anxiety, and BPRS depression. A significant group-by-age interaction continued to be observed only for the ED measure.

Within the EOP group, APO was significantly inversely correlated with performance on SC (r=-0.300, $p<0.05$) and ANT (r=-0.338, $p<0.05$), controlling for the effects of age and gender. In contrast to our predictions, earlier onset was associated with improved performance (Figure 4A-B). All other correlations with neurocognitive or social cognitive measures were not significant in the EOP group (all *p*-values > 0.05). Among 22q11DS patients who had comorbid psychotic diagnoses (n=8), APO significantly correlated with FAS (r=0.939, $p<0.05$) and ER40 (r=0.891, $p<0.05$); unlike the pattern in EOP, earlier onset age was associated with worse performance (Figure 4C-D). All other correlations with neurocognitive/social cognitive measures were not significant in the 22q11DS group (all *p*-values > 0.05).

Analysis II: Prediction of Psychotic Symptoms. Among the cognitive measures for which both EOP and 22q11DS patients evidenced significant differences from healthy controls (i.e., all but MR, ANT, ED40, and ED), significant correlations among the EOP group between cognitive measures and total positive symptoms were observed for SC (r=-0.304, $p<0.05$), Vocab (r=-0.369, $p<0.01$), IQ (r=-0.368, $p<0.01$), and TASIT (r=-0.328, $p<0.05$) scores. Similar to the EOP group, significant correlations among 22q11DS patients were also observed between positive symptoms with Vocab (r=-0.329, $p<0.05$) and IQ (r=-0.336, $p<0.05$); 22q11DS patients additionally showed significant correlations with VLT (r=-0.415, $p=0.001$), LNS (r=-0.303, $p<0.05$), and FAS (r=-0.270, $p<0.05$). In all instances, greater psychotic symptom severity was associated with poorer performance. See Table 6 for full results.

Correlation comparisons using the Fisher r-to-z' transformation were conducted on the correlations that were significant in both clinical groups (Vocab and IQ). Across both measures, the correlations were not significantly different between groups (Vocab: z=-0.228, p=0.82; IQ: z=-0.171, p=0.86).

Analysis III: Prediction of Functional Outcome. Interactions of age-by-group and group-by-initial functioning were not significant in any model, and were thus removed from all subsequent analyses. See Table 7 for all results, as outlined below.

Prediction of Global Functioning (GAF). Global functioning at follow-up was significantly predicted by the overall models (neurocognition: $F(8, 116) = 28.576$, $p<0.001$; social cognition: $F(8, 111) = 25.653$, $p<0.001$). However, neither neurocognition or social cognition had significant main effects in the overall model predicting global functioning (GAF) at follow-up. Instead, a significant interaction of group-by-time delay was observed (neurocognition: $\beta=0.572$, $p<0.05$; social cognition: $\beta=0.599$, $p<0.05$). Follow-up contrasts indicated that only healthy controls evidenced a significant relationship between follow-up GAF scores and time in both models, such that as time between assessments increased, functioning at follow-up decreased (neurocognition: r=-0.501, $p<0.001$; social cognition: r=-0.502, $p<0.001$).

Prediction of Social Functioning (GF:S). Social functioning at follow-up was also significantly predicted by both overall models (neurocognition: $F(8, 116) = 25.294$, $p<0.001$; social cognition: $F(8, 111) = 23.326$, $p<0.001$), but was not significantly predicted by neurocognition or social cognition at initial assessment. A significant interaction of group-by-time between assessments (neurocognitive: $\beta=0.615$, $p<0.05$; social cognition: $\beta=0.607$, $p<0.05$) was observed across both models (Figure 5). Follow-up contrasts for the group-by-time interaction showed that again, only healthy controls evidenced a significant association between

follow-up GF:S scores and time across models (neurocognitive: r=-0.453, $p<0.001$; social cognition: r=-0.431, $p=0.001$). Specifically, as the time interval between assessments increased, functioning decreased in controls. The interaction of initial GF:S-by-time also significantly predicted social functioning at follow-up in both models (neurocognition: $\beta=0.685$, $p<0.01$ (Figure 6A); social cognition: $\beta=0.666$, $p<0.01$ (Figure 6B)). Lower functioning at initial assessment was associated with lower functioning at follow-up, with the relationship becoming stronger as the time delay increased. Furthermore, the highest functioning individuals at initial assessment were more likely to show reductions in GF:S scores over time, though to a lesser extent when the delay between assessments was short versus long.

Prediction of Role Functioning (GF:R). Role functioning at follow-up was similarly significantly predicted by the overall models (neurocognition: $F(6, 118) = 43.396$, $p<0.001$; social cognition: $F(6, 113) = 38.490$, $p<0.001$). No significant interactions were observed and these terms were thus dropped from the final models. Significant main effects of neurocognition ($\beta=0.166$, $p<0.05$), initial GF:R scores ($\beta=0.549$, $p<0.001$), group ($\beta=-0.144$, $p<0.05$), and time ($\beta=-0.158$, $p<0.01$) were observed in the model predicting follow-up role functioning. Specifically, better neurocognitive performance at initial assessment was associated with better role functioning at follow-up. In the social cognition model, only initial GF:R scores ($\beta=0.624$, $p<0.001$), group ($\beta=-0.162$, $p<0.05$), and time ($\beta=-0.175$, $p<0.01$) significantly predicted follow-up role functioning. Across both models, better role functioning at initial assessment was associated with better role functioning at follow-up. Regarding effects of group in both models, HCs were more likely to have higher role functioning at follow-up as compared to both patient groups. Additionally, better role functioning at follow-up was associated with a shorter time delay between assessments, across groups.

Post-hoc Examination of Clinical Symptomatology. Post-hoc analyses were conducted to further examine the unexpected association between poorer functioning with greater time delay between assessments. In particular, we examined whether this relationship was attributable to greater symptomatology at follow-up. To do this, separate correlations were conducted within each participant group between positive symptoms at follow-up and time delay between assessments, controlling for the effects of age and gender. Across all participant groups, positive symptoms at follow-up did not correlate with time delay (Controls: r=-0.032, p=0.796; 22q11DS: r=0.078, p=0.676; EOP: r=0.056, p=0.803), suggesting there was not a simple relationship between time delay and increased symptomatology.

Discussion

This study investigated how the clinical and cognitive profile of individuals with EOP compares to those with 22q11DS, a genetically defined high risk group for psychosis, relative to healthy controls. We also evaluated whether there is phenotypic overlap between EOP and 22q11DS by looking for similar patterns of relationships between psychotic symptoms with neurocognition and social cognition across the clinical groups. Lastly, we examined whether cognition at initial assessment predicted global, social, and/or role functioning at follow-up. To our knowledge, this is the first study to broadly compare clinical and neurocognitive profiles of EOP and a representative sample of 22q11DS patients. It is also the first to assess relationships between neurocognition at initial assessment and functioning at follow-up across these groups.

The study revealed several new findings: first, groups differed on all initial assessment measures, with age only playing a significant interaction role in a social cognition measure (emotion discrimination). Additionally, adjusting for overall IQ only affected the observed

significant group differences in working memory (LNS) and emotional recognition (ER40) tasks, suggesting that differences in the majority of specific cognitive abilities in EOP and 22q11DS participants are not fully accounted for by differences in global intellectual function.

Secondly, APO showed an unexpected relationship in the EOP cohort, such that earlier onset was associated with better task performance on two measures, symbol coding (SC) and animal naming test (ANT). In contrast, and in line with our predictions, among the small sample of 22q11DS patients with an overt psychotic disorder, earlier APO was related to greater impairment on verbal fluency and emotion recognition tasks.

Thirdly, significant correlations among the EOP group emerged between total positive symptoms and SC, vocabulary, IQ, and TASIT scores. Among 22q11DS patients, significant correlations emerged between positive symptoms and vocabulary, IQ, VLT, LNS, FAS, ER40, and ED scores. Comparable relationships between neurocognitive impairments and positive psychotic-like symptoms were observed between the EOP and 22q11DS patient groups. This suggests phenotypic overlap, as a similar pattern of cognitive deficits are relevant to psychotic symptom development in both groups.

Finally, in contrast to our hypotheses, cognition at initial assessment largely did not predict functioning at follow-up, when controlling for other key variables. Only in one analysis was this hypothesis confirmed; better neurocognitive performance at initial assessment was associated with better role functioning at follow-up.

Largely consistent with our hypothesis, patients with 22q11DS performed significantly worse relative to EOP patients on all domains except verbal skills, albeit not verbal memory, and processing speed. Specifically, at initial assessment, individuals with 22q11DS evidenced greater impairment than EOP patients on most tasks except a phonemic verbal fluency task (ANT), for

which EOP patients performed worse. There were no significant differences between clinical groups on two measures of processing speed, including with set-shifting (Trails A and B). Lastly, while differential developmental patterns were not observed among the large majority of measures, a significant group-by-age interaction was found for ED. However, this effect should be interpreted with caution, as the age range among EOP patients is much smaller than that of the other two participant groups. Therefore, the observed steep slope may be driven by edge effects on that smaller range. Overall, these cognitive results are fairly consistent with literature suggesting that verbal skills and processing speed are particular areas of impairment in EOP relative to adult-onset SZ (Basso et al., 1997; Frangou, 2010).

Results also largely confirmed our hypothesis that individuals with EOP would evidence greater impairment on all clinical measures. Interestingly, however, 22q11DS and EOP patients did not differ on adolescent-specific measures of social or role functioning at initial assessment. This was true despite greater clinical impairment in the EOP group across all other domains, including on measures of anxiety and depression. These results suggest that both clinical groups have poor social and role functioning, though perhaps for different reasons (e.g., greater clinical impairment in EOP patients versus greater cognitive impairment in 22q11DS patients).

Our secondary analyses indicate significant main effects of IQ on almost all neurocognitive and social cognitive measures, though it largely did not entirely account for group differences on specific cognitive measures (with the exception of the LNS and ER40 tasks). However, our prediction that earlier APO would correlate with greater cognitive impairment was surprisingly not confirmed among EOP patients, as earlier APO was associated with better performance on measures of processing speed (SC) and verbal fluency (ANT). In contrast, among 22q11DS patients, earlier onset was associated with greater impairment on a

different measure of verbal fluency (FAS) and emotion recognition (ER40). Our results from EOP patients do not agree with previous literature suggesting that early age at onset is associated with poorer cognitive performance (Basso et al., 1997; Frangou, 2010; Hoff et al., 1996; Rajji et al., 2009).

However, our study was only the second one (Hoff et al., 1996), to our knowledge, to analyze APO as a continuous variable within an adolescent-onset group (rather than a categorical comparison of EOP versus adults with schizophrenia). Hoff et al. (1996) utilized a sample of individuals with ages of illness onset ranging from 7 to 29 years; in contrast to our findings, their result indicated later age at onset was associated with better performance on processing speed tasks (e.g., Trails B, Symbol Digit Modalities Test), as well as a finger tapping motor task. Therefore, our sample evidenced more limited variation in onset age, relative to the majority of prior studies. It is also plausible that greater impairment based on age at illness onset may become apparent only later in the illness trajectory, suggesting that future studies utilizing longer follow-up periods would be beneficial. However, it is important to note that our results would not survive correction for multiple comparisons, and APO analyses within the 22q11DS sample were conducted on a very small subset of patients with comorbid psychosis disorders. Thus, results are exploratory and difficult to fully interpret.

We also evaluated whether the domains showing significant impairment in clinical groups (i.e, vocabulary, IQ, working memory, declarative memory, verbal fluency, processing speed, and ToM) were associated with psychotic symptoms in both EOP and 22q11DS groups. Our hypothesis was only partially confirmed. Among EOP patients, psychotic symptoms correlated with both ToM and processing speed, but only with one of three processing speed measures (SC). We also observed correlations between psychotic symptoms and both IQ and

vocabulary. Among 22q11DS patients, additional significant correlations emerged with verbal fluency, working memory, and emotion recognition/discrimination measures. However, in line with our prediction, EOP and 22q11DS patients did not show differences in correlation patterns for the overlapping measures of vocabulary and IQ, suggesting that the relationship between psychotic symptoms and these cognitive domains is similar for EOP and 22q11DS patients.

Although we did not observe relationships between symptoms and all of the predicted areas of psychosis-related deficits, results are consistent with literature suggesting that low IQ (including verbal IQ) and ToM deficits have been predictive of psychosis among 22q11 patients (Gothelf et al., 2013; T. Green et al., 2009; Jalbrzikowski et al., 2012; Vorstman et al., 2015). However, as very few studies have looked at more than just general intellectual function among patients with 22q11DS, it is possible that stronger relationships with other specific cognitive abilities may exist. Thus, this study represents a relatively novel contribution. Additionally, processing speed has been shown to predict psychosis emergence among clinical high-risk populations (e.g., Cannon et al., 2016; Riecher-Rössler et al., 2009). Overall, results suggest that there are shared phenotypic qualities between EOP and 22q11DS patients, highlighting the utility of 22q11DS as a genetic high-risk model of psychosis.

Our last aim was to evaluate whether neurocognitive performance at initial assessment predicted social and role functioning at follow-up; this hypothesis was largely unsupported by the current results. Neurocognitive at initial assessment was only predictive of follow-up role functioning, and did not predict global functioning or social functioning at follow-up. Social cognition did not predict any measures of functioning. This is not consistent with prior studies with adult-onset (Allott et al., 2011; Couture et al., 2006; Fett et al., 2011b; Hoe et al., 2012; Horan et al., 2011) and EOP patients (Bachman et al., 2012) that have suggested a relationship

between cognition and social/community functioning. However, prior literature among adults with SZ has been inconsistent, with many null relationships being reported as well (Allott et al., 2011). Given our use of adolescent-specific functioning measures, it seems that neurocognition in this cohort is only closely associated with academic (i.e., role) functioning.

Moreover, the majority of prior studies have not examined time interval as a predictor, which emerged as a significant factor in our models. Additionally, the follow-up time intervals of these studies ranged from 0 to 15+ years. Although there were group differences in prediction results, the time between initial and follow-up assessments emerged as a robust predictor of functioning over time. Specifically, only healthy controls evidenced a significant relationship between follow-up GAF and GF:S scores and time, such that as time between assessments increased, functioning decreased. It is possible that patients are less likely than controls to evidence changes in functioning as a function of time delay due to higher rates of stabilization through sources such as medication and outpatient therapy, though our study did not directly assess for this. We also observed that the amount of social functioning change (i.e., increase/decrease) between assessments was related to time interval between assessments. For example, participants who began with higher functioning were more likely to show a decline when the assessment delay was greater. It is possible that individuals who are more clinically unstable may be less likely to return to the clinic on time for future appointments for various reasons. However, post-hoc analyses suggested that the time delay was not associated with clinical symptomatology across all participant groups, which does not support this interpretation.

This study has several limitations which must be noted. In particular, while the sample size is larger than prior studies, it is likely under-powered for some analyses (i.e., age at psychosis onset, and modeling interactions). HCs and 22q11DS patients also evidenced a wider

age range compared to EOP patients. Our study also utilized a cross sectional rather than longitudinal design for assessing overall group differences in clinical and cognitive measures. Additionally, the longitudinal predictions of functioning at follow-up were greatly influenced by the observed assessment time delay. Lastly, a limitation exists in combining different measures for particular domains, as measures were confounded with group. Future directions include increasing sample size, for adequately powered analyses of 22q11DS patients with and without psychotic diagnoses, and investigating the relationship of cognition to other measures of pediatric/adolescent functioning (e.g., adaptive behavior). Prospective longitudinal studies over a longer follow-up period will also be important to understand cognitive and symptomatic changes in relation to functional changes. Nevertheless, this study offers a unique look into a broad comparison of deficits in EOP and 22q11DS samples relative to healthy controls and the utility of initial cognitive deficits in predicting future outcome.

Table 1

Demographic Information Characterizing Study Sample at Initial Assessment

	Controls (*N*=126)	22q11DS Patients (*N*=61)	EOP Patients (*N*=51)	*p*-value
Mean age, years (± SD)	17.92(4.18)	16.18(4.53)	15.85(1.63)	<0.001*
Number female (%)	63(50.0)	34(55.7)	25(49.0)	NS
Number left-hand dominant (%)	6(4.84)[+]	5(8.77)	4(10.26)	NS
Mean IQ (± SD)	110.23(16.21)	76.87(13.95)	99.14(15.33)	<0.001**
Mean participant education, years (± SD)	11.03(3.94)[+++]	8.34(3.50)[++]	9.31(2.05)	<0.001*
Mean parental education, years (± SD)	6.69(1.53)[+]	6.67(1.41)	6.69(1.47)	NS
Race/Ethnicity (%)				<0.01*
Caucasian, Non-Hispanic	49(38.9)	42(68.9)	18(35.3)	
Caucasian, Hispanic	29(23.0)	10(16.4)	14(27.5)	
African-American	17(13.5)	1(1.6)	7(13.7)	
Asian-American/Pacific Islander	14(11.1)	1(1.6)	2(3.9)	
Other	17(13.5)	7(11.5)	10(19.6)	
Primary Psychotic Diagnoses (%)				
Schizophrenia	0(0)	3(5.26)	20(51.28)	
Psychotic Disorder NOS	0(0)	3(5.26)	3(7.69)	
Schizoaffective disorder	0(0)	2(3.51)	11(28.21)	
Schizophreniform disorder	0(0)	0(0)	5(12.82)	
Mean Age of Overt Psychosis Onset (±SD) [range]	N/A	13.75(2.87)[1] [10-19]	14.37(1.67) [11-17]	
Mean SIPS Positive Symptoms (±SD) [range]	1.11(1.59) [0-8]	6.20(6.43) [0-28]	17.96(5.56) [2-29]	<0.001**
Mean Global Assessment of Functioning Scores (±SD) [range]	83.27(10.42) [43-95]	53.36(14.40) [21-85]	41.54(11.48) [20-71]	<0.001**
Mean Global Functioning: Social Scores (±SD) [range]	8.60(0.96) [6-10]	6.43(1.64) [2-9]	5.78(1.90) [2-10]	<0.001*; <0.05^

Mean Global Functioning: Role Scores (±SD) [range]	8.69(1.04) [4-10]	5.13(1.85) [1-9]	5.18(1.94) [1-9]	<0.001*

[1]Based on patients with comorbid psychotic diagnoses (n=8).
*= significant differences between controls and each patient group
**=significant difference between all contrast groups
^=significant difference between 22q and EOP
Missing data: [+](n=1) [++](n=4) [+++](n=5)

Table 2

Specific Neurocognitive Tests Administered at Initial Assessment, by Group (n, %)

Measure	Controls (n=126)	22q11DS Patients (n=61)	EOP Patients (n=51)
WASI Vocabulary	125(99.2)	61(100)	51(100)
WASI Matrix Reasoning	118(93.7)	61(100)	51(100)
Trails A	125(99.2)	60(98.4)	51(100)
Trails B	120(95.2)	59(96.7)	50(98.0)
CPT – Identical Pairs	78(61.9)	45(73.8)	46(90.2)
D-KEFS Category Fluency Test: Animal Naming	125(99.2)	61(100)	51(100)
D-KEFS Letter Fluency Test: FAS	120(95.2)	61(100)	50(98.0)
Symbol Coding			
BACS Symbol Coding	88(69.8)	55(90.2)	51(100)
WISC-IV Coding	12(9.5)	6(9.8)	0(0)
WAIS-III Coding	25(19.8)	0(0)	0(0)
Verbal Learning			
CVLT	89(70.6)	61(100)	0(0)
HVLT	36(28.6)	0(0)	51(100)
Letter Number Span			
WISC-IV Letter Number Span	1(0.8)	6(9.8)	0(0)
University of Maryland Letter Number Span	88(69.8)	55(90.2)	51(100)

Table 3

(A) Correlations between Cognitive Measures (z-scores) within Composite Domains among Healthy Controls

		Neurocognitive Composite Domain											Social Cognitive Composite Domain		
		Vocab	MR	IQ	LNS	VLT	ANT	FAS	Trails A[1]	Trails B[1]	SC	CPT	TASIT[1]	ER40	ED
Neurocognitive Composite Domain	Vocab	-	0.683***	0.825***	0.652***	0.386***	0.291***	0.590***	0.320***	0.324***	0.514***	0.738***	0.550***	0.450***	0.579***
	MR	0.683***	-	0.765***	0.521***	0.342***	0.120	0.400***	0.363***	0.388***	0.564***	0.583***	0.459***	0.466***	0.532***
	IQ	0.825***	0.765***	-	0.428***	0.459***	0.303***	0.424***	0.486***	0.476***	0.373***	0.495***	0.404***	0.330***	0.563***
	LNS	0.652***	0.521***	0.428***	-	0.299**	0.327**	0.538***	0.128	0.336**	0.544***	0.694***	0.480***	0.255*	0.424***
	VLT	0.386***	0.342***	0.459***	0.299**	-	0.345***	0.251**	0.297***	0.343***	0.319***	0.331**	0.299***	0.111	0.259*
	ANT	0.291***	0.120	0.303***	0.327**	0.345***	-	0.209*	0.090	0.140	0.047	0.222	0.164	0.109	0.295**
	FAS	0.590***	0.400***	0.424***	0.538***	0.251**	0.209*	-	0.274**	0.336**	0.376***	0.540***	0.509***	0.457***	0.335**
	Trails A[1]	0.320***	0.363***	0.486***	0.128	0.297***	0.090	0.274**	-	0.710***	0.287***	0.206	0.216*	0.054	0.154
	Trails B[1]	0.324***	0.388***	0.476***	0.336**	0.343***	0.140	0.336***	0.710***	-	0.266**	0.300**	0.242*	-0.091	0.206
	SC	0.514***	0.564***	0.373***	0.544***	0.319***	0.047	0.376***	0.287***	0.266**	-	0.663***	0.392***	0.298**	0.408***
	CPT	0.738***	0.583***	0.495***	0.694***	0.331**	0.222	0.540***	0.206	0.300**	0.663***	-	0.521***	0.457***	0.410***
Social Cognitive Composite Domain	TASIT[1]	0.550***	0.459***	0.404***	0.480***	0.299***	0.164	0.509***	0.216*	0.242*	0.392***	0.521***	-	0.354***	0.373***
	ER40	0.450***	0.466***	0.330**	0.255*	0.111	0.109	0.457***	0.054	-0.091	0.298**	0.457***	0.354***	-	0.302**
	ED	0.579***	0.532***	0.563***	0.424***	0.259*	0.295**	0.335**	0.154	0.206	0.408***	0.410***	0.373***	0.302**	-

*p<0.05 **p<.01 ***p<.001

[1]In the transformed version of this variable, lower/negative numbers reflect better performance.

Vocab=Wechsler Abbreviated Scale of Intelligence Vocabulary subtest; *MR*=Wechsler Abbreviated Scale of Intelligence Matrix Reasoning subtest; *CPT*=Continuous Performance Task – Identical Pairs; *ANT*=D-KEFS Category Fluency Test – Animal Naming; *FAS*=D-KEFS Letter Fluency; SC=Symbol coding from WISC or BACS; *VLT*=Verbal learning test from CVLT or HVLT; *LNS*=Letter number span from WISC or LNS; *TASIT*=The Awareness of Social Interferences Test; *ER40*=Penn Emotion Recognition task; *ED*=Penn Emotion Discrimination task

(B) Correlations between Cognitive Measures (z-scores) within Composite Domains among 22q11DS Patients

		Neurocognitive Composite Domain										Social Cognitive Composite Domain		
		Vocab	MR	IQ	LNS	VLT	ANT	FAS	Trails A[1]	Trails B[1]	SC	CPT	TASIT[1]	ER40	ED
Neurocognitive Composite Domain	Vocab	-	0.642***	0.771***	0.591***	0.432***	0.429***	0.560***	0.260*	0.196	0.572***	0.478***	0.584***	0.564***	0.225
	MR	0.642***	-	0.872***	0.634***	0.413***	0.191	0.403***	0.322*	0.334**	0.479***	0.373*	0.418***	0.348**	0.245
	IQ	0.771***	0.872***	-	0.576***	0.475***	0.2226	0.402***	0.296*	0.282*	0.378**	0.288	0.461***	0.420***	0.257
	LNS	0.591***	0.634***	0.576***	-	0.503***	0.3438**	0.597***	0.439***	0.469***	0.686***	0.534***	0.408**	0.479***	0.276*
	VLT	0.432***	0.413***	0.475***	0.503***	-	0.520***	0.367**	0.337**	0.209	0.470***	0.357*	0.350**	0.354**	0.385**
	ANT	0.429***	0.191	0.226	0.348**	0.520***	-	0.501***	0.204	0.196	0.425***	0.201	0.309*	0.206	0.032
	FAS	0.560***	0.403***	0.402***	0.597***	0.367**	0.501***	-	0.281*	0.273*	0.567***	0.455**	0.214	0.322*	0.208
	Trails A[1]	0.260*	0.322*	0.296*	0.439***	0.337**	0.204	0.281*	-	0.504***	0.529***	0.398**	0.084	0.415***	-0.062
	Trails B[1]	0.196	0.334**	0.282*	0.469***	0.209	0.196	0.273*	0.504***	-	0.433***	0.467***	0.371**	0.291*	0.187
	SC	0.572***	0.479***	0.378**	0.686***	0.470***	0.425***	0.567***	0.529***	0.433***	-	0.642***	0.421***	0.400**	0.178
	CPT	0.478***	0.373*	0.288	0.534***	0.357*	0.201	0.455**	0.398**	0.467***	0.642***	-	0.382**	0.448**	0.265
Social Cognitive Composite Domain	TASIT[1]	0.584***	0.418***	0.461***	0.408**	0.350**	0.309*	0.215	0.084	0.371**	0.421***	0.382**	-	0.475***	0.252
	ER40	0.564***	0.348**	0.420***	0.479***	0.354**	0.206	0.322*	0.415***	0.291*	0.400**	0.448**	0.475***	-	0.390**
	ED	0.225	0.245	0.257	0.276*	0.385**	0.032	0.208	-0.062	0.187	0.178	0.265	0.252	0.390**	-

*$p<0.05$ **$p<.01$ ***$p<.001$

[1]In the transformed version of this variable, lower/negative numbers reflect better performance.

Vocab=Wechsler Abbreviated Scale of Intelligence Vocabulary subtest; *MR*=Wechsler Abbreviated Scale of Intelligence Matrix Reasoning subtest; *CPT*=Continuous Performance Task – Identical Pairs; *ANT*=D-KEFS Category Fluency Test – Animal Naming; *FAS*=D-KEFS Letter Fluency; SC=Symbol coding from WISC or BACS; *VLT*=Verbal learning test from CVLT or HVLT; *LNS*=Letter number span from WISC or LNS; *TASIT*=The Awareness of Social Interferences Test; *ER40*=Penn Emotion Recognition task; *ED*=Penn Emotion Discrimination task

C) Correlations between Cognitive Measures (z-scores) within Composite Domains among EOP Patients

		Neurocognitive Composite Domain											Social Cognitive Composite Domain		
		Vocab	MR	IQ	LNS	VLT	ANT	FAS	Trails A[1]	Trails B[1]	SC	CPT	TASIT[1]	ER40	ED
Neurocognitive Composite Domain	Vocab	-	0.355*	0.834***	0.498***	0.467***	0.331*	0.306*	0.427**	0.462***	0.335*	0.304*	0.514***	0.203	0.719***
	MR	0.355*	-	0.603***	0.479***	0.373**	0.163	0.253	0.307*	0.469***	0.258	0.213	0.396**	0.373*	0.320*
	IQ	0.834***	0.603***	-	0.545***	0.496***	0.338*	0.382**	0.520***	0.612***	0.364**	0.276	0.549***	0.250	0.566***
	LNS	0.498***	0.479***	0.545***	-	0.372**	0.355*	0.429**	0.360**	0.418**	0.523***	0.490***	0.478***	0.320*	0.382**
	VLT	0.467***	0.373**	0.496***	0.372**	-	0.461***	0.290*	0.464***	0.639***	0.401**	0.280	0.391**	0.376**	0.488***
	ANT	0.331*	0.163	0.338*	0.355*	0.461***	-	0.309*	0.256	0.404**	0.471***	0.407**	0.291*	0.299*	0.283
	FAS	0.306*	0.253	0.382**	0.429**	0.290*	0.309*	-	0.008	0.014	0.223	0.327*	0.254	0.356*	0.307*
	Trails A[1]	0.427**	0.307*	0.520***	0.360**	0.464***	0.256	0.008	-	0.727***	0.504***	0.379**	0.476***	0.043	0.437**
	Trails B[1]	0.462***	0.469***	0.612***	0.418**	0.639***	0.404**	0.014	0.727***	-	0.469***	0.431**	0.415**	0.218	0.344*
	SC	0.335*	0.258	0.364**	0.523***	0.401**	0.471***	0.223	0.504***	0.469***	-	0.524***	0.495***	0.340*	0.455***
	CPT	0.304*	0.213	0.276	0.490***	0.280	0.401**	0.327*	0.379**	0.431**	0.524***	-	0.317*	0.368*	0.297
Social Cognitive Composite Domain	TASIT[1]	0.514***	0.396**	0.549***	0.478***	0.391**	0.291*	0.254	0.476***	0.415**	0.495***	0.317*	-	0.446**	0.499***
	ER40	0.203	0.373*	0.250	0.320*	0.376**	0.299*	0.356*	0.043	0.218	0.340*	0.368*	0.446**	-	0.353*
	ED	0.719***	0.320*	0.566***	0.382**	0.488***	0.283	0.307*	0.437**	0.344*	0.455***	0.297	0.499***	0.353*	-

*$p<0.05$ **$p<.01$ ***$p<.001$

[1]In the transformed version of this variable, lower/negative numbers reflect better performance.

Vocab=Wechsler Abbreviated Scale of Intelligence Vocabulary subtest; *MR*=Wechsler Abbreviated Scale of Intelligence Matrix Reasoning subtest; *CPT*=Continuous Performance Task – Identical Pairs; *ANT*=D-KEFS Category Fluency Test – Animal Naming; *FAS*=D-KEFS Letter Fluency; SC=Symbol coding from WISC or BACS; *VLT*=Verbal learning test from CVLT or HVLT; *LNS*=Letter number span from WISC or LNS; *TASIT*=The Awareness of Social Interferences Test; *ER40*=Penn Emotion Recognition task; *ED*=Penn Emotion Discrimination task

Table 4

Group Differences at Initial Assessment

Measure	Group		Age		Gender		Group*Age	
	F(*df*)	ηp^2	*F*(*df*)	ηp^2	*F*(*df*)	ηp^2	*F*(*df*)	ηp^2
P sxs	266.76(2, 226)***	0.702	0.260(1, 226)	0.001	2.35(1, 226)	0.010	--	--
N sxs	145.13(2, 225)***	0.563	0.30(1, 225)	0.001	4.73(1, 225)*	0.021	--	--
D sxs	92.56(2,225)***	0.451	0.00(1, 225)	0.000	12.72(1, 225)***	0.054	--	--
G sxs	90.42(2, 225)***	0.446	2.26(1, 225)	0.010	1.32(1, 225)	0.006	--	--
GAF	259.72(2, 225)***	0.698	0.06(1, 225)	0.000	1.26(1, 225)	0.006	--	--
GF:S	87.25(2, 224)***	0.438	0.33(1, 224)	0.001	2.15(1, 224)	0.010	--	--
GF:R	153.92(2, 224)***	0.579	0.275(1, 224)	0.001	2.19(1, 224)	0.010	--	--
BPRS_anx	43.48(2, 193)***	0.311	1.58(1, 193)	0.008	1.74(1, 193)	0.009	--	--
BPRS_dep	46.21(2, 193)***	0.324	9.27(1, 193)**	0.046	0.11(1, 193)	0.001	--	--
Vocab	86.06(2, 232)***	0.426	34.69(1, 232)***	0.130	0.02(1, 232)	0.000	--	--
MR	84.70(2, 225)***	0.430	9.38(1, 225)**	0.040	0.26(1, 225)	0.001	--	--
IQ	89.35 (2, 232)***	0.435	0.10(1, 232)	0.000	0.22(1, 232)	0.001	--	--
LNS	29.77(2, 196)***	0.233	18.73(1, 196)***	0.087	0.47(1, 196)	0.002	--	--
VLT	37.03(2, 232)***	0.242	0.05(1, 232)	0.000	5.57(1, 232)*	0.023	--	--
ANT	18.77(2, 232)***	0.139	0.00(1, 232)	0.000	0.68(1, 232)	0.003	--	--
FAS	39.09(2, 226)***	0.257	21.42(1, 226)***	0.087	2.00(1, 226)	0.009	--	--
Trails A	34.69(2, 231)***	0.231	0.80(1,231)	0.003	0.88(1, 231)	0.004	--	--

Trails B	37.76(2, 224)***	0.252	1.43(1, 224)	0.006	0.39(1, 224)	0.002	--	--
SC	62.98(2, 232)***	0.352	49.98(1, 232)***	0.177	9.50(1, 232)**	0.039	--	--
CPT	34.88(2, 164)***	0.298	37.92(1, 164)***	0.188	1.45(1, 164)	0.009	--	--
TASIT	45.39(2, 210)***	0.302	18.02(1, 210)***	0.079	7.81(1, 210)**	0.036	--	--
ER40	16.88(2, 181)***	0.157	13.31(1, 181)***	0.068	0.18(1, 181)	0.001	--	--
ED	2.59(2, 174)	0.029	10.82(1, 174)***	0.059	1.07(1, 174)	0.006	3.75(2, 174)*	0.041

*p<0.05 **p<.01 ***p<.001

P, N, D, & G sxs= Positive, negative, disorganized, and general symptoms from the Structured Interview for Prodromal Syndromes (SIPS); *GAF*=Global Assessment of Functioning; *GF:S*=Global Functioning: Social scale; *GF:R*= Global Functioning: Role scale; *BPRS_anx*=BPRS anxiety item; *BPRS_dep*=BPRS depression item; *Vocab*=Wechsler Abbreviated Scale of Intelligence Vocabulary subtest; *MR*=Wechsler Abbreviated Scale of Intelligence Matrix Reasoning subtest; *CPT*=Continuous Performance Task – Identical Pairs; *ANT*=D-KEFS Category Fluency Test – Animal Naming; *FAS*=D-KEFS Letter Fluency; *SC*=Symbol coding (WISC /BACS); *VLT*=Verbal learning test from CVLT or HVLT; *LNS*=Letter number span from WISC or LNS; *TASIT*=The Awareness of Social Interferences Test; *ER40*=Penn Emotion Recognition task; *ED*=Penn Emotion Discrimination task.

Partial η^2 (ηp^2) provides a measure of effect size for group differences; values over 0.14 are considered large effects.

Table 5

Group Differences at Initial Assessment, Controlling for IQ

Measure	Group		Age		Gender		IQ		Group*Age	
	F(*df*)	ηp^2	*F*(*df*)	ηp^2	*F*(*df*)	ηp^2	*F*(*df*)	ηp^2	*F*(*df*)	ηp^2
P sxs	260.62 (2, 224)***	0.699	0.15(1, 224)	0.001	2.72(1, 224)	0.012	17.78(1, 224)***	0.074	--	--
N sxs	114.35(2, 223)***	0.506	0.43(1, 223)	0.002	5.17(1, 223)*	0.023	10.41(1, 223)***	0.045	--	--
D sxs	62.26(2,223)***	0.358	0.02(1, 223)	0.000	13.69(1, 223)***	0.058	12.14(1, 223)***	0.052	--	--
G sxs	70.61(2, 223)***	0.338	2.38(1, 223)	0.011	1.44(1, 223)	0.006	1.76(1, 223)	0.008	--	--
GAF	190.60(2, 223)***	0.631	0.01(1, 223)	0.000	1.49(1, 223)	0.007	19.65(1,223)***	0.081	--	--
GF:S	54.93(2, 222)***	0.331	0.19(1, 222)	0.001	2.34(1, 222)	0.010	21.98(1,222)***	0.090	--	--
GF:R	89.23(2, 222)***	0.446	0.40(1, 222)	0.002	2.35(1, 222)	0.010	9.38(1, 222)**	0.041	--	--
BPRS_anx	33.09(2, 192)***	0.256	1.62(1, 192)	0.008	1.66(1, 192)	0.009	0.85(1,192)	0.004	--	--
BPRS_dep	44.92(2, 192)***	0.319	9.26(1, 192)**	0.046	0.10(1, 192)	0.001	0.13(1,192)	0.001	--	--
Vocab	3.31(2, 231)*	0.028	124.47(1, 231)***	0.350	1.18(1, 231)	0.005	684.05(1,231)***	0.748	--	--
MR	19.13(2, 224)***	0.146	18.47(1, 224)***	0.076	0.33(1, 224)	0.001	295.63(1,224)***	0.569	--	--
LNS	1.30(2, 195)	0.013	25.23(1, 195)***	0.115	0.40(1, 195)	0.002	68.08(1,195)***	0.259	--	--
VLT	5.12(2, 231)**	0.042	0.01(1, 231)	0.000	8.52(1, 231)**	0.036	66.24(1,231)***	0.223	--	--
ANT	22.10(2, 231)***	0.161	0.01(1, 231)	0.000	1.00(1, 231)	0.004	21.31(1,231)***	0.084	--	--
FAS	4.30(2, 225)*	0.037	24.50(1, 225)***	0.098	3.05(1, 225)	0.013	50.45(1,225)***	0.183	--	--
Trails A	12.00(2, 230)***	0.094	0.69(1,230)	0.003	1.66(1, 230)	0.007	56.00(1,230)***	0.196	--	--
Trails B	9.68(2, 223)***	0.080	1.16(1, 223)	0.005	0.60(1, 223)	0.003	54.86(1,223)***	0.197	--	--

SC	13.84(2, 231)***	0.107	57.90(1, 231)***	0.200	12.89(1, 231)***	0.053	48.05(1,231)***	0.172	--	--
CPT	4.74(2, 163)**	0.055	49.90(1, 163)***	0.234	1.55(1, 163)	0.009	42.20(1,163)***	0.206	--	--
TASIT	5.06(2, 209)**	0.046	20.90(1, 209)***	0.091	9.03(1, 209)**	0.041	53.01(1,209)***	0.202	--	--
ER40	1.22(2, 180)	0.013	14.54(1, 180)***	0.075	0.10(1, 180)	0.001	23.90(1,180)***	0.117	--	--
ED	4.32(2, 173)*	0.048	15.50(1, 173)***	0.082	0.92(1, 173)	0.005	56.97(1, 173)***	0.248	4.64(2, 173)*	0.051

*p<0.05 **p<.01 ***p<.001

P, N, D, & G sxs= Positive, negative, disorganized, and general symptoms from the Structured Interview for Prodromal Syndromes (SIPS); *GAF*=Global Assessment of Functioning; *GF:S*=Global Functioning: Social scale; *GF:R*= Global Functioning: Role scale; *BPRS_anx*=BPRS anxiety item; *BPRS_dep*=BPRS depression item; *Vocab*=Wechsler Abbreviated Scale of Intelligence Vocabulary subtest; *MR*=Wechsler Abbreviated Scale of Intelligence Matrix Reasoning subtest; *CPT*=Continuous Performance Task – Identical Pairs; *ANT*=D-KEFS Category Fluency Test – Animal Naming; *FAS*=D-KEFS Letter Fluency; *SC*=Symbol coding (WISC /BACS); *VLT*=Verbal learning test from CVLT or HVLT; *LNS*=Letter number span from WISC or LNS; *TASIT*=The Awareness of Social Interferences Test; *ER40*=Penn Emotion Recognition task; *ED*=Penn Emotion Discrimination task.

Partial η^2 (ηp^2) provides a measure of effect size for group differences; values over 0.14 are considered large effects.

Table 6

Correlations between Cognitive Measures and Positive Psychotic Symptoms[1]

	22q11DS Patients		EOP Patients	
Measure	Pearson correlation (*r*)	*p*-value	Pearson correlation (*r*)	*p*-value
Vocab	-0.329	<0.05	-0.369	<0.01
IQ	-0.336	<0.05	-0.368	<0.01
LNS	-0.303	<0.05	-0.085	NS (0.56)
VLT	-0.415	0.001	-0.227	NS (0.113)
FAS	-0.270	<0.05	0.079	NS (0.589)
Trails A[2]	0.022	NS (0.873)	0.154	NS (0.287)
Trails B[2]	0.061	NS (0.657)	0.213	NS (0.143)
SC	-0.258	NS (0.055)	-0.304	<0.05
CPT	-0.163	NS (0.285)	-0.103	NS (0.502)
TASIT[2]	0.235	NS (0.081)	0.345	<0.05

[1]Correlations included measures for which both patient groups showed significant impairment relative to controls

[2]In the transformed version of this variable, lower/negative numbers reflect better performance.

Vocab=Wechsler Abbreviated Scale of Intelligence Vocabulary subtest; *LNS*=Letter number span from WISC or LNS; *VLT*=Verbal learning test from CVLT or HVLT; *FAS*=D-KEFS Letter Fluency; *SC*=Symbol coding from WISC or BACS; *CPT*=Continuous Performance Task – Identical Pairs; *TASIT*=The Awareness of Social Interferences Test.

Table 7

Predicting Functional Outcome[1]

Outcome Measure	Predictors	Neurocognitive Model (n=68 HC, 33 22q11DS, 24 EOP) β	Social Cognitive Model (n=63 HC, 33 22q11DS, 24 EOP) β
Follow-up GAF	Cognition	0.103	0.018
	Initial GAF	0.240	0.274
	Group	-0.608*	-0.640*
	Time Delay	-0.658*	-0.676*
	Age	-0.112	-0.088
	Gender	-0.021	-0.020
	GAF*Time	0.421	0.421
	Group*Time	0.572*	0.599*
Follow-up GF:S	Cognition	0.019	0.011
	Initial GF:S	0.018	0.034
	Group	-0.685**	-0.680**
	Time Delay	-1.005***	-0.973***
	Age	0.013	0.012
	Gender	-0.010	-0.012
	GF:S*Time	0.685**	0.666**
	Group*Time	0.615*	0.607*
Follow-up GF:R	Cognition	0.166*	0.015
	Initial GF:R	0.549***	0.624***
	Group	-0.144*	-0.162*
	Time Delay	-0.158**	-0.175**
	Age	-0.103	-0.071
	Gender	-0.012	-0.009

*p<0.05 **p<.01 ***p<.001

[1]n=125 for neurocognitive models; n=120 for social cognitive models.

Figure 1. *Group-by-Age Interaction for the Penn Emotion Discrimination (ED) Measure* ($F(2, 174)=3.75$, $p<0.05$).

Results from the initial assessment score linear regressions show the effect of age to be greatest for the EOP group.

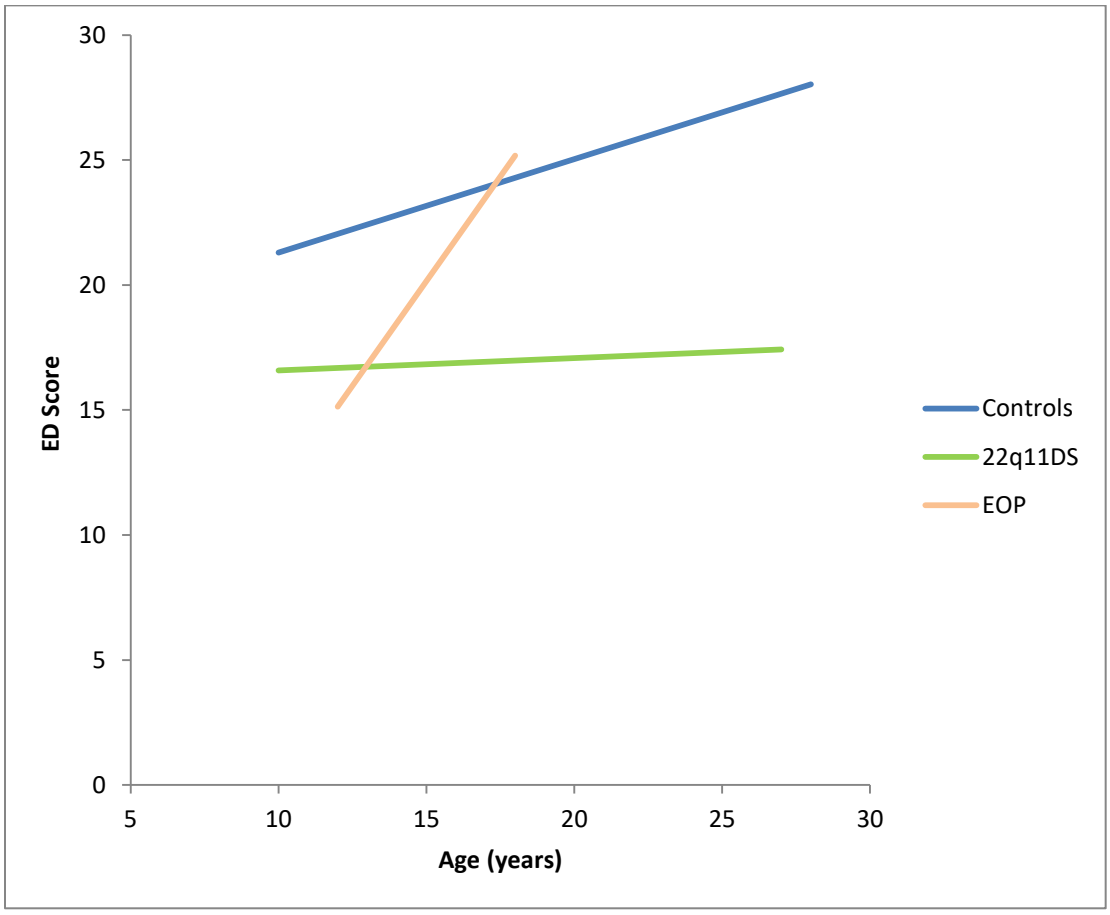


Figure 2. *Initial Assessment z-score Plot – Clinical Measures.*

The graph depicts the group z-score means for each clinical measure; significant pairwise comparisons between the EOP and 22q11DS patient groups are indicated (Bonferroni-corrected: *p<0.05 ***p<0.001). Patients with EOP evidenced significant impairment compared to 22q11DS patients on all measures, except ratings of social and role functioning. Healthy controls significantly differed from both patient groups (p<0.001) on all measures except on a rating of depression (BPRSdep), in which there was no difference between controls and 22q11DS patients. While statistics are based on the regression models covarying for age and gender, z-scores are plotted for visualization purposes only. Note that negative scores on all measures indicate more severe symptomatology relative to controls. *GAF*=Global Assessment of Functioning; *GF:S*=Global Functioning: Social scale; *GF:R*= Global Functioning: Role scale; *BPRS_anx*=BPRS anxiety item; *BPRS_dep*=BPRS depression item.

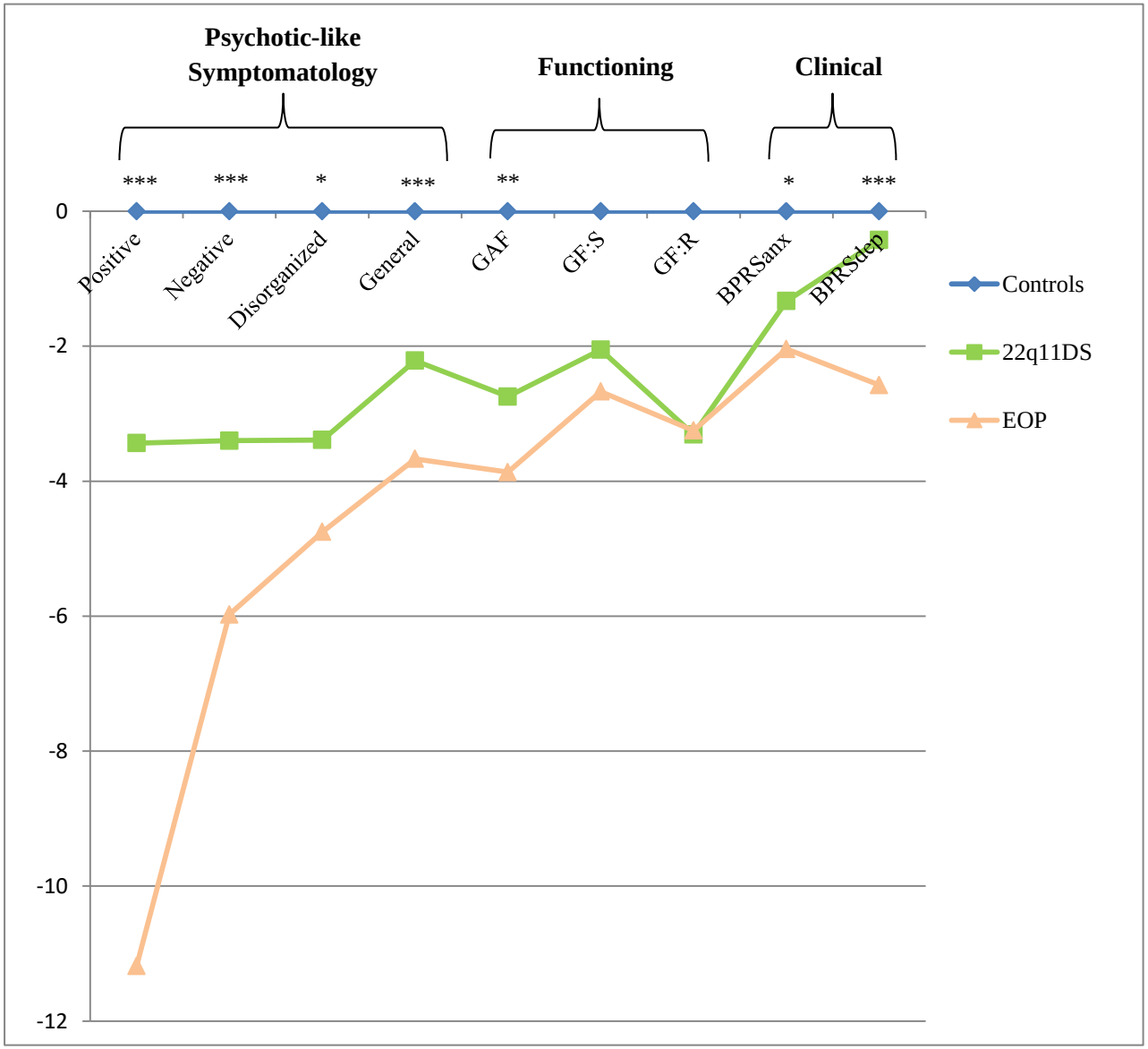

Psychotic-like Symptomatology
Functioning
Clinical
***
***
*
***
**
*
***
0
-2
-4
-6
-8
-10
-12
Positive
Negative
Disorganized
General
GAF
GF:S
GF:R
BPRSanx
BPRSdep
Controls
22q11DS
EOP

Figure 3. *Initial Assessment z-score Plot – Cognitive Measures.*

The graph depicts the group z-score means for each neurocognitive and social cognitive measure and pairwise comparisons between the EOP and 22q11DS patient groups (Bonferroni-corrected: *p<0.05 ***p<0.001). Patients with EOP evidenced significant differences compared to 22q11DS patients on all measures except two measures of processing speed (Trails A & B). Healthy controls significantly differed from both patient groups (p<0.01, at least) on all measures except MR, ER40, and ED, on which there were no difference between controls and EOP patients, as well as on ANT, for which no difference was observed between controls and 22q11DS patients. While statistics are based on the regression models covarying for age and gender, z-scores are plotted for visualization purposes only. Note that negative scores on all measures indicate more severe deficits relative to controls. *Vocab*=Wechsler Abbreviated Scale of Intelligence Vocabulary subtest; *MR*=Wechsler Abbreviated Scale of Intelligence Matrix Reasoning subtest; *CPT*=Continuous Performance Task – Identical Pairs; *ANT*=D-KEFS Category Fluency Test – Animal Naming; *FAS*=D-KEFS Letter Fluency; SC=Symbol coding from WISC or BACS; *VLT*=Verbal learning test from CVLT or HVLT; *LNS*=Letter number span from WISC or LNS; *TASIT*=The Awareness of Social Interferences Test; *ER40*=Penn Emotion Recognition task; *ED*=Penn Emotion Discrimination task.

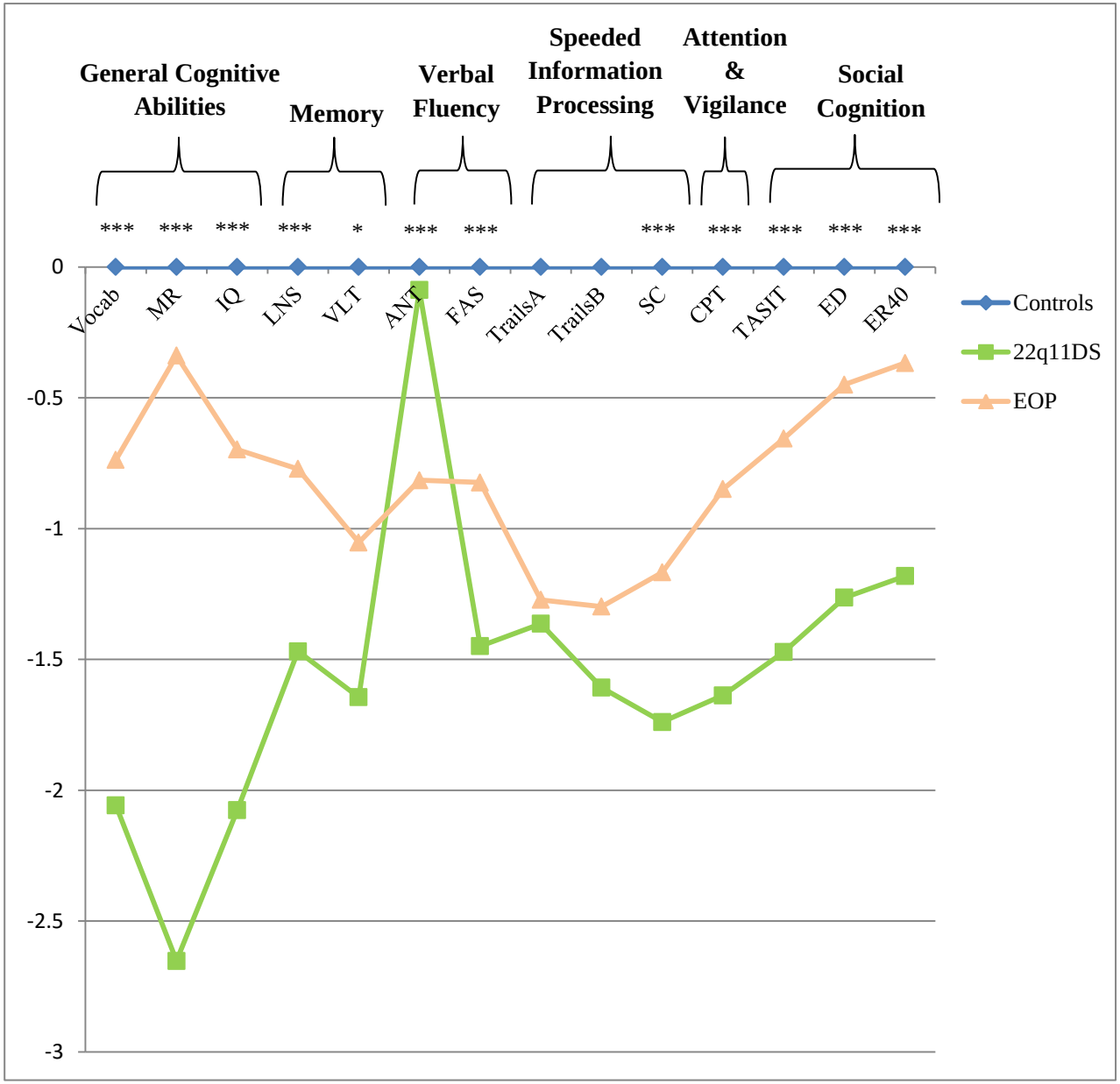
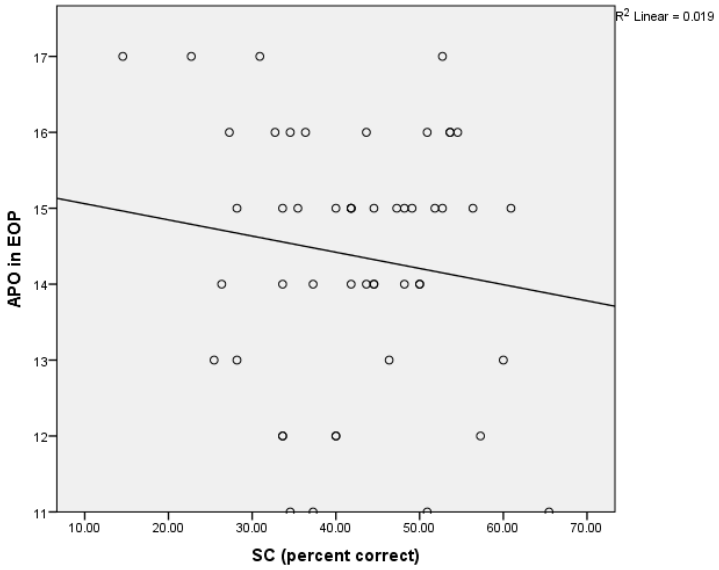

General Cognitive Abilities
Memory
Verbal Fluency
Speeded Information Processing
Attention & Vigilance
Social Cognition
*** *** *** *** * *** *** *** *** *** *** ***
0
-0.5
-1
-1.5
-2
-2.5
-3
Vocab
MR
IQ
LNS
VLT
ANT
FAS
TrailsA
TrailsB
SC
CPT
TASIT
ED
ER40
Controls
22q11DS
EOP

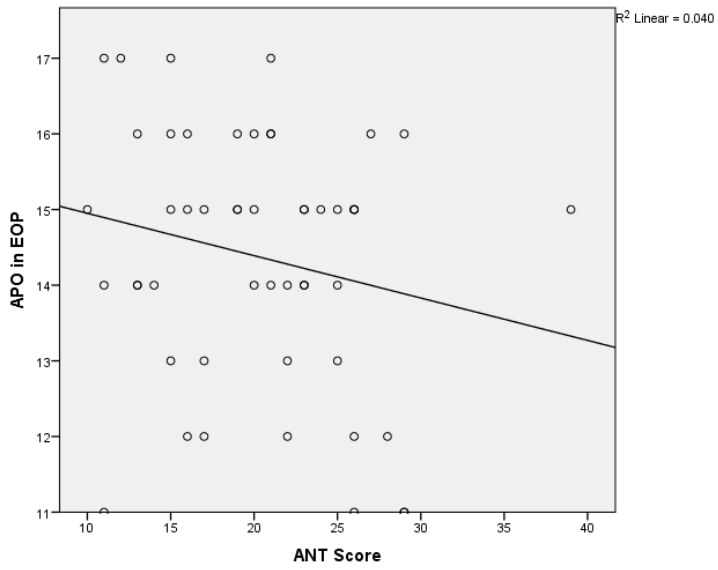
Figure 4. *Association between APO and Cognition in EOP Patients and 22q11DS Patients with Comorbid Psychosis.*

Among EOP patients, earlier age of psychosis onset was associated with better performance on specific cognitive measures. The first panel (A) depicts the significant correlation between APO and SC (r=-0.300, $p<0.05$); the second panel (B) depicts the significant association between APO and ANT (r=-0.338, $p<0.05$) in EOP. In contrast, among 22q11DS patients who had comorbid psychotic diagnoses (n=8), earlier age of psychosis onset was associated with worse performance on particular cognitive measures. The third panel (C) depicts the significant correlation between APO and FAS ($r=0.939$, $p<0.05$); the fourth panel (D) depicts the significant correlation between APO and ED40 ($r=0.891$, $p<0.05$) in 22q11DS patients with psychosis. Note that plots are for visualization purposes only and do not include covariates.

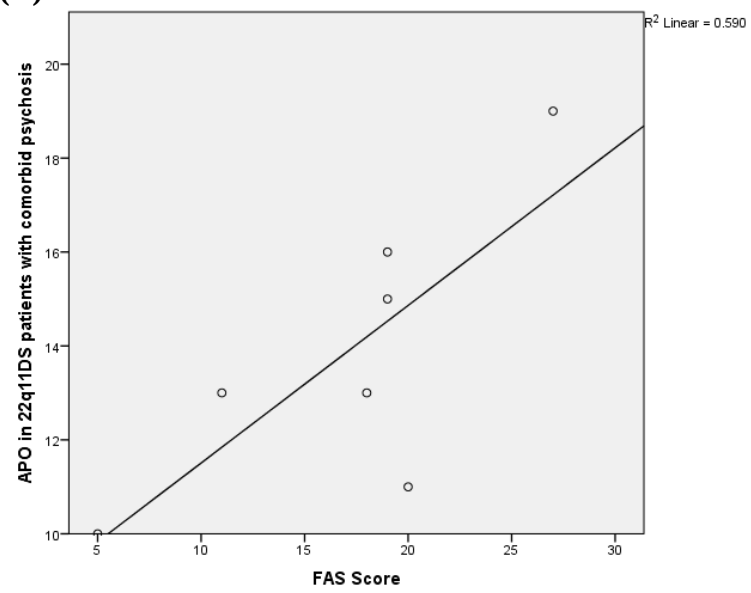
(A)



(B)



(C)


R² Linear = 0.590
APO in 22q11DS patients with comorbid psychosis
FAS Score
10
12
14
16
18
20
5
10
15
20
25
30

(D)

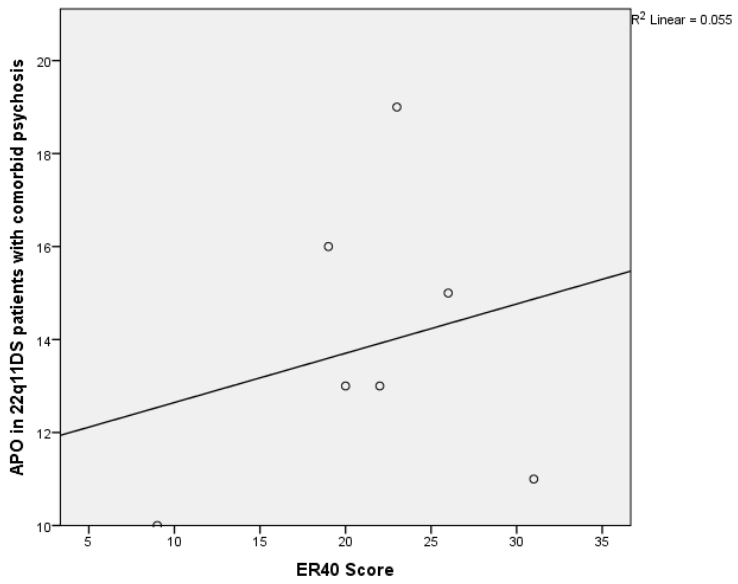

R² Linear = 0.055
APO in 22q11DS patients with comorbid psychosis
ER40 Score
10
12
14
16
18
20
5
10
15
20
25
30
35

Figure 5. *Group-by-Time Interaction.*

A significant interaction of group-by-time delay between assessments (p<0.05) was observed in the prediction of follow-up Global Functioning: Social (GF:S) Scores. As the plots for the neurocognitive and social cognitive models were identical, only one is shown for visualization purposes.

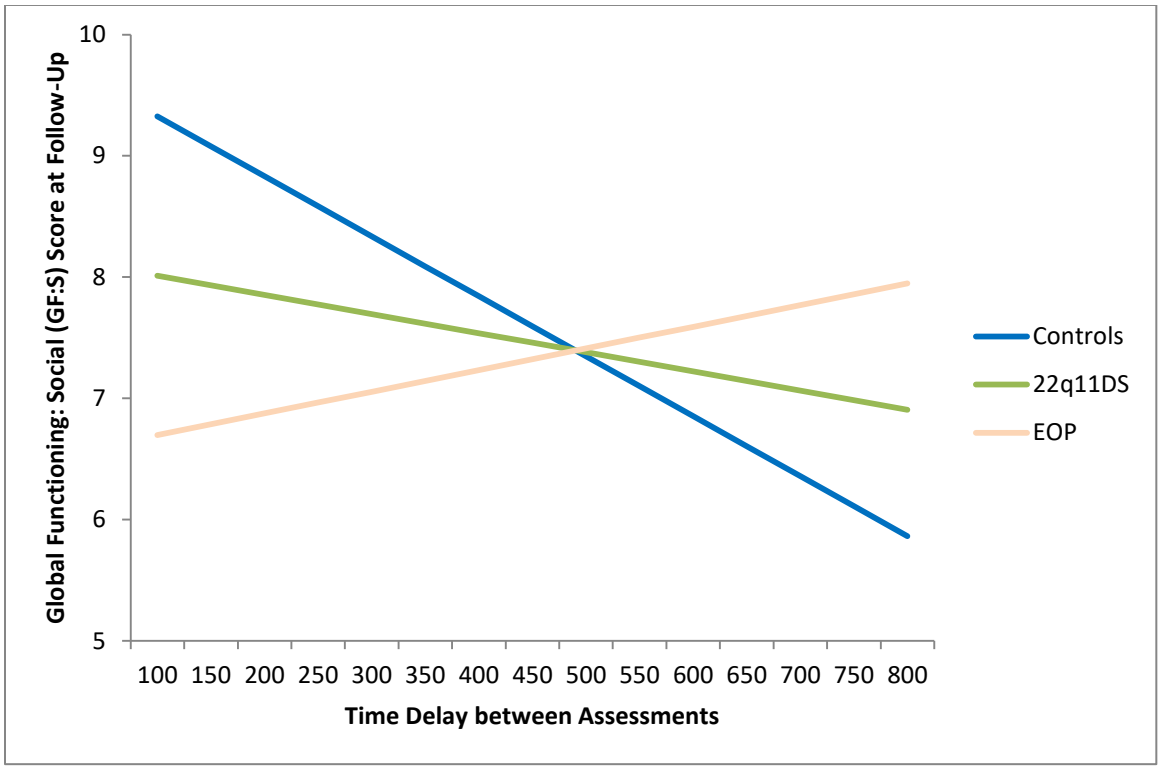
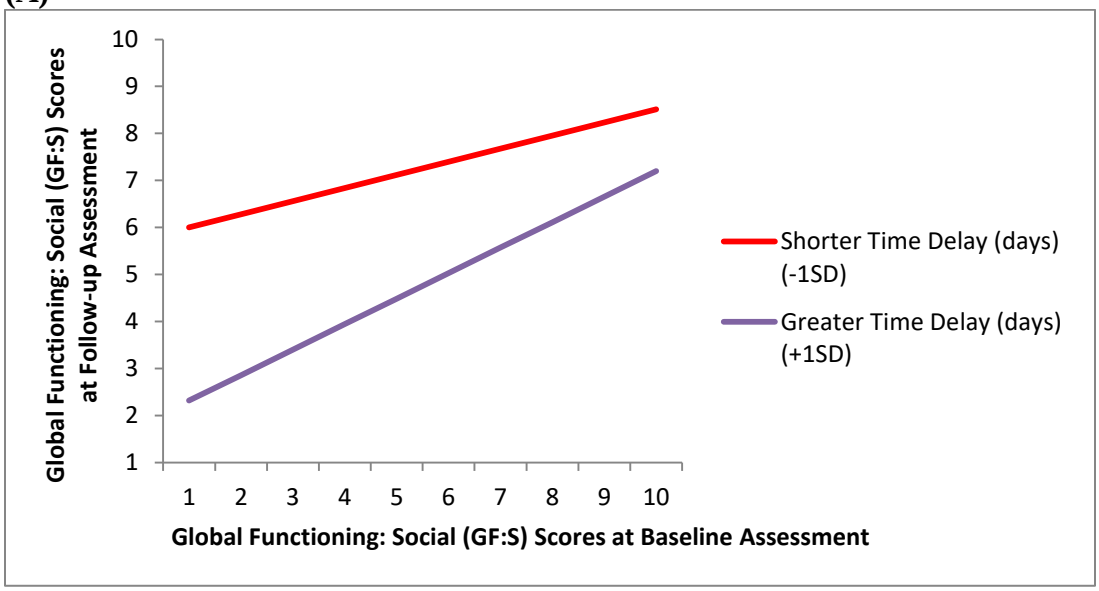
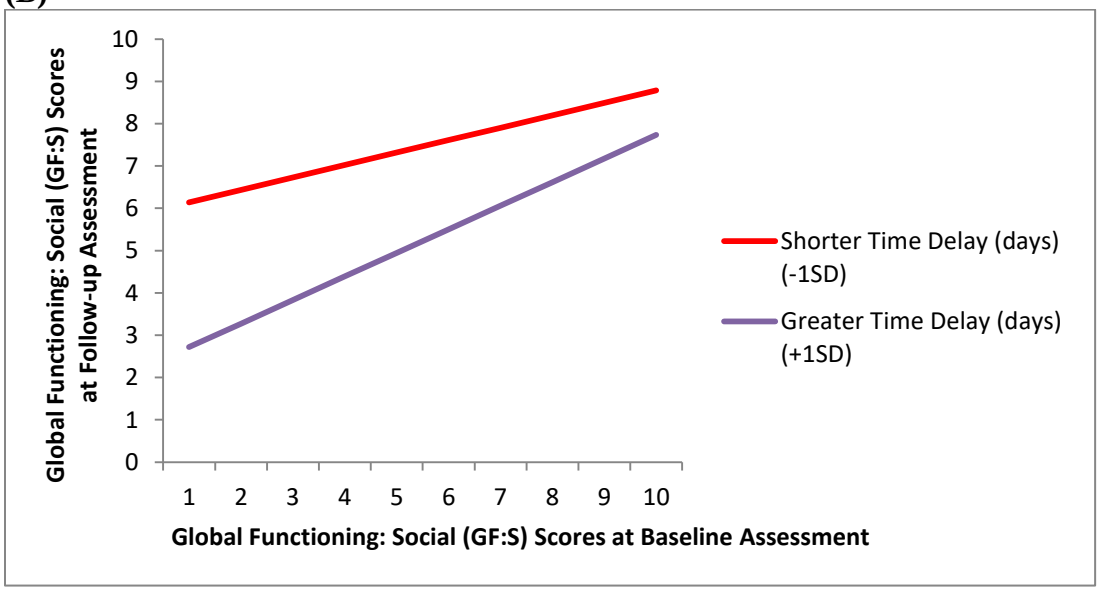


Figure 6. *Initial Assessment Global Functioning: Social (GF:S) Scores-by-Time Interaction.* The first panel (A) depicts the prediction of social functioning at follow-up by the interaction of initial GF:S and time between assessments in the neurocognition regression model (β=0.685, $p<0.01$). The second panel (B) depicts the comparable interaction in the social cognition regression model (β=0.666, $p<0.01$).

(A)



(B)



STUDY 3: COGNITIVE TRAINING FOR EARLY-ONSET PSYCHOSIS

Abstract

Plasticity-based cognitive training (CT) is a behavioral intervention based on neuroplasticity models that attempts to treat neurocognitive deficits associated with various neurological and psychiatric disorders such as schizophrenia. However, this approach has yet to be attempted with early-onset psychosis (EOP) patients. The current study therefore sought to investigate the feasibility of conducting plasticity-based CT in patients with EOP, and evaluate the factors that may moderate treatment-associated changes in cognition and functioning. Results demonstrated that 53.85% of the 13 initial participants completed at least 10 hours of training, with only 31% completing 30 hours. Boredom was noted to be a particular concern. Parent surveys indicated that all participants required encouragement and reminders in order to train. Repeated measures ANCOVAs revealed higher post-training social functioning scores relative to pre-training scores, as well as decreased general and anxiety symptoms following training. Additionally, pre-CT scores on measures of disorganized symptoms and multiple cognitive measures (IQ, vocabulary, processing speed, working memory, sustained attention, verbal fluency, and emotion recognition) were negatively associated with changes over time in each respective domain; in other words, the better the pre-training scores were, the more likely scores were to decrease over time, while low pre-CT scores were more likely to improve.. Lastly, age at initial assessment was correlated with pre- to post-CT decreases in general symptoms and improvement in working memory performance. Earlier age at psychosis onset was associated with less improvement in social and role functioning from pre- to post-assessments, greater disorganized and general symptoms, and a decline in performance on matrix reasoning and working memory tasks. Overall, this study provides a first step in evaluating plasticity-based CT feasibility in an EOP

sample; results highlight the unique training considerations for adolescents with EOP, including the importance of parental support, intrinsic motivation, and baseline functioning level.

Keywords: cognitive training, neuroplasticity, schizophrenia, neurocognition, functioning

Introduction

Cognitive Training for Schizophrenia

Cognitive training (CT), also referred to as cognitive rehabilitation, cognitive enhancement, or cognitive remediation (Hogarty, Flesher, Ulrich, et al., 2004), is a behavioral training intervention that seeks to target a broad range of cognitive processes in an effort to promote improvements in multiple cognitive domains (e.g., memory, attention, social cognition), as well as to improve overall functioning in everyday life. CT is used to treat neurocognitive deficits that may have resulted from a range of neurological and psychiatric disorders or other organic brain injuries. Specifically, CT aims to help regain lost cognitive skills, aid in the acquisition of new skills, and/or improve adaptive role and social functioning (Laatsch, Thulborn, Krisky, Shobat, & Sweeney, 2004; Wykes & Spaulding, 2011).

While CT has been applied to a range of neurologic and neuropsychiatric disorders, it is of particular interest as a possible intervention for individuals with schizophrenia (SZ), given the enduring and treatment-resistant cognitive deficits associated with the disorder (Frazier et al., 2012; Keefe et al., 2012). Specifically, patients with SZ typically have some degree of global cognitive impairment (~1 SD below population norms, on average), accompanied by significant impairments in specific cognitive domains (long-term memory, working memory, attention, and verbal fluency) (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Heinrichs & Zakzanis, 1998), as well as deficits in social cognition (Penn, Sanna, & Roberts, 2008).

Further, regardless of age, gender, or illness duration, the degree of deficit in verbal fluency, verbal memory/learning, visual memory/learning, reasoning & problem solving, attention & vigilance, and particularly social cognition among patients with SZ is associated with poorer functioning in the areas of: community functioning, social behavior, social problem

solving, and social skills, as per a recent meta-analytic review of cross-sectional associations (Fett et al., 2011). A review of longitudinal work has similarly implicated cognitive deficits as a predictor of poor community functioning 6 months to 10 years following initial evaluation (Green, Kern, & Heaton, 2004). More recent research has highlighted the role of social cognition as a mediator of the relationship between neurocognition and global functioning/ symptomatology, again emphasizing the role of social cognition and neurocognition in predicting long-term outcome (Lam, Raine, & Lee, 2014; Schmidt, Mueller, & Roder, 2011). Thus, an essential need in the field is to identify treatment methods that improve cognition, which in turn may stave off associated functional declines.

Several meta-analyses have recently examined the effectiveness of computerized CT for improving cognition in patients with SZ (McGurk et al., 2007; Thorsen et al., 2014; Wykes et al., 2011); these studies indicate significant treatment-associated gains in the domains of attention, processing speed, verbal memory and working memory in patients with SZ, with small to medium effect sizes (Cohen's *d*s ranging from 0.38 to 0.54). The largest effect sizes (medium, *d*s between 0.5 to 0.6) to date have been observed in the domain of social cognition (Grynszpan et al., 2011). Small to medium effect sizes have also been observed in clinical and functional outcome measures assessed at 6-month to 2-year follow-up periods, specifically in: daily functioning (d=0.35-0.37), overall cognition (d=0.4-0.45), and clinical symptoms (positive, negative, and general) (d=0.28) (McGurk et al., 2007; Thorsen et al., 2014; Wykes et al., 2011). Across meta-analyses, no significant effect of CT on visual learning and memory has been found (McGurk et al., 2007; Wykes et al., 2011). Effect sizes for these meta-analyses were calculated by contrasting treatment group means with comparison group means, with the comparison group

consisting of heterogeneous treatment conditions (e.g., treatment-as-usual, placebo, vocational training, etc.).

In order to further examine the extent of possible treatment-associated gains, the role of phase of illness in CT effectiveness has been considered; the effects of 12 weeks of CT were compared between early-course patients (e.g., within five years of their initial psychotic episode) and chronic patients (more than 15 years of illness) (Bowie, Grossman, Gupta, Oyewumi, & Harvey, 2014). While both groups improved cognitively, the early-course cohort demonstrated greater gains in processing speed and executive functioning, as well as better post-treatment adaptive function and real-world work skills (Bowie et al., 2014). This suggests that CT for SZ is most effective when delivered early in the course of illness (Bowie et al., 2014). Relatedly, the effects of CT appear limited in older individuals with SZ (ages ~40 and up) as compared to younger patients (under 40), regardless of initial intelligence, as the older cohorts do not demonstrate significant effects of CT on the majority of cognitive domains and/or clinical symptomatology (Wykes et al., 2009; Kontis, Huddy, Reeder, Landau, & Wykes, 2013; McGurk & Mueser, 2008). Results are consistent with work suggesting increased plasticity in learning among younger individuals (Dennis & Cabeza, 2011). However, other work has shown significant improvements in memory, executive function, and social functioning among chronic patients below the age of 55 years that persisted at 6-month follow-up evaluations (Penadés et al., 2006). This suggests that CT is still feasible in this group, but may require more intensive and concentrated training (i.e., Penadés et al.'s 40 sessions vs. Kontis et al.'s 20 sessions), in line with the idea that older patients (who, on average, have suffered symptoms for more time) have had a longer duration of continuous, maladaptive information-processing that may be less malleable.

Plasticity-Based CT

Of note, the training approaches described above have been heterogeneous, using a variety of techniques. The current project focuses on a distinct training approach which is based on neuroplasticity models (e.g., Buonomano & Merzenich, 1998; Merzenich, Van Vleet, & Nahum, 2014; Nahum, Lee, & Merzenich, 2013). The exercises created for this plasticity-based CT approach were derived from the principle that early perceptual information processing deficits may underlie higher-order cognitive processes, given that cortical representations of sensory input are known to be impaired in patients with SZ (Barch & Carter, 1998; Butler et al., 2007, 2009; Carter et al., 1998; Javitt, Liederman, Cienfuegos, & Shelley, 1999; Martínez et al., 2008; Schechter, Butler, Silipo, Zemon, & Javitt, 2003). Therefore, in order to durably increase the efficiency of higher order or "top down" processes affected in SZ (i.e., executive functions, pattern recognition, metacognition, working memory), CT must first target lower level or "bottom up" processes (i.e., speed and accuracy of perception, temporal and spatial resolution, stimuli signal strength) in order to improve related cortical representations (Adcock et al., 2009; Fisher, Holland, Merzenich, & Vinogradov, 2009; Keshavan, Vinogradov, Rumsey, Sherrill, & Wagner, 2014; Subramaniam et al., 2012; Vinogradov et al., 2012).

This CT approach is based on the theory that precision of sensory representation is an important determinant of cognitive performance (Adcock et al., 2009). As such, drawing on the brain's ability to adapt following exposure to novel experiences and input, the impaired information processing and underlying inefficient neural circuitry in SZ can be modified through the learning process associated with the CT tasks (Fisher et al., 2009; Keshavan et al., 2014; Vinogradov et al., 2012). In order to maximize performance improvement and increase the generalization of skills among patients with SZ, the training is additionally intensive,

constrained, and consists of (initially) exaggerated sensory stimuli with gradual and adaptive increases in level of task difficulty (e.g., stimuli presented more rapidly and/or take on more naturalistic appearance) in order to incentivize and motivate (Adcock et al., 2009; Vinogradov et al., 2012). Therefore, through the enriched, controlled learning environment that is provided, there is now evidence that this specific CT for SZ can modulate the underlying neural substrates of cognitive domains, perceptual abnormalities, and behavioral dysfunction experienced by patients, ultimately leading to behavioral and functional changes (Fisher et al., 2013; Keshavan et al., 2014; Laatsch et al., 2004; Rabipour & Raz, 2012).

With these principles in mind, the plasticity-based CT approach was developed to specifically focus on two key perceptual areas for patients with SZ: abnormal processing of auditory information, which is thought to underlie verbal learning and memory deficits, and deficits in social cognition, such as impaired theory of mind skills (representation of self and others' mental states). In the auditory domain, computerized tasks entail discriminating between sound stimuli with varying frequencies or between similar-sounding phonemes, with the task becoming progressively and adaptively more difficult over the course of training (e.g., by shortening inter-stimulus intervals) (Fisher et al., 2009; Fisher, Holland, Subramaniam, & Vinogradov, 2010). Such auditory and working memory tasks are employed to induce changes in the resolution of auditory cortical representations (Fisher et al., 2009). In the social cognition tasks, emotions presented through audio or video clips must be recognized/labeled (Hooker et al., 2012, 2013; Sacks et al., 2013; Subramaniam et al., 2012). As mentioned above, since higher-order facial discrimination abilities also rely upon visuospatial skills, deficits in this area are first addressed by improving visual attention and contrast sensitivity (Vinogradov et al., 2012).

Through the implementation of these methods, plasticity-based CT has been shown to result in neurocognitive improvement in adult-onset SZ patients. In particular, patients receiving this CT program have demonstrated: 1) increases in a composite neurocognitive score, driven by gains in verbal learning, social cognition, and reasoning/problem-solving domains (Keefe et al., 2012); 2) improvement on an auditory discrimination task (Keefe et al., 2012; Murthy et al., 2012); 3) improved visual learning (Sacks et al., 2013; Surti, Corbera, Bell, & Wexler, 2011); 4) increased verbal working memory, verbal learning and memory, and global cognition (Adcock et al., 2009; Fisher et al., 2009; Sacks et al., 2013); and 5) decreased symptomatology and improvements in processing speed, problem solving, and social cognition (Sacks et al., 2013). Furthermore, cognitive improvement predicted improvement in functioning (quality of life) at 6-month follow-ups following CT completion; gains in verbal learning and memory were also observed to persist over this time period (Adcock et al., 2009; Fisher et al., 2010; Genevsky, Garrett, Alexander, & Vinogradov, 2010).

Mechanisms underlying Cognitive Improvement

Naturally, the underlying neural mechanisms of observed behavioral changes are an area of intense interest. Studies that have employed functional magnetic resonance imaging (fMRI) before and after plasticity-based CT have identified changes in neural activity that are associated with CT. For example, the pre/post-training performance (from baseline to follow-up, 16 weeks later) on an untrained *N*-back working memory functional MRI (fMRI) task was compared between three groups: 15 SZ patients receiving 80 hours of CT emphasizing auditory/verbal, visual, and social cognition (e.g., facial emotion recognition) processing; 13 patients receiving access to 80 hours of commercial computer games; and 12 healthy controls who did not receive any treatment (Subramaniam et al., 2014). Following training, only patients who received the

targeted CT demonstrated improved performance on the working memory task, with corresponding increases in left middle frontal gyri (MFG) activation, an area associated with working memory. CT patients also displayed a significant correlation between increased performance on the fMRI task and change in right MFG activity, which was also observed in healthy controls. This association was additionally found to predict better working memory skills and occupational functioning at a follow-up evaluation six months following CT completion (Subramaniam et al., 2014). Using identical study procedures (i.e., pre/post-CT MRI scans to evaluate changes in neural activity), only patients receiving the CT demonstrated improvement in reality monitoring (i.e., differentiating the source of internal from external experiences) and associated increased activity in the medial prefrontal cortex (mPFC), a brain region implicated in social cognitive processing; these findings similarly predicted increased social functioning six months later, suggesting lasting effects (Subramaniam et al., 2012).

Additional examinations of the neural underpinnings of social cognition changes following CT have been conducted. As compared to 11 adult patients with SZ receiving 50 hours of commercial computer games, 11 patients undergoing 50 hours of plasticity-based auditory and social cognition training demonstrated greater post-training increases in postcentral gyrus activity (an area associated with facial emotion recognition) during an fMRI task requiring identification of both negative and positive emotions (Hooker et al., 2012). Both groups also showed correlations between pre/post changes in neural activity and behavior, such that increased neural activity in the postcentral gyrus was associated with improvement on a neurocognitive measure of emotion perception. In a related examination of the same cohorts, as compared to the general computer games group, CT patients demonstrated greater post-training increases in accurate recognition of expressions of happiness, surprise, and fear that correlated

with increased activation within the amygdala, putamen, and mPFC (Hooker et al., 2013). The CT group also exhibited behavioral improvement on the same neurocognitive measure of emotion perception. Taken together, these studies demonstrate the enhanced functioning of neural structures and successive improved neurocognitive skills and/or functioning following CT.

CT for Early-Onset Psychosis

Recent studies have begun to investigate the potential benefits of CT among patients with early-onset psychosis (EOP), defined based on the development of overt psychotic symptoms prior to the age of 18 (Holzer et al., 2014; Puig et al., 2014; Wykes et al., 2007). Such patients present with more severe neurocognitive deficits as compared to the adult-onset form of illness, particularly in memory, processing speed, and executive function domains (Frangou, 2010; Rajji, Ismail, & Mulsant, 2009). Auditory hallucinations, predominant negative symptoms, and decreased social adjustment and communication are additional hallmarks of the disorder (Kyriakopoulos & Frangou, 2007). Both clinical and neurocognitive features of EOP have been shown to predict future functioning outcomes; specifically, processing speed has been shown to predict social functioning one year later, and social cognition, including subareas of social perception, emotion perception, theory of mind, and attributional style have correlated with several aspects of functioning including social milieu behavior, community functioning, social skills and social problem solving (Bachman et al., 2012; Couture, Penn, & Roberts, 2006; Fett et al., 2011). CT-focused intervention in youth with EOP is therefore of particular interest, as the period of increased brain plasticity and ongoing neural development during adolescence (Blakemore, 2012; Kolb & Gibb, 2011; Spear, 2000) may potentially allow for greater cognitive gains.

While plasticity-based CT has not yet been applied directly to an EOP sample, one recent study utilized a combined adolescent/young adult recent-onset SZ cohort to examine outcomes in neurocognitive measures, clinical symptoms, and global functioning (Fisher et al., 2014). Patients were randomized to one of two groups and compared: playing 20 to 40 hours of commercial computer games (e.g., Hangman; checkers), or receiving 20 to 40 hours of computerized CT. Similar to methods described above, CT in this study utilized verbal and auditory working memory tasks theorized to improve the resolution of auditory cortical representations, with the goal of affecting downstream processes of verbal learning and auditory processing. All training was conducted on study-provided laptops in the home environment, with the exception of 1 patient who preferred to work in the clinic. Participants were called 1-2 times weekly by staff to discuss progress and provide coaching, when needed. Of the 121 patients randomized to the two groups, there were 40 patients in each group (66% total) who completed the required 20 to 40 hours of training, while three patients in each group completed less than 20 hours. Overall, 33 participants withdrew (27%), and one patient from each group (1.65% total) was subsequently excluded due to medication changes.

Results demonstrated effects of CT in study completers on global cognition (d = 0.73), verbal memory (d = 0.69), and problem solving (d = 0.46). Additionally, CT treatment response (i.e., increased cognitive gains) was found to be predicted by both higher reward anticipation at baseline and improved target engagement (faster auditory processing speed), suggesting that learning potential may be affected by motivation. However, no significant effect on role and social functioning was found for up to 8 weeks of training, which may be due to the lack of training specifically focused on social cognition, or other psychosocial training that better

promotes generalization (Fisher et al., 2014). Regardless, CT-related effects on neurocognition remained even when controlling for general computer game access.

Current Study

Findings from the single study that have investigated plasticity-based CT in adolescents/young adults with recent-onset SZ suggest that it is as beneficial for improving neurocognition among this population as it is for adult-onset patients, though its effectiveness for achieving functional gains remains questionable. The lack of significant functional improvement may be due to differing operational definitions of social and role functioning gains between adolescents and adults. The failure to take into account potential effects of differing ages of illness onset may also be contributing to heterogeneous results. Therefore, additional insight into individual subject characteristics predicting outcome may be useful. Furthermore, this approach has yet to be attempted in a cohort identified on the basis of early onset illness. Correspondingly, the purpose of the current study was to:

1. Conduct a pilot study to assess the feasibility of conducting 30 hours of a neuroplasticity-based CT intervention emphasizing auditory information processing and social cognition in patients with EOP, given the established impairments in both of these domains, and their potential role in future functioning. In the context of this feasibility-based study, we did not include a control condition. We predicted that CT intervention would prove feasible to implement in this cohort, as verified by the completion of the CT program by participants. We also predicted that ratings on program experience would be high for ease of training, but moderate on self-reported improvements.
2. Examine the extent to which plasticity-based CT may treat neurocognitive, social cognitive, and global functioning deficits associated with early-onset schizophrenia-

spectrum disorders. In particular, we aimed to focus on factors that moderate treatment-associated changes. We postulated that the training would result in measurable improvements in neurocognition and clinical functioning/symptomatology, particularly in the CT targeted domains of social cognition, verbal learning/memory, and problem-solving. We also predicted that self-rated reward anticipation would be correlated with treatment gains, given previous literature (Fisher et al., 2014).

3. Examine the respective effects of age and age of psychosis onset (APO) on cognitive and clinical improvement. Based on the premise that younger patients may have increased neuroplasticity (Blakemore, 2012; Kolb & Gibb, 2011; Spear, 2000), we predicted that cognitive change will be inversely correlated with age (i.e., younger participants would show greater cognitive improvement). However, given evidence that earlier symptom onset is associated with more severe cognitive and clinical deficits (Eggers & Bunk, 1997; Kao & Liu, 2010), possibly reflecting increased disruption of typical neurodevelopmental processes, we explored the effects of APO on CT response, with the prediction that earlier APO may be associated with reduced treatment gains.

Methods

Participants

In an effort to obtain initial estimates of effect size and feasibility, we recruited 16 English-speaking, clinically-stable patients with psychosis-spectrum disorders who were participating in a larger, ongoing study for adolescents with psychotic illness aged 12-18 years old (UCLA Adolescent Brain–Behavior Research Clinic; ABBRC). However, 3 participants declined to begin the cognitive training program following initial evaluations, resulting in 13

final participants. See Table 1 for demographic and diagnostic information. Patients with past substance abuse diagnoses were permitted to participate if they were free of substance abuse for the preceding six months; patients with substance dependence diagnoses were excluded. Patients with evidence of known neurological conditions (e.g., epilepsy), significant head injuries, or intellectual disability were also excluded. Informed consent was provided by all participants, and by their parents for participants under the age of 18, using procedures approved by UCLA's Institutional Review Board. Participants were reimbursed for their participation in all assessments and for hourly training.

Materials and Procedures

Participants completed clinical and neuropsychological (NP) assessments within three months prior to beginning the CT program and repeated assessments within three months following the completion of CT. However, delays in the administration of the post-CT assessment occurred for two participants, and post-training assessments could not be obtained for the majority of participants who dropped out of the study prematurely (n=5/6). See Table 2 for all training information. Diagnoses for all participants upon study entry were determined using the Structured Clinical Interview for DSM-IV Axis I diagnoses (SCID-IV; First, Spitzer, Gibbon, & Williams, 1997) and by review of medical records when available; final diagnoses required consensus among supervising clinical psychologists. All diagnostic and neuropsychological assessment measures used have been previously described in detail (Bachman et al., 2012).

Pre/Post Clinical Assessments

All measures were administered at both pre- and post-CT assessments. All participants were rated on the Global Assessment of Functioning Scale (GAF; (T. J. Miller et al., 2002) to determine overall level of functioning. Role and social functioning were evaluated using the

Global Functioning: Role Scale (GF:R) and Global Functioning: Social Scale (GF:S), which measures functioning on a scale from 1-10, with one representing extreme dysfunction and ten representing superior functioning). Current level of symptomatology (within the current month of the clinical assessment) was determined via the Structured Interview for Prodromal Syndromes (SIPS) (McGlashan, Miller, Woods, Hoffman, & Davidson, 2001). This measure evaluates positive, negative, disorganized, and general symptoms on a scale from 0-6, with zero representing an absence of symptoms and six referring to a severe and psychotic level of symptoms. The SIPS also encompasses a range of symptom severity; 0-2 representing an absence of clinically significant prodromal symptoms, 3-5 representing subthreshold (prodromal) symptoms, and 6 suggesting a psychotic level. For the purposes of this study, the sum of symptom scores within each dimension (positive, negative, general, and disorganized) was calculated and analyzed separately. Additionally, participants were interviewed with the Extended Brief Psychiatric Rating Scale (BPRS; Lukoff, Liberman, & Nuechterlein, 1986) which assesses symptom severity across multiple domains (ratings from 1-7, with one representing the absence of a symptom and seven representing an extremely severe symptom). Scores on anxiety (BPRS anx) and depression (BPRS dep) domains were entered into analyses; these particular symptom domains were identified due to their relation to EOP symptomatology, and because these symptom domains are not covered by the SIPS (Achim et al., 2011; Buckley, Miller, Lehrer, & Castle, 2009; Siris, 2000).

Participants additionally completed two self-report measures to assess for behavioral inhibition and behavioral activation (BIS/BAS Scale; Carver & White, 1994) as well as anticipatory and consummatory aspects of pleasure (Temporal Experience of Pleasure Scale (TEPS); Gard, Gard, Kring, & John, 2006) (see Appendices 1 and 2). The BIS/BAS involved

participants rating the truth of statements on a scale of 1 (very true for me) to 4 (very false for me); the TEPS asked participants to respond to how true statements were for them over the past week from 1 (very false for me) to 6 (very true for me). Questionnaires were scored on the following dimensions/scales: BIS total score (BIStotal), BAS fun seeking (BASfun), BAS drive (BASdrive), BAS reward responsiveness (BAS reward), TEPS anticipatory, and TEPS consummatory.

At the conclusion of training, participants (n=8) and their parent/guardian completed additional self-report measures assessing overall training experience across several domains (e.g.., interest, scheduling, software, etc.; see appendices 3 and 4). These measures could not be obtained for participants who dropped out of the study prematurely and/or who were lost to follow-up and thus did not complete post-training assessments (n=5/6).

Pre/Post Neuropsychological Assessments

All participants completed the standard research neuropsychological battery consistent with the larger ABBRC UCLA study (Bachman et al., 2012). This included measures of general cognitive abilities (Wechsler Abbreviated Scale of Intelligence (WASI) – Vocabulary and Matrix Reasoning (MR) subtests and Full Scale IQ),), single-word reading (Wide Range Achievement Test-4 (WRAT)), visuomotor sequencing and set-shifting speed (Trails A and B), psychomotor speed (Brief Assessment of Cognition in Schizophrenia (BACS) – Symbol-Coding subtest), sustained attention (Continuous Performance Task – Identical Pairs (CPT-IP), verbal fluency (semantic: Category Fluency Test – Animal Naming; phonetic: FAS), nonverbal working memory (Wechsler Memory Scales-3 (WMS) – Spatial Span subtest), and memory (verbal episodic: Hopkins Verbal Learning Test (HVLT)); visual episodic: Brief Visuospatial Memory Test (BVMT); auditory: University of Maryland – Letter Number Span (LNS)). Where available,

published age-normed T- or z-scores were entered into analyses (WASI IQ, vocab, matrix reasoning, WRAT, Trails A/B, HVLT, ANT, spatial span); all other measures utilized z-scores derived from a normative model based on our UCLA ABBRC control sample (BACS, LNS, BVMT, CPT-IP). Therefore, higher scores on all measures indicated better performance.

Social cognition was assessed via Part 3 of The Awareness of Social Inferences Test (TASIT; McDonald, Flanagan, Rollins, & Kinch, 2003), the Penn Emotion Recognition Test (ER40; Kohler, Bilker, Hagendoorn, Gur, & Gur, 2000), and the Penn Emotion Differentiation Task (EMODIFF (ED); Erwin et al., 1992). The TASIT is a computerized task believed to assess one's ability to comprehend the intentions of others, particularly how one comprehends white lies or sarcasm. The task consists of 16 vignettes (each lasting between 15-60 seconds), eight of which show an individual telling a lie, while the other eight display an interaction in which someone uses sarcasm. After viewing each vignette, an assessor asked the participant four yes/no questions related to the scene: 1) what someone is doing to another person in the scene, 2) what someone is trying to say to the other person, 3) what one of the individuals in the scene is thinking, and 4) what one of the characters in the vignette is feeling. After task completion, an overall score (total correct) was calculated (maximum=64) and entered into analyses. The TASIT has shown adequate reliability and validity with brain-injured patients (McDonald et al., 2006), and has been used with adolescents at clinical high-risk for psychosis, along with first-episode and chronic patients with schizophrenia (Green et al., 2011).

The Penn ER40 task is a computerized emotion identification task in which 40 color photographs of adult faces, varying in race and gender, are randomly presented. Participants were asked to identify the emotion of each face (happy, sad, anger, fear, or no emotion) and were given as long as needed to respond (total maximum score=40, each emotion presented 8 times).

The Penn EMODIFF (ED) task is a computerized emotion differentiation task in which individuals are presented with two black and white faces of the same person and are asked to choose which of the two faces displayed expresses an emotion more intensely (e.g., more happy, more sad), or decide that the two faces are equally happy or sad (total maximum score=40). Both measures have shown adequate construct validity and test-retest reliability (Carter et al., 2009; Rojahn, Gerhards, Matlock, & Kroeger, 2000), have been widely used in studies with schizophrenia patients (e.g., Butler et al., 2009; Sachs, Steger-Wuchse, Kryspin-Exner, Gur, & Katschnig, 2004; Silver, Shlomo, Turner, & Gur, 2002), as well as in adolescents (Roddy et al., 2012; Schenkel, Pavuluri, Herbener, Harral, & Sweeney, 2007). Scores representing the total number correct on ED and ER40 tasks were entered into subsequent analyses.

CT Program

Training was conducted on iPads provided by the ABBRC clinic using the free brainHQ™ application by Posit Science Corporation®. Based on prior auditory CT research leading to sustained verbal memory improvements (Adcock et al., 2009; Fisher et al., 2014, 2013, 2009), a specific training module was developed by Dr. Sophia Vinogradov and her team at the University of California – San Francisco. The training initially consisted of 30 hours (completed by n=4 participants), divided into 20 hours of targeted auditory/working memory tasks (i.e., “Fine Tuning,” “Memory Grid,” “Sound Sweeps,” & “Syllable Stacks”) and 10 hours of targeted social cognition tasks (i.e., “Looky Lou,” “Recognition,” “Face to Face,” “Face Facts,” “Face Poke,” “Voice Choice,” “Social Scenes,” & “Say What”). However, training was later modified to 10-15 hours (10 auditory + 5 social, or 10 auditory only) in an attempt to bolster recruitment efforts and reduce patient burden (completed by n=3 participants) (see Table 2).

Auditory tasks contained stimulus sets spanning the acoustic organization of speech, starting with improving basic processing of auditory information and working memory skills and then increasing verbal learning and memory demands (Fisher et al., 2009). For example, early exercises required participants to distinguish, with increasing accuracy and speed, between two difficult-to-distinguish phonemes or similar sounding words (e.g., "ka" and "ga"; rake and lake) (see Figure 1-2), make gradually more difficult distinctions between frequency modulation "sweeps" of auditory stimuli increasing or decreasing in frequency, and match sounds on a spatial grid (Fisher et al., 2009). More advanced tasks consisted of listening to and following sequences of verbal instructions, while additional working memory and attention tasks asked participants to spatially match or visually track stimuli (see Figures 3-4). Social cognition tasks also progressively increased in level of difficulty, and included tasks such as requiring participants to match faces with previously read facts (see Figure 5), match the emotion on one face to another face (see Figure 6), and identify emotions in vocal expressions (see Figure 7) (e.g., Subramaniam et al., 2012). Available tasks varied from week to week depending on the participant's progress (e.g., total number of hours trained to that point).

Tasks were designed to be continuously adaptive to participants' ability, such that following a participant's ability to achieve a threshold of 80-85% correct performance, task difficulty within a level was varied parametrically according to ongoing performance. Each task also consisted of multiple levels that were successively 'unlocked' when the prior level was completed. Correct performance was rewarded through the accumulation of points and visual/auditory graphics. Participants at the start of the study were instructed to complete a minimum of two hours per week, in sessions no less than 30 minutes each, for a maximum total of 15 weeks of training. For later participants who were asked to complete 15 hours in total, 1

hour per week was required, for a continued total of 15 weeks of training. Patients were told that the number of hours completed took precedence over the number of levels or number of tasks completed, although they were encouraged to try each available task. Patients who failed to demonstrate ongoing training progress (e.g., at least a month of no training) were removed from the study and/or were lost to follow-up (n=6).

Participants completed in-clinic training when possible (n=7), or were given an iPad for at-home training (n=6). For participants training at home, progress was monitored remotely by study personnel, who contacted participants weekly for progress updates and to complete a Weekly Check-In Questionnaire assessing for use of other electronic and gaming devices (see Appendix 5). Participants training in clinic were supervised by an undergraduate-level research assistant, who also assisted in the completion of the Weekly Check-In Questionnaire. De-identified training data (e.g., hours trained; modules completed) was stored via secure network servers and encrypted software provided by the brainHQ™ program.

Statistical Analyses

Analysis I: CT Program Feasibility. All statistical analyses were performed using SPSS software v. 20 (Chicago, Illinois). Overall CT program feasibility for EOP patients was evaluated based on the percentage of participants completing the full training (10-15, or 30 hours) and pre/post-training assessments. Additionally, mean scores on post-training patient and parent self-report measures were evaluated regarding overall program experience (e.g., ease of training, interest in training, and self-reported improvements in functioning).

Analysis II: CT-related Effects. CT success was further gauged by comparing pre/post clinical and NP measures. Repeated-measures ANCOVAs were conducted to assess for any differences in each measure before and after CT intervention, controlling for age and hours

trained. Partial η^2 (η_p^2) values were calculated as measures of effect size. Directional change scores for all clinical and NP measures between pre- and post-training assessments were then calculated as an indication of treatment effect. Follow-up Pearson correlations evaluated whether self-rated motivation (BIS/BAS) and/or pleasure (TEPS) at baseline correlated with significant treatment gains (i.e., change scores) revealed through the above ANCOVAs. Additional Pearson correlations tested whether baseline clinical and/or neurocognitive measures were associated with treatment changes in that domain. To further explore the potential effects of age and total hours of training, these correlations were then re-run as partial correlations. Effect sizes (Cohen's *d*) were computed using the absolute value of mean change scores from post- to pre-training, divided by the change score standard deviation. Due to the exploratory nature of these analyses, we did not correct for multiple comparisons (n=32 ANCOVAs and 32 Pearson correlations total).

Analysis III: Effects of Age and APO. Pearson correlations were run to examine whether age and age of psychosis onset (APO) were separately associated with treatment-associated change. Specifically, we examined the relationships between age at study start and change in NP measures and change in clinical measures, including BIS/BAS and TEPS questionnaires (i.e., difference scores). Identical correlations were conducted between APO and clinical and NP difference scores. As above, corrections for multiple comparisons were not made to these exploratory analyses (n= 60 total comparisons).

Results

Analysis I: CT Program Feasibility. At the end of the program, 7 out of 13 participants (53.85%) were deemed to have completed their required training. Specifically, 4 participants (30.77%) were able to complete 30 hours of training (20 auditory/working memory, 10 social), 1

(7.69%) completed 15 hours, and 2 (15.38%) completed between 10 and 15 hours (see Table 2 for full training information). Out of the 6 participants who prematurely ended their program involvement (e.g., less than 10 hours of training), 4 participants identified their reasons for early termination; responses could be not obtained for 2 participants who were lost to follow-up. Additionally, two participants who completed between 10-15 hours similarly were asked to provide reasons for completing fewer than 30 hours. Thus, 6 total responses were obtained. The majority of the 6 responders (66.7%) rated boredom to be the primary problem, though other reasons were also endorsed by at least one patient (i.e., symptoms got in the way; participant was hospitalized; didn't have time; didn't think training would help; training was too difficult). Follow-up analyses suggested participants who completed at least 10 hours of training (n=7) showed trends for having higher pre-training IQ ($t(11)=-2.206$, $p=0.05$) and global functioning (GAF) ($t(11)=-2.085$, $p=0.061$) compared to those who did not complete the CT program (n=6). No other significant group differences across demographic and clinical variables (age, gender, race, education, APO, diagnosis, SIPS positive symptoms, GF:S, and GF:R) were observed.

8 participants (61.54%), including one who dropped out of the study early, and their parents completed post-training evaluations related to overall program experience (Table 3). Post-CT patient surveys (Appendix 3) revealed that program interest/enjoyment and ease of scheduling were both largely rated to be poor (i.e., "a little bit of the time"). Satisfaction regarding training effects, including feeling it was helpful and effective, was slightly higher and rated to be "about half the time." Details related to the CT software (e.g., use of iPad, easy to understand instructions) were the highest on average, with participants indicated satisfaction around "half" to "most of the time." Almost all participants indicated they were unlikely to use the program again outside of a research setting, and that training was not a high priority

compared to other daily activities. In contrast, participants on average endorsed greater likelihood of recommending the CT program to others (i.e., “about half the time” to “most of the time”). Almost all participants endorsed needing training reminders, particularly from parents and research staff, and that techniques such as putting alarms on phones were helpful. They also reported interferences to training, such as forgetting to do it and not enjoying it. At times, program glitches due to updated application versions also caused frustration and reluctance to train. Most participants also reported wanting program changes, including reduced training requirements, increased education about the program, and greater feedback about progress. Additional suggestions included providing information about how much training time is left in each module and making the training more interesting/less repetitive. Some participants stated interest in an interactive program that would allow them to connect with and/or play against other participants in the study. A minority of participants endorsed CT benefits, such as seeing improvements in cognition after a few weeks of consistent training. Positives to the program included the ease of the BrainHQ application use/navigation and the ability to gain gold stars with CT progress.

Parent surveys (Appendix 4) indicated that all participants received encouragement to complete exercises ranging from once a week to multiple times a day. Half of the parents also provided reminders from once a week to 2-3 times a day. On a scale from 1(no improvement) to 5(much improvement), average improvements across a range of domains (i.e., symptoms, functioning, quality of life, attention, memory, problem solving, processing speed, overall cognitive) placed in the moderate range. Three parents reported “much improvement” in an additional area of improvement of increased self-confidence. In contrast with patient ratings, the majority of parents (62.5%) endorsed interest in having their children use the CT program again

outside of a research study, and that they would recommend the program to others. In addition to aforementioned improvements, parents reported benefits of having different/more structured activities during the day, particularly for those that were no longer in school.

Parents identified numerous suggestions for improvements, including increasing the incentive/payment distribution to be more frequent, diversifying the tasks/exercises, and making the exercises more current/relevant to today's technology/game-like. Additional recommendations focused on reducing patient frustration by decreasing required training time per session and allowing them to get "credit" for time spent training even if modules were not completed, as training time was not recorded if all trials of a given activity were not finished. Similarly, parents highlighted the need for greatly improved displays that would better show the patient's progress and goals, including time completed, time left, exercises completed, and exercises coming next. The majority of parents noted the frustrating aspect of training and lack of patient motivation, which led to training becoming a source of stress for some participants and/or their families. Thus, one parent suggested providing more direct feedback from staff and CT software about the "real-world connection" between the exercises and any direct impact on their day-to-day life.

Analysis II: CT-related Effects. Repeated-measures ANCOVAs for participants with post-training assessments (n=8) revealed post-training GF:S scores were significantly higher than pre-training GF:S scores ($F(1,5)=6.721$, $p<0.05$, $\eta_p^2=0.573$), controlling for age and total hours of training. SIPS general symptoms ($F(1,5)=8.212$, $p<0.05$, $\eta_p^2=0.622$) and BPRS anxiety symptoms ($F(1,5)=15.921$, $p=0.01$, $\eta_p^2=0.761$) also showed significant differences between assessments, with reduced symptomatology demonstrated after CT. All other ANCOVAs for clinical, NP, social cognitive, and/or behavioral measures were nonsignificant.

Pearson correlations demonstrated that pre-CT scores on each respective measure were negatively associated with changes over time in the following domains: SIPS disorganized symptoms (r=-0.755, $p<0.05$, $d=0.69$), IQ (r=-0.738, $p<0.05$, $d=0.08$), vocabulary (r=-0.805, $p<0.05$, $d=0.12$), Trails A (r=-0.832, $p=0.01$, $d=0.12$), Trails B (r=-0.851, $p<0.01$, $d=0.75$), BACS (r=-0.833, $p=0.01$, $d=0.24$), spatial span (r=-0.782, $p<0.05$, $d=0.77$), LNS (r=-0.745, $p<0.05$, $d=0.08$), CPT (r=-0.898, $p<0.01$, $d=0.94$), FAS (r=-0.861, $p<0.01$, $d=0.62$), and ER40 (r=-0.840, $p<0.01$, $d=0.79$) (Figure 8a-k). Specifically, the better the pre-training scores were, the more likely scores were to decrease over time, while low pre-CT scores were more likely to improve. Due to too few observations, correlations could not be conducted for BIS/BAS or TEPS measures. Additionally, due to a bimodal distribution, correlations could not be conducted for GF:R. However, only BPRS anxiety (r=-0.891, $p<0.05$), Trails A (r=-0.858, $p<0.05$), CPT (r=-0.815, $p<0.05$), FAS (r=-0.953, $p<0.01$), and ER40 (r=-0.895, $p<0.05$), survived partial correlations controlling for age and hours of training.

Analysis III: Effects of Age and APO. Age at baseline and APO were significantly correlated (r=0.858, $p<0.05$). Age at baseline was significantly correlated with changes in SIPS general symptoms (r=-0.801, $p<0.05$), and LNS scores (r=0.721, $p<0.05$) (Figure 9a-b). Specifically, as age increased, LNS scores were more likely to improve from pre- to post-CT assessments; however, older age at baseline was associated with a decrease in general symptoms from pre- to post-CT assessments. All other correlations between age and changes in clinical, neuropsych/social cognitive, and/or behavioral scores were non-significant. Due to a bimodal distribution of GF:S change, correlations could not be conducted for this measure.

Age of psychosis onset significantly correlated with changes in GF:R scores (r=0.735, $p<0.05$), SIPS disorganized symptoms (r=-0.752, $p<0.05$), SIPS general symptoms (r=-0.881,

$p<0.01$), matrix reasoning scores (r=0.706, $p=0.05$), and LNS scores (r=0.782, $p<0.05$) (Figure 10a-e). Specifically, earlier age of psychosis onset was associated with less improvement in social and role functioning scores, an increase in disorganized and general symptomatology, and a decline in performance on MR and LNS tasks from pre- to post-assessments. All other correlations between APO and changes in clinical, NP/social cognitive, and/or behavioral scores were nonsignificant. Due to a bimodal distribution of GF:S change, correlations could not be conducted for this measure.

Discussion

To our knowledge, this study was the first to examine the feasibility of implementing iPad-administered plasticity-based CT in a sample of adolescents with EOP. We also evaluated the degree to which neurocognitive, social cognitive, and global functioning deficits associated with early-onset psychosis could be addressed by the CT program, and what role age and age of psychosis onset may have on outcomes. Overall, the study revealed that: 1) hypotheses about the feasibility of CT implementation in this population were unsupported, with the majority of participants unable to complete 30 hours of CT; however, ratings of program experience were largely in line with predictions; 2) while CT was associated with some improvement in clinical symptomatology and social functioning, the majority of predicted changes in cognitive areas were not found, contrary to the adult-SZ literature; 3) As predicted, age was negatively correlated with clinical symptoms, meaning that older age at baseline was associated with a decrease in symptoms from pre- to post-CT assessments, but was positively correlated with working memory; 4) Earlier age of psychosis onset was associated with reduced gains in cognition and functioning, and with increased clinical symptomatology over time.

In contrast with initial predictions, CT completion rates were lower than expected and training activity was fairly inconsistent. In particular, periods of inactivity were observed even for participants that eventually completed training. Participants' primary complaints included boredom, lack of motivation to train, and the low priority of training relative to other daily responsibilities. Both participants and parents alike indicated that updating the training interface to be more videogame-like would be useful, such as including more visually dynamic tasks, having more intrinsic program rewards (e.g., beating levels), and allowing families to gain direct and immediate information on progress, both overall and within a given training session. Feedback also suggested that a more interactive program might aid in motivation and interest, such as having the ability to connect with other individuals training, and possible play against each other, so long as consent to do so was previously provided. Post-training surveys further suggested that the current structure of extrinsic rewards via study reimbursements was not helpful, as it was too delayed when given only at the end of the study. Instead, families suggested more regular dispensing of gift cards, for example, might have increased engagement. However, the need for consistent payment in order to engage EOP participants highlights the potential limitations of the current iteration of the CT program, and the difficulties that likely would be encountered if long-term implementation was attempted in the absence of such rewards.

Of note, however, parents tended to rate the CT program more favorably than participants in post-training surveys. Many families commented that they saw changes that the patient did not see and/or could not appreciate. This suggests that additional psychoeducation to participants about the potential benefits may be helpful, though it is unclear to what extent participants' level of insight about improvements would improve even then. Additionally, it is important to note that research suggests that parents often overestimate treatment effects (S. A. Miller, Manhal, &

Mee, 1991), and that interpretations about improvements are limited in the absence of a control group.

Study results also indicated that in-clinic training was far superior to training that was attempted in the home environment. In the latter instance, participants' success often depended upon the level of support parents provided, including whether alarms or timers for training were set, if parents were available to sit with participants during training to provide encouragement, and if additional rewards were provided. Given these findings, it is likely that the current iteration of iPad-based CT training would require ongoing 1:1 supervision and dedicated training time, particularly if conducted in the home setting. This has important implications for the potential transition of the program into community settings, as initial attempts indicated limited feasibility.

Results regarding changes in scores from pre- to post-CT are more difficult to interpret, particularly given the lack of a control group. However, in general, aspects of general symptomatology and social functioning seemed to improve over time, consistent with previous literature on CT-related decreases in symptoms and improved functioning within the adult literature (Adcock et al., 2009; Fisher et al., 2010; Genevsky et al., 2010; Sacks et al., 2013). However, changes in social cognition or processing speed were not found, in contrast with findings from the adult literature (Hooker et al., 2013; Keefe et al., 2012; Sacks et al., 2013). In part, this may be related to the difference in the number of variables controlled for in analyses, as the large majority of those studies did not factor in aspects such as APO, as the current study did. Of note, however, while the adult SZ literature compared two groups, this analysis consisted of a within-group comparison only. Additionally, while repeated-measures analyses controlled for the total hours of training in the current study, it may also be important to account for the amount of

time (e.g., in weeks) actually taken to complete those hours, given the significant variability present. As the current study sample size did not allow for more sophisticated models, future studies should consider altering the CT program to boost recruitment.

Interestingly, participants who completed training showed a trend for higher global functioning and IQ. This may be an important factor to consider when identifying participants who might be able to engage most effectively with the program. However, it is worth noting that these individuals with EOP could have also improved in symptoms or functioning over time even without the training; without the comparison to a control group, it is difficult to ascertain what changes were directly related to the CT. Our goal in this initial study was to assess feasibility for conducting a larger, controlled trial. Thus, in addition to potentially modifying the BrainHQ interface, it will be important to add a control group to future studies to further assess the comparability of results with those from adult SZ CT studies.

Not surprisingly, pre-CT scores seemed to dictate the amount of change for many measures across clinical and neurocognitive/social cognitive domains, such that participants who had lower scores or lower functioning were more likely to improve over time relative to participants who were doing better at the start. These effects were less apparent after controlling for age, APO, and total training time. Although prior studies particularly have not focused on age or APO, our results suggest these are important considerations for some measures. However, results also suggest that correlations between pre-CT scores and changes in those domains are likely reflective of a regression to the mean effect. As indicated previously, comparisons to a control group are necessary to further evaluate this area.

Further examination of the effects of age demonstrated that predictions were partially supported; negative correlations were observed between age and symptoms as expected, but

increased age at study entry was associated with better working memory performance. In contrast, the hypothesis regarding APO was largely supported; earlier APO was associated with reduced cognitive and functioning gains, and correlated with increased symptomatology over time. This is consistent with literature suggesting earlier psychosis onset represents a more severe form of illness (Eggers & Bunk, 1997; Kao & Liu, 2010), and highlights that the current iteration of CT may be less effective for this population.

In conclusion, this study provided an important first step in evaluating plasticity-based CT feasibility in an EOP sample. Results highlight the unique training considerations for adolescents with EOP, including the importance of parental support, intrinsic motivation, and baseline functioning. Our study also suggests that future directions should focus on identifying how to maximize the impact of a relatively shorter duration of training, and to evaluate appropriate training time "doses" that may lead to improvements among this population in comparison to a control group. As previously highlighted, modifications to the current BrainHQ CT program will also be important for bolstering recruitment and therefore sample sizes, increasing engagement, allowing for more consistent training, and improving feasibility odds for community implementation. After a more thorough investigation of potential CT-related gains in EOP, future studies should conduct follow-up evaluations following a post-training delay, comparable to what is being attempted in adults. This will aid in determinations of whether any such gains can be sustained, and to help consider the potential generalizability of training gains to day-to-day life skills and 'real world' functioning.

Table 1

Demographic Information Characterizing Baseline Study Sample

	EOP Patients (N=13)
Mean age, years (± SD)	15.96(2.30)
Number female (%)	2(15.4)
Number left-hand dominant (%)	2(15.4)
Mean baseline IQ (± SD)	104.69(11.06)[1]
Mean participant education, years (± SD)	10.23(2.01)
Mean parental education, years (± SD)	14.85(3.47)
Race/Ethnicity (%)	
Caucasian, Non-Hispanic	8(61.5)
Caucasian, Hispanic	5(38.5)
DSM-IV-TR Diagnoses (%)	
Schizophrenia	8(61.5)
Schizoaffective, Bipolar Type	1(7.7)
Schizoaffective, Depressive Type	1(7.7)
Psychosis NOS/Unspecified Psychotic Disorder	3(23.1)
Comorbid Diagnoses	13(100)
ASD	3(23.1)
Anxiety disorders	9(69.2)
PTSD	1(7.7)
Depression disorders	5(38.5)
ADHD	2(15.4)
Substance disorders	3(23.1)
Eating disorders	1(7.7)
Mean APO (± SD)	13.81(1.91)
Primary Medications (%)	
Atypical Antipsychotic	11(84.5)
Anticonvulsant/Mood Stabilizer	1(7.7)

Stimulant	1(7.7)
Concurrent Medication (%)	10(76.9)
Typical Antipsychotic	1(7.7)
Anticonvulsant/Mood stabilizer	3(23.1)
SSRI/SNRI/other anxiolytics	6(46.2)
MAOi/other antidepressants	1(7.7)
Anticholinergic	3(23.1)
Other	3(23.1)
Mean Total SIPS Positive Symptoms (± SD)	12.23(8.11)
Mean GAF (± SD)	49.00(15.09)*

SIPS=Structured Interview for Prodromal Syndromes; GAF=Global Assessment of Functioning

[1]Trend towards group differences in completers (n=7) vs. non-completers (n=6). IQ: t(11)=-2.206, *p*=0.050; GAF: t(11)=-2.085, *p*=0.061.

Table 2

Cognitive Training Information

	CT completers (N=7)	**CT non-completers (N=6)**
Mean total time training, hours (± SD)	23.00(9.25)	2.66(1.94)
[range]	[10.15-30.63]	[0.68-5.55]
Mean total training, weeks (± SD)	27.55(14.30)	6.83(7.17)
[range]	[3.57-43.71]	[1.00-16.29]
Mean training rate, hours/week (± SD)	1.31(1.34)	0.59(0.32)
[range]	[0.34-4.27]	[0.28-1.07]
Training completion, by hours (%)		
30+	4(57.14)	0(0.0)
15.0-29.9	1(14.29)	0(0.0)
10.0-14.9	2(28.57)	0(0.0)
5.0-8.9[1]	0(0.0)	1(16.67)
0.1-4.9[1]	0(0.0)	5(83.33)
Early completion/termination reasons[2]		
Training was boring	2(100.0)	2(50.0)
Symptoms got in the way	1(50.0)	1(25.0)
Hospitalized	0(0.0)	1(25.0)
Didn't have time	1(50.0)	0(0.0)
Didn't think the training will help	1(50.0)	0(0.0)
Training was too difficult	1(50.0)	0(0.0)
Delay between assessments and CT start/end (± SD)		
[range]		
Pre-assessment	26.43(25.69)	29.17(22.59)
	[5.00-69.0]	[3.00-70.00]
Post-assessment	39.29(35.92)[3]	378.00(NA)[4]
	[11.00-103.00]	[NA]

[1]Participants who trained for less than 10.0 hours in total were considered to have dropped from the study prematurely.

[2]Patients were asked to select all applicable answers; total % may be greater than 100. Of the 6 participants who terminated the program prior to 10 hours of training, responses were missing for 2 patients (n=4 responders). Participants who completed 10-15 hours of training were also asked to respond (n=2 responders). In total, 6 responses were obtained.

[3]Neuropsych assessment took place 6 months after post-clinical assessment for 1 patient due to scheduling conflicts

[4]Post-training assessment data were only available for one participant who prematurely terminated. It was conducted almost one year following CT completion due to initial loss to follow-up.

Table 3

CT Program Evaluation Summary

	EOP Patients (N=8)
Patient Survey, mean responses (± SD)	
Program interest/enjoyment[1]	7.00(2.62)
Scheduling[1]	8.88(6.18)
Software/Instructions[2]	17.25(5.37)
Effect of the training[2]	12.00(8.25)
Other[3]	
Use program again	0.88(1.13)
Recommend program to others	2.50(1.31)
Training as a high priority	1.37(1.51)
Needed training reminders	
Yes (%)	6(75.0)
Felt other things interfered with training	
Yes (%)	5(62.5)
Changes to program[4]	
Training for less time each day	1.63(1.19)
Training for fewer days each week	1.63(1.06)
Getting more feedback about how training is helping	2.13(0.84)
Knowing more about how training is supposed to be helpful	1.88(0.99)
Parent Survey, mean responses	
Provided encouragement	
Yes (%)	8(100.0)
Provided reminders	
Yes (%)	4(50.0)
Improvements(± SD)[5]	
Symptoms	3.38(1.41)
Functioning at school	3.50(1.41)

Social functioning	3.13(1.64)
Overall quality of life	3.25(1.49)
Attention	3.63(1.69)
Memory	3.38(1.92)
Problem solving	3.38(1.69)
Speed of processing	3.50(1.77)
Overall cognition	3.50(1.77)
Other (confidence)	5.00(0.00)
Use program again	
Yes (%)	5(62.5)
Recommend program to others	
Yes (%)	5(62.5)

[1]Composite of 5 questions rated on a Likert scale 0(None of the time) to 4(All of the time): total sum ranges from 0-20; higher scores indicate best ratings.

[2]Composite of 6 questions rated on a Likert scale 0(None of the time) to 4(All of the time): total sum ranges from 0-24; higher scores indicate best ratings.

[3]Individual questions rated on a Likert scale 0(None of the time) to 4(All of the time); higher scores indicate best ratings.

[4]Individual questions rated on a Likert scale 0(Not at all better) to 3(A lot better); higher scores indicate best ratings.

[5]Individual questions rated on a Likert scale 1(No improvement) to 5(Much improvement) ; higher scores indicate best ratings.

Figure 1. *BrainHQ iPad Display: "Fine Tuning" Neurocognitive Task*

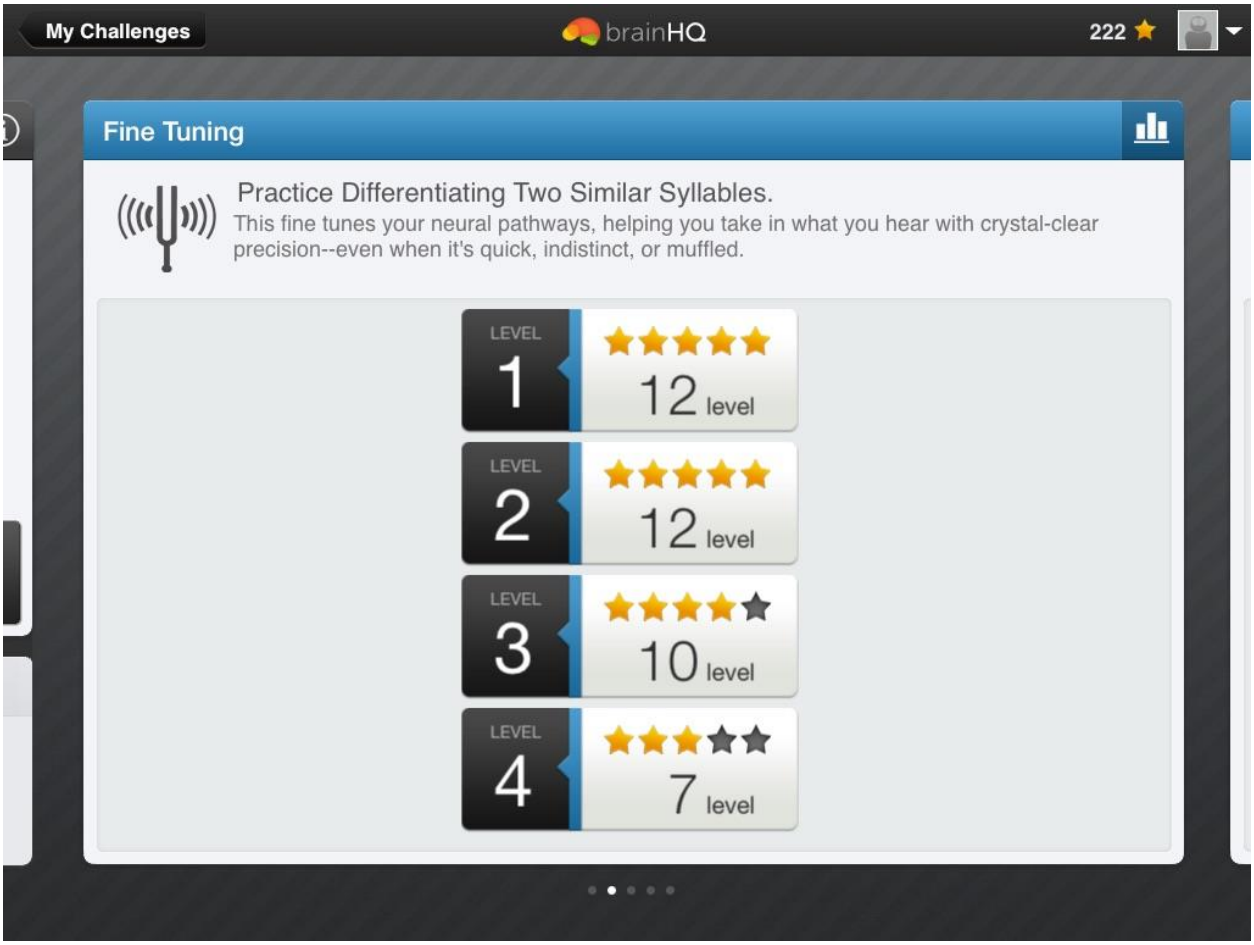
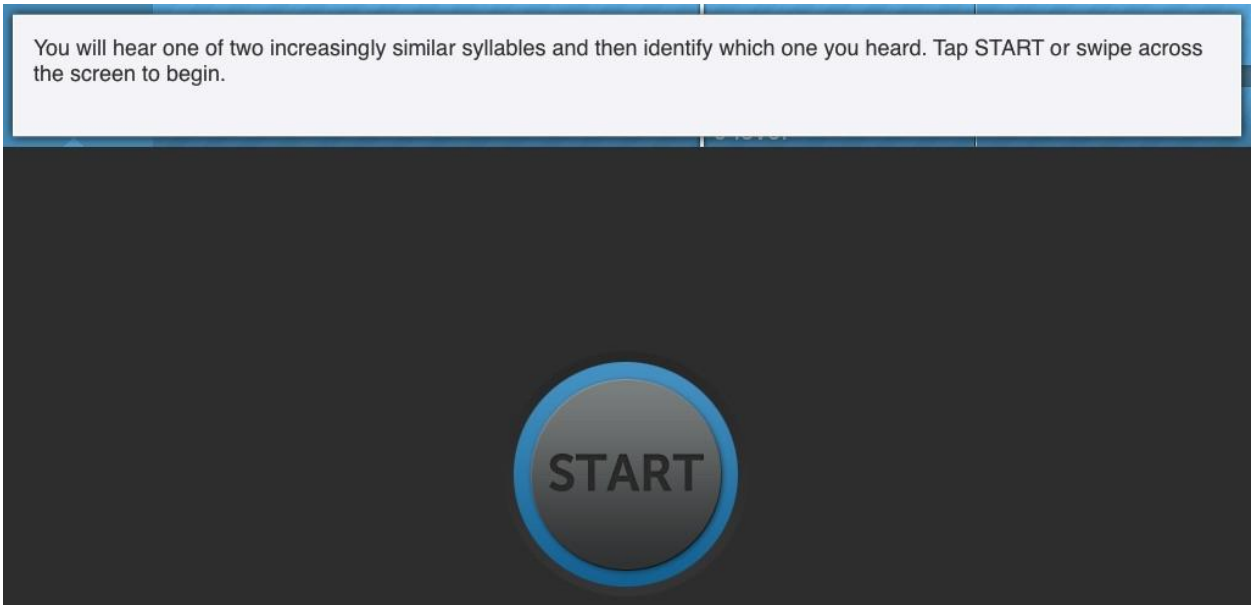


Figure 2. *BrainHQ CT Instructions "Fine Tuning" Neurocognitive Task*



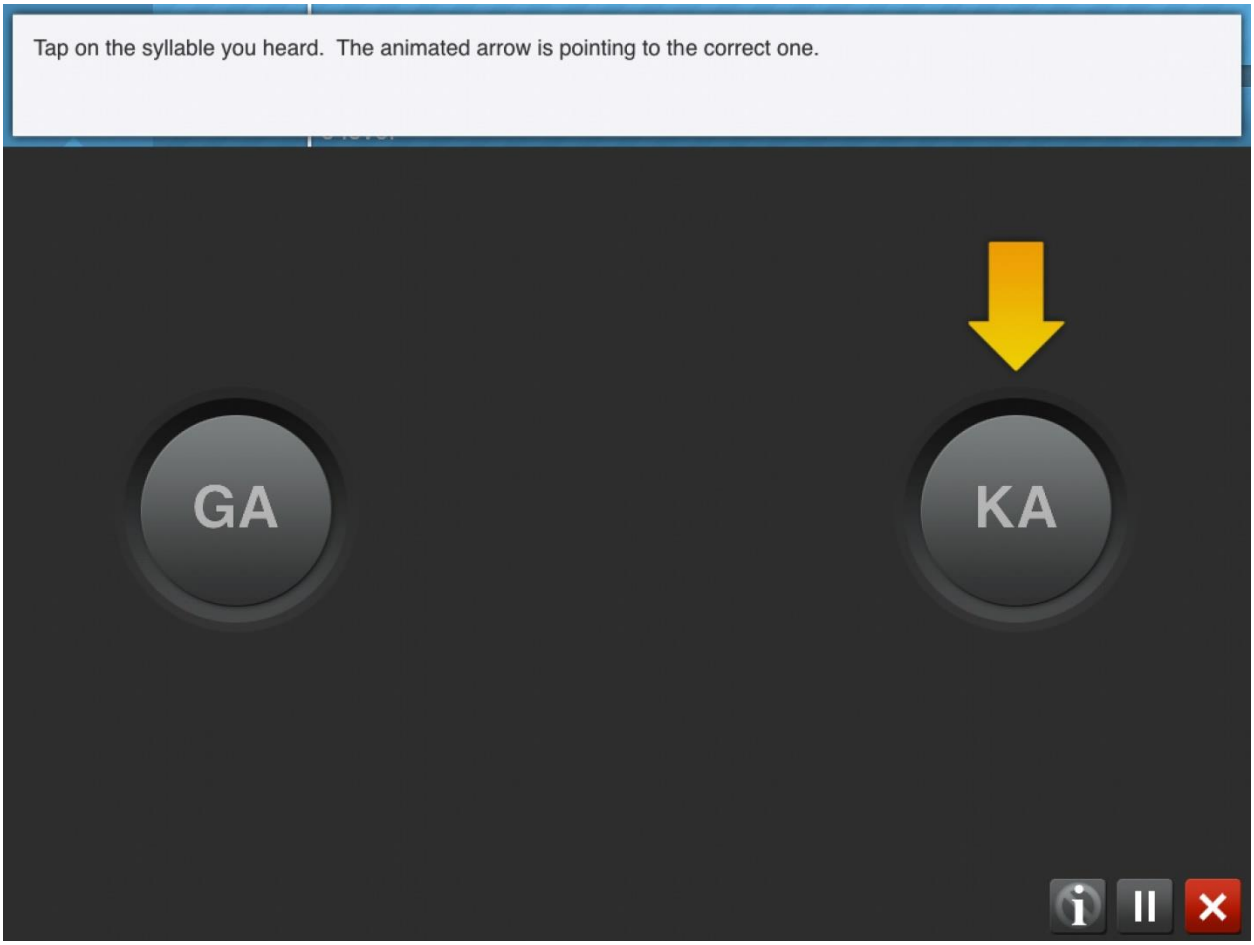


Figure 3. *Brain HQ Detailed Description: "Target Tracker" Neurocognitive Task*

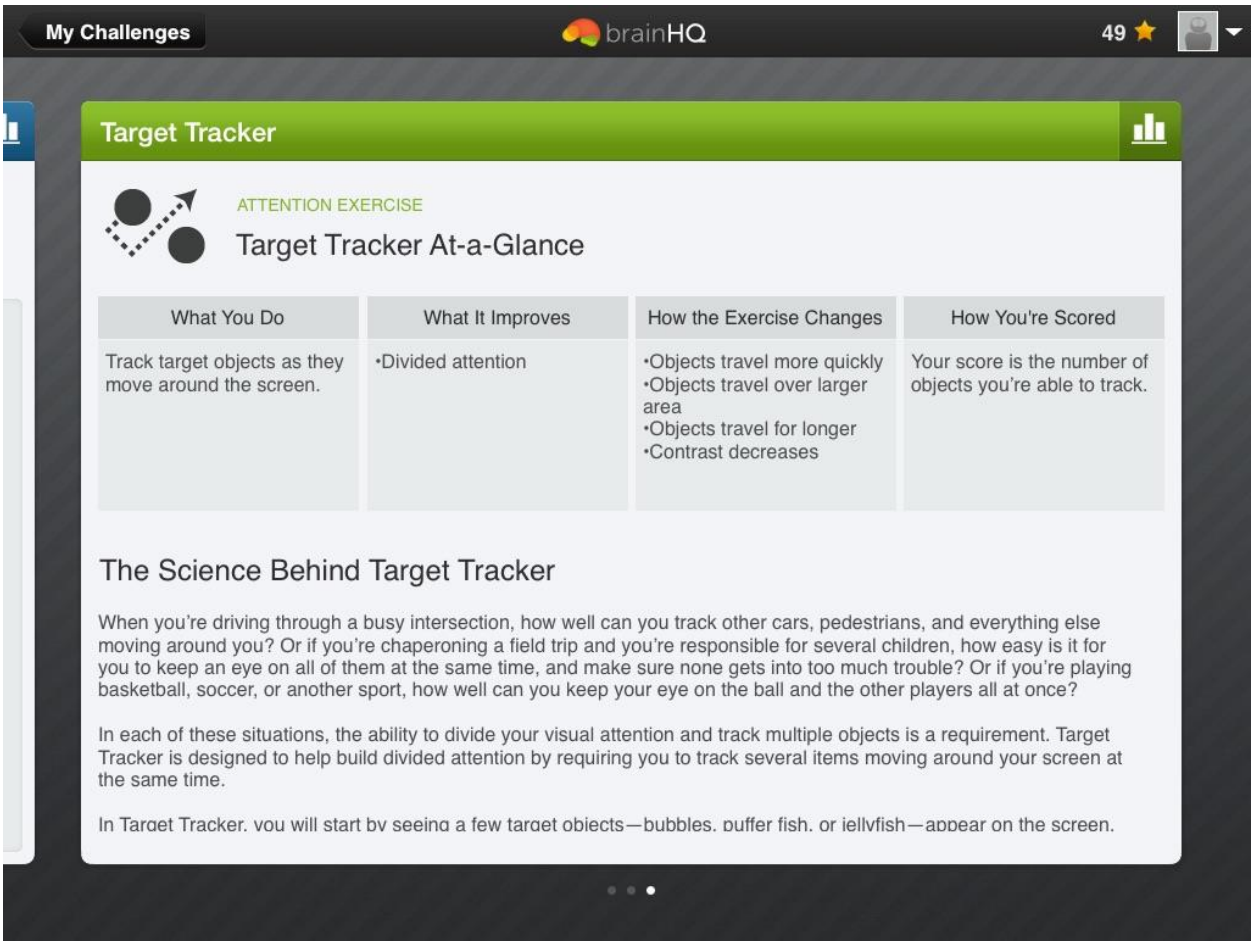
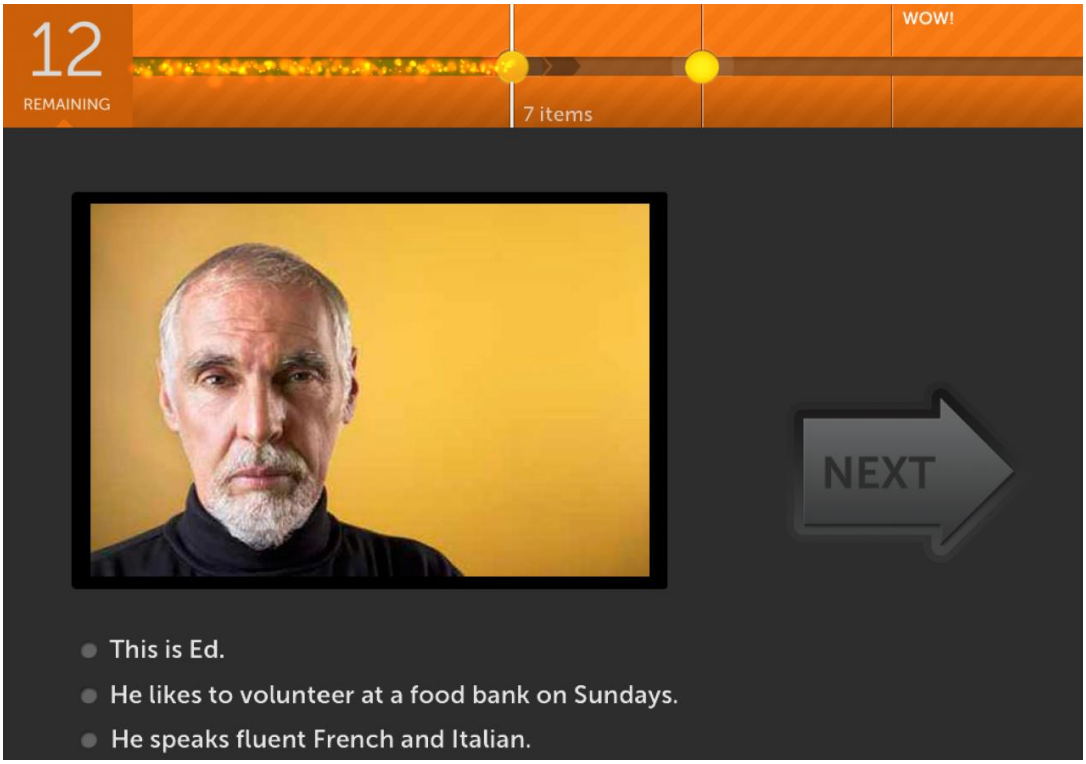

My Challenges
brainHQ
49
Target Tracker
ATTENTION EXERCISE
Target Tracker At-a-Glance
What You Do
What It Improves
How the Exercise Changes
How You're Scored
Track target objects as they move around the screen.
•Divided attention
•Objects travel more quickly
•Objects travel over larger area
•Objects travel for longer
•Contrast decreases
Your score is the number of objects you're able to track.
The Science Behind Target Tracker
When you're driving through a busy intersection, how well can you track other cars, pedestrians, and everything else moving around you? Or if you're chaperoning a field trip and you're responsible for several children, how easy is it for you to keep an eye on all of them at the same time, and make sure none gets into too much trouble? Or if you're playing basketball, soccer, or another sport, how well can you keep your eye on the ball and the other players all at once?
In each of these situations, the ability to divide your visual attention and track multiple objects is a requirement. Target Tracker is designed to help build divided attention by requiring you to track several items moving around your screen at the same time.
In Target Tracker, you will start by seeing a few target objects—bubbles, puffer fish, or jellyfish—appear on the screen.

Figure 4. *BrainHQ CT Instructions "Target Tracker" Neurocognitive Task*

Figure 5. *BrainHQ CT Example "Face Facts" Social Cognitive Task*



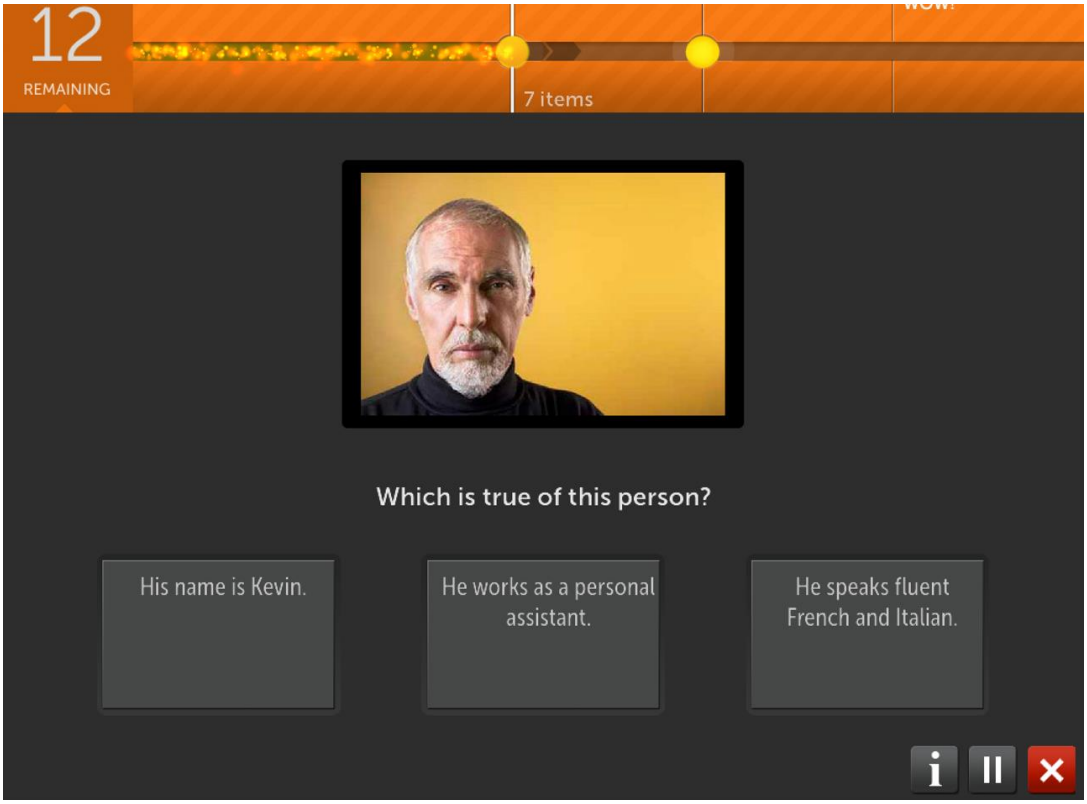
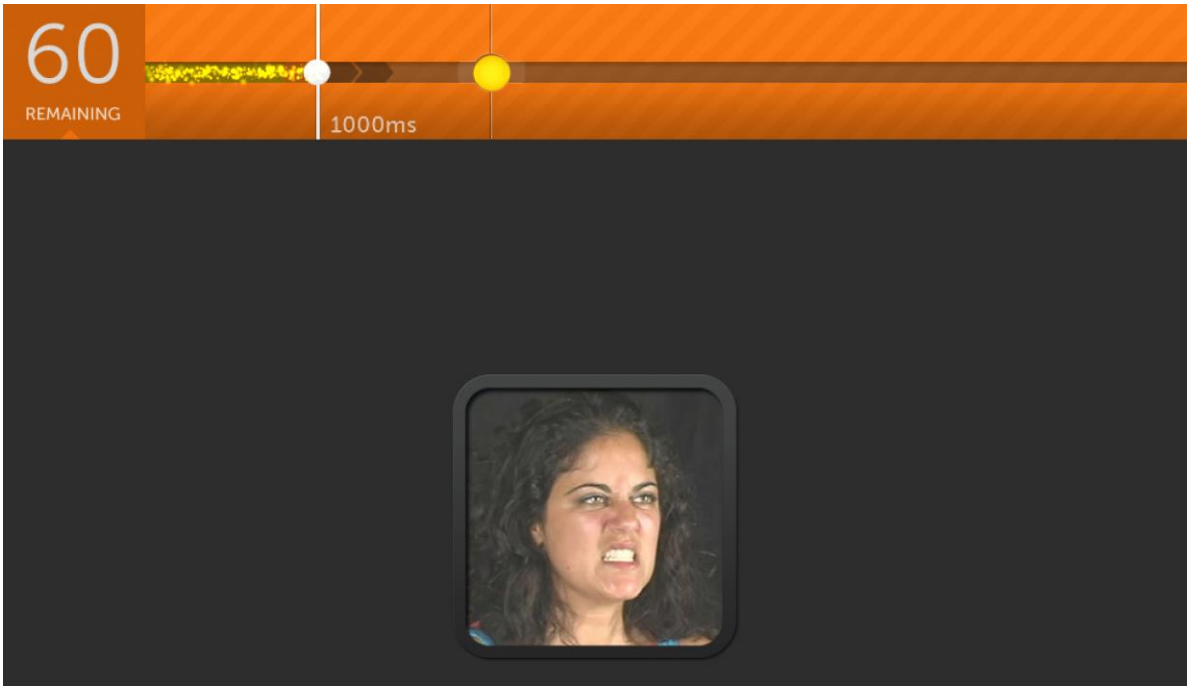


Figure 6. *BrainHQ CT Example "Face To Face" Social Cognitive Task*


60
REMAINING
1000ms

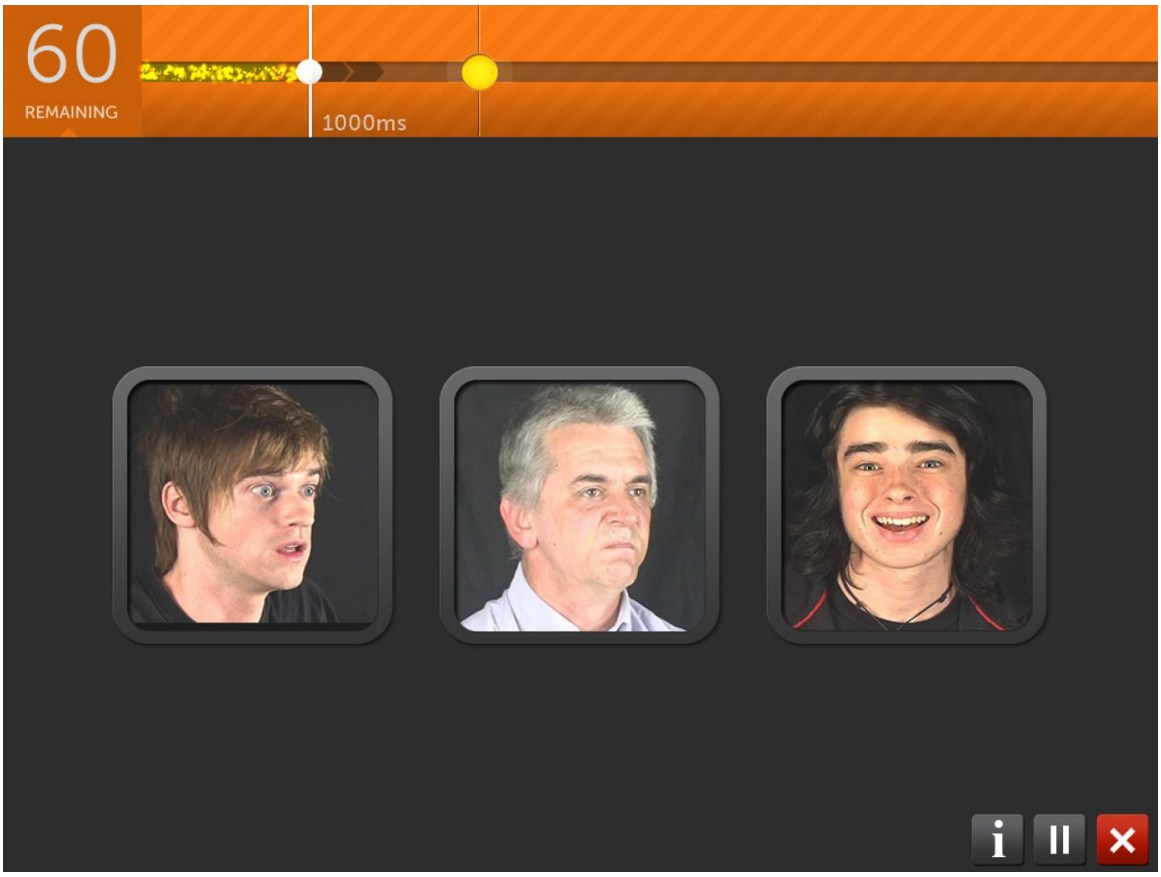

60
REMAINING
1000ms

Figure 7. *BrainHQ CT Example "Target Tracker" Social Cognitive Task*

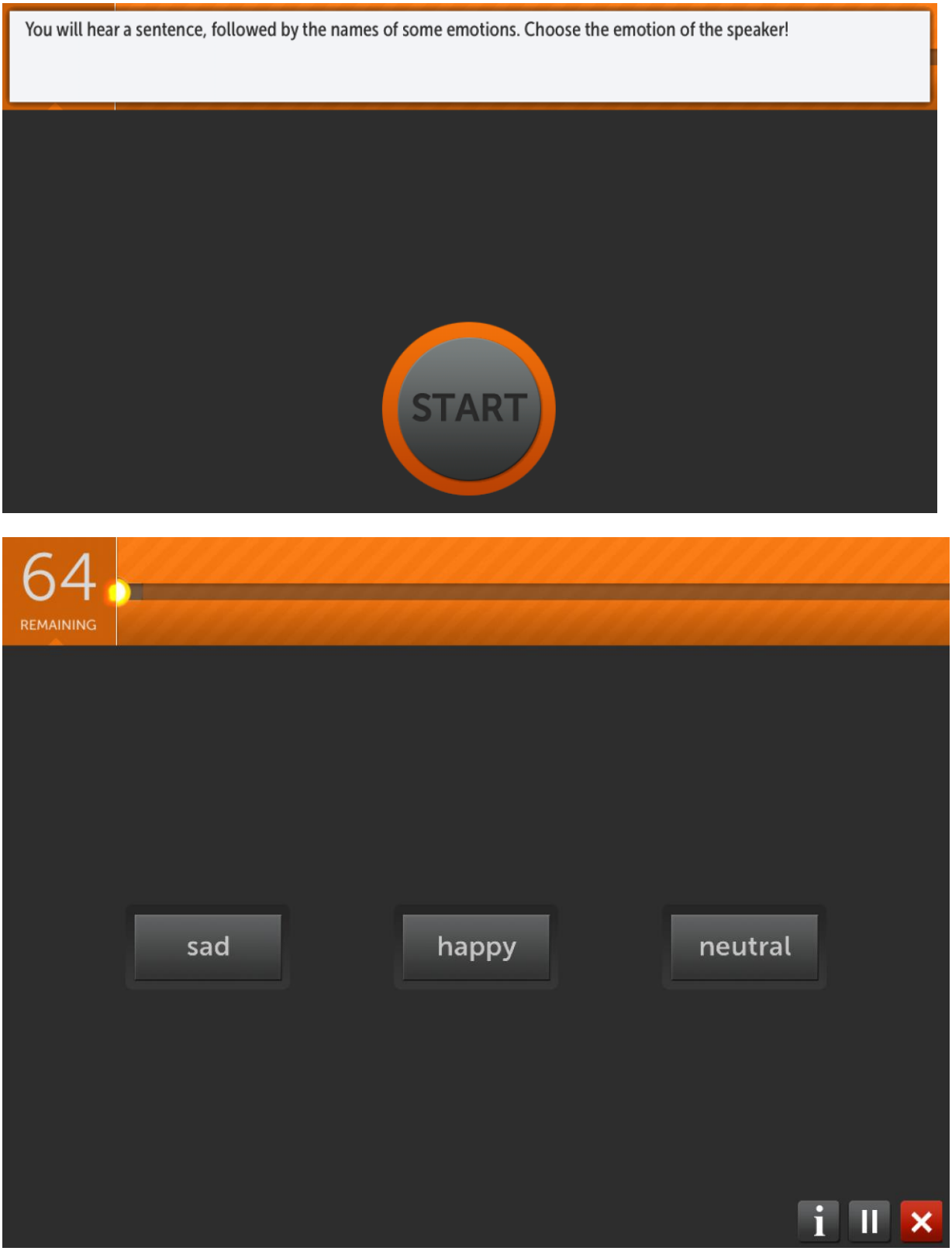
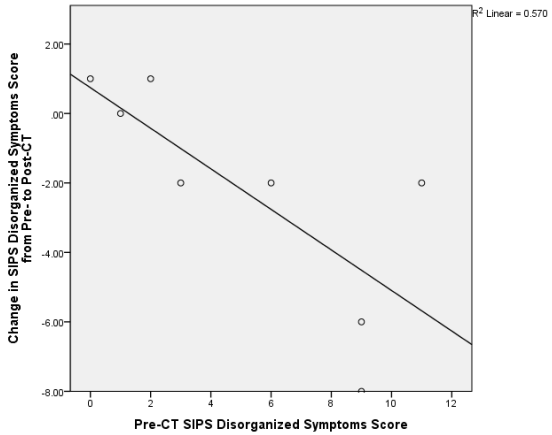
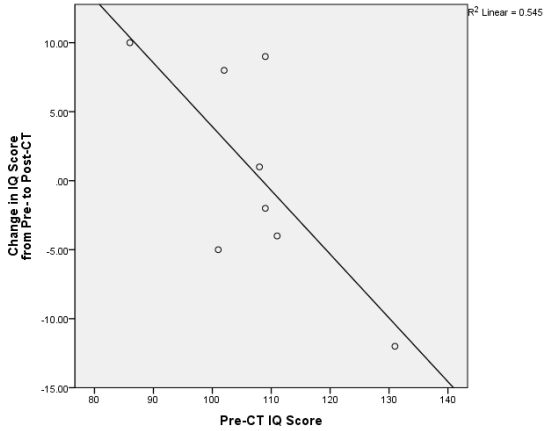
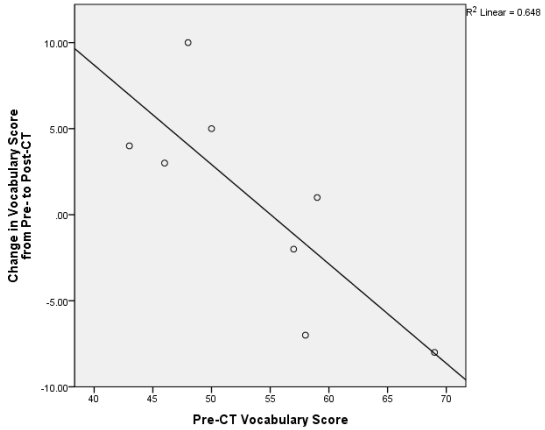


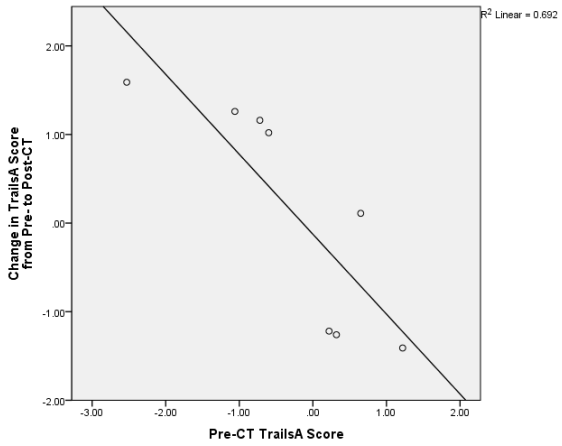
Figure 8a-k. *Correlation Plots between Pre-CT Scores and Change Scores across Domains.*

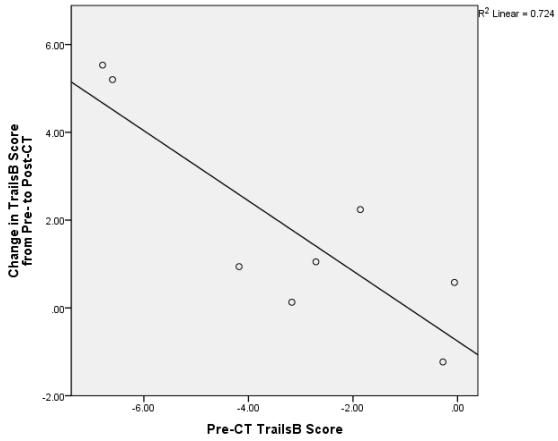
A positive change score reflects improvement from pre- to post-CT assessments. Negative scores at pre-CT assessment reflect negative age-normed z-scores of patients relative to healthy controls. The better the pre-training scores were, the more likely scores were to remain stable or decrease over time; low pre-CT scores were more likely to improve. *IQ*=Wechsler Abbreviated Scale of Intelligence; *Vocabulary*=Wechsler Abbreviated Scale of Intelligence Vocabulary subtest; *BACS*=Symbol coding; *Spatial Span*=Wechsler Memory Scales-3 Spatial Span subtest; *LNS*=Letter number span; *CPT*=Continuous Performance Task – Identical Pairs; *FAS*=D-KEFS Letter Fluency; *ER40*=Penn Emotion Recognition task.

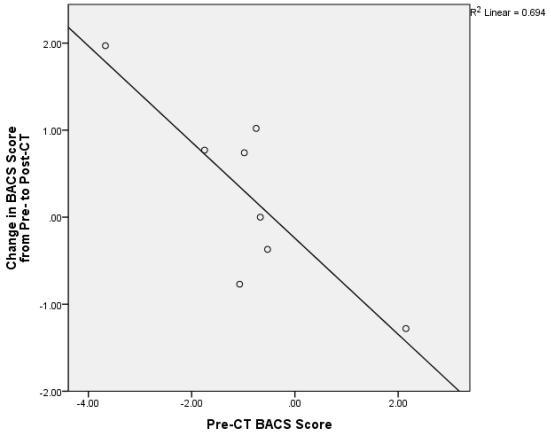


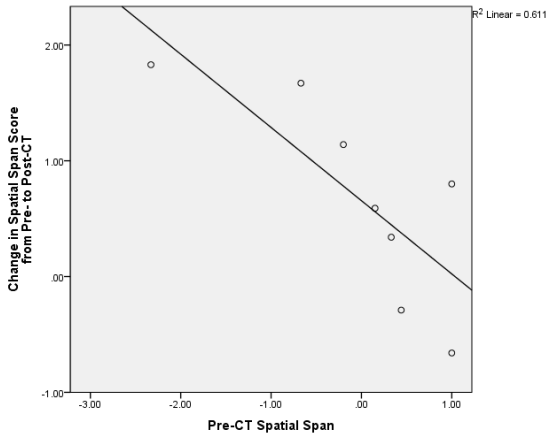


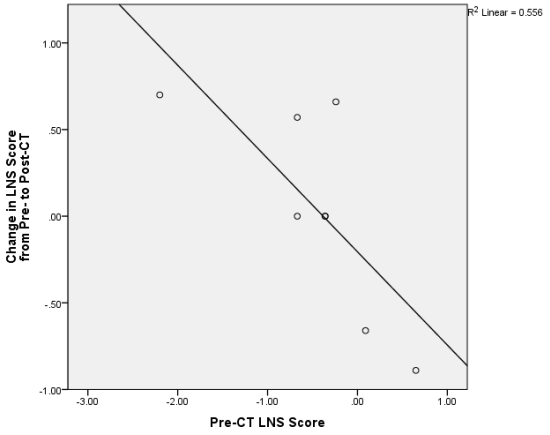


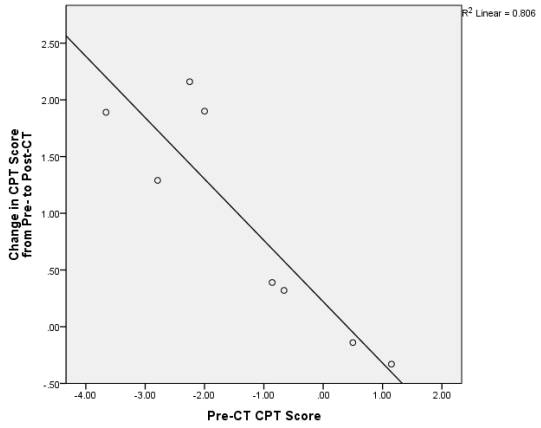

R² Linear = 0.692
Change in TrailsA Score from Pre- to Post-CT
Pre-CT TrailsA Score

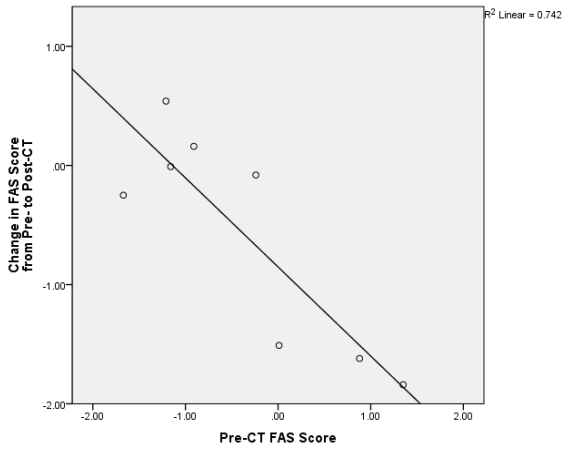

R² Linear = 0.724
Change in TrailsB Score from Pre- to Post-CT
Pre-CT TrailsB Score


R² Linear = 0.694
Change in BACS Score from Pre- to Post-CT
Pre-CT BACS Score


R² Linear = 0.611
Change in Spatial Span Score from Pre- to Post-CT
Pre-CT Spatial Span


R² Linear = 0.556
Change in LNS Score from Pre- to Post-CT
Pre-CT LNS Score


R² Linear = 0.806
Change in CPT Score from Pre- to Post-CT
Pre-CT CPT Score


R² Linear = 0.742
Change in FAS Score from Pre- to Post-CT
1.00
.00
-1.00
-2.00
-2.00
-1.00
.00
1.00
2.00
Pre-CT FAS Score

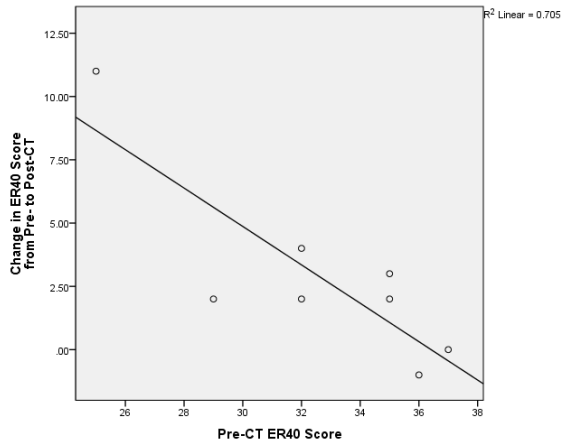

R² Linear = 0.705
Change in ER40 Score from Pre- to Post-CT
12.50
10.00
7.50
5.00
2.50
.00
26
28
30
32
34
36
38
Pre-CT ER40 Score

Figure 9a-b. *Correlation Plots between Age and Change Scores across Domains.*

A positive change score reflects improvement from pre- to post-CT assessments. Increasing age at baseline was associated with a decrease in general symptoms from pre- to post-CT assessments; however, as age at baseline increased, LNS scores were more likely to improve from pre- to post-CT assessments. *LNS*=Letter number span.

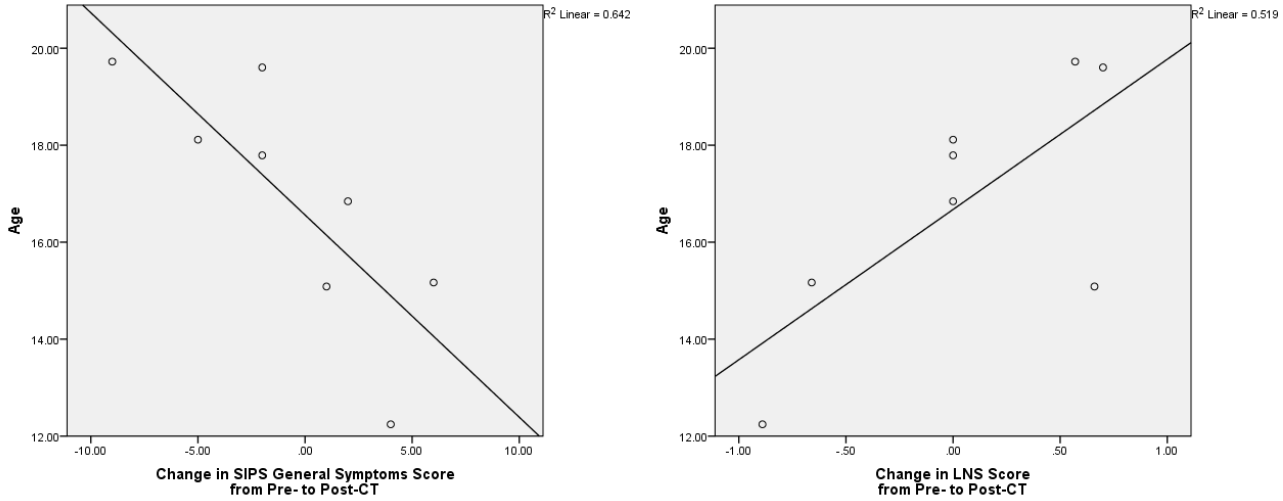
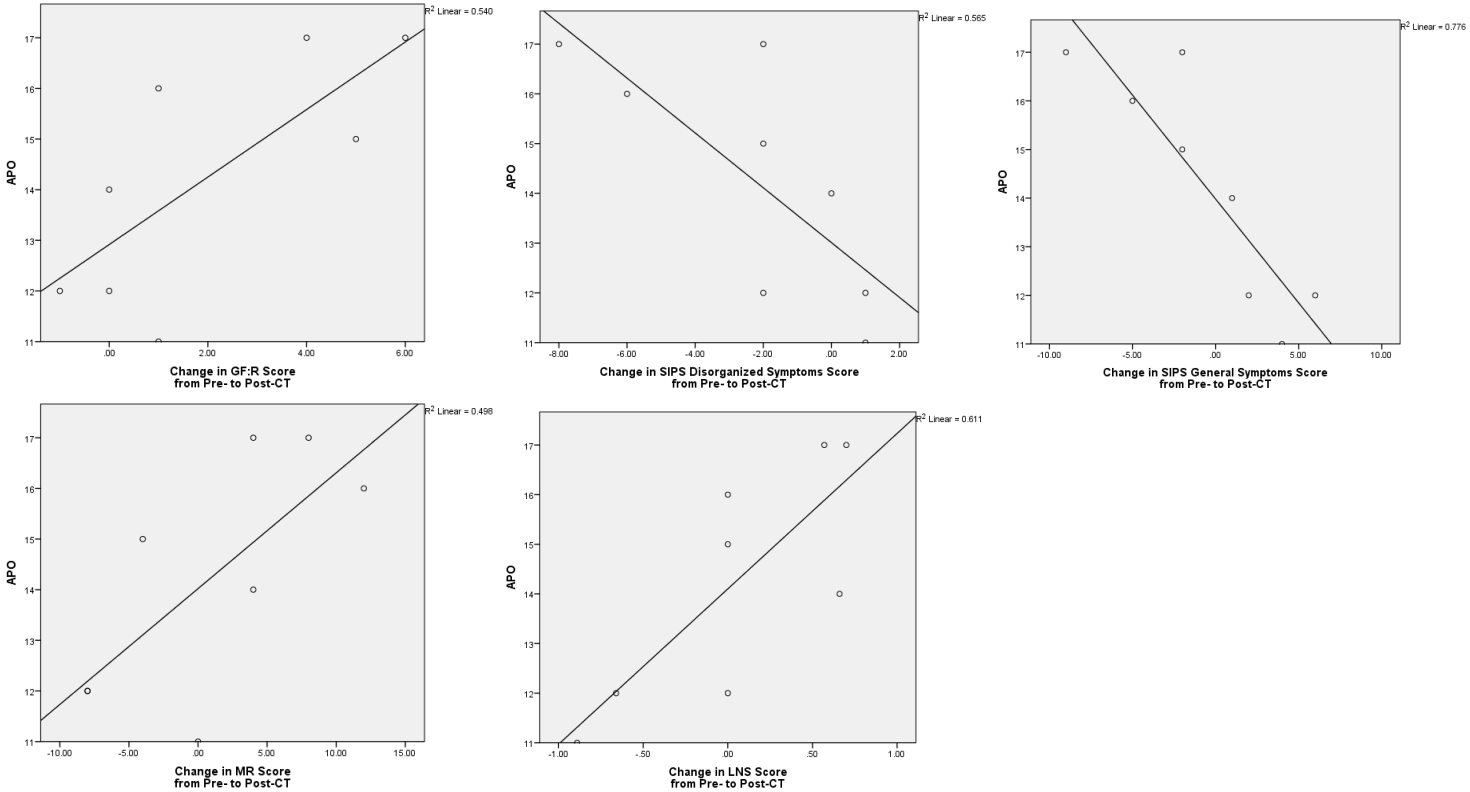


Figure 10a-e. *Correlation Plots between Age at Psychosis Onset (APO) and Change Scores across Domains.*

A positive change score reflects improvement from pre- to post-CT assessments. Earlier APO was associated with less improvement in role functioning scores from pre- to post-assessments, greater disorganized and general symptomatology at post- compared to pre-assessment, and increased deficits on MR and LNS tasks at post- versus pre-CT evaluations. *GF:R*=Global Assessment of Functioning: Role Scale. *MR*=Wechsler Abbreviated Scale of Intelligence Matrix Reasoning subtest; *LNS*=Letter number span.



Appendix 1

BIS/BAS Questionnaire

Subject ID#_____ Time Point_____ Date_____

BIS/BAS

Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says. Please respond to all items. Do *not* leave any blank. Choose only *one* response to each statement. Please be as accurate and honest as you can be. Respond to each item as if it were the only item. That is, don't worry about being "consistent" in your responses. Choose from the following four response options:

Very true for me	Somewhat true for me	Somewhat false for me	Very false for me
1	2	3	4

1. _____ Even if something bad is about to happen to me, I rarely experience fear or nervousness
2. _____ I go out of my way to get things I want.
3. _____ When I'm doing well at something, I love to keep at it.
4. _____ I'm always willing to try something new if I think it will be fun.
5. _____ When I get something I want, I feel excited and energized.
6. _____ Criticism or scolding hurts me quite a bit.
7. _____ When I want something, I usually go all-out to get it.
8. _____ I will often do things for no other reason than that they might be fun.
9. _____ If I see a chance to get something I want, I move on it right away.
10. _____ I feel pretty worried or upset when I think or know somebody is angry at me.
11. _____ When I see an opportunity for something I like, I get excited right away.
12. _____ I often act on the spur of the moment.
13. _____ If I think something unpleasant is going to happen I usually get pretty "worked up."
14. _____ When good things happen to me, it affects me strongly.
15. _____ I feel worried when I think I have done poorly at something.
16. _____ I crave excitement and new sensations.
17. _____ When I go after something, I use a "no holds barred" approach.
18. _____ I have very few fears compared to my friends.
19. _____ It would excite me to win a contest.
20. _____ I worry about making mistakes.

Appendix 2

TEPS Questionnaire

TEPS STATE

DIRECTIONS: Please read each statement carefully and decide how true that statement has been for you in past week. Please respond to *all items*. In the rare case where you have ***never*** had the experience described, think about the most similar experience you've had and make your response. Do *not* leave any blank. Choose only *one* response to each statement. Don't worry about being consistent in your responses. Choose from the following 6 response options and CIRCLE your response to the right of the item.

1	2	3	4	5	6
very false for me	moderately false for me	slightly false for me	slightly true for me	moderately true for me	very true for me

In the past week…		**In the past week…**	
1. if I were to hear about a new movie coming out starring my favorite actor, I would get very excited to see it.	1 2 3 4 5 6	10. I've noticed that I get so excited before important days or events that I can hardly sleep.	1 2 3 4 5 6
2. I have enjoyed experiences like taking deep breaths of fresh air when I walk outside.	1 2 3 4 5 6	11. when I'm about to do something fun, I can hardly wait.	1 2 3 4 5 6
3. the smell of freshly cut grass (or the outdoors) has been enjoyable to me.	1 2 3 4 5 6	12. I've noticed that I really enjoy the feeling of a good yawn.	1 2 3 4 5 6
4. I have been looking forward to a lot of things.	1 2 3 4 5 6	13. I've noticed that I don't look forward to things like eating out at restaurants.	1 2 3 4 5 6
5. I have enjoyed the touch of others.	1 2 3 4 5 6	14. I've noticed that I love the sound of rain on the windows (or other outdoor sounds) when I'm lying in my warm bed.	1 2 3 4 5 6
6. I have noticed that looking forward to a pleasurable experience is in itself pleasurable.	1 2 3 4 5 6	15. when I think about eating my favorite food, I can almost taste how good it is.	1 2 3 4 5 6
7. I have found a hot cup of coffee or tea very satisfying.	1 2 3 4 5 6	16. when I'm ordering something off the menu, I imagine how good it will taste.	1 2 3 4 5 6
8. I have noticed that when I think of something tasty, like a chocolate chip cookie, I have to have one.	1 2 3 4 5 6	17. I've noticed that things like the sound of crackling wood in the fireplace can be very relaxing.	1 2 3 4 5 6
9. I have appreciated the beauty of the outdoors.	1 2 3 4 5 6	18. when something exciting is coming up in my life, I really look forward to it.	1 2 3 4 5 6

Appendix 3

Patient Post-CT Survey

Follow-up iPad Training Survey

ABBRC Study Participant ID: _____ Date: _____

We'd like to know how things went with the iPad training as part of this study.

When you did the iPad training, how much of the time did you feel that…		none of the time	a little bit of the time	about half the time	most of the time	all of the time
Interest/Enjoyment						
1.	the training was interesting?	0	1	2	3	4
2.	the training was fun?	0	1	2	3	4
3.	the training was satisfying?	0	1	2	3	4
4.	the training was enjoyable?	0	1	2	3	4
5.	the training was easy?	0	1	2	3	4
Scheduling						
6.	it's was easy to do the training for two hours per week?	0	1	2	3	4
7.	the application made it quick and easy for you to play every time?	0	1	2	3	4
8.	the application fit easily into your weekly schedule?	0	1	2	3	4
9.	it was easy to do the training for at least 30 minutes at a time?	0	1	2	3	4
10.	the training session passed by quickly?	0	1	2	3	4
Software/Instructions						
11.	It was easy to use the iPad?	0	1	2	3	4
12.	the training software was easy to navigate?	0	1	2	3	4
13.	you needed to use the help button ("?") to find things on the application?	0	1	2	3	4
14.	the training instructions were easy to understand?	0	1	2	3	4
15.	the application conveniently helped you remember where you last left off in your training session?	0	1	2	3	4
16.	the application graphics were attractive?	0	1	2	3	4
Effect of the Training						
17.	you were making progress?	0	1	2	3	4
18.	the training session felt helpful to you?	0	1	2	3	4
19.	the training was effective?	0	1	2	3	4
20.	the training improved your thinking and memory?	0	1	2	3	4

21.	the training helped you do well at school or at work?	0	1	2	3	4
22.	the training was having a positive effect on your daily life?	0	1	2	3	4
Other						
23.	you would use the training even if you were not part of the study?	0	1	2	3	4
24.	you would recommend this training to others?	0	1	2	3	4
25.	the training was a high priority, compared to your other activities?	0	1	2	3	4

26. Did anyone remind you to do the training?

no = 0	yes = 1

If YES, who?

parent	no = 0	yes = 1
other family member	no = 0	yes = 1
friend	no = 0	yes = 1
therapist	no = 0	yes = 1
educational support staff	no = 0	yes = 1
someone else	no = 0	yes = 1

27. Was there anything that kept you from doing the iPad training according to the schedule – two hours a week, at least 30 minutes a session?

no = 0	yes = 1

If YES, did the following keep you from doing the training according to schedule:

Getting access to the iPad	no = 0	yes = 1
Remembering to do the training	no = 0	yes = 1
Not enjoying the training	no = 0	yes = 1

Did anything else keep you from doing the training according to schedule? If YES, list:

We are interested in how we can improve the iPad training for future users.

Based on your experience, would changing any of the following things about the training help to make it better and easier to use?

		not at all better	a little bit better	somewhat better	a lot better
28.	training for less time each day?	0	1	2	3

	(even if that meant training for more days)				
29.	training for fewer days each week? (even if that meant training for more weeks)	0	1	2	3
30.	getting more feedback about how training is affecting your thinking and memory?	0	1	2	3
31.	knowing more about how the training is supposed to be helpful?	0	1	2	3
33.	Is there anything else that would make the training better and easier to use?				

34.	What did you like best about the application?

For early drop-outs only:

35.	Why did you decide to stop training? Please respond here and circle all that apply below:

Moved away	=1
Training was boring	=2
Symptoms got in the way	=3
Hospitalized	=4
Didn't have time	=5
Don’t think the training will help	=6
Training was too difficult	=7

Appendix 4

Parent/Caregiver Post-CT Survey

Parent/Caregiver Survey	Page | **157**
ABBRC Study. Participant ID: _____	Date: _____

We'd like to know how things went with your child as part of this study.

1.	Did you provide encouragement to complete the exercises?	no = 0	yes = 1
	If YES, how often?	_____ times per week OR _____ times per month	
2.	Did you provide reminders to complete the exercises?	no = 0	yes = 1
	If YES, how often?	_____ times per week OR _____ times per month	

For questions 3 - 12, please tell us whether you noticed improvement in the following. (please circle one):

		No improvement		Moderate improvement		Much improvement	N/A
3.	Symptoms	1	2	3	4	5	
4.	Functioning at school	1	2	3	4	5	
5.	Social functioning	1	2	3	4	5	
6.	Overall quality of life	1	2	3	4	5	
7.	Attention	1	2	3	4	5	
8.	Memory	1	2	3	4	5	
9.	Problem solving	1	2	3	4	5	
10.	Speed of processing	1	2	3	4	5	
11.	Overall cognition	1	2	3	4	5	
12.	Other: _____	1	2	3	4	5	

13.	Would you use this program outside of a research study?	no = 0	yes = 1
14.	Would you recommend this program to others?	no = 0	yes = 1
15.	Do you have any suggestions for improvements?		

Appendix 5

Weekly Computer Use Survey

Weekly Computer Use Survey	Page | **159**
ABBRC Study	Participant ID: _____

Research assistant: These questions only pertain to non-CogRem computer usage (i.e., participant responses should not include brainHQ usage). You may need to remind the participant throughout the interview that their answers should **not** include brainHQ app usage.

Date of Form Completion	__/__-__/__/-__/__/__/__/ MM – DD – YYYY
Have your medications changed in the past week? (If yes, list changes- med names/dosages)	□ Yes: _____ _____ _____ □ No
Where do you have computer access?	
Other than the iPad we gave you for the study, in the past week, how often did you use a computer or mobile computing device (e.g. iPad)? (Select one)	□ No computer use □ 1 day this week □ 2 days □ 3 days □ 4 days □ 5 days □ 6 days □ 7 days this week
On the days you used a computer or mobile computing device, how many hours per day did you use it? (Select one)	□ No computer use □ 1 hour per day □ 2 hours □ 3 hours □ 4 hours □ 5 hours □ 6 hours □ 7 hours □ 8 hours □ 9 hours □ 10 hours per day □ Other

If "Other", please specify:	
In the last week, what did you most often use the computer for? (Select one)	□ Searching for information online □ Online shopping □ Email, Correspondence □ Music or Movie Streaming □ Social Networking □ Games □ Other
In the last week, how many days did you play video games? Remember, the iPad brain training game doesn't count for this total.	□ No video games □ 1 day this week □ 2 days □ 3 days □ 4 days □ 5 days □ 6 days □ 7 days this week
How many hours per day did you play video games?	□ No video game use □ 1 hour per day □ 2 hours □ 3 hours □ 4 hours □ 5 hours □ 6 hours □ 7 hours □ 8 hours □ 9 hours □ 10 hours per day □ Other
If "Other", please specify:	

If you played either video or computer games, please list them and the average time you played them per day:	Game 1:_____ Hours per day:_____ Game 2: _____ Hours per day: _____ Game 3: _____ Hours per day: _____ Game 4: _____ Hours per day: _____
How many hours over the past week have you been in school?: *(ask participant to make their best guess if they don't know)*	_____
How many hours over the past week have you been in work?: *(if applicable; ask participant to make their best guess if they don't know)*	_____
Form Completed by:	_____

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