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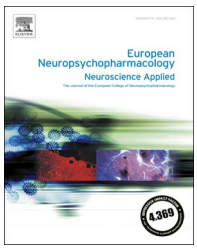

Neurocognitive profile in psychotic versus nonpsychotic individuals with 22q11.2 deletion syndrome

Ronnie Weinberger[a], James Yi[b,c], Monica Calkins[b], Yael Guri[a], Donna M. McDonald-McGinn[d,e], Beverly S. Emanuel[d,e], Elaine H. Zackai[d,e], Kosha Ruparel[b], Miri Carmel[a,f], Elena Michaelovsky[a,f], Abraham Weizman[a,f,g], Ruben C. Gur[b,c], Raquel E. Gur[b,c], Doron Gothelf[a,h,*]

[a]*Sackler Faculty of Medicine, Tel Aviv University, Israel*
[b]*Department of Psychiatry, Neuropsychiatry Section, Perelman School of Medicine, University of Philadelphia Pennsylvania, Philadelphia, PA, USA*
[c]*Department of Child and Adolescent Psychiatry, Children's Hospital of Philadelphia, Philadelphia, PA, USA*
[d]*Division of Human Genetics, The Children's Hospital of Philadelphia, Philadelphia, PA, USA*
[e]*Department of Pediatrics, Perelman School of Medicine, University of Philadelphia Pennsylvania, Philadelphia, PA, USA*
[f]*Felsenstein Medical Research Center, Sackler Faculty of Medicine, Tel Aviv University, Petah Tikva, Israel*
[g]*Research Unit, Geha Mental Health Center, Petah Tikva, Israel*
[h]*The Child Psychiatry Unit, Edmond and Lily Sapfra Children's Hospital, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel*

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Abstract
The 22q11.2 deletion syndrome (22q11DS) is associated with increased rates of psychotic disorders and cognitive deficits, but large scale studies are needed to elucidate their interaction. The objective of this two-center study was to identify the neurocognitive phenotype of individuals with 22q11DS and psychotic disorders. We hypothesized that psychotic 22q11DS individuals compared to nonpsychotic deleted individuals would have more severe neurocognitive deficits, especially in executive function and social cognition. These deficits would be present when compared to IQ- matched individuals with Williams Syndrome (WS).
Three groups were ascertained from the Tel Aviv and Philadelphia centers: 22q11DS individuals with a psychotic disorder (n=31), nonpsychotic 22q11DS (n=86) and typically-developing controls (TD, n=828). In Tel Aviv a group of individuals with WS (n=18) matched in IQ to the

*Corresponding author at: The Child Psychiatry Unit, Edmond and Lily Sapfra Children's Hospital, Sheba Medical Center Hashomer, Ramat Gan, Israel. Fax: +972 0 35302593.
E-mail address: gothelf@post.tau.ac.il (D. Gothelf).

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22q11DS psychotic group was also included. The Penn Computerized Neurocognitive Battery (CNB) was used to assess a wide-range of cognitive functions and all patients underwent structured psychiatric evaluations. 22q11DS individuals performed poorly on all CNB domains compared to TD. Participants with 22q11DS and psychosis, compared to nonpsychotic 22q11DS, had more severe deficits in global neurocognitive performance (GNP), executive function, social cognition and episodic memory domains. The primary deficits were also significant when comparing the Tel Aviv 22q11DS psychotic group to IQ-matched individuals with WS. In conclusion, 22q11DS individuals with a psychotic disorder have specific neurocognitive deficits that are reliably identified cross nationality using the CNB. These cognitive dysfunctions should be further studied as potential endophenotypes of psychosis in 22q11DS and as targets for intervention.

1. Introduction

The 22q11.2 deletion syndrome (22q11DS) is one of the most common genetic syndromes, occurring in up to 1 in 1000 live births (Grati et al., 2015). It is characterized by multiple medical symptoms, including cardiac disorders, palatal abnormalities and hypocalcemia (Bassett et al., 2011; Furuya et al., 2015; McDonald-McGinn et al., 2015). Most individuals with 22q11DS cope with cognitive deficits in attention, executive function, complex cognition, social cognition and memory (Azuma et al., 2015; Gur et al., 2014b; Simon et al., 2005). In addition, psychiatric comorbidities are very common and include attention deficit/hyperactivity disorder (ADHD), depression and anxiety disorders (Schneider et al., 2014a). The syndrome is also associated with high prevalence of psychotic disorders. By adulthood about one-third of individuals with 22q11DS develop a psychotic disorder, most often schizophrenia (Gothelf et al., 2013) representing an approximately ~10-fold increase risk compared to individuals with other developmental disabilities (Hemmings, 2006).

Premorbid neurocognitive deficits in attention, verbal memory and executive function, are prominent features of schizophrenia in the general population. Some of those domains, including working memory and executive function deficits, are endophenotypes of the disorder (Tan et al., 2009).

The associations among cognitive deficits, psychosis risk and psychotic disorders have been previously studied in 22q11DS (Chow et al., 2006; Gothelf et al., 2007; van Amelsvoort et al., 2004). These studies investigated premorbid cognitive deficits as predictors for later development of psychosis (Antshel et al., 2010; Gothelf et al., 2007; Vorstman et al., 2015; Yuen et al., 2013) and focused primarily on IQ measures. They found that individuals with 22q11DS who later develop psychotic disorders or prodromal syndrome have lower baseline verbal IQ (VIQ) and more robust age associated decline in VIQ compared to 22q11DS individuals who do not develop psychotic disorders (Antshel et al., 2010; Gothelf et al., 2007; Gothelf et al., 2013; Green et al., 2009). A large sample of individuals with 22q11DS followed longitudinally, replicated these finding (Vorstman et al., 2015) and demonstrated that the decline in VIQ as early as 11 years old, was associated with later development of psychotic disorders. Such findings are consistent with reports of substantial neuropsychological decline in schizophrenia in the general population from the premorbid to the post-onset period (Meier et al., 2014).

Few studies have investigated a broad cognitive profile in individuals with 22q11DS and psychotic disorders (Chow et al., 2006; Gothelf et al., 2013; Green et al., 2009; van Amelsvoort et al., 2004). The studies that examined psychotic patients with 22q11DS did not use a single battery, and applied several tests from various cognitive batteries, including nonstandardized measures, combining computerized and noncomputerized tests (Chow et al., 2006; van Amelsvoort et al., 2004). These studies reported that individuals with psychotic disorders and 22q11DS, compared with non-psychotic 22q11DS individuals, had poorer motor skills and more deficits in verbal learning and social cognition (Chow et al., 2006). Deficits in spatial working memory, strategy formation, attention and visual recognition have also been reported in individuals with 22q11DS and psychotic disorders (van Amelsvoort et al., 2004). To better characterize the cognitive deficits in psychotic individuals with 22q11DS, it is important to employ a single computerized comprehensive neurocognitive battery and to include both healthy and developmentally delayed controls.

In addition to being the first study to use a comprehensive computerized cognitive battery for 22q11D psychotic individuals, the current study is also the first to compare cognitive characteristics in 22q11DS psychotic individuals with an IQ matched group of individuals with another common microdeletion disorder. Williams syndrome (WS) is an optimal control group for psychotic patients with 22q11DS because the mean IQ of individuals with WS is ~60 (Mervis et al., 2000), which is similar to the reported IQ of 22q11DS individuals with psychotic disorders (Vorstman et al., 2015). Additionally, individuals with 22q11DS and WS have a high prevalence of similar physical comorbidities including cardiac deficits, feeding difficulties, and calcium abnormalities (Zarchi et al., 2014). The two groups also share high rates of psychiatric disorders and problems with peer relations (Zarchi et al., 2014).

The aim of the present two-site study was to characterize the cognitive phenotype of individuals with 22q11DS and psychotic disorders by comparing them to age-matched 22q11DS individuals without psychotic disorders, to

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