European Neuropsychopharmacology (2017) 27, 928–939

www.elsevier.com/locate/euroneuro

A Polygenic Risk Score of glutamatergic SNPs associated with schizophrenia predicts attentional behavior and related brain activity in healthy humans

Antonio Rampino[a], Paolo Taurisano[a], Giuseppe Fanelli[a], Mariateresa Attrotto[a,b], Silvia Torretta[a], Linda Antonella Antonucci[a], Grazia Miccolis[a], Giulio Pergola[a], Gianluca Ursini[c], Giancarlo Maddalena[a,b], Raffaella Romano[a], Rita Masellis[b], Pasquale Di Carlo[a], Patrizia Pignataro[a], Giuseppe Blasi[a,b], Alessandro Bertolino[a,b,*]

[a]*Department of Basic Medical Science, Neuroscience and Sense Organs – University of Bari "Aldo Moro", Piazza Giulio Cesare 11, 70124 Bari, Italy*
[b]*Psychiatry Unit – Bari University Hospital, Piazza Giulio Cesare 11, 70124 Bari, Italy*
[c]*Lieber Institute for Brain Development, Johns Hopkins University Medical Campus, 21205 Baltimore, MD, USA*

Received 6 December 2016; received in revised form 13 April 2017; accepted 10 June 2017

KEYWORDS
Glutamate;
Working memory;
Attention;
Schizophrenia;
Prefrontal;
Cortex

Abstract
Multiple genetic variations impact on risk for schizophrenia. Recent analyses by the Psychiatric Genomics Consortium (PGC2) identified 128 SNPs genome-wide associated with the disorder. Furthermore, attention and working memory deficits are core features of schizophrenia, are heritable and have been associated with variation in glutamatergic neurotransmission. Based on this evidence, in a sample of healthy volunteers, we used SNPs associated with schizophrenia in PGC2 to construct a Polygenic-Risk-Score (PRS) reflecting the cumulative risk for schizophrenia, along with a Polygenic-Risk-Score including only SNPs related to genes implicated in glutamatergic signaling (Glu-PRS). We performed Factor Analysis for dimension reduction of indices of cognitive performance. Furthermore, both PRS and Glu-PRS were used as predictors of cognitive functioning in the domains of Attention, Speed of Processing and Working Memory. The association of the Glu-PRS on brain activity during the Variable Attention Control (VAC) task was also explored. Finally, in a second independent sample of healthy volunteers we sought to

*Corresponding author at: Department of Basic Medical Sciences, Neuroscience and Sensory Organs, University of Bari, 'Aldo Moro', Piazza Giulio Cesare, 11, 70120 Bari, Italy.
E-mail address: alessandro.bertolino@uniba.it (A. Bertolino).

http://dx.doi.org/10.1016/j.euroneuro.2017.06.005

confirm the association between the Glu-PRS and both performance in the domain of Attention and brain activity during the VAC.

We found that performance in Speed of Processing and Working Memory was not associated with any of the Polygenic-Risk-Scores. The Glu-PRS, but not the PRS was associated with Attention and brain activity during the VAC. The specific effects of Glu-PRS on Attention and brain activity during the VAC were also confirmed in the replication sample.

Our results suggest a pathway specificity in the relationship between genetic risk for schizophrenia, the associated cognitive dysfunction and related brain processing.

1. Introduction

Schizophrenia is a brain disease with an important genetic component accounting for 65–80% of heritability (Lichtenstein et al., 2009; Sullivan et al., 2012, 2003). There is evidence that genetic risk for schizophrenia results by a collective burden of many low-penetrance gene mutations together with a small number of highly penetrant mutations (Purcell et al., 2009). Consistently, Genome Wide Association Studies (GWAS) have confirmed that a considerably high number of Single Nucleotide Polymorphisms (SNPs) distributed across the entire genome is associated with the disorder. For example, recent analyses by the Schizophrenia Working Group of the Psychiatric Genomics Consortium on almost 37,000 cases and 113,000 controls (PGC2) have identified 128 SNPs, occurring in 108 loci that are genome-wide associated with the disorder (Schizophrenia Working Group of the Psychiatric Genomics, 2014). In order to test the polygenic burden of this disease, previous studies have captured the en masse additive variation across nominally associated loci into quantitative scores (Polygenic Risk Scores -PRSs), and related the scores to disease state in independent samples (Cross-Disorder Group of the Psychiatric Genomics et al., 2013, Ripke et al., 2013). These scores are constructed from alleles showing association with schizophrenia in GWAS and thus reflect additive genetic risk for the disease and represent a powerful tool to understand the genetic underpinnings of schizophrenia. Nevertheless, these cumulative non-specific indices of genetic risk do not provide any specific insight into the biology associated with these genetic variants. One possible way to overcome such a limitation is to consider alleles associated with known specific biological pathways and use them to construct pathway-specific PRSs. Moreover, it is possible to hypothesize that PRSs recapitulating variation in a specific signaling pathway and associated with a disease are more strongly associated with distinct specific endophenotypes of the same disease as compared with the en masse PRS by virtue of their biological specificity. In line with such a hypothesis, studies have demonstrated that disruption in specific neuronal signaling pathways is associated with variation in endophenotypes of schizophrenia (Allen et al., 2009, Cannon, 2005), including cognitive deficits typical of the disorder. Therefore, it is plausible to hypothesize that PRSs built on genetic variants belonging to specific pathways can predict variation in these phenotypes more robustly than risk scores reflecting the overall risk for the disorder.

Among cognitive deficits that are endophenotypes of schizophrenia (Bertolino and Blasi, 2009), impairments in attention and WM are well established. Several studies have identified attention as a cognitive domain that encompasses the primary deficiencies of schizophrenia (Nuechterlein et al., 2004). Consistently, schizophrenia patients perform poorer than healthy controls at the Continuous Performance Test (CPT) (Cornblatt and Malhotra, 2001), a task that is used to assess attention performance in humans. Consistently, neuroimaging studies have reported modification in prefrontal cortex processing of attention stimuli in patients with schizophrenia (Blasi et al., 2010; Delawalla et al., 2008).

Similarly, robust deficits in WM have been identified in schizophrenia patients relative to healthy controls. In fact, as described in two comprehensive meta-analyses (Lee and Park, 2005; Forbes et al., 2009), deficits in working memory are present in schizophrenia across a number of measures, specifically, tasks assessing maintenance and/or manipulation of auditory, visual, lexical, or semantic information. Consistently, imaging studies have shown prefrontal activity during WM to be altered in patients with the disorder (Callicott et al., 1998).

A number of studies have also suggested that variation in attention and WM performance is associated with modulation in glutamatergic signaling both in animal models and humans. In fact, studies in rodents have demonstrated that acute administration of the noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist ketamine inhibits sustained attention in rats performing a visual signal detection task (Hillhouse et al., 2015) and that the repeated administration of ketamine can impair the ability to sustain attention as assessed in the five-choice serial reaction time task (5-CSRTT) (Nikiforuk and Popik, 2014). Furthermore, the same ketamine administration protocol induces deficits in mice attention set-shifting abilities as assessed with the attention set-shifting task (ASST), an effect that is alleviated by the subsequent administration of antipsychotic medication (Kos et al., 2011). In humans, studies have demonstrated that NMDA antagonists including ketamine and phencyclidine exacerbate psychosis in patients with schizophrenia (Malhotra et al., 1997). Furthermore, these molecules induce in healthy subjects phenomena reminiscent of positive and negative symptoms (Krystal et al., 1994), as well as cognitive dysfunction reminiscent of that associated with the disorder, especially in the domain of attention (Lieberman et al., 2008, Malhotra et al., 1996). Among others, deficits in strategic shifting of visual attention (Fuchs et al., 2015) and goal-driven biases in orienting