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Meta-analysis on the association between genetic polymorphisms and prepulse inhibition of the acoustic startle response

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ABSTRACT

Sensorimotor gating measured by prepulse inhibition (PPI) of the acoustic startle response (ASR) has been proposed as one of the most promising electrophysiological endophenotypes of schizophrenia. During the past decade, a number of publications have reported significant associations between genetic polymorphisms and PPI in samples of schizophrenia patients and healthy volunteers. However, an overall evaluation of the robustness of these results has not been published so far. Therefore, we performed the first meta-analysis of published and unpublished associations between gene polymorphisms and PPI of ASR. Unpublished associations between genetic polymorphisms and PPI were derived from three independent samples. In total, 120 single observations from 16 independent samples with 2660 study participants and 43 polymorphisms were included. After correction for multiple testing based on false discovery rate and considering the number of analyzed polymorphisms, significant associations were shown for four variants, even though none of these associations survived a genome-wide correction ($P < 5 * 10^{-8}$). These results imply that PPI might be modulated by four genotypes – *COMT* rs4680 (primarily in males), *GRIK3* rs1027599, *TCF4* rs9960767, and *PRODH* rs385440 – indicating a role of these gene variations in the development of early information processing deficits in schizophrenia. However, the overall impact of single genes on PPI is still rather small suggesting that PPI is – like the disease phenotype – highly polygenic. Future genome-wide analyses studies with large sample sizes will enhance our understanding on the genetic architecture of PPI.

1. Introduction

Prepulse inhibition (PPI) of the acoustic startle response (ASR) is defined as a substantial reduction of the startle amplitude that occurs when a startling stimulus is preceded within a timeframe of 20–500 ms by a stimulus of lower intensity than the startling stimulus (Graham 1975). PPI has been shown to occur across species ranging from mollusks and fishes to mammals including non-human and human primates (Burgess and Granato 2007; Frost et al. 2003; Hoffman and Searle 1965; Ison and Leonhard 1970; Krauter et al. 1973; Linn and Javitt 2001). Animal studies carried out predominantly in rodents suggested that PPI is regulated by a cortico-striato-pallido-pontine (CSPP) circuitry including frontal and mediotemporal regions, ventral striatum, ventral pallidum, and pontine regions of the brainstem (Fendt et al. 2001; Swerdlow et al. 2001). Within the CSPP circuit, several neurotransmitters have been demonstrated to play a major role in the mediation of PPI such as dopamine, noradrenaline, serotonin, acetylcholine, glutamate, and γ-aminobutyric acid (GABA) (Geyer et al. 2001; Koch 1999). Consequently, PPI has been proposed as a "window" into brain chemistry potentially allowing the identification of

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neuropharmacological alterations in specific psychiatric disorders with PPI abnormalities (Braff 2010). In fact, lower PPI levels have been reported for several neuropsychiatric disorders (Braff et al. 2001; Kohl et al. 2013; Quednow 2008), but were replicated best for schizophrenia spectrum disorders (e.g., Braff et al. 1992; Cadenhead et al. 1993; Kumari et al. 2000; Ludewig et al. 2003; Parwani et al. 2000; Quednow et al. 2006; Swerdlow et al. 2014). Given that PPI shows such a robust association with schizophrenia and because it is heritable (Anokhin et al. 2003; Greenwood et al. 2007, 2016; Willott et al. 1994, 2003), reduced in unaffected relatives of schizophrenia patients (Cadenhead et al. 2000; Kumari et al. 2005), and already decreased in early (prodromal) stages of the disease (Quednow et al. 2008a; Ziermans et al. 2011, 2012), PPI was suggested as an promising candidate of an intermediate or endophenotypic marker in genetic studies of schizophrenia (Braff and Light 2005; Gottesman and Gould 2003). Specifically, the substantial heritability of PPI in humans – ranging from 29% to 50% across a number studies – suggests PPI as a favorable target for genetic analyses (Anokhin et al. 2003; Greenwood et al. 2007; Hasenkamp et al. 2010; Seidman et al. 2015). Additionally, it was recently shown that PPI revealed substantially increased heritability (47%) in 97 families multiply affected by schizophrenia when compared with a 96 families, in which only a single individual was affected (2%). This finding further promotes the assumption that a commonality of genes underlies both schizophrenia and PPI (Greenwood et al. 2016).

The endophenotype concept assumes that an endophenotypic marker is a heritable, quantifiable, and stable trait, which is determined by a smaller number of genes compared to the respective complex disease phenotype (Braff et al. 2007). Accordingly, in the last decade several research groups aimed to identify gene effects on the expression of PPI. The first positive findings were published in 2008, where associations of PPI with single nucleotide polymorphisms (SNPs) of the neuregulin-1 (*NRG1*, rs3924999) (Hong et al. 2008), catechol-*O*-methyltransferase (*COMT*, rs4680) (Roussos et al. 2008b), dopamine D3 receptor (*DRD3*, rs6280) (Roussos et al. 2008a), and the serotonin-2A receptor (*5-HT2AR*, rs6311/6313) gene (Quednow et al. 2008b) have been reported from hypothesis-driven single association studies. Since then a number of further single association studies reported significant associations of PPI with numerous SNPs, which mainly have been identified as schizophrenia risk genes previously (for a list of studies and SNPs see Tables 1 and 2, respectively). The only SNPs that have been replicated in at least two independent samples so far are *CHRNA3* (rs1051730) (Petrovsky et al. 2010), *5-HT2AR* (rs6311/6313) (Quednow et al. 2008b, 2009), *COMT* (rs4680) (Liu et al. 2013; Quednow et al. 2009, 2010; Roussos et al. 2008b), *NRG1* (rs3924999) (Hong et al. 2008), *TCF4* (rs9960767) (Quednow et al. 2011), and *DRD2* (rs1800497) (Volter et al. 2012). However, for most of these SNPs also negative findings have been reported. Most recently, the first explorative genome-wide association study (GWAS) identified two non-coding loci (rs61810702 and rs4718984) that were co-localized with expression quantitative trait loci related with the gene expression of nerve growth factor (*NGF*) and calneuron 1 (*CALN1*) genes. Additionally, a higher polygenic risk score for schizophrenia was associated with lower PPI (Roussos et al. 2016).

The heterogeneity of these genetic results implies i) that there are probably no single genes with a high impact on PPI and ii) that there are likely also some false positive results considering that – from today's perspective – many of the previous studies are strongly underpowered and lack replication samples (Button et al. 2013). One way to reduce the number of false positive (but also false negative) results in psychiatric genetics is the application of a meta-analysis, in which all available data are included (Levinson 2005; Lohmueller et al. 2003). Therefore, we performed a systematic meta-analysis of all genotype-SNP associations published so far using a weighted *Z*-method approach (Stouffer et al. 1949). We additionally included three independent data sets coming from samples that have been published before for reporting of genotype-PPI associations but for which also yet unpublished genotype or GWAS data existed (Petrovsky et al. 2010; Quednow et al. 2008b, 2009, 2010, 2011; Roussos et al. 2016). Genetic variants were included into the analysis if they were available in at least two independent samples. In order to control for multiple comparisons, a false discovery rate (FDR) method based on estimation of tail area-based FDR was applied (Strimmer 2008). The aim of this systematic meta-analysis was the identification of the most robust i.e., significant genotype-PPI associations.

Table 1
Summary list of published and unpublished studies included in meta-analysis. HC = healthy controls, SCZ = patients with schizophrenia.

Reference	Sample (location)	Sample number	Analyzed *n*
(Brauer et al. 2009)	HC (Giessen)	1	81
(Greenwood et al. 2012)	SCZ (San Diego)	2	219
(Hong et al. 2008)	HC (Maryland)	3	63
	SCZ (Maryland)	4	113
(Hokyo et al. 2010)	HC (Osaka)	5	71
	SCZ (Osaka)	6	81
(Liu et al. 2013)	SCZ (Guangdong)	7	140
(Montag et al. 2008)	HC (Bonn-Montag)	8	96
(Petrovsky et al. 2010)	HC (London)	9	96
	SCZ (Bonn)	10	68
(Petrovsky et al. 2013)	HC (Bonn)	11	63
(Quednow, Ettinger, Kumari, unpublished data)	HC (London)	9	100
(Quednow and Wagner, unpublished data)	SCZ (Bonn)	10	107
(Quednow et al. 2008b)	SCZ (Bonn)	10	68
(Quednow et al. 2009)	HC (London)	9	99
(Quednow et al. 2010)	SCZ (Bonn)	10	71
(Quednow et al. 2011)	HC (London)	9	98
	SCZ (Bonn)	10	105
(Roussos et al. 2008a)	HC (Crete)	12	101
(Roussos et al. 2008b)	HC (Crete)	12	93
(Roussos et al. 2009a)	HC (Crete)	12	217
(Roussos et al. 2011)	HC (LOGOS)	13	445
(Roussos et al. 2016)	HC (LOGOS GWAS)	14	686
(Shi et al. 2016)	SCZ (Beijing)	15	77
(Volter et al. 2012)	HC (London)	9	96
	HC (Munich)	16	101

Varying sample sizes among single samples (e.g., sample nr. 10: range $n = 68–107$) are explained by different schizophrenia spectrum diagnoses included or because genotype was only available in a subsample (e.g., due to genotyping failures).

2. Methods

2.1. Eligibility criteria

Human association studies (single associations and GWAS) with genetic variants reporting *P*-values and direction of effect for PPI-genotype associations in samples of healthy controls or patients with schizophrenia spectrum disorders. To be included, a gene variant must have been available in at least two independent samples.

2.2. Information sources and search strategy

With the search term ((“prepulse inhibition” OR “sensorimotor gating”) AND (mutation OR polymorphism OR polymorphisms OR snp OR snps OR gene OR genotype) NOT (rats OR rat OR mice OR mouse)) NOT review[ptyp]), 63 articles have been identified initially by a MEDLINE search (PubMed.gov). Only studies reporting *P*-values of genetic effects on PPI in healthy volunteers and patients with schizophrenia spectrum disorders were included. Studies investigating PPI-gene associations in pregnant women or individuals with developmental disorders (e.g., with 22q11 syndrome) were excluded. With this procedure, we identified 19 original articles reporting SNP-PPI associations (Table 1). After checking, if at least two *P*-values of a specific genotype-PPI and from independent samples are available (e.g., in

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