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 Therefore, we performed the first meta-analysis of published and unpublished associations between gene polymorphisms and PPI of ASR. Unpublished associations between genetic polymorphisms and PPI were derived from three independent samples.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 2,660 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.

Keywords

Prepulse inhibition; startle; sensorimotor gating; polymorphism; SNP; genotype; gene; mutation; schizophrenia; psychosis; endophenotype; intermediate phenotype; meta-analysis

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 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 **Table 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.

Methods

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.

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 two publications or in a publication and an unpublished data set), 120 single observations from 16 independent samples with 2,660 study participants and 43 polymorphisms were included in the meta-analysis (**Table 2**).

Inclusion of unpublished data

The authors included unpublished genotype-PPI association data from three samples that have been published before: (1) the LOGOS sample recruited in Crete, Greece, consisting of healthy volunteers (max. n=686) (Roussos et al., 2016), (2) a sample of healthy volunteers (max. n=100) from London, UK (Petrovsky et al., 2010; Quednow et al., 2009; 2011), and (3) a sample of patients with schizophrenia spectrum disorders (max. n=107) from Bonn, Germany (Petrovsky et al., 2010; Quednow et al., 2008b; 2010; 2011). P-values of yet unpublished genotype-PPI associations have been calculated using the same statistical approach as previously reported, e.g., using the same covariates such as sex, smoking status, and antipsychotic medication (London and Bonn samples: Quednow et al., 2011). The final studies, cohorts and number of samples per study included in the meta-analysis is shown in **Table 1** and **2**.

Statistical Analysis

We sum the association evidence across studies using a weighted *Z*-method approach where every study is weighted by the effective sample size (Stouffer et al., 1949). Briefly, in each study, we convert P_i *P*-values into Z_i signed *Z*-scores based on the Δ_i direction of effect using the following equation:

$$Z_i = \phi^{-1}\left(\frac{P_i}{2}\right) * sign(\Delta_i).$$

We then estimate overall *Z* score by summing *Z*-scores for each genetic polymorphism using weights proportional to the square-root of the sample size for each study:

$$Z = \frac{\sum_i Z_i w_i}{\sqrt{\sum_i w_i^2}},$$

where $w_i = \sqrt{N_i}$ and N_i is the sample size of study *i*. Finally, the overall *Z* score is converted back to overall *P*-value for a given genotype based on:

$$P = 2\,\Phi(|-Z|).$$

For multiple testing correction, we applied FDR at combined *P*-values estimated based on fdrTool in R (Strimmer, 2008). The Cohen's *d* effect sizes for the strengths of association were estimated from *Z*-values according to Rosenthal (1984). For estimation of effect sizes in schizophrenia GWAS study we used the average odds ratio of 1.1 across all genome-wide significant SNPs and estimated Cohen's d based on:

$$d = LogOddsRatio\ x\ \frac{\sqrt{3}}{\pi}$$

As sex effects are well-documented for the rs4680 *COMT* SNP (Tunbridge and Harrison, 2011), and as strong sex differences in rs4680 *COMT* effects on PPI were recently reported in a non-trivial sample of healthy subjects (Swerdlow et al., 2017), we additionally analyzed sex effects for this SNP only. Based on the existing studies, we are well powered to study the *COMT* association in males only as the majority of the included samples with known gender (92% or 870 out of 943) were males.

Results

In this study, we examined the associations of SNPs and PPI of ASR. We evaluated a total of 43 SNP-PPI associations, while for each SNP two to six samples were available (mean 2.8, standard deviation 1.1, median 2.0 samples). Statistical significance was defined as an FDR-adjusted p-value of 0.05 or smaller. At this threshold, four index SNPs were significant. The strongest association was between *COMT* rs4680 and PPI ($P = 5.5*10^{-5}$, FDR = 0.002, Cohen's $d = 0.28$) in male samples only (**Table 2**). The other three loci with significant association with PPI were: *GRIK3* rs1027599 ($P = 0.004$, FDR = 0.045, Cohen's $d = 0.19$), *TCF4* rs9960767 ($P = 0.006$, FDR = 0.050, Cohen's $d = 0.19$) and *PRODH* rs385440 ($P = 0.006$, FDR = 0.050, Cohen's $d = 0.27$). As expected, the detected Cohen's *d* effect sizes are small according to the definition of Cohen (1988) and none of these associations survived a genome-wide correction ($P < 5*10^{-8}$). Notably, we also found a significant effect for *COMT* rs4680 in both males and females, but with smaller effect size that did not survive multiple testing corrections ($P = 0.01$, FDR = 0.057, Cohen's $d = 0.15$), indicating a putative gender-specific effect of *COMT* on PPI.

Discussion

The aim of this meta-analysis was the identification of robust associations between gene polymorphisms and PPI of the ASR. Given that PPI was repeatedly proposed as an endophenotype of schizophrenia (Braff et al., 2007), this investigation might elucidate which genes may robustly contribute to the low PPI levels of schizophrenia patients and presumably to the disease itself. We thus analyzed published and unpublished data resulting in the inclusion of 120 single observations from 16 independent samples with 2,660 study participants and 43 polymorphisms. After multiple testing corrections based on an FDR approach, four polymorphisms were significantly associated with PPI. In males, the *COMT* rs4680 (Val158Met) polymorphism showed the strongest association with PPI (P = $5.5*10^{-5}$, FDR = 0.002, Cohen's d = 0.28), while the *COMT* gene effect was barely not significant (P = 0.01, FDR = 0.057, Cohen's d = 0.15) in the mixed-gender sample. Carriers of the *COMT* rs4680 G (valine) allele showed lower PPI levels than carriers of the A (methionine) allele. Moreover, *GRIK3* rs1027599 (P = 0.004, FDR = 0.045, Cohen's d = 0.19), *TCF4* rs9960767 (P = 0.006, FDR = 0.050, Cohen's d = 0.19), and *PRODH* rs385440 (P = 0.006, FDR = 0.050, Cohen's d = 0.27) showed significant association with PPI. Regarding *GRIK3* rs1027599, the T allele carriers showed lower PPI, while the same was true for TCF4 rs9960767 C and PRODH rs385440 A allele carriers. In fact, when the widely accepted threshold for genome-wide multiple corrections ($P < 5*10^{-8}$) is applied, none of the results is powerful enough to survive. However, it has to be taken into account that the power of this meta-analysis (sample size range: N=436 to 1224) was much lower, e.g., compared to previously published mega-analyses in schizophrenia genetics, including ten thousands of participants (Ripke et al., 2013; Steinberg et al., 2011). Nevertheless, the effect sizes of the significant SNPs in the present meta-analysis are small (Cohen's d = 0.19 to 0.28) in the sense of Cohen's definition (Cohen, 1988) but relatively strong considering the strengths of genetic associations commonly shown in meta-analysis of GWAS in schizophrenia (Cohen's d = 0.05 based on Schizophrenia Working Group of the Psychiatric Genomics, 2014).

The *COMT* gene effect on PPI is highly plausible as the COMT enzyme is involved in in the metabolic inactivation of dopamine and norepinephrine in regions with a low density of dopamine and noradrenaline transporters specifically in the frontal cortex (Rivett et al., 1982). The rs4680 polymorphism leads to an amino acid substitution of methionine for valine changing the metabolic rate of the enzyme. Consequently, compared to methionine homozygotes, valine homozygotes have a 3 to 4-fold stronger COMT enzyme activity and, thus, an increased catabolism of catecholamines in the frontal cortex (Lachman et al., 1996). Animal and human studies suggest that PPI is critically modulated by dopamine and noradrenaline neurotransmission at several stages of the CSPP circuit (Geyer et al., 2001; Swerdlow et al., 2001). Moreover, *COMT* messenger RNA is highly expressed in the prefrontal cortex and the hippocampus and less in the striatum, the ventral tegmental area, or the substantia nigra (Tunbridge et al., 2006). Considering that these structures are participating in the CSPP circuit, it is likely that the *COMT* polymorphism influences PPI at the prefrontal or hippocampal level (Swerdlow et al. 2001; Quednow et al, 2010). Specifically, lower prefrontal dopamine concentrations probably contribute to reduced PPI levels in valine allele carriers as is was shown that reduced dopamine activity in the prefrontal cortex goes along with a disruption of PPI (Bubser and Koch, 1994; Ellenbroek et al., 1996; Zavitsanou et al., 1999). In addition, drug-induced inhibition of the COMT enzyme with tolcapone leads to PPI enhancement only in the *COMT* Val carriers (Bitsios and Roussos, 2011; Giakoumaki et al., 2008; Roussos et al., 2009b). In line with these human data, it was shown that the effects of *COMT* inhibition by tolcapone on amphetamine-modified PPI were categorically different in rat strains exhibiting low vs. high levels *Comt* expression in the forebrain (Swerdlow et al., 2013). Moreover, genetic associations between *COMT* and psychiatric phenotypes frequently display sex differences (Tunbridge and Harrison, 2011). Accordingly, *COMT* rs4680 genotype effects on PPI have been demonstrated particularly in males, while the gene effects were absent, less strong, or even reversed in females (Montag et al., 2008; Quednow et al., 2009; 2010; Roussos et al., 2008b; Swerdlow et al., 2017). Finally, *COMT* rs4680 has been proposed to be a risk gene for schizophrenia for a long time but recent meta-analytical results are conflicting (Gonzalez-Castro et al., 2016; Taylor, 2017). Again, associations between *COMT* rs4680 and schizophrenia or schizotypy have been demonstrated primarily in males but not females (for reviews see Tunbridge and Harrison, 2011). Thus, the sex-specific effect of the *COMT* rs4680 on PPI shown here is in agreement with a variety of previous findings.

The *GRIK3* gene encodes the glutamate ionotropic receptor kainate type subunit 3, which is one of three principal subunits (GRIK1-3) of the tetrameric kainate/AMPA receptors. Two further auxiliary subunits of these receptors exist (GRIK4-5) (Fernandez et al 2009, Neuron). GRIK3-containing receptors differ from other kainate/AMPA receptors as they can only be activated by fast and strong glutamate releases. Moreover, they have some special electrophysiological properties suggesting that GRIK3-containing receptors have specialized presynaptic functions (Perrais et al., 2009). Decreased expression of GRIK3 in the prefrontal cortex and hippocampus of schizophrenia patients have been shown (Hu et al., 2015): While there are no published positive associations of the *GRIK3* rs1027599 SNP with psychiatric disorders so far, other *GRIK3* SNPs have been associated with schizophrenia (Begni et al., 2002; Kilic et al., 2010) and major depression (Schiffer and Heinemann, 2007), previously. Moreover, sporadic deletion in chromosome 1p34.3 involving *GRIK3* was reported for a girl with developmental delay (Takenouchi et al., 2014). Interestingly, in a recent twin study, a *GRIK3* gene set was associated with overall startle responses (Vaidyanathan et al., 2014), raising the question if the association with PPI shown here is rather an epiphenomenon of changes in startle reactivity (Csomor et al., 2008). Moreover, the kainate antagonist LY382884 reduced both exaggerated ASR and PPI deficits observed in mice with genetically reduced NMDA receptor expression (Duncan et al., 2010). However, these results might be explained by the changes in ASR again, as strongly elevated startle responses can result in low PPI levels also in mice (Csomor et al., 2008).

TCF4 belongs to the superfamily of basic Helix-Loop-Helix (bHLH) transcription factors that can act as a transcriptional repressor or activator in a context specific fashion. It can be considered as an integrator ('hub') of several bHLH networks controlling critical steps of various developmental and plasticity related transcriptional programs in neurons (Quednow et al., 2014). Haploinsufficiency of the *TCF4* gene causes the Pitt-Hopkins syndrome – a severe neurodevelopmental disease characterized by mental retardation, microcephaly, epilepsy, facial dysmorphisms, and intermittent hyperventilation –, suggesting that *TCF4* is critical for the development of the mammalian nervous system (de Pontual et al., 2009; Zweier et al., 2007). Three large but also partially overlapping meta-analyses of GWAS consistently identified that common *TCF4* polymorphisms are associated with the risk of schizophrenia (Schizophrenia Psychiatric Genome-Wide Association Study, 2011; Stefansson et al., 2009; Steinberg et al., 2011). In these analyses, two SNPs at the intron located between the internal exon 4 and internal exon 5 of human *TCF4* gene on chromosome 18q21.2 (rs9960767, rs17512836) and an intragenic SNP near the *TCF4* gene (rs4309482) have shown the strongest association with the disease (Schizophrenia Psychiatric Genome-Wide Association Study, 2011; Stefansson et al., 2009; Steinberg et al., 2011). Several subsequent studies replicated schizophrenia-*TCF4* gene associations in independent samples: (1) Two studies in Han Chinese (in which the rs9960767 SNP is not polymorphic) identified *TCF4* rs2958182 (Li et al., 2010) as well as rs9320010, rs7235757, and rs1452787 (Li et al., 2016) to be associated with schizophrenia. (2) In a discovery sample from Ireland and a replication sample including non-overlapping samples from the Psychiatric GWAS Consortium (PGC), two intronic *TCF4* SNPs (again rs9960767 and rs17594526) passed the genome-wide significance threshold of $p<5*10^{-8}$ (Irish Schizophrenia Genomics and the Wellcome Trust Case Control, 2012). (3) In a recent family-based linkage meta-analysis a further *TCF4* SNP was identified (rs1261117) as linked to schizophrenia (Aberg et al., 2013). These results have contributed to the view that *TCF4* SNPs belong to the best-replicated schizophrenia susceptibility genes. A potential disturbance of TCF4 function in schizophrenia would be in line with the assumption that schizophrenia is a neurodevelopmental disorder (Quednow et al., 2014); however, the exact functional impact of the discussed TCF4 SNPs has still to be elucidated. Finally, transgenic mice moderately overexpressing *TCf4* in the brain as well as *TCf4* haploinsufficient mice both display profound reductions in PPI (Brzozka et al., 2010; Kennedy et al., 2016). Beyond PPI, *TCF4* SNPS including rs9960767 have been shown to be associated with another proposed endophenotype of schizophrenia: P50 suppression also called "sensory gating"; however, this association was only present in smoking individuals but not in never-smokers (Quednow et al., 2012). Taken together, the significant association of *TCF4* rs9960767 and PPI in human cohorts reported here is neurobiologically and pathophysiologically plausible as well.

PRODH encodes the enzyme proline oxidase, which is involved, among other functions, in the conversion of proline to D-1-pyrroline-5-carboxylate (P5C) in mitochondria. P5C is subsequently converted to glutamate or GABA, two neurotransmitters critically implicated in the pathophysiology of schizophrenia (Roussos et al., 2009a). Together with *COMT*, *PRODH* is located at 22q11 and, thus, both genes belong to the ~30 genes affected by the 22q11 deletion syndrome (Velo-Cardio-Facial or DiGeorge syndrome). Individuals with a 22q11 deletion syndrome show a strongly elevated risk for schizophrenia symptoms (Prasad et al., 2008) as well as reductions of PPI (Sobin et al., 2005a, b). In addition, rodent models of the 22q11 syndrome are associated with deficits in PPI (Diamantopoulou et al., 2017; Didriksen et al., 2017; Gogos et al., 1999). Previous studies suggested a possible role of the *PRODH* gene variations, in the pathogenesis of schizophrenia. Specifically, *PRODH* haplotypes consisting of rs372055 (1945T>C), rs450046 (1766A>G), and rs385440 (1852G>A) SNPs were significantly associated with schizophrenia, indicating that the alleles 1945C, 1766G, and 1852A are overtransmitted in schizophrenia patients (Li et al., 2004; Liu et al., 2002). The haplotypes, which included rs385440, is associated with *PRODH* hyperactivity potentially resulting in reduced proline levels and increased P5C/Glu availability in the central nervous system (Phang et al., 2008) and these changes might induce changes in the modulation of PPI (Roussos et al., 2009a). As both *COMT* and *PRODH* SNPs seem to have an impact on PPI and given that these genes are within 22q11 locus, further studies should investigate gene-gene interactions of both variants with regard to PPI.

Limitations of our meta-analysis include the small number of included studies and sample sizes making the estimates of effect sizes less reliable. Moreover, for most of the SNPs only two independent samples were available. It should be noticed, that the *PRODH* effect on PPI was indeed similarly strong as the *COMT* effect in males but that the *PRODH* sample size was nevertheless the lowest amongst all analyzed SNPs. Thus, the *PRODH* effect is likely less reliable than the *COMT* effect. Moreover, similar as for *PRODH*, the *GRIK* effect was calculated from only two studies, while three studies were included for *TCF4* and four regarding *COMT* (in males, and six for COMT including females). Consequently, the *GRIK* effects might also be less robust compared to *TCF4* and *COMT* (in males). Finally, we used a weighted *Z*-method approach using reported p-values to calculate the meta-analysis and consequently, statistical differences between studies (e.g., regarding the inclusion of different sets of covariates) have not been considered. Accordingly, as we did not use the original data sets of previously published work we were not able to adjust the results for the common confounding factors affecting PPI, such as gender and menstrual cycle, smoking, startle magnitude, as well as medication (Quednow, 2008). Particularly in patient samples, PPI-gene associations could have been masked by the potential PPI-enhancing impact of antipsychotic medication (Quednow et al., 2006; 2008a). However, several previous studies have controlled for such confounding factors and reported adjusted p-values, but not all. The additional analyses of so far unpublished data from patients with schizophrenia spectrum disorders reported in the present paper in fact considered smoking, sex, and antipsychotic medication status as covariates and only the adjusted p-values were used for the meta-analysis. Nevertheless, the overall strength of the gene effects might have been biased by confounding factors such as antipsychotic medication. Another limitation is that the included studies employed a variety of different PPI setups. Given that it has not been investigated systematically yet, which PPI parameters (e.g., prepulse and pulse intensities, stimulus-onset asynchrony, number of stimuli, intertrial intervals) might provide an optimal signal-to-noise ratio with regard to gene effects (or if genes might specifically influence PPI at various conditions), it remains unclear how the heterogeneity of PPI setups used in the included studies might have affected our results.

Beyond PPI, several further electrophysiological “gating” or filtering” paradigms have been proposed as potential endophenotypes and clinical biomarkers of schizophrenia, such as P50 suppression, P300 and P3a, and mismatch negativity (MMN) (Light and Swerdlow, 2015). Many studies have investigated the associations between polymorphisms and these electroencephalographic measures but no meta-analysis has been performed for any of these markers yet (Owens et al., 2016). Specifically, the MMN and the P3a event related potential component might be highly promising targets for future endophenotype-related genetic meta-analyses given that both are strongly, robustly, and stably affected in schizophrenia patients and both show considerable heritability (Light and Swerdlow, 2015; Light et al., 2015). However, a recent well-powered study demonstrated significant difficulty in the identification of genetic associations between 108 schizophrenia risk loci, a polygenic risk score for schizophrenia, and 17 electrophysiological schizophrenia endophenotypes, challenging the endophenotype concept (Liu et al., 2017) – albeit neither PPI, MMN, nor P3a (but P300) have been included in this analysis. Thus, future studies have to reveal if these most promising endophenotype candidates are more useful to decompose the genetic basis of schizophrenia or if they have at least a clinical relevance (Light and Swerdlow, 2015).

Taken together, the present meta-analysis revealed that four SNPs located on genes that have been associated with schizophrenia previously, are robustly correlated with the expression of PPI in humans as well. These associations are neurobiologically plausible as the respective gene products have been shown to be involved in the CSPP circuit processing PPI (Geyer et al., 2001; Koch, 1999; Swerdlow et al., 2001). Although the effect sizes of the gene effects on PPI are relatively strong (at least when compared to the extremely weak gene effects shown in meta-analysis of GWAS in schizophrenia) none of the results would have survived a strict genome-wide correction of the alpha-level. This indicates that PPI – like schizophrenia itself – is highly polygenic. Thus, the question that still has to be answered in the future is whether the hitherto proposed schizophrenia endophenotypes are in fact less polygenic as the complex disease phenotype, so that endophenotypes can be used to predict the risk for schizophrenia or if they can be used to discover new neurobiological treatment targets.

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Tables

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 diagnosis included or because genotype was only available in a subsample (e.g., due to genotyping failures).

Table 2. Combined and Z-scores and P-values across genotypes where data were available at least in two independent samples. The signed *Z*-score indicates the direction of association among genotype and PPI. Negative *Z*-scores indicate decreased PPI in the reference compared to the alternative allele; Positive *Z*-scores indicate increased PPI in the reference compared to the alternative allele. Results with false discovery rate (FDR) ≤ 0.05 are in bold.

SNP	Gene	Number of studies	Total sample	Reference allele	Combined Z-score	Cohen's d	Combined P-value	FDR
rs4680 (only males)	***COMT***	**4**	**870**	**A**	**4.03**	**0.28**	**5.51E-05**	**0.002**
rs1027599	***GRIK3***	**2**	**905**	**C**	**2.87**	**0.19**	**0.004**	**0.045**
rs9960767	***TCF4***	**3**	**889**	**C**	**-2.77**	**0.19**	**0.006**	**0.050**
rs385440	***PRODH***	**2**	**436**	**A**	**-2.75**	**0.27**	**0.006**	**0.050**
rs533337	*GRIK3*	2	905	A	2.64	0.18	0.008	0.055
rs4680	*COMT*	6	1,179	A	2.58	0.15	0.010	0.057
rs13101891	*GRID2*	2	905	G	-2.41	0.16	0.016	0.067
rs1800497	*DRD2*	5	1,047	A2	-2.40	0.15	0.017	0.067
rs4782262	*GRIN2A*	2	905	C	2.36	0.16	0.018	0.069
rs876848	*GAD2*	2	905	T	-2.27	0.15	0.023	0.074
rs1044396	*CHRNA4*	3	863	T	-2.26	0.15	0.024	0.075
rs1923292	*SLC1A2*	2	905	G	-2.15	0.14	0.032	0.097
rs40184	*SLC6A3*	3	998	A	2.14	0.14	0.033	0.100
rs4852550	*CTNNA2*	2	905	T	-2.06	0.14	0.039	0.118
rs308787	*GRM5*	2	905	G	2.04	0.14	0.041	0.122
rs3924999	*NRG1*	5	1,180	A	-2.03	0.12	0.042	0.126
rs8068673	*PAFAH1B1*	2	905	C	2.01	0.13	0.045	0.132
rs6277	*DRD2*	4	905	G	-2.00	0.13	0.046	0.135
rs701567	*DAOA*	2	905	G	1.91	0.13	0.057	0.162
rs1587526	*GRIK3*	2	905	A	1.90	0.13	0.057	0.163
rs894829	*CTNNA2*	2	905	G	-1.89	0.13	0.059	0.167
rs1266475	*PAFAH1B1*	2	905	C	1.88	0.13	0.060	0.169
rs6311	*5HT2AR*	3	851	A	1.87	0.13	0.062	0.173
rs1051730	*CHRNA3*	4	902	T	-1.79	0.12	0.074	0.200
rs6994992	*NRG1*	3	1,224	T	-1.79	0.10	0.074	0.202

rs10095556	*NRG1*	2	905	G	1.72	0.11	0.086	0.226
rs12685902	*GRIN3A*	2	905	C	-1.68	0.11	0.094	0.242
rs11782671	*NRG1*	2	905	T	1.66	0.11	0.098	0.250
rs9297186	*NRG1*	2	905	A	1.59	0.11	0.111	0.275
rs778294	*DAOA*	3	1,003	A	1.36	0.09	0.175	0.373
rs6280	*DRD3*	4	1,070	G	-1.34	0.08	0.181	0.381
rs8081803	*PAFAH1B1*	2	905	C	1.21	0.08	0.225	0.433
rs6313	*5HT2AR*	5	1,151	T	1.12	0.07	0.265	0.474
rs2619539	*DTNBP1*	4	1,105	C	-0.99	0.06	0.324	0.524
rs2008626	*NRG1*	2	905	C	-0.97	0.06	0.334	0.532
rs1368909	*CTNNA2*	2	905	C	-0.93	0.06	0.350	0.544
rs165599	*COMT*	3	928	G	-0.81	0.05	0.417	0.586
rs3814614	*GRID1*	2	905	C	0.79	0.05	0.431	0.595
rs7555221	*GRIK3*	2	905	C	-0.56	0.04	0.578	0.663
rs4648317	*DRD2*	4	948	G	-0.52	0.03	0.601	0.672
rs2619528	*DTNBP1*	4	941	G	0.49	0.03	0.625	0.680
rs1486009	*DRD3*	2	905	G	-0.48	0.03	0.634	0.683
rs4584372	*NOS1AP*	2	905	C	-0.34	0.02	0.736	0.715
rs1011313	*DTNBP1*	4	1,108	A	0.08	0.01	0.933	0.760