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Genetic underpinnings of schizophrenia-related electroencephalographical intermediate phenotypes: A systematic review and meta-analysis

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ABSTRACT

Although substantial research into genetics of psychotic disorders has been conducted, a large proportion of their genetic architecture has remained unresolved. Electroencephalographical intermediate phenotypes (EIP) have the potential to constitute a valuable tool when studying genetic risk loci for schizophrenia, in particular P3b amplitude, P50 suppression, mismatch negativity (MMN) and resting state power spectra of the electroencephalogram (EEG). Here, we systematically reviewed studies investigating the association of single nucleotide polymorphisms (SNPs) with these EIPs and meta-analysed them when appropriate. We retrieved 45 studies (N = 34,971 study participants). Four SNPs investigated in more than one study were genome-wide significant for an association with schizophrenia and three were genome-wide suggestive, based on a lookup in the influential 2014 GWAS (Ripke et al., 2014). However, in our meta-analyses, rs1625579 failed to reach a statistically significant association with p3b amplitude decrease and rs4680 risk allele carrier status was not associated with p3b amplitude decrease or with impaired p50 suppression. In conclusion, evidence for SNP associations with EIPs remains limited to individual studies. Careful selection of EIPs and SNPs, combined with consistent reporting of effect sizes, directions of effect and p-values would aid future meta-analyses.

1. Introduction

Schizophrenia is a complex psychiatric disorder, the primary clinical characteristics of which are positive symptoms (e.g. hallucinations and delusions), negative symptoms (e.g. flattened affect) and cognitive symptoms (e.g. cognitive deficits) (Insel, 2010). These symptoms are highly disabling and quality of life is generally severely impaired: the World Health Organization estimates schizophrenia as the 17th leading cause of years lived with disability globally (Mathers et al., 2018). Heritability estimates, based on twin studies, generally fluctuate around 70–80% (Hilker et al., 2018; Sullivan et al., 2003). Recently, progress has been made towards understanding the genetic complexity of schizophrenia (Burmeister et al., 2008; Insel, 2010; Pardiñas et al., 2018; Ripke et al., 2014), most notably by identifying 158 independent loci associated with schizophrenia through large genome-wide association studies (GWAS) (Pardiñas et al., 2018; Ripke et al., 2014). Another genome-wide analysis of copy number variants (CNVs) reported eight novel loci implicated in schizophrenia (Schizophrenia Workgroup of the Psychiatric Genomics Consortium, 2016).

Another potentially powerful way to study the genetic underpinnings of schizophrenia is by targeting intermediate phenotypes (Gottesman and Gould, 2003; Owens et al., 2016; B. I. Turetsky et al., 2007). An intermediate phenotype implies a genetic link between a heritable trait and a disorder (Rasetti and Weinberger, 2011): often neuroimaging or neurocognitive measures of brain function that lie in the expression pathway from genetic liability to disorder. Intermediate phenotypes may be of use for psychiatric genetics as they are quantitative and generally phenotypically (and therefore possibly genetically)

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less complex than psychiatric disorders (Gottesman and Gould, 2003; Walters and Owen, 2007).

Electrophysiological measures (in particular P3b event-related potentials (ERP), mismatch negativity (MMN), P50 suppression and resting state electroencephalography (EEG) characteristics, such as power spectra) are among the most promising intermediate phenotypes in schizophrenia research. Generally, electrophysiological intermediate phenotypes are stable over time, state-independent, reliable and associated with the phenotype of interest. Moreover, electrophysiological abnormalities in such intermediate phenotypes of schizophrenia are more prevalent in first-degree relatives of these patients than in the general population, but less prevalent and pronounced compared to their relatives with schizophrenia (Owens et al., 2016).

P3b amplitude is an ERP elicited by a change in the sensory environment, with an average peak onset latency of 300 ms - 450 ms after stimulus presentation (Light et al., 2012; Owens et al., 2016; Polich, 2007; B. I. Turetsky et al., 2007). P3b amplitude is typically assessed in a visual or auditory oddball paradigm (Polich, 2007; Turetsky et al., 2007): the subject is asked to respond to a deviant (infrequently appearing) stimulus in a sequence of standard (frequently appearing) stimuli; this elicits the P3b amplitude which reaches its peak at parietal lobes. Simultaneously, this deviant stimulus triggers a P3a amplitude that not only precedes the P3b amplitude but is also more frontally oriented. However, given that the p3a amplitude is overshadowed by the P3b amplitude, it is usually either assessed with an oddball paradigm where subjects do not need to respond to the oddball (deviant) stimulus, or by adding a second, task-irrelevant but salient and rare (deviant) stimulus to an oddball paradigm in which the P3b is assessed as well (Polich, 2007). P3a occurs earlier (220 ms – 280 ms; Squires et al., 1975), has a more frontal-central scalp topography, and is subject to habituation (reduction over time), while the P3b occurs later (300 ms – 450 ms post stimulus), has a central-parietal topography, and is not sensitive to habituation (Owens et al., 2016; B. I. Turetsky et al., 2007). Schizophrenia research mainly focuses on the P3b ERP. A diminished P3b amplitude (compared to healthy controls) is the most reliable and stable irregularity in the oddball evoked potentials in schizophrenia (Earls et al., 2016; Jeon and Polich, 2003; Light et al., 2012; Qiu et al., 2014; Turetsky et al., 2007). Over the past years, research has shown that P3b amplitude is a viable intermediate phenotype in schizophrenia research: it is heritable (M. H. Hall et al., 2006; Weisbrod et al., 1999), relatively stable over time, state-independent (e.g. Oranje et al., 2017), reliable (Light et al., 2012; Turetsky et al., 1998), and relatives of schizophrenia patients show a reduced P3b amplitude compared to healthy controls (Earls et al., 2016; Weisbrod et al., 1999).

Mismatch negativity (MMN) is a negative deflection that appears automatically in an individual's EEG as a result of a change detection in the perceived environmental stimuli; it is often referred to as the brain's orienting reflex. In MMN paradigms the subject is usually distracted from the stimulus, e.g. by showing a muted video with the request not to pay attention to the stimuli of the oddball task (Näätänen et al., 2007). MMN is attenuated in schizophrenia patients compared to healthy controls (Erickson et al., 2016; Owens et al., 2016; B. I. Turetsky et al., 2007). Most characteristics of the MMN fit the endophenotype criteria: there is considerable heritability and reliability (M. H. Hall et al., 2006), it is relatively stable over time (Light et al., 2012), and relatives of patients show an intermediate response and prevalence (Jessen et al., 2001; Şevik et al., 2011). However MMN is state-dependent, since medication can ameliorate (e.g. Oranje et al., 2017) and psychotic states can aggravate its deficits in schizophrenia (Shinozaki et al., 2002). There is considerable methodological diversity in auditory oddball paradigms used to measure MMN. Varying intensity (e.g. Näätänen et al., 1978), duration (e.g. Paavilainen et al., 1989) and frequency (e.g. Sams et al., 1985) have all been used to achieve the oddball effect and some studies have used a mixture of oddball stimuli (e.g. Zarchi et al., 2013). MMNs induced using different oddball paradigms do not share all properties (Nagai et al., 2013), despite the fact that many studies compare them directly, mix them or use them interchangeably.

Another characteristic that is usually diminished in schizophrenia patients is P50 suppression (Owens et al., 2016). The basis for P50 suppression is the phenomenon that an individual's EEG response to the second of two identical stimuli is normally reduced within a certain time frame. P50 suppression is most frequently assessed by presenting two identical auditory stimuli with inter-stimulus interval of 500 ms. An individual's response to the first, or conditioning stimulus (C), is larger than to the second, or testing (T), stimulus. Although the whole EEG response to the second stimulus appears to be reduced, this starts with the P50 ERP. P50 suppression is normally expressed as the ratio of T/C, while C-T is sometimes used as a complementary measure (Owens et al., 2016; B. I. Turetsky et al., 2007). The T/C ratio is higher in schizophrenia patients than in controls, indicating reduced suppression of the second stimulus in schizophrenia (e.g. Oranje et al., 2017). Generally, P50 suppression is thought to be a measure of sensory gating, a mechanism that protects an individual's brain of sensory overload by filtering out irrelevant environmental stimuli before they reach consciousness (Adler et al., 1982; Brockhaus-Dumke et al., 2008). Unlike the P3b ERP, P50 suppression has received some critique as an intermediate phenotype for schizophrenia: it has a relatively low test-retest reliability (Light et al., 2012), is not always found diminished in schizophrenia patients (During et al., 2014) and conflicting heritability estimates are reported (Greenwood et al., 2007; M. H. Hall et al., 2006).

Over the past decade, resting state EEG (rs-EEG) has become increasingly popular in schizophrenia research (Boutros et al., 2008; Coburn et al., 2006; Hughes and John, 1999; Ranlund et al., 2014; Scott R Sponheim et al., 2000). EEG reflects local field potentials generated by synchronous activity of large populations of neurons (Lopes da Silva, 2013). Quantitative analysis of frequency bands, for example to characterize the relative contribution of different frequencies to the full power spectrum of the signal may be used to provide more sophisticated insight into neurophysiology of schizophrenia. It shows slowing of the EEG power spectrum in schizophrenia, and may even be used to predict transition to psychosis in high risk populations (van Tricht et al., 2014). Schizophrenia patients generally show increased activity in delta and theta bands compared to healthy controls (Begić et al., 2011; Harris et al., 2006; Hong et al., 2012; Ranlund et al., 2014; Winterer et al., 2001). With regard to alpha and beta bands, there is less consensus as both decreases (Begić et al., 2011; Harris et al., 2006; Scott R Sponheim et al., 2003) and absences of case-control differences have been reported (Ranlund et al., 2014), while in the beta range, increases (Begić et al., 2011; Wuebben and Winterer, 2001), decreases (John et al., 1994) and absences of case-control differences have been reported (Hong et al., 2012; Mientus et al., 2002; Ranlund et al., 2014; SCOTT R Sponheim et al., 1994; Winterer et al., 2001).

Given the potential of the abovementioned electrophysiological measures to serve as intermediate phenotypes, genetic research into these intermediate phenotypes could shed light on genetic factors associated with schizophrenia. To the best of our knowledge, no systematic review or meta-analysis is available on these genetic underpinnings of schizophrenia-related electrophysiological measures, although a recent review did sum up the evidence for each EEG measure as an endophenotype for schizophrenia (Owens et al., 2016). Therefore, we systematically collected all studies investigating a relationship between SNPs and selected EIPs; p3b amplitude, P50 suppression, MMN amplitude and resting EEG.

2. Methodology

2.1. Search

Here, we abide by the PRISMA guidelines for systematic reviews and meta-analyses (http://www.prisma-statement.org/). Our PubMed search was carried out on Sept 22nd 2019 (using the search string in

Supplementary data S1). We looked for (genome-wide) association studies between common genetic variants and electrophysiological intermediate phenotypes. Articles were included in our systematic review if: 1) the study was based on a study population consisting of healthy humans or humans with psychotic symptoms; and 2) the study reported on a SNP and a genetic association with the specified electrophysiological intermediate phenotypes. Exclusion criteria were: 1) animal studies; and/or 2) articles written in other languages than English; and/or 3.) articles including patients suffering from organic psychoses. In addition to the search described above, we screened reference lists for additional articles fulfilling our inclusion criteria.

Additional inclusion criteria were used for meta-analyses: 1) SNPs were analysed in two or more independent studies per intermediate phenotype; 2) studies investigated the same EIP; P3b amplitude, P50 suppression, or MMN amplitude; 3) studies were comparing groups of individuals with the same genotype (e.g. reference allele homozygotes vs. risk allele carriers); and 4.) the studies reported the *p*-value and direction of effect. Additionally, we did not compare studies that used different oddball paradigms to induce MMN, as the literature is not unequivocal about their similarities (Nagai et al., 2013).

Where studies investigating p300 did not specifically report whether they measured p3a or p3b component of P300, we attempted to extract data using the study methods. We characterised the signal as p3b if it was most prominent in parietal electrodes, was a task-relevant stimulus requiring active action or was reported in the 300 ms–800 ms window after stimulus presentation.

2.2. Statistical analyses

Our outcome variable was the presence of an association between a SNP and one of the intermediate phenotypes. METAL meta-analysis software was used to perform the meta-analyses (version 2011; Willer et al., 2010). Input data for METAL in this study were: *p*-values, the number of participants (N) and the direction of effect. Direction of effect was based on either F or beta value (if reported) or on the mean values of the electrophysiological measure of the individual genotype groups.

2.3. SNP look-up

We performed a look up of SNPs reported in the largest published schizophrenia GWAS by the Psychiatric Genomics Consortium (2018), to see whether genome-wide significant ($P \leq 5 \times 10^{-8}$) and suggestively significant SNPs ($P > 5 \times 10^{-8}$ and $P \leq 10^{-5}$, respectively) were studied in association with our intermediate phenotypes of interest. Candidate SNPs that were studied in relation to p3b amplitude in two or more studies were also looked up in Malone et al., 2014 GWAS (Malone et al., 2014).

2.4. Quality assessment

A single assessor performed quality assessment of all retrieved studies, using Q-Genie assessment tool (Sohani et al., 2015). Q-Genie scores were calculated for each study and a qualitative descriptor of “poor”, “moderate” or “good” was attributed to each study according to the score.

3. Results

3.1. Descriptive statistics

We retrieved five genome-wide studies (four GWASs and one linkage study) comprising 22,803 subjects (Greenwood et al., 2013; Hall et al., 2015; Konte et al., 2017; Malone et al., 2014; Smit et al., 2018) and 40 candidate SNP studies comprising 4565 patients and 7603 controls (Fig. 1; Supplementary data S2), resulting in a total N of 12,168 subjects. Two SNPs met our predefined inclusion criteria for meta-analysis: rs4680 (*COMT*) in relation to p3b amplitude and p50 T/C ratio and rs1625579 in relation to p3b amplitude (Table 3). Two studies (Del Re et al., 2014; Horikoshi et al., 2019) reported on rs4680 and MMN. However, the methodology used to measure MMN differed significantly between them, making them unsuitable for meta-analytic comparison (Table 4).

3.2. Genome-wide studies

The only retrieved genome wide linkage analysis investigated 12 endophenotypes of schizophrenia, including the electrophysiological intermediate phenotype P50 (Greenwood et al., 2013). No single genomic location reached genome-wide significance linkage (LOD score > 3.6) to the P50 suppression intermediate phenotype and no suggestive linkage signals were found to the P50 suppression response (operationalized as LOD scores of > 2.2).

We retrieved four GWASs, investigating the relationship between P50 suppression, P3b amplitude or rest EEG and SNPs in schizophrenia. The largest GWAS ($n = 4211$) reported no genome-wide significant association with the P3b (Malone et al., 2014). In a candidate SNP analysis within the same study population, none of 176 SNPs were associated with the P3b amplitude. P50 suppression, MMN and rs-EEG were not investigated in this study.

In a more modestly sized GWAS (M.-H. Hall et al., 2015) comprising 392 subjects (schizophrenia patients and healthy controls combined) the authors reported an association between P50 suppression and nine different SNPs on chromosome 14 in the LOC105370605, nearby the fibronectin leucine rich transmembrane protein 2 (*FLRT2*) gene (*p*-values ranging from 1.27^{-9} to 1.36^{-8}, and absolute beta-values from 19.8 to 21.39). Risk alleles were associated with higher sensory gating. All of the SNPs were in high linkage disequilibrium (LD) and the results suggest that these SNPs reflect a single association signal at this locus (chromosome 14). The p3b amplitude did not display genome-wide significant evidence for an association to any SNPs. MMN and rs-EEG intermediate phenotypes were not investigated in this study.

A recent GWAS (Konte et al., 2017) comprising 315 subjects (241 controls, 74 schizophrenia patients) investigated the genetic association of auditory evoked early gamma-band response. No significant associations between SNPs and the auditory evoked were found in this study. The patient group showed stronger signals compared to healthy controls. The strongest, albeit non-significant signal found in this study ($P = 3.8 \times 10^{-6}$) mapped onto the Neuregulin 2 gene (*NRG2*).

Another GWAS studied tissue-specific SNP-imputation of gene expression (Smit et al., 2018) in relation to rest EEG in 8425 subjects. This study looked at SNPs relevant to a range of intermediate phenotypes and psychiatric conditions. SNPs related to expression of GNL3 and ITIH4 in frontal cortical tissue were significant for changes in alpha-power. These genes have been linked to schizophrenia and bipolar disorder (Ohi et al., 2016; Yang et al., 2019)

3.3. Quality assessment

All 45 studies were quality assessed. Out of 45 studies, 28 contained control groups. 33 studies ranked as “poor”, 10 as “moderate” and only 2 as “good”. The average score across all the studies was 32, which corresponds to “poor” quality and standard deviation was 4.9. One study involved in meta-analysing the effect of rs4680 on p50 T/C ratio was assessed as “moderate” quality. Other studies involved in meta-analyses were “poor”. For details see Supplement S3.

3.4. Candidate SNP studies

3.4.1. P3b

In total, 18 articles were retrieved (see Supplementary data S2a for an overview). As shown in Table 1 several SNPs have been investigated

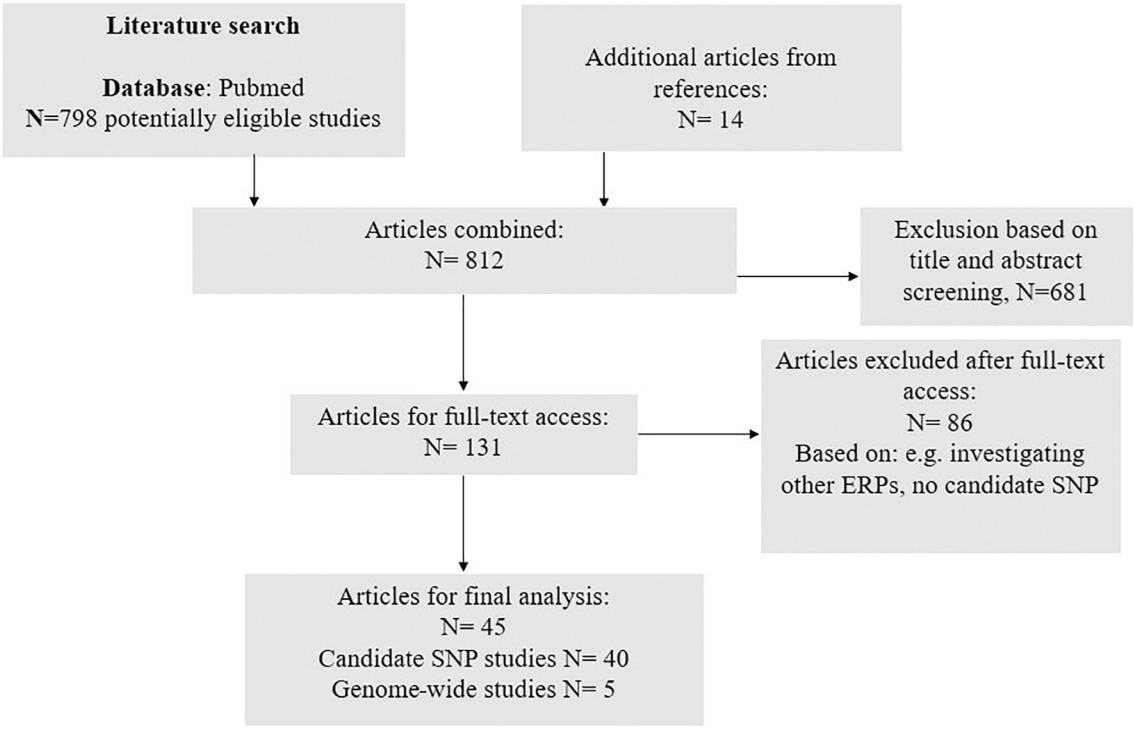

Fig. 1. Flowchart of search.

in two or more studies. For two SNPs (rs4680 and rs1625579) sufficient numbers of studies allowed for a meta-analysis.

Four studies on the association of rs4680 (contained in *COMT*) with p3b fulfilled our criteria for meta-analysis inclusion. Two of them compared reference allele homozygotes to risk allele homozygotes (Gallinat et al., 2003; Golimbet et al., 2006). Golimbet et al., reported an increased p3b amplitude in risk allele homozygotes in the subgroup of healthy relatives of schizophrenia patients (n = 79) as the only statistically significant ERP-SNP association (p = .004). Gallinat et al., studied 170 schizophrenia patients and 49 healthy controls. They reported a decrease in p3b amplitude in risk allele homozygotes (p = .003). Meta-analysis of these results showed no statistically significant association between rs4680 and P3b amplitude in comparing risk and reference allele homozygotes (p = .29; Table 3).

Two papers described association analysis of rs4680 with P3b amplitude in all three genotypic groups – reference allele homozygotes, heterozygotes and risk allele homozygotes (Bramon et al., 2006; Del Re et al., 2014). Together these studies included 130 schizophrenia patients, 94 healthy relatives and 108 healthy controls. Both studies found an association between rs4680 risk allele and decreased P3b amplitude, however, neither result was statistically significant. Meta-analysis of these studies also yielded a non-significant result (p = .38; Table 3).

Two studies compared rs1625579 reference allele homozygotes to risk allele carriers (Decoster et al., 2012; Del Re et al., 2014). Decoster et al., found a significant increase in p3b amplitude in risk allele carriers (0.0048), whilst Del Re et al., found a non-significant decrease (p = .12). In total these studies looked at 404 schizophrenia patients and 75 healthy controls. Meta-analysis of these results showed no statistically significant association between rs1625579 risk allele and P3b amplitude reduction (p = .13; Table 3).

Table 1
SNPs that were investigated in relation to p3b in more than one study. Only studies reporting direction of effect are included. Where multiple electrodes or genotypic comparisons were tested, we only report the most significant finding. Look-up: indicates if SNP is genome-wide significant or suggestive in Ripke et al., 2014 GWAS; HR: healthy relatives; SCZ: schizophrenia patients; HC: healthy controls; NS: not significant; +: increase in p3b amplitude; −: decrease in p3b amplitude; *: study included in meta-analysis.

SNP	Gene	Study	Study population (N)	Direction	p-value	Look-up
rs4680	*COMT*	Golimbet et al., 2006*	HR (79)	+	0.004	NS
		Gallinat et al., 2003*	SCZ (170); HC (49)	–	0.003	
		Ehlis et al., 2007	SCZ (56)	–	< 0.05	
		Heitland et al., 2013	HCS (52)	+	0.008	
		Bramon et al., 2006*	SCZ (62) & HR (94) & HC (33)	–	0.72	
		del Re et al., 2014*	SCZ (68); HC (75)	–	0.35	
rs1344706	*ZNF804A*	O'Donoghue et al., 2014	SCZ (60); HC (90)	–	0.02	Significant
		del Re et al., 2014	SCZ (68); HC (75)	+	0.13	
rs1625579	*MIR137HG*	del Re et al., 2014*	SCZ (68); HC (75)	–	0.12	Significant
		Decoster et al., 2012*	SCZ (336)	+	0.0048	
rs7914558	*CNNM2*	Del Re et al., 2014	SCZ (68); HC (75)	+	0.71	Significant
rs7004633	*MMP16*	Del Re et al., 2014	SCZ (68); HC (75)	+	0.41	Suggestive
rs548181	*STT3A*	del Re et al., 2014	SCZ (68); HC (75)	+	0.91	NS
rs12966547	*TCF4*	del Re et al., 2014	SCZ (68); HC (75)	–	0.84	Significant
rs6265	*BDNF*	Decoster et al., 2012	SCZ (336)	+	0.0068	NS

Table 2
SNPs that were investigated in relation to p50 T/C ratio in more than one study. Only studies reporting directions of effect are included. Where study was conducted in multiple electrodes, we only report those with lowest *p*-value. Look-up: indicates if SNP is genome-wide significant or suggestive in Ripke et al., 2014 GWAS HR: healthy relatives; SCZ: schizophrenia patients; HC: healthy controls; BD: bipolar disorder patients; NS: not significant; +: increase in p50 T/C ratio; −: decrease in p50 T/C ratio; *: study included in meta-analysis.

SNP	Gene	Study	Study population (N)	Direction	p-value	Look-up
rs4680	*COMT*	Ancén et al., 2011*	BD (122); HC (95)	−	0.02	NS
		Demily et al., 2016*	SCZ(94)	+	0.46	
		Lu et al., 2007*	SCZ (42); HC (25)	−	0.02	
		Majic et al., 2011*	SCZ (282)	+	0.69	
		Mao et al., 2016	SCZ (372); HC (391)	−	0.62	
rs9960767	*TCF4*	Quednow et al., 2012	HC (1821)	+	0.000045	Suggestive
rs17512836	*TCF4*	Quednow et al., 2012	HC (1821)	+	0.0002	Suggestive
rs883473	*CHRNA7*	/	/	/	/	NS

3.4.2. P50

Sixteen studies investigated candidate SNPs in relation to p50 suppression using either S2-S1 difference score or T/C ratio. Table 2 shows SNPs that have been investigated in two or more studies. See Supplementary data S2b for a summary of all SNPs investigated for association with p50 suppression. Due to methodological differences between studies, it was not possible to meta-analyse studies investigating rs9960767, rs883473 and rs17512836. However, for the rs4680, sufficient data was collected for meta-analysis. Four studies (Ancén et al., 2011; Demily et al., 2016; Lu et al., 2007; Majic et al., 2011) tested the association between p50 T/C ratio and rs4680 by comparing all three genotypic groups. Two of these reported an association between decreased p50 T/C ratio and rs4680 risk allele (Ancén et al., 2011; Lu et al., 2007), whilst two reported an increase in p50 T/C ratio associated with rs4680 risk allele (Demily et al., 2016; Majic et al., 2011). In total these studies investigated 551 subjects (324 schizophrenia patients, 122 bipolar disorder patients and 105 healthy controls). The result of our meta-analysis indicates no association between the rs4680 polymorphism and P50 suppression ($p = .25$).

3.4.3. MMN

A total of three studies reported on the mismatch negativity intermediate phenotype (Del Re et al., 2014; Horikoshi et al., 2019; Lin et al., 2014). Overall, 22 SNPs were investigated in these 3 studies (see Supplementary data S2c). Lin et al. used a paradigm with varied tone duration to show that reference homozygotes of rs2240158 SNP (part of GRIN3B gene) display significantly smaller MMN amplitudes compared to risk allele carriers (Lin et al., 2014; see Table 4). Two studies tested for MMN association with rs4680 (Del Re et al., 2014; Horikoshi et al., 2019) and neither of them found a significant association between rs4680 and MMN. Horikoshi et al. varied duration to introduce deviant stimuli, whereas Del Re et al. varied pitch. Due to this difference they were not meta-analysed together.

3.4.4. Resting-state EEG

A total of three studies investigated the association between resting state EEG spectra and a single SNP: the rs4680 SNP in the *COMT* gene (Venables et al., 2009; Veth et al., 2014; Wacker and Gatt, 2010). In a study investigating 44 schizophrenia patients, delta and theta activity was altered in schizophrenia patients carrying the risk allele for schizophrenia (Venables et al., 2009). In addition, in a study of 383 healthy participants converging evidence was found regarding the delta activity in risk allele carriers. For theta activity the association reached a tendency to statistical significance (Wacker and Gatt, 2010). Another study, investigating 413 healthy participants could not detect an association between alpha peak frequency and the risk allele carriers for the rs4680 *COMT* SNP (Veth et al., 2014). We were not able to conduct a meta-analysis on these studies as they compared different genotypic groups and EIPs.

Table 4
SNPs that were investigated in relation to MMN amplitude in more than one study. SCZ; schizophrenia, HC; healthy control. Where study was conducted in multiple electrodes, we only report those with lowest p-value. HC: healthy controls; SCZ: schizophrenia patients; +: increase in MMN amplitude; −: decrease in MMN amplitude; NR: not reported; NS: not significant.

SNP	Gene	Study	Study population (N)	Direction	p-value
Rs4680	*COMT*	del Re et al., 2014	SCZ (68); HC (75)	+	0.96
		Horikoshi et al., 2019	SCZ (49)	+	0.28

3.5. SNP look-up

Our look-up in the PGC-SCZ2 database indicated that four out of 11 SNPs reported in two or more studies that we retrieved were genome-wide significant for schizophrenia (see SNPs printed in red in Table 1; $P < 5 \times 10^{-8}$). In addition, three SNPs were genome-wide suggestive for schizophrenia (SNPs printed in blue in Tables 1 and 2, $5 \times 10^{-8} < P < 1 \times 10^{-5}$). Four studies were published in 2014 (the year of the influential GWAS (Ripke et al., 2014) or later (Del Re et al., 2014; M. H. Hall et al., 2014; O'Donoghue et al., 2014; Saville et al., 2015) and two before 2014 (Decoster et al., 2012; Quednow et al., 2012).

None of the 11 SNPs reported in our retrieved studies showed genome-wide significance in our look-up in the 2014 GWAS of SNPs underpinning p3b amplitude (Malone et al., 2014).

Table 3
Results of meta-analyses. Directions of effect indicate directions of effect of individual studies used in the meta-analyses. HC: healthy controls; SCZ: schizophrenia patients; +: increase in ERP measure; −: decrease in ERP measure.

SNSNP	Gene	ERP	Genotypic comparison	Number of studies	Number of subjects	p-value	Directions of effect
rs4680	*COMT*	p3b amplitude	AA vs GG	2	298	0.29	- +
rs4680	*COMT*	p3b amplitude	AA vs AG vs GG	2	384	0.38	–
rs4680	*COMT*	p50 T/C ratio	AA vs GG vs GG	4	565	0.25	- - + +
rs1625579	*mir-137*	p3b amplitude	CC vs AC and AA	2	479	0.13	- +

4. Discussion

Our systematic review focused on the genetic association between electrophysiological intermediate phenotypes of schizophrenia (P3b, P50 suppression, MMN, and rs-EEG) and single nucleotide polymorphisms in patients with psychosis and healthy controls. Due to high diversity in study design and strict inclusion criteria, we were only able to conduct four meta-analyses of two SNPs' association with selected endophenotypes. All meta-analyses failed to reach statistical significance, therefore the evidence for association of SNPs with selected EIPs remained limited to individual studies.

It is important to note that 33 out of 45 retrieved studies ranked as "poor" on Q-Genie quality assessment tool. This highlights the difficulty in directly comparing studies and interpreting their results. It also reflects potential difficulties in interpreting meta-analysis results when the reliability of results across studies involved in the same meta-analysis is variable.

Two studies reported on rs1625579 which is found in the coding region of *miR-137*, a gene implicated in schizophrenia (Liu et al., 2019; Ripke et al., 2014; Ripke, S., Sanders, A. R., Kendler, K. S., Levinson, D. F., Sklar, P., Holmans, P. A., … Consortium, T. S. P. G.-W. A. S. (GWAS), 2011; Rasetti and Weinberger, 2011). (Liu et al., 2019) have recently identified dorsolateral prefrontal cortex connectivity as a potential endophenotype linking miR-137 expression and schizophrenia. Somewhat counter-intuitively, Decoster et al. (2012) have reported an association between rs1625579 risk allele and increased p3b amplitude. However, in our meta-analysis of the two studies, the risk allele was not associated with p3b amplitude.

rs4680 is found in the coding region of *COMT*. Our meta-analysis results did not find any statistically significant association between rs4680 and P3b amplitude. However, it is important to note that only two studies in one genotypic comparison and three in another were suitable for inclusion. rs4680 risk allele has been implicated in schizophrenia and its treatment resistance (Sagud et al., 2018; Williams et al., 2007), hence it would be consistent for rs4680 risk allele carriers to have decreased P3b amplitudes. This association was studied in ten papers, however only two studies (Ehlis et al., 2007; Gallinat et al., 2003) reported a decrease in p3b amplitude in risk allele carriers, whilst two reported an increase (Golimbet et al., 2006; Heitland et al., 2013). Our meta-analysis of the association between p50 T/C ratio and rs4680 found no change in p50 suppression in risk allele carriers, compared to reference heterozygotes. Individual studies also reported conflicting results (Table 2). We therefore conclude that there is no strong evidence available for p50 suppression in association with rs4680, despite a strong theoretical rationale.

22 SNPs were investigated in the context of the MMN, and one reached statistical significance: rs2240158 (Lin et al., 2014) (Table 4). Rs4680 was the only SNP studied in more than one publication, however, the differences in MMN paradigms made studies hard to compare and impossible to integrate into a meta-analysis.

For the resting EEG intermediate phenotype two studies seem to converge on an association between theta and delta activity and the rs4680 SNP (Venables et al., 2009; Wacker and Gatt, 2010), however they could not be compared in a meta-analysis, due to inclusion of different genotypic groups in either study.

Interestingly, several SNPs that were investigated in more than one study were genome-wide suggestive or genome-wide significant for association with schizophrenia (Table 1, Table 2) in the influential 2014 GWAS (Ripke et al., 2014), but were not associated with any schizophrenia related EIPs in other GWAS studies (Greenwood et al., 2013; M.-H. Hall et al., 2015; Konte et al., 2017; Malone et al., 2014). This could be due to significantly higher power of the 2014 GWAS (n = 150,064). However, it is also possible that no firm EIP-SNP associations exist. It is important to note that Ripke et al. study could in itself introduce significant selection bias in interpreting the results of our review, as the SNPs reported by Ripke et al. were more likely to be studied as a consequence of that publication, increasing the likelihood of obtaining significant results in individual SNP-ERP association studies. However, only three studies that addressed SNPs studied in more than one study (Table 1, Table 2, Table 4) were published after 2014 (Bertelsen et al., 2015; Demily et al., 2016; Mao et al., 2016).

There are several caveats to interpreting our results. Firstly, we focused only on SNPs, excluding studies looking at structural variation, e.g. microdeletions associated with schizophrenia such as the 22q11.2 deletion syndrome (e.g. Flomen et al., 2013; McDonald-McGinn et al., 2015; Zarchi et al., 2013). Secondly, differences in experimental paradigms and designs severely limited the potential number of meta-analyses we could conduct. Thirdly, the meta-analyses only included sample sizes, directions of effect and *p*-values. Consistent reporting of effect sizes could have greatly benefitted the meta-analyses. Unfortunately, differences in how effect sizes were reported, selective reporting and overall scarcity of studies that reported them at all prevented us from visually examining or quantifying publication bias. In addition, unknown population stratification effects could have increased or reversed SNP effects in the studies of complex traits, even if a relatively homogenous sample was being studied (Abdellaoui et al., 2013). It is important to bear in mind that candidate gene studies generally report relatively large effect sizes (and even false-positives) compared to genome-wide studies (Anokhin, 2014), although there is some agreement between SNPs implicated in schizophrenia by GWAS and candidate-gene studies (Farrell et al., 2015). We have also noticed that exact p-values are reported more often when the results are statistically significant. Because exact p-values were required for our meta-analysis, this means that significant results were more likely to be included. Similarly, where direction of effect was not clear, we were unable to include the results in a meta-analysis. This was most common in MANOVA comparisons of three genotypic groups in those studies, where heterozygotes were associated with lower or higher p3b amplitudes then both homozygous groups. Lastly, we directly compared ERPs obtained from different EEG electrodes. Whilst we can be confident that they measured the same ERP, there are important differences between them (such as prominence of p3b amplitude) that may influence the results when directly comparing the studies.

5. Conclusion

Despite an extensive body of studies, there is at present no conclusive evidence of an association between any SNPs to any of the electrophysiological intermediate phenotypes that we reviewed in this manuscript. We show that despite individual findings, rs1625579 association with p3b amplitude does not reach statistical significance after meta-analysis. Likewise, rs4680 is not significantly associated with p3b decrease or p50 T/C ratio, despite multiple studies investigating these associations. Perhaps the main reason for lack of statistically significant SNP-EIP associations is the presence of statistical and methodological heterogeneity between the studies, but it may also be true that no such associations exist. Review by Owens et al. (2016) provides some more practical guidelines to achieve higher homogeneity between ERP studies. We note that future comprehensive reviews of literature and future meta-analyses would be made easier by consistent reporting of p-values and directions of effect and consistent selection of genotypic groups for statistical analyses.

Contributors

Authors J. O. Nuninga, J. J. Luykx and J. Hederih wrote the study protocol. Author J. O. Nuninga wrote the first draft of the manuscript and J. Hederih wrote the further versions. Author K. Van Eijk contributed to the statistical analyses. Authors D. J. Smit, E. van Dellen, B. Oranje and J. J. Luykx contributed extensively to the text and its revision. All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2020.110001.

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