Is auditory processing measured by the N100 an endophenotype for psychosis? A family study and a meta-analysis

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Abstract

Background. The N100, an early auditory event-related potential, has been found to be altered in patients with psychosis. However, it is unclear if the N100 is a psychosis endophenotype that is also altered in the relatives of patients.

Methods. We conducted a family study using the auditory oddball paradigm to compare the N100 amplitude and latency across 243 patients with psychosis, 86 unaffected relatives, and 194 controls. We then conducted a systematic review and a random-effects meta-analysis pooling our results and 14 previously published family studies. We compared data from a total of 999 patients, 1192 relatives, and 1253 controls in order to investigate the evidence and degree of N100 differences.

Results. In our family study, patients showed reduced N100 amplitudes and prolonged N100 latencies compared to controls, but no significant differences were found between unaffected relatives and controls. The meta-analysis revealed a significant reduction of the N100 amplitude and delay of the N100 latency in both patients with psychosis (standardized mean difference [s.m.d.] = −0.48 for N100 amplitude and s.m.d. = 0.43 for N100 latency) and their relatives (s.m.d. = −0.19 for N100 amplitude and s.m.d. = 0.33 for N100 latency). However, only the N100 latency changes in relatives remained significant when excluding studies with affected relatives.

Conclusions. N100 changes, especially prolonged N100 latencies, are present in both patients with psychosis and their relatives, making the N100 a promising endophenotype for psychosis. Such changes in the N100 may reflect changes in early auditory processing underlying the etiology of psychosis.

Introduction

Breakthroughs have been made on our understanding of the genetic basis of psychosis, with 287 genomic loci for schizophrenia and 64 loci for bipolar disorder discovered (Mullins et al., 2021; Trubetskoy et al., 2022), as well as rare variants affecting 10 genes associated with schizophrenia (Singh et al., 2022). Nevertheless, more research is still needed to explain how such genetic risk is conferred on the clinical phenotypes of psychosis. One possible approach is the use of endophenotypes for psychosis, which are intermediate phenotypes that bridge the gap between the genetic variants and clinical phenotypes of psychosis (Gottesman & Gould, 2003; Gottesman & Shields, 1973; Gould & Gottesman, 2006). Although the concept was initially proposed to aid gene discovery, the goal of endophenotype research now has shifted to understanding the neurobiological mechanisms linked to the genetics and phenotypes of psychosis (Hall & Smoller, 2010). Endophenotype deficits observed in both patients and their unaffected relatives could serve as biomarkers of genetic predisposition toward the disease and provide mechanistic insights (Gottesman & Gould, 2003; Gottesman & Shields, 1973; Gould & Gottesman, 2006).

Event-related potentials (ERPs) are changes in the electroencephalogram (EEG) triggered by stimuli such as perception or cognitive tasks and constitute promising endophenotypes for psychosis. This technology is ubiquitous, non-invasive, and due to its millisecond temporal resolution, allows the real-time investigation of perception and

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cognition. Since deficits in auditory processing (e.g. auditory hallucinations) are core features of psychosis (Waters et al., 2012), research on auditory ERPs is important to unravel their underlying mechanisms. A few auditory ERPs, such as the mismatch negativity and the P300 (Blakey et al., 2018; Bramon et al., 2005; Earls, Curran, & Mittal, 2016; Erickson et al., 2016), are considered endophenotypes for psychosis as they are impaired in both patients with psychosis and their relatives. However, compared to other ERPs, the N100 waveform has been relatively less researched as a potential endophenotype for psychosis. The N100 is a change in EEG that occurs very consistently at about 100 ms following any kind of auditory stimulus and is related to the processing of auditory information at an early stage.

The N100 is mainly generated from the primary and association auditory cortices (Liasis, Towell, Alho, & Boyd, 2001; Näätänen, 1992; Näätänen & Picton, 1987), and was found to be altered in patients with psychosis. It is commonly measured by three paradigms: the passive listening paradigm (where a series of identical stimuli are presented), the auditory oddball paradigm (where a few target stimuli are randomly embedded in a series of standard stimuli), and the paired-click paradigm (where pairs of two consecutive stimuli are presented). A review by Rosburg, Boutros, and Ford (2008) concluded that patients had reduced N100 amplitudes compared to controls, but such deficits were more robust in studies that employed longer interstimulus intervals (>1 s) (Rosburg et al., 2008). When focusing on the paired click paradigm, Rosburg (2018) found that patients with psychosis had reduced N100 amplitudes to the first stimulus (S1), but no significant differences between patients and controls were found for N100 amplitudes to the second stimulus (S2) (Rosburg, 2018). This important observation challenged the view that patients had N100 sensory gating impairment measured by the S2/S1 ratio, but is in line with findings from the passive listening and auditory oddball paradigms. By contrast, relatively few studies examined the N100 latency, an EEG correlate of reaction time, with some reporting N100 delays in patients compared to controls (Adler & Gattaz, 1993; Adler, Adler, Schneck, & Armbruster, 1990; Ahveninen et al., 2006; Frangou et al., 1997; Iyer, Boutros, & Zouridakis, 2012).

The N100 is heritable, making it a potential endophenotype indicative of genetic risk for psychosis. Twin studies showed a heritability of 60–70% for the N100 amplitude (Ahveninen et al., 2006; O'Connor, Morzorati, Christian, & Li, 1994) and 56% for the N100 latency (O'Connor et al., 1994) in the auditory oddball paradigm at the Cz electrode, while the heritability of the N100 amplitude to S1 in the paired click paradigm was estimated to be 73% at Cz (Anokhin, Vedeniapin, Heath, Korzyukov, & Boutros, 2007). However, whether the N100 is impaired in the relatives of patients with psychosis remains unclear. While some studies reported a reduction in the N100 amplitude and a prolongation in the N100 latency in the relatives of patients (Ahveninen et al., 2006; Ethridge et al., 2015; Force, Venables, & Sponheim, 2008; Foxe et al., 2011; Frangou et al., 1997; Lebedeva & Orlova, 2001; Pokorny & Sponheim, 2022; Simons et al., 2011; Turetsky et al., 2008), others did not find such differences (Blackwood, Clair, Muir, & Duffy, 1991; Ford et al., 2013; Karoumi et al., 2000; Leicht et al., 2011; Pokorny & Sponheim, 2022; Simons et al., 2011; Sumich et al., 2008; Waldo, Adler, & Freedman, 1988; Winterer et al., 2001), and there have been no systematic reviews or meta-analyses summarizing the literature so far.

Therefore, the current study aims to examine whether the N100 meets the criteria to be an endophenotype for psychosis by comparing the N100 in patients with psychosis and their relatives with controls. To achieve this, we first analyzed EEG data from a family study conducted by our team and performed a systematic review and meta-analysis to combine our results with all available N100 literature.

Methods and materials

Family study: participants

Our family study is an international collaboration among three research institutes at two research sites: University College London (London, UK), King's College London (London, UK), and McLean Hospital at Harvard Medical School (Belmont, MA, USA). The study was approved by local ethics committees at both research sites and all participants provided written consent before assessments. Both research sites recruited patients with psychosis and controls, while the London site also recruited the unaffected relatives of patients. Patients and their relatives were recruited by clinical teams at mental health services in London and Belmont, while controls were recruited in local communities via advertisements. Psychotic disorders were diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 1994), and validated by structured clinical interviews (Andreasen, Flaum, & Arndt, 1992; Endicott & Spitzer, 1978; Kay, Fiszbein, & Opler, 1987; Spitzer, Williams, Gibbon, & First, 1992; Williams et al., 1992; Wing et al., 1990). Controls in the study did not have any personal or family histories of psychosis. Unaffected relatives recruited in London were the first-degree relatives of the patients without personal histories of psychosis. Details of recruitment can be found in online Supplementary Material.

Family study: EEG recording and processing

Participants' EEG was recorded using the auditory oddball paradigm with similar parameters at both research sites. Stimuli in the paradigm were 400 binaural 80 dB tones, including 20% (London) or 15% (Belmont) target tones of 1500 Hz randomly embedded in the standard tones of 1000 Hz. The interstimulus interval was 1.8–2.2 s. Participants were instructed to press a button when they detected a target tone. EEG data were referenced to the left earlobe or an average of mastoids and bandpass filtered between 0.1 and 30 (London) or 20 (Belmont) Hz. Eye blinks and other artifacts were removed using independent component analysis (Delorme & Makeig, 2004; Pion-Tonachini, Kreutz-Delgado, & Makeig, 2019) in London and by a regression-based method (Gratton, Coles, & Donchin, 1983) in Belmont. After baseline correction, N100 amplitudes, and latencies to the standard stimuli were measured at the Cz electrode at both research sites. N100 amplitudes were measured as the most negative peak amplitude in a window from 50 to 200 ms post-stimulus. N100 latencies were measured as the interval between the N100 peak and stimulus onset. Details of EEG recording and processing can be found in online Supplementary Material.

Family study: group comparisons

We compared the N100 amplitude and latency across three clinical groups using linear regression models. N100 amplitude or

latency was included as the outcome variable in the model, and clinical group (patients/relatives/controls) was included as the main explanatory variable. Controls were set as the reference group in the model. We also added age, sex, and research site as covariates in the model, since they could be potential confounders for group differences in the N100. To minimize heterogeneity caused by experimental differences between the two sites, N100 amplitudes and latencies were standardized across groups within each site before the analysis.

Meta-analysis: literature search

As the power to detect N100 differences across groups in our family study was limited by its modest sample size, we conducted a meta-analysis to combine the results of our family study and any suitable previously published family studies. Before conducting the literature search and meta-analysis, we registered the protocol of the meta-analysis on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=163195).

We searched PsycINFO (Ovid interface, 1806 onward, multipurpose search), Embase (Ovid interface, 1974 onward, multipurpose search), and PubMed (text-word search), using the following search terms: (psychosis OR psychoses OR psychotic OR schizophreni* OR bipolar) AND (N1 OR N100) AND (relative* OR famil*). Searches were restricted to English language and human studies. The last search was conducted on January 11, 2023.

Meta-analysis: inclusion and exclusion criteria

Eligible studies should focus on participants aged 18 or above with no neurological disorders, intellectual disability, or hearing loss. Studies must be family studies involving the relatives of patients with psychosis. Patients must be diagnosed with schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, psychotic disorder not otherwise specified, or bipolar disorder. As there were limited studies in this field, although we initially planned to include only unaffected relatives, studies with affected relatives were still included if the majority of the relatives were unaffected, and we excluded those studies in further sensitivity analyses. Controls should have no personal or family histories of psychosis. As we were interested in the N100 deficits related to auditory processing, studies using non-auditory paradigms were excluded.

Meta-analysis: data collection and extraction

Initial search results were exported to EndNote X9 (https://endnote.com/) for deduplication and uploaded to Rayyan (https://rayyan.qcri.org/) for screening. Three researchers (B.W., H.A., and L.V.) screened all titles and abstracts independently, and all papers were double-screened. We then downloaded the full-text articles for the studies and assessed them for final inclusion. We also checked the references of the full-text articles for additional eligible studies. Discrepancies were resolved by discussion between the three researchers, and a fourth senior researcher (E.B.) was consulted when required.

For each eligible study, we extracted the following information: (1) author(s) and year of publication; (2) sample size and characteristics; (3) paradigm (e.g. oddball, paired click, or talk-listen), electrode(s), and N100 measure (e.g. amplitude or latency); (4) means and S.D.s of N100 amplitudes and/or latencies in patients,

relatives, and controls; (5) standardized mean differences (S.M.D.s) between groups when (4) was not available. Missing data were requested by emailing the authors of eligible studies.

Meta-analysis: statistical analysis

We pooled the S.M.D.s of our family study and all eligible previous studies in a meta-analysis using the metafor package in R 4.0.2 (R Core Team, 2020; Viechtbauer, 2010). When no S.M.D.s were provided by a primary study, we calculated S.M.D.s using Cohen's d (Cohen, 1988) based on the mean and S.D. of each group, or from the S.D. of the outcome variable and the unstandardized regression coefficient in regression models. We used random-effects models to calculate the pooled effect sizes using the DerSimonian–Laird method (DerSimonian & Laird, 1986) and assessed heterogeneity by the I^2 statistics (Higgins & Thompson, 2002; Higgins, Thompson, Deeks, & Altman, 2003).

The primary meta-analysis compared the N100 amplitude and latency between patients and controls as well as between relatives and controls. We also conducted sensitivity analyses excluding samples with affected relatives and broad clinical status (i.e. participants with other neuropsychiatric conditions, such as minor brain injuries and low IQ). Since all but two studies used the auditory oddball paradigm and its variants, we performed subgroup analyses including only those studies and excluding two studies using the paired-click paradigm.

Meta-analysis: assessment of study quality and publication bias
All studies included in the qualitative synthesis were assessed by the Newcastle–Ottawa scale (Wells et al., 2000). The scale has a maximum score of nine stars indicative of optimal case–control designs and appraises four domains: selection of participants (four stars), comparability across groups (two stars), and ascertainment of outcome/exposure (three stars). We also assessed publication bias in the literature by funnel plots (Light, Richard, Light, & Pillemer, 1984).

Results

Family study: sample overview

A total of 523 participants in our family study were analyzed, including 220 from London and 303 from Belmont. In total, 243 patients, 86 relatives, and 194 controls were included in the analysis. Descriptive statistics of age, sex, N100 amplitude, and N100 latency by clinical group in the two samples are shown in Table 1.

Family study: group comparisons

For the N100 amplitude, linear regression revealed that patients had significantly reduced N100 amplitudes compared to controls (S.M.D.: −0.21, 95% CI: −0.40 to −0.02, $p = 0.027$), but no significant differences were found between relatives and controls for N100 amplitude (S.M.D.: −0.06, 95% CI: −0.35 to 0.22, $p = 0.664$). Similarly, we found that patients had significantly prolonged N100 latencies (S.M.D.: 0.22, 95% CI: 0.03–0.41, $p = 0.025$), but no significant differences were found between relatives and controls for the N100 latency (S.M.D.: 0.10, 95% CI: −0.18 to 0.39, $p = 0.476$). We also tested the interactions between group × age, sex × age, and sex × age, but those interactions were generally not significant.

Table 1. Sample characteristics by clinical group and research site

Variable	London				Belmont		
	Patients ($n = 67$)	Relatives ($n = 86$)	Control ($n = 67$)	Total ($n = 220$)	Patients ($n = 176$)	Controls ($n = 127$)	Total ($n = 303$)
Mean (S.D.) age (years)	39.6 (11.4)	47.2 (13.8)	43.8 (14.1)	43.9 (13.5)	40.8 (14.0)	30.2 (11.1)	36.3 (13.9)
Sex							
Female	34 (51%)	46 (53%)	35 (52%)	115 (52%)	80 (45%)	76 (60%)	156 (51%)
Male	33 (49%)	40 (47%)	32 (48%)	105 (48%)	96 (55%)	51 (40%)	147 (49%)
Mean (S.D.) N100 amplitude (μV)	8.51 (4.05)	8.92 (3.81)	9.26 (3.73)	8.90 (3.86)	3.69 (3.15)	4.69 (2.87)	4.11 (3.07)
Mean (S.D.) N100 latency (ms)	98.59 (12.37)	97.34 (12.61)	95.50 (13.94)	97.16 (12.96)	99.47 (16.77)	95.33 (11.17)	97.73 (14.81)

Meta-analysis: study selection

A total of 415 studies were identified from our literature search, with three additional studies identified through other resources (two by reference checking and our family study). A total of 334 studies were left after deduplication. After screening titles and abstracts, we included 31 studies for full-text screening. In total, 17 studies (including our family study) were included in the qualitative synthesis, and 14 of the 17 studies (including our family study) were included in the meta-analysis. Figure 1 shows the PRISMA flow diagram of the selection process (Moher et al., 2009).

Meta-analysis: study characteristics

Table 2 summarizes information about the 17 studies included in the qualitative synthesis after the full-text screening. All studies included three clinical groups except Lebedeva and Orlova (2001), which compared relatives and controls only. All 17 studies included in the qualitative synthesis measured N100 amplitudes, and 11 studies measured N100 latencies. The N100 was measured at Cz in most studies, although some studies included more electrodes (mostly Fz and Pz) or computed the N100 based on principal component analysis. Three types of tasks were used to measure the N100: the auditory oddball paradigm or its variants, the paired click paradigm, and the talk-listen task (where the N100 response to an individual's own speech is compared with the N100 during listening).

Meta-analysis: results

N100 data were available for meta-analysis from 14 studies including our family study. The pooled sample for meta-analysis included 999 patients, 1192 relatives, and 1253 controls. All 14 studies provided data for N100 amplitude, while data for N100 latency were also available from eight studies. N100 data measured at Cz to the standard stimuli in the oddball paradigm or to S1 in the paired click paradigm were used when available in the meta-analysis. Otherwise, N100 data at different electrodes or in other conditions were also used, and the specific data used for each study in the meta-analysis are specified in Table 2.

We identified one outlier study with unusually small S.D.s for the N100 latency (Frangou et al., 1997). We calculated new corrected S.D.s treating the original S.D.s as S.E.s, and used the corrected S.D.s for the meta-analysis. We also performed separate analyses using the uncorrected data and sensitivity analyses

excluding this outlier study for the primary meta-analysis. Those analyses yielded consistent results with the primary meta-analysis (online Supplementary Material; Figs S1 and S2).

For the primary meta-analysis comparing patients with psychosis and controls in family studies, we found very strong evidence that patients had reduced N100 amplitudes compared to controls with a medium effect size (S.M.D.: -0.48; 95% CI -0.59 to -0.36; $p < 0.001$; $I^2 = 31\%$; Fig. 2a). Similarly, we found evidence that patients with psychosis had longer N100 latencies than controls with a medium effect size (S.M.D.: 0.43; 95% CI 0.03–0.82; $p = 0.034$; $I^2 = 86\%$; Fig. 2b). The sensitivity analysis excluding participants with broad clinical status showed consistent results with the primary analysis (online Supplementary Fig. S3).

Figure 3 shows the forest plots of the primary meta-analysis comparing relatives and controls. For the N100 amplitude, we found evidence that relatives had significantly smaller N100 amplitudes than controls with a small effect size (S.M.D.: -0.20; 95% CI -0.35 to -0.05; $p = 0.011$; $I^2 = 60\%$; Fig. 3a). The meta-analysis also revealed that relatives had significantly longer N100 latencies than controls with a small effect size (S.M.D.: 0.33; 95% CI 0.16–0.50; $p < 0.001$; $I^2 = 25\%$; Fig. 3b). However, in the sensitivity analysis excluding samples with affected relatives and with broad clinical status, we found that the difference in N100 amplitudes between unaffected relatives and controls became no longer significant (S.M.D.: -0.27; 95% CI -0.62 to 0.08; $p = 0.129$; $I^2 = 74\%$; online Supplementary Fig. S4A). Nevertheless, the sensitivity analysis excluding samples with affected relatives showed consistent results with the primary analysis for the N100 latency (S.M.D.: 0.40; 95% CI 0.19–0.61; $p < 0.001$; $I^2 = 23\%$; online Supplementary Fig. S4B).

As all but two studies used the oddball paradigm or its variants to measure the N100, we conducted subgroup analyses excluding two studies using the paired click paradigm (Turetsky et al., 2007; Waldo et al., 1988). All subgroup analyses comparing the N100 and latency across the three clinical groups yielded consistent results with the primary analyses (online Supplementary Material; Figs. S5–S6).

Meta-analysis: risk of bias assessment

The number of stars scored by each study on the Newcastle-Ottawa Scale is presented in Table 2. No studies scored nine stars as experimental EEG studies typically do not report
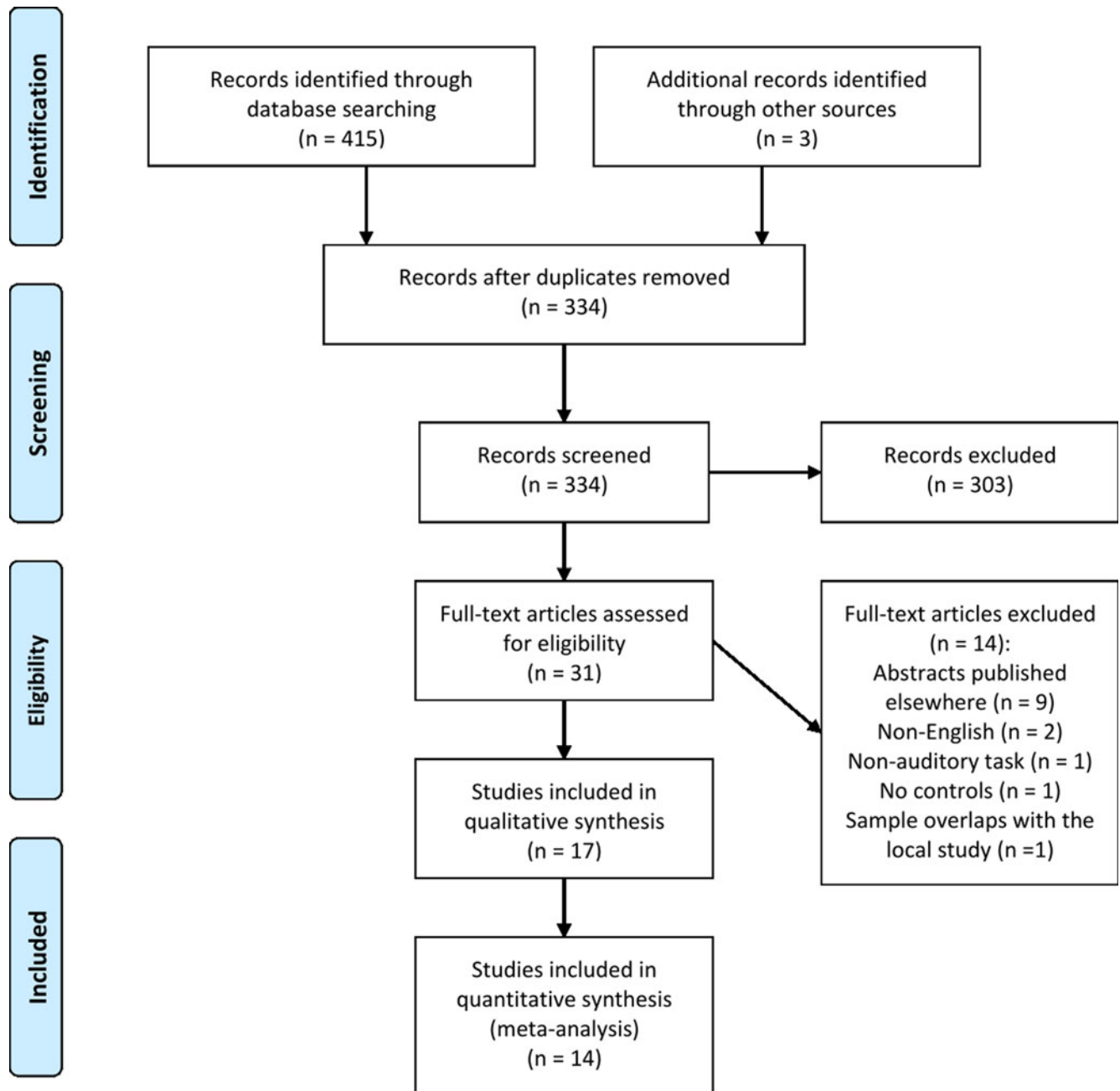
Figure 1. PRISMA flow diagram of study selection (Moher et al., 2009).

no-response rates (commonly recorded in epidemiological studies), but it is an item in the Newcastle-Ottawa Scale. Other common sources of potential bias identified by the scale included no independent validation of cases apart from record linkage or self-report, no description of case or control ascertainment (whether participants were recruited from hospitals or communities), and no controlling for age or sex in statistical analysis.

Funnel plots assessing publication bias for the primary meta-analysis are shown in online Supplementary Fig. S7. Studied in most analyses showed a relatively symmetrical pattern, which is typically interpreted as no evidence of publication bias. However, publication bias may still exist, especially for the meta-analysis of N100 amplitude comparing patients and

controls, since studies with smaller samples reported slightly bigger effect sizes than the larger studies.

Discussion

In the current study, we examined the N100 amplitude and latency as potential endophenotypes for psychosis. Our multicenter family study and the meta-analysis confirmed that patients with psychosis had reduced N100 amplitudes and prolonged N100 latencies compared to controls of moderate severity. The meta-analysis including our family study with previously published data found that the relatives of patients with psychosis also had similar, yet milder deficits in the N100 amplitude and

Table 2. Summary of the 17 studies included in the qualitative synthesis

Study	Sample size			Task	Electrode	N100 Measure	Main findings	Inclusion in meta-analysis	NOS total no. stars
	Patients	Relatives	Controls						
Ahveninen et al. (2006)	23 schizophrenia	23 co-twins (10 monozygotic; 13 dizygotic)	40 (20 twin pairs; 9 monozygotic & 11 dizygotic)	Oddball (no action) 20% target; 80% standard ISI = 0.5 s	FC1, FCz, FC2, C1, Cz, and C2	N100 amplitude and latency to standard stimuli	Patients and their co-twins had significantly reduced N100 amplitudes compared to controls. The N100 latency was significantly longer in patients than controls.	Included (amplitude averaged across electrodes; latency at FCz)	8
Blackwood et al. (1991)	96 schizophrenia	150 for N100 latency; 149 for N100 amplitude [a]	211	Oddball (silently count) 10% target; 90% standard ISI = 0.9 s	Cz	N100 amplitude and latency to standard stimuli	N100 amplitudes were reduced in patients with schizophrenia compared to controls. No evidence of deficits in relatives.	Included (Cz)	5
Ethridge et al. (2015)	229 schizophrenia; 188 bipolar disorder	First-degree relatives of patients with schizophrenia: 264; bipolar disorder: 239 [a]	284	Oddball (press button) 15% target; 85% standard ISI = 1.3 s	All electrodes using PCA	N100 amplitude to standard stimuli	In the final model of linear discriminant analysis, N100 amplitude significantly discriminated patients with schizophrenia, patients with bipolar disorder, and relatives of patients with schizophrenia from controls.	Included (PCA; effect sizes comparing patients with schizophrenia and their relatives with controls)	8
Force et al. (2008)	19 schizophrenia; 18 bipolar disorder	First-degree relatives of patients with schizophrenia: 37; bipolar disorder: 25 [a]	36	Two-dimensional dichotic listening task (press button) 10% target; 10% unattended deviant; 80% standard ISI = 1.1–1.6 s	Cz	N100 amplitude to all stimuli	Patients with schizophrenia and relatives of patients with schizophrenia showed reduced N100 amplitudes compared to controls across conditions.	Included (Cz, data combining all conditions)	6
Ford et al. (2013)	30 schizophrenia; 19 schizoaffective	Unaffected first-degree relatives of	43	Talk–listen	Fz, FCz, and Cz	N100 amplitude to both	N100 suppression was greater in controls than	Not included. Unable to obtain data.	7

	disorder; 39 bipolar disorder	patients with schizophrenia: 30; schizoaffective disorder: 23; bipolar disorder: 50				conditions and N100 suppression (Talk - Listen)	patients with schizophrenia and patients with bipolar disorder. Patients showed reduced N100 amplitudes in the listen condition. No evidence of N100 suppression deficits in relatives.		
Foxe et al. (2011)	35 chronic schizophrenia; 30 first-episode schizophrenia	30 unaffected first-degree relatives	22	Oddball (press button) 17% target; 83% standard ISI = 1.5 s	FC1, FCz, and FC2	N100 amplitude to standard stimuli	All three groups showed a reduction in N100 amplitude compared to controls.	Included (FCz; data for relatives & controls)	6
Frangou et al. (1997)	33 schizophrenia	57 first-degree relatives [a]	32	Oddball (press button) 16.7% target; 83.3% standard ISI = 2 s	Fz, Cz, and Pz	N100 amplitude and latency to target stimuli	Patients with schizophrenia showed reduced N100 amplitudes and prolonged N100 latencies than relatives and controls at several electrodes. No evidence of deficits in relatives.	Included (Cz)	8
Karoumi et al. (2000)	21 schizophrenia	21 unaffected siblings	21	Oddball (press button) 20% target; 80% standard	Fz, Cz, and Pz	N100 amplitude and latency to standard stimuli	Patients with schizophrenia showed reduced N100 amplitudes compared to controls at Cz. No evidence of deficits in relatives.	Included (Cz)	4
Lebedeva et al. (2001)	NA	30 unaffected relatives (15 parents; 15 children or siblings)	Two groups of 15 (matched to the two relative groups)	Oddball (press button) 20% target; 80% standard ISI = 1.5 s	F3, F4, C3, Cz, C4, P3, Pz, and P4	N100 amplitude and latency to standard and target stimuli	Relatives of patients with schizophrenia showed smaller N100 amplitudes and longer N100 latencies than controls at some electrodes.	Included (Pz)	4
Leicht et al. (2011)	17 schizophrenia	17 unaffected siblings	17	Tone discrimination (press button) 2 pitches, 50% each (both	Cz	N100 amplitude and latency	Patients with schizophrenia showed a significant reduction in N100 amplitude than controls. No	Included (Cz, data combining both conditions)	6

Table 2. (Continued.)

Study	Sample size			Task	Electrode	N100 Measure	Main findings	Inclusion in meta-analysis	NOS total no. stars
	Patients	Relatives	Controls						
				required responses)			evidence of deficits in relatives.		
				ISI = 2.5–7.5 s					
Pokorny et al. (2022)	90 schizophrenia; 53 bipolar disorder	72 first-degree relatives of patients with schizophrenia [a]	90	Directed attention oddball listening task (press button)	64/128 electrodes using PCA	N100 amplitude to all stimuli	Irrespective of the condition, patients with schizophrenia showed reduced N100 amplitudes than controls. No evidence of deficits in relatives.	Included (PCA, only data for attended stimuli were used)	6
				10% target; 10% unattended deviant; 40% attended standard; 40% unattended standard					
				ISI = 1.2–1.5s					
Simons et al. (2011)	17 schizophrenia; 1 schizophreniform disorder; 2 schizoaffective disorder; 2 psychotic disorder not otherwise specified	31 unaffected siblings	39	Oddball (press button)	Cz, Fz, and Pz	N100 amplitude and latency to standard and target stimuli	Patients and relatives showed longer N100 latencies than controls to both standard and target stimuli.	Included (Cz)	8
				12.5% target; 87.5% standard					
				ISI = 1 s					
Sumich et al. (2008)	18 schizophrenia	18 unaffected siblings	18	Go and No-Go versions of the oddball paradigm (press button)	Electrodes in three hemispheres (left, right, and midline)	N100 amplitude and latency to target stimuli	Relatives of patients with schizophrenia had larger N100 amplitudes than patients and controls in the Go task.	Not included. Unable to obtain data.	6
				20% rare; 80% frequent					
Turetsky et al. (2008)	142 schizophrenia (58 broad clinical status; 84 narrow clinical status)	373 unaffected relatives (130 parents; 243 siblings; 178 broad clinical status; 195 narrow clinical status)	221	Paired click	Cz	N100 amplitude to S1 and S2; S2/S1 ratio	Patients with schizophrenia had reduced N100 amplitudes to S1 compared to controls in both broad and narrow clinical status groups. Relatives of patients with schizophrenia only showed reduced N100 amplitudes to S1 compared to controls in broad	Included (Cz, data from both broad and narrow clinical status groups)	8

							clinical status groups.	
Waldo et al. ([1988](#))	13 schizophrenia	20 first-degree relatives (9 without P50 gating deficit; 11 with P50 gating deficit)	32	Paired click	Cz	N100 amplitude to S1 and S2; S2/S1 ratio; N100 latency to S1	Patients with schizophrenia had smaller N100 amplitudes to S1 than other groups. Relatives of patients with schizophrenia with P50 gating deficit had larger N100 amplitudes to S1 than controls. Patients with schizophrenia had the shortest N100 latency to S1.	Included (Cz)	4
Winterer et al. ([2001](#))	42 schizophrenia	62 unaffected siblings	34	Oddball (silently count) 20% target; 80% standard ISI = 1–1.5 s	16 electrodes	N100 amplitude and latency to standard and target stimuli	No differences between any groups.	Not included. Unable to obtain data.	7
Our family study	243 psychosis	86 unaffected first-degree relatives	194	Oddball (press button) 15% to 20% target; 80% to 85% standard ISI = 1.8–2.2 s	Cz	N100 amplitude and latency to standard stimuli	Patients with psychosis had reduced N100 amplitudes and prolonged N100 latencies compared to controls. No differences in N100 between relatives and controls.	Included (Cz)	8

[a]Indicates that some relatives in the study had psychosis. ISI, interstimulus interval; S1 and S2, stimulus 1 and 2 in the paired click paradigm; PCA, principal component analysis; NOS, Newcastle-Ottawa Scale.

Note. This table summarizes the 17 studies included in the qualitative synthesis with their sample characteristics, methodology, main findings, whether they were included in the meta-analysis, and study quality assessed by the Newcastle-Ottawa Scale. A maximum of nine stars can be awarded by the Newcastle-Ottawa Scale, indicating optimal case-control designs.
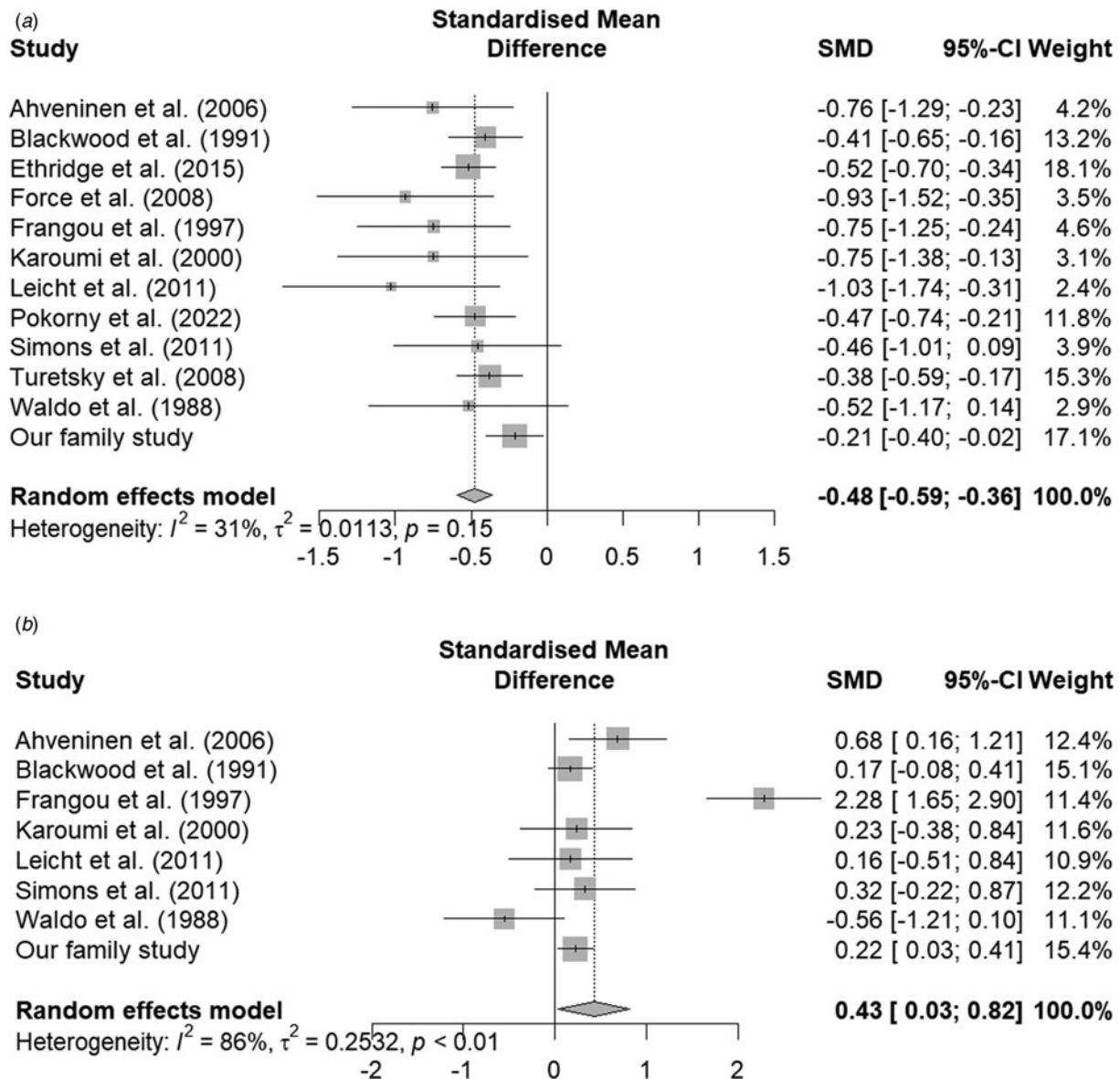
Figure 2. Forest plots comparing the N100 amplitude between 999 patients and 1216 controls (a) and the N100 latency between 466 patients and 585 controls (b). s.m.d., standardized mean difference.

latency, although only delays in the N100 latency remained significant after excluding affected relatives.

Our findings are in line with previous studies that reported reduced N100 amplitudes in patients consistently (Rosburg, 2018; Rosburg et al., 2008), and suggest that patients with psychosis may also have prolonged N100 latencies, which has been less researched in previous literature. We also provided further evidence that the N100 might not only be a biomarker associated with psychosis status (altered in patients with psychosis), but also an endophenotype that indicates psychosis genetic risk (altered in relatives). Our sensitivity analyses suggest that of the two biomarkers, the N100 latency is more robust as an endophenotype of genetic predisposition to psychosis since its results remained unchanged after excluding studies with affected relatives. Such prolongation in the N100 latency observed in patients and unaffected relatives may reflect delays in auditory processing, which is related to the genetic risk of psychosis.

There are several theories explaining the underlying mechanisms of N100 deficits in psychosis. First, as the N100 and P200 constitute the N1-P2 complex that can be clinically used to measure hearing thresholds (Lightfoot, 2016), the N100 deficits may be an indicator of subclinical hearing impairment, given how hearing impairment is associated with an increased risk of psychosis in epidemiological studies (Linszen, Brouwer, Heringa, & Sommer, 2016). Moreover, the N100 deficits are more commonly observed at longer interstimulus intervals (>1 s) in previous studies, possibly due to the larger N100 amplitudes induced by longer interstimulus intervals, which provide more power to detect group differences. This might indicate that patients take longer to recover from the previous N100 response than controls (Hari, Kaila, Katila, Tuomisto, & Varpula, 1982; Imada, Watanabe, Mashiko, Kawakatsu, & Kotani, 1997; Rosburg, 2018; Rosburg, Zimmerer, & Huonker, 2010; Shagass & Schwartz, 1963). This explanation might be better illustrated by the paired click
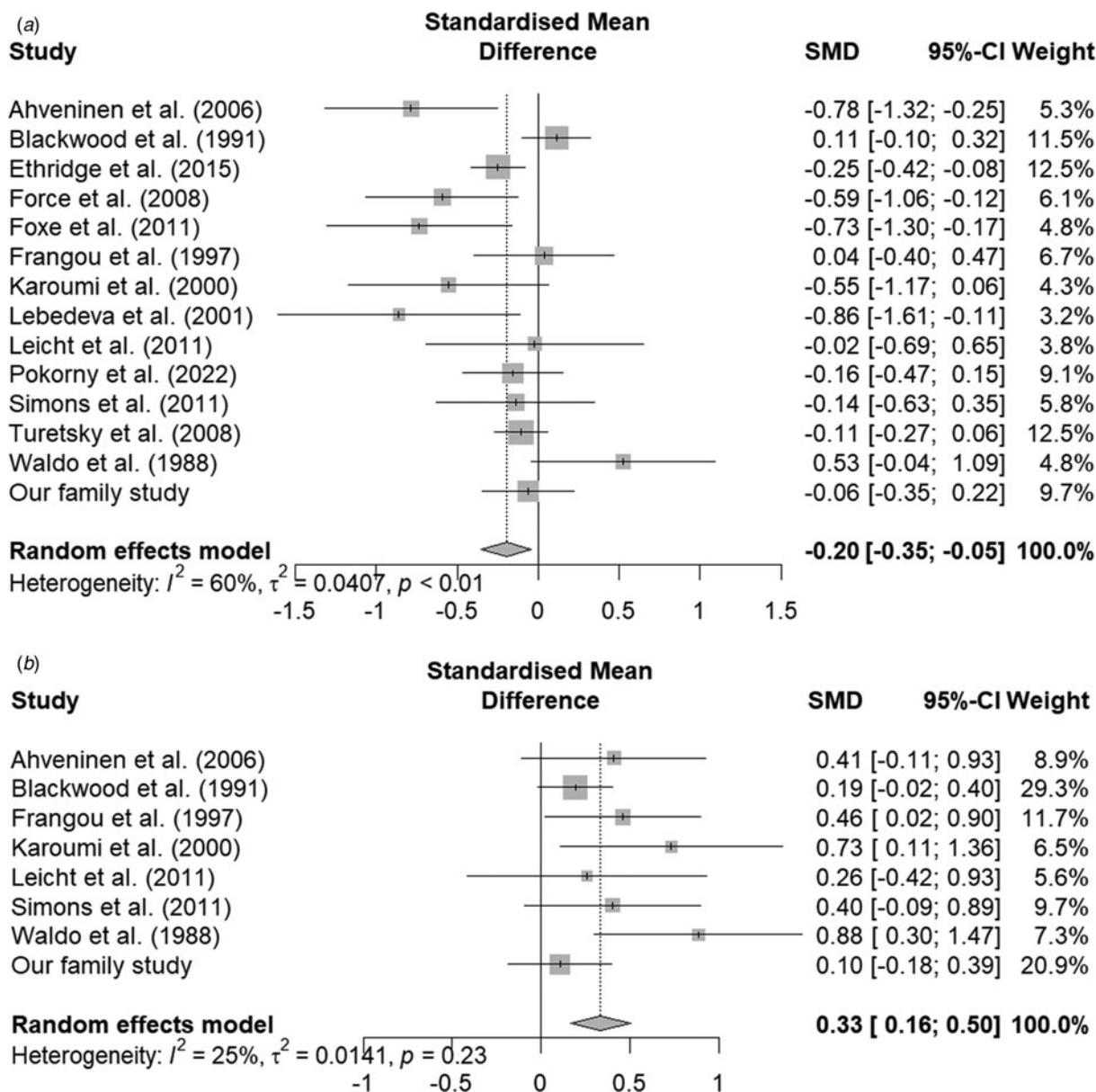
Figure 3. Forest plots comparing the N100 amplitude between 1192 relatives and 1253 controls (a) the N100 latency between 402 relatives and 585 controls (b). s.m.d., standardized mean difference.

paradigm, which can be viewed as a series of auditory stimuli presented with two different interstimulus intervals (usually about 0.5 s $v.$ 10 s) (Rosburg, 2018). Although the N100 occurs at a relatively early stage of auditory processing, the involvement of higher functions of the brain cannot be ruled out, since previous research suggests that the N100 might be modulated by attention (Hillyard, Hink, Schwent, & Picton, 1973; Rosburg et al., 2008). As most included studies measured the N100 triggered by standard rather than target stimuli, our meta-analysis indicates that patients with psychosis and their relatives have impaired responses to external sounds generally, possibly reflecting deficits in early auditory perception and/or attention. Future studies using dynamic causal modeling may help further unravel the role of the N100 in auditory processing in psychosis, and the method has been successfully applied to other ERPs, such as the mismatch negativity (Garrido, Kilner, Kiebel, & Friston, 2009; Ranlund et al., 2016).

The underlying neurobiology of the N100 deficits in psychosis remains unclear. Since N-methyl-D-aspartate (NMDA) glutamate receptors are implicated in the etiology of psychosis (Kantrowitz, 2019), a few studies investigated the effect of NMDA receptor antagonists on the N100 in animal models and human participants but reported mixed results (Connolly et al., 2004; Ehrlichman, Maxwell, Majumdar, & Siegel, 2008; Javitt, Jayachandra, Lindsley, Specht, & Schroeder, 2000; Umbricht et al., 2000). There is also evidence suggesting a link between the N100 amplitude and the *CHRNA4* gene, which encodes the nicotinic acetylcholine receptor alpha4 subunit (Espeseth, Endestad, Rootwelt, & Reinvang, 2007; Mobascher et al., 2016). However, two candidate gene studies examining this association between the N100 and *CHRNA4* reported results in opposite directions (Espeseth et al., 2007; Mobascher et al., 2016).

A limitation of the meta-analysis is the different definitions of relatives across studies. Some studies included a few relatives

affected by psychosis, which could have led to bias. Additionally, the N100 measured in different generations of participants could be confounded by potential yet not fully characterized age-related decline (Gmehlin, Kreisel, Bachmann, Weisbrod, & Thomas, 2011; Lijffijt et al., 2009). Moreover, as some patients and affected relatives included in the meta-analysis were on psychotropic medication, the N100 changes in patients and relatives might be confounded by medication effect. However, since we conducted sensitivity analyses on exclusively unaffected relatives and the results remained unchanged for the N100 latency, the N100 latency might be a trait marker independent of psychosis state and medication effect. Another limitation of the meta-analysis is that the methods used to measure the N100 varied greatly across studies. Two different paradigms (oddball and paired click) were employed by studies included in the meta-analysis, which reflect different underlying constructs reflected by the N100 (early auditory processing and sensory gating). Such methodological differences could also explain the high heterogeneity revealed by I^2 in some of our analyses. Since the N100 is often measured as a by-product in the oddball and paired-click paradigms, more studies comparing relatives and controls which employ standardized tasks specifically designed for the N100 (e.g. containing only standard tones with long interstimulus) are still needed and would advance reproducibility.

Our family study with 523 participants is one of the largest investigations of EEG in psychosis. However, potential confounders might exist in our family study as participants were recruited from two sites. To reduce heterogeneity, we measured the N100 using the same time window with similar collection and processing procedures, while also controlling for study site as a covariate in the regression model. We only had 86 relatives, which limited the power to detect deficits in this group, and therefore we conducted the meta-analysis combining ours and all previous family studies. With 999 patients, 1192 relatives, and 1253 controls, this is the first meta-analysis on the N100 in psychosis comparing all three clinical groups and one with a substantial size.

We conclude that both patients with psychosis and their relatives have reduced N100 amplitudes and prolonged N100 latencies. This makes the N100, especially the N100 latency (prolonged even in unaffected relatives), a promising endophenotype for psychosis. Neurophysiology offers a non-invasive imaging method well suited to multi-systems and cross-species comparisons. We need further cellular, animal, and human investigations of the N100 as a biomarker of perception and cognition and to elucidate the aetiological mechanisms in psychosis.

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