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Probing the relative contribution of the first and second responses to sensory gating indices: A meta-analysis

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Abstract

Sensory gating deficit in schizophrenia patients has been well-documented. However, a central conceptual issue, regarding whether the gating deficit results from an abnormal initial response (S1) or difficulty in attenuating the response to the repeating stimulus (S2), raise doubts about the validity and utility of the S2/S1 ratio as a measure of sensory gating. This meta-analysis study, therefore, sought to determine the consistency and relative magnitude of the effect of the two essential components (S1 and S2) and the ratio. The results of weighted random effects meta-analysis revealed that the overall effect sizes for the S1 amplitude, S2 amplitude, and P50 S2/S1 ratio were − 0.19 (small), 0.65 (medium to large), and 0.93 (large), respectively. These results confirm that the S2/S1 ratio and the repeating (S2) stimulus differ robustly between schizophrenia patients and healthy controls in contrast to the consistent but smaller effect size for the S1 amplitude. These findings are more likely to reflect defective inhibition of repeating redundant input rather than an abnormal response to novel stimuli.

Descriptors: Sensory gating, Schizophrenia, P50, Gating out

Deficits in both the early pre-attentive stage and later evaluative processes of information processing are well-documented in schizophrenia patients (e.g., Turetsky, Bilker, Siegel, Kohler, & Gur, 2009). The putative mechanism underlying these deficits is the inability to inhibit irrelevant or redundant information inflow (Venables, 1964). This inhibitory control, or gating of neuronal responses to afferent information, is believed to be essential for sustaining attention in a changing environment and for appropriate responses to afferent stimuli (Hubel & Wiesel, 1959). It has been argued that the sensory gating problem may result from neuronal hyper-excitability due to a flaw in neuronal inhibitory pathways of cortical and sub-cortical areas (Adler et al., 1982; Flach et al., 1996; Freedman, Waldo, Bickford-Wimer, & Nagamoto, 1991).

To study this sensory gating mechanism, an auditory P50 conditioning (S1)-testing (S2) paradigm is often used while recording the electroencephalogram (EEG) (Adler et al., 1982; Freedman et al., 1987, 1991). In this paired stimulus paradigm (PSP), two identical auditory stimuli are presented as pairs (500 ms apart between clicks or sounds) with an inter-trial interval (ITI) of 8 to 10 s between the pairs (e.g., Freedman et al., 1987; Zouridakis & Boutros, 1992). The P50 mid-latency auditory evoked response (MLAER) attained from the PSP is the most positive peak approximately 40–90 ms after the onset of auditory stimuli (e.g., Boutros, Korzyukov, Jansen, Feingold, & Bell, 2004). The degree of sensory gating, denoted as T/C ratio or S2/S1 ratio, is determined by the ratio of the amplitude of the P50 response to the testing click (T or S2) to the amplitude of the P50 response to the conditioning click (C or S1; e.g., Freedman et al., 1987). In healthy individuals, the S2 amplitude is usually diminished by over 60% of the S1 amplitude (Moxon, Gerhardt, Gulinello, & Adler, 2003). In schizophrenia patients, however, the amount or percent of the S2 amplitude decrement over the S1 amplitude has not been clearly documented.

Despite the publication of three meta-analyses supporting the presence of P50 sensory gating deficit in schizophrenia patients (Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004; de Wilde, Bour, Dingemans, Koelman, & Linszen, 2007a; Patterson et al., 2008), there are methodological and conceptual concerns regarding the use of the T/C or S2/S1 ratio. These concerns include the low noise to signal ratio (SNR), the low test–retest reliability in healthy controls (Fuerst, Gallinat, & Boutros, 2007; Rentzsch, Jockers-Scherübl, Boutros, & Gallinat, 2008; Smith, Boutros, & Schwarzkopf, 1994), and the lack of blinding during data collection in some studies (Boutros, 2008). Other methodological concerns, such as use of antipsychotic medication and illness duration, were not found to be important in the three prior meta-analyses (Bramon et al., 2004; de Wilde et al., 2007a; Patterson et al., 2008). Both de Wilde et al. (2007a) and Patterson et al. (2008) proposed specific recommendations for future sensory gating research to address methodological issues (see de Wilde et al., 2007a; Patterson et al., 2008 for details). However, none of

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these meta-analyses have addressed conceptual issues of sensory gating.

The central conceptual factor is the relative magnitude of both the responses to S1 and S2 stimuli to the noted decreased decrement of the response to S2 stimuli in schizophrenia patients as compared to the decrement of S2 responses recorded from healthy control subjects. This decrement is most commonly assessed by dividing the amplitude of the responses to S2 by the amplitudes of the responses to S1. Although the S2/S1 ratio is most widely used to assess gating, the S1-S2 mathematical difference has also been used (Smith et al., 1994). The more widely employed ratio is taken as an operational measure of the brain's habituation or gating capacity. An elevated ratio is taken to denote decreased brain ability to habituate or suppress irrelevant or redundant incoming sensory input (Freedman et al., 1987). An elevated ratio can result from an abnormally low response to S1 stimuli, or a decreased attenuation of the S2 response. The physiological implications of the two scenarios are different and significantly impact the understanding of the physiological deviations (Boutros et al., 2009). We have previously proposed that two physiological aberrations, abnormally low S1 responses and abnormally decreased ability to suppress S2 responses, are demonstrated in schizophrenia patients and that these two abnormalities may or may not be completely independent (Boutros et al., 2009). We propose that, on a fundamental level, if there is no gating abnormality, the ratio should remain low no matter how small the response to S1 is, unless there is a yet unidentified floor effect. Similarly, if a gating deficit exists, the amplitude decrement from S1 to S2 should remain small no matter how large the response to S1 is.

Stemming from earlier work (Jansen, Hegde, & Boutros, 2004) and more recent work (Turetsky et al., 2009), this issue is critical to the P50 gating literature. For instance, both Blumenfeld and Clementz (2001) and Jansen et al. (2004) asserted that a decreased S1 amplitude in schizophrenia patients is the major determinant of the elevated P50 S2/S1 ratio noted in these individuals. Moreover, Johannesen et al. (2005) noticed an abnormally small S1 response in the presence of a normal S2 response leading to a high P50 S2/S1 ratio among schizophrenia patients, and their findings are further supported by a recent study (i.e., Brenner et al., 2009).

Studies questioning the relative importance of the S1 amplitudes, however, indicate that poor sensory gating, i.e., high P50 S2/S1 ratio, is not associated with the S1 amplitude (Clementz, Geyer, & Braff, 1997; Jin et al., 1997). Also, Freedman et al. (1987) indicated that poor sensory gating is a result of a lack of gating out the redundant S2 stimuli. Thus, a significant disagreement exists regarding whether the P50 S2/S1 ratio is the result of a defective response to S1 stimuli or a hitherto unidentified interaction between the S1 and S2 responses in both schizophrenia patients and healthy subjects (e.g., Blumenfeld & Clementz, 2001; Boutros & Belger, 1999; Clementz et al., 1997; Jin et al., 1997; Johannesen et al., 2005).

It is thus fundamental for future sensory gating research utilizing the PSP to establish whether the paradigm examines the habituation process (i.e., the degree of decrement from S1 to S2) or that the decrement noted is simply a reflection of the abnormal response to S1 stimuli. A consistently stronger association of S1 values compared to that of S2 and the S2/S1 ratios would support the latter possibility and throw serious doubt regarding the implications of the PSP abnormalities reported in association with schizophrenia. Therefore, the purpose of this meta-analysis is to ascertain the relative magnitude of the S1, S2, and S2/S1 effect sizes.

Method

Literature Search

The literature search began with three published meta-analyses of sensory gating in schizophrenia patients and healthy controls (i.e., Bramon et al., 2004; de Wilde et al., 2007a; Patterson et al., 2008). The Bramon et al. (2004) study searched sensory gating papers published between January 1994 and August 2003 in the databases MEDLINE and SCIENCE CITATION INDEX using the keywords: P50 AND [Psychosis OR Schizophrenia]. They also carried out a search for papers published between January and August 2003 in several journals and included 20 studies in their analysis. The de Wilde et al. (2007a) study used the keywords P50 and schizophrenia to conduct a search for papers published between 1982 and October 2006 in the databases MEDLINE, PUBMED, and Science Direct, and crossed-referenced citations. They included 34 studies in their analysis. The Patterson et al. (2008) study reviewed studies published between 1982 and 2006 as found in PUBMED. They included 39 studies in their analyses. Across these three meta-analyses, 52 studies were included.

For our meta-analysis, we started with these 52 studies and added 18 studies published between January 2007 and December 2009 found in the databases MEDLINE, PUBMED, and Science Direct using the keywords P50 sensory gating and schizophrenia. Thus, there was the potential for 70 studies to be analyzed before subsequent review for inclusion.

Inclusion Criteria

As some studies did not include sufficient information for analysis, we established *a priori* the following inclusion criteria: (1) report separately the number of participants in each of the schizophrenia and healthy control groups, (2) report separately the mean and standard deviation (*SD*) of the S1 and S2 P50 amplitudes in each of the schizophrenia and healthy control groups, and (3) report separately the mean and *SD* of P50 S2/S1 ratio in each of the schizophrenia and healthy control groups. If studies reported P50 amplitudes and ratios in plots or graphed the findings only, they were not included in the analysis.

After carefully reviewing the articles based on these inclusion criteria, 35 articles (publications) were included in this meta-analysis with a total number of 58 different comparisons between schizophrenia patients and healthy controls. The 58 different comparisons were obtained as some of the articles included more than one schizophrenia patient group. Among these 35 articles, four had been included in all three previously published meta-analyses, nine were included in at least two meta-analyses, and four were in only one previously published meta-analysis. Thus, 18 out of the 35 included articles were not included in any of the three previous meta-analyses.

Data Collected

Prior to analysis, reported standard errors of mean were converted to standard deviations. Reported P50 suppression rates were converted to the S2/S1 ratio by subtracting the S2 percent reduction from 100% and dividing by 100. Thus, a 35% reduction in S2 would convert to a 0.65 ratio.

Meta-Analysis Procedure and Data Analysis

Consistent with the three meta-analysis studies of P50 sensory gating in schizophrenia patients (i.e., Bramon et al., 2004; de Wilde et al., 2007a; Patterson et al., 2008), the effect sizes for the means of the S1 amplitude, S2 amplitude, and S2/S1 ratio were calculated using Cohen's *d*, or the difference between the mean of control group and the mean of schizophrenia group divided by the pooled standard deviation. In addition, random effects meta-analysis was used, consistent with two of the previous studies (Bramon et al., 2004; Patterson et al., 2008). The random effects meta-analysis assumes that true effect size has normal distribution from a population of studies investigated and provides an overall mean estimation of effect size and its confidence interval. Although the fixed effect analysis was conducted and used the inverse variance method of weighting, only the results of the random effects models are present. The models were weighted using the DerSimonian-Laird method (DerSimonian & Laird, 1986).

As suggested by de Wilde et al. (2007a), we calculated the overlap statistic (OL%) to examine the overlap in the P50 measure distribution between schizophrenia patients and healthy controls. When *d* is zero, there is 100% overlap between the two groups. If *d* is one, it equates to 44.6% overlap (Zakzanis, 2001). Publication bias was examined by calculating the number of unpublished studies, or Nfs (Orwin, 1983), needed to obtain a small effect size (Cohen, 1988), and by examining funnel plots. Homogeneity was tested using the Q statistic, with the magnitude of homogeneity quantified with I^2. Effect size calculations were conducted using MIX Pro 2.0 software (BiostatXL.com) and the OL% was calculated using Excel software (Microsoft), a spreadsheet designed by DeCoster and Iselin (Stat-Help.com).

Results

Table 1 presents the means of the reported P50 S2/S1 ratios and amplitudes for both schizophrenia patients and healthy controls from the 35 articles (58 comparisons). For healthy controls, the mean S1 amplitude ranged from 0.79 μV to 5.93 μV, the mean S2 amplitude ranged from 0.18 μV to 2.89 μV, and the mean P50 S2/S1 ratio ranged from 0.16 to 0.94. Among the schizophrenia patients, the mean S1 amplitude ranged from 1.40 μV to 6.39 μV, the mean S2 amplitude ranged from 0.80 μV to 3.73 μV, and the mean P50 S2/S1 ratio ranged from 0.32 to 1.42. Among the 58 comparisons, schizophrenia patients had a smaller mean S1 amplitude than controls in 38 comparisons (65.52%). For the S2, schizophrenia patients had a larger mean S2 amplitude than controls in 52 out of 58 comparisons (89.66%). For the S2/S1 ratio, schizophrenia patients had a larger mean ratio than healthy controls in 56 comparisons (96.55%).

Figure 1a, 1b, and 1c present the forest plots of the effect size for the S1 amplitude, S2 amplitudes, and S2/S1 ratio, respectively. Each square is located at the estimate of the effect size with the size of the square proportional to the sample size. The blue horizontal lines indicate the 95% confidence interval of the effect size for each comparison. The red line indicates the estimated effect size with its corresponding prediction interval. Table 2 presents the effect sizes of the S1 amplitude, S2 amplitude, and P50 S2/S1 ratio for 58 comparisons between schizophrenia patients and healthy controls. The effect size for the S1 amplitude from the random effects model was -0.19 with the standard error of 0.049 and the 95% confidence interval of -0.29 to -0.10. The OL statistic ranged from 38.78% to 100% (mean = 76.83% ± 15.72%). For the combined effect size, the OL statistic showed that there was 85.74% overlap in the mean S1 amplitude between schizophrenia patients and healthy controls. There was an indication of heterogeneity in the S1 amplitude across the studies, Cochrane $Q = 116.69$, $p < .0005$, $I^2 = 51.15\%$. The Orwin's Nfs for publication bias showed that there were no additional studies needed to support the null hypothesis of at least a small effect size ($d = 0.2$) as the combined effect size was small; the funnel plot of the S1 amplitude (see Figure 2) supported the lack of publication bias due to a symmetrical distribution.

For the S2 amplitude, the effect size in each comparison ranged from -0.42 to 4.53. The effect size for the S2 amplitude from the random effects model was 0.65 with the standard error of 0.084 and the 95% confidence interval of 0.48 to 0.81. The OL statistic ranged from 1.18% to 100% (mean = 63.59% ± 24.30%). For the combined effect size, the OL statistics showed that there was 59.62% overlap in the mean S2 amplitude between schizophrenia patients and healthy controls. There was also an indication of heterogeneity, Cochrane $Q = 344.61$ $p < .0005$, $I^2 = 83.46\%$. The Orwin's Nfs indicated that 131 studies were necessary to reduce the combined effect size of the S2 amplitude to a small effect size. The funnel plot of the S2 amplitude (see Figure 3) did not suggest a publication bias.

For the P50 S2/S1 ratio, the effect size in each comparison ranged from -0.29 to 3.97. The effect size from the random effects model was 0.93 with the standard error of 0.088 and a 95% confidence interval of 0.75 to 1.10. The OL statistics showed an overlap of 2.42% to 98.28% with the mean of 51.44% ± 23.63%, indicating a 47.37% overlap in the P50 S2/S1 ratio between schizophrenia patients and healthy controls. There was also a lack of homogeneity across the 58 comparisons among the 35 articles, Cochrane $Q = 368.74$, $p < .0005$, $I^2 = 84.54\%$. The funnel plot of the S2/S1 ratio (see Figure 4) displayed a clear asymmetric pattern, suggesting a publication bias against findings of small or absent effects.

Examination of Heterogeneity in S1 Amplitude, S2 Amplitude, and P50 S2/S1 Ratio

To investigate possible sources for the heterogeneity of the S1 amplitude, S2 amplitude, and P50 S2/S1 ratio between schizophrenia patients and healthy controls, we stratified the comparison by research groups (assessing the impact of different protocols, such as Colorado group, as was done in two of the three prior meta-analyses: de Wilde et al., 2007a; Patterson et al., 2008) and limited the analysis to one comparison from each publication. In addition, we investigated whether use of blinding to diagnostic group when measuring P50 amplitude or type of medication for the patients with schizophrenia were potential sources for the heterogeneity. As the research group and blinding were the only moderators to have a more than 10% effect on the effect sizes, Table 3 presents the results of the effect sizes (the same random effects weighted procedure), Cochrane Q, and I^2 for the S2/S1 ratio and the S1 and S2 amplitudes for these moderators. The results showed that larger values of the effect sizes were obtained from the Colorado group than those from other research groups. However, regardless of the research group, the effect size for S1 amplitude was smaller than that for S2 amplitude or for the P50 S2/S1 ratio.

Table 1. *Means (Standard Deviations) of Both S1 and S2 Amplitudes (in μV) and P50 S2/S1 Ratios for Both Schizophrenia Patients and Healthy Controls in Each Study*

Study	Number of subjects in data analysis	S1 amplitude	S2 amplitude	S2/S1 ratio
Adler et al. (2004)	177 healthy controls	3.00 ± 1.50	0.60 ± 0.07	0.198 ± 0.210
	132 schizophrenia patients (all)	2.40 ± 1.80	1.70 ± 1.70	0.789 ± 0.646
	88 schizophrenia patients (atypical antipsychotic)	2.20 ± 1.40	1.40 ± 1.20	0.704 ± 0.537
	34 schizophrenia patients (typical antipsychotic)	2.70 ± 2.60	2.30 ± 2.70	1.1101 ± 0.879
	10 schizophrenia patients (no medication)	3.10 ± 1.70	2.10 ± 1.40	0.741 ± 0.278
Arnfred et al. (2003)	22 healthy controls	2.52 ± 1.39	1.01 ± 0.84	0.40 ± 0.30
	12 schizophrenia patients	2.56 ± 1.63	0.89 ± 0.71	0.32 ± 0.24
Becker et al. (2004)	25 healthy controls	5.44 ± 2.72	2.23 ± 1.78	0.44 ± 0.27
	25 schizophrenia patients (atypical antipsychotic)	6.39 ± 3.96	3.73 ± 4.18	0.57 ± 0.41
	25 schizophrenia patients (typical antipsychotic)	4.34 ± 2.70	2.94 ± 1.41	0.82 ± 0.45
Boutros et al. (1991)	13 healthy controls	5.93 ± 3.08	2.89 ± 1.39	0.52 ± 0.15
	13 paranoid schizophrenia patients (typical antipsychotic)	4.05 ± 2.30	2.37 ± 1.60	0.59 ± 0.22
	13 undifferentiated schizophrenia patients (typical antipsychotic)	2.93 ± 1.92	2.91 ± 1.09	1.26 ± 0.71
Boutros and Belger (1999)	12 healthy controls	3.30 ± 2.10	1.00 ± 0.08	0.51 ± 0.44
	12 schizophrenia patients (typical antipsychotic)	2.50 ± 1.80	3.30 ± 1.90	1.42 ± 0.58
Boutros et al. (2004)	23 healthy controls	2.60 ± 2.30	1.30 ± 1.40	0.54 ± 0.38
	23 schizophrenia patients (atypical antipsychotic)	2.60 ± 1.60	2.00 ± 1.90	0.80 ± 0.69
Boutros et al. (2009)	31 healthy controls—Mean of all days base-to-peak measure	3.10 ± 2.20	1.20 ± 1.20	0.41 ± 0.33
	35 schizophrenia patients (atypical antipsychotic)—Mean of all days base-to-peak measure	2.30 ± 2.40	1.80 ± 2.60	0.79 ± 0.53
	36 healthy controls—Mean of all days peak-to-peak measure (for T/C ratio: 35 healthy controls)	2.80 ± 2.50	1.40 ± 1.50	0.67 ± 0.60
	35 schizophrenia patients (atypical antipsychotic)—Mean of all days peak-to-peak measure	2.90 ± 2.70	2.00 ± 2.00	0.79 ± 0.65
Brenner et al. (2009)	19 healthy controls	4.62 ± 2.58	0.94 ± 0.89	0.94 ± 2.54
	18 schizophrenia patients (medicated)	4.28 ± 2.46	2.35 ± 2.11	0.73 ± 0.71
Brockhaus-Dumke, Mueller et al. (2008a)	32 healthy controls	3.90 ± 2.25	1.83 ± 1.44	0.4019 ± 0.3862
	32 schizophrenia patients	3.46 ± 2.63	1.75 ± 1.41	0.6877 ± 0.5613
Brockhaus-Dumke, Schultz-Lutter et al. (2008b)	41 healthy controls (for S2 amplitude and T/C ratio: 35 healthy controls)	3.12 ± 1.50	1.44 ± 1.06	0.43 ± 0.28
	14 chronic schizophrenia patients (for S2 amplitude: 13 chronic schizophrenia patients; for T/C ratio: 12 chronic schizophrenia patients)	2.00 ± 0.84	1.89 ± 1.39	0.85 ± 0.42
	29 schizophrenia patients (antipsychotic-naive) (for S2 amplitude and T/C ratio: 21 schizophrenia patients)	3.14 ± 1.75	1.96 ± 1.32	0.65 ± 0.38
Clementz et al. (1998a)	36 healthy controls	4.23 ± 1.33	0.95 ± 1.01	0.231 ± 0.222
	36 schizophrenia patients (28 medicated; 8 unmedicated)	3.50 ± 1.26	1.99 ± 1.23	0.612 ± 0.465
Clementz et al. (1998b)	45 healthy controls	4.16 ± 1.20	1.21 ± 0.97	0.299 ± 0.228
	44 schizophrenia patients (medicated)	3.35 ± 1.14	1.88 ± 0.92	0.594 ± 0.316
Clementz and Blumenfeld (2001)	20 healthy controls	2.30 ± 0.80	0.80 ± 0.50	0.38 ± 0.24
	20 schizophrenia patients (14 atypical, 6 typical antipsychotic)	1.80 ± 0.80	0.80 ± 0.50	0.48 ± 0.27
Devrim-Üçok et al. (2008)	24 healthy controls	3.89 ± 2.00	1.97 ± 1.34	0.59 ± 0.44
	16 acute schizophrenia patients (medicated)	2.91 ± 2.37	2.33 ± 1.24	0.96 ± 0.58
	16 post-acute schizophrenia patients (medicated)	3.08 ± 1.52	1.47 ± 0.96	0.60 ± 0.49
de Wilde et al. (2007b)	28 healthy controls	2.02 ± 1.20	0.93 ± 1.01	0.4313 ± 0.3822
	27 healthy siblings of schizophrenia patients	2.18 ± 1.44	0.82 ± 0.77	0.4164 ± 0.4215
	53 inpatient schizophrenia patients (medicated)	2.05 ± 1.41	1.11 ± 1.05	0.6502 ± 0.5582
Fresán et al. (2007)	17 healthy controls	3.00 ± 2.00	1.00 ± 0.90	0.30 ± 0.10
	14 violent schizophrenia patients (unmedicated)	3.80 ± 2.00	2.90 ± 1.70	1.00 ± 0.80
	18 nonviolent schizophrenia patients (unmedicated)	2.70 ± 2.00	1.70 ± 1.20	1.00 ± 1.30
Ghisolfi et al. (2004)	24 healthy controls	5.40 ± 2.94	2.00 ± 0.98	0.444 ± 0.235
	12 schizophrenia patients	4.10 ± 1.73	3.20 ± 1.04	0.883 ± 0.436
Ghisolfi et al. (2006)	28 healthy controls	5.60 ± 2.90	2.10 ± 1.10	0.454 ± 0.209
	28 schizophrenia patients (medicated)	5.20 ± 3.10	3.30 ± 1.80	0.792 ± 0.373
Guterman and Josiassen (1994)	10 healthy controls	5.51 ± 3.18	1.75 ± 1.28	0.37 ± 0.28
	10 schizophrenia patients	4.93 ± 4.02	2.81 ± 2.05	1.25 ± 2.26
Hong et al. (2004)	16 healthy controls	3.00 ± 1.60	1.10 ± 0.90	0.39 ± 0.34
	23 schizophrenia patients (medicated)	3.30 ± 2.20	1.80 ± 1.10	0.65 ± 0.39
Hong et al. (2008)	70 healthy controls	4.04 ± 3.10	2.01 ± 1.67	0.56 ± 0.33
	74 healthy relatives of schizophrenia patients	3.31 ± 2.75	2.01 ± 2.41	0.60 ± 0.34
	102 schizophrenia patients (medicated)	3.91 ± 3.53	2.32 ± 2.83	0.62 ± 0.30
Hong et al. (2009)	62 healthy controls	2.50 ± 1.47	1.45 ± 1.18	0.4122 ± 0.3382
	65 schizophrenia patients (baseline)	2.27 ± 1.34	1.95 ± 1.12	0.9419 ± 0.6131
	65 schizophrenia patients (atypical antipsychotic after baseline)	2.04 ± 1.13	1.64 ± 1.07	0.8481 ± 0.5538
Jin et al. (1997)	10 healthy controls	5.60 ± 2.97	2.19 ± 1.80	0.37 ± 0.20
	10 schizophrenia patients (medication-free for 5 days)	3.34 ± 1.74	2.34 ± 1.74	0.73 ± 0.35
Johannesen et al. (2005)	38 healthy controls	2.14 ± 0.64	1.19 ± 0.65	0.5757 ± 0.3314
	37 schizophrenia patients (all; medicated)	1.87 ± 0.54	1.25 ± 0.56	0.6899 ± 0.3081
	11 nonparanoid schizophrenia patients (medicated)	1.99 ± 0.44	1.36 ± 0.42	0.6873 ± 0.1868
	26 paranoid schizophrenia patients (medicated)	1.83 ± 0.57	1.20 ± 0.61	0.6910 ± 0.3503
Kathmann and Engel (1990)	22 healthy controls	3.00 ± 1.41	2.10 ± 0.94	0.73 ± 0.39
	18 schizophrenia patients (medicated)	2.60 ± 0.85	2.10 ± 1.70	0.947 ± 0.82
Kisley et al. (2003)	10 healthy controls, non-REM	1.51 ± 0.62	0.67 ± 0.81	0.39 ± 0.35
	10 healthy controls, REM	0.79 ± 0.29	0.18 ± 0.18	0.20 ± 0.22

Table 1. (Contd.)

Study	Number of subjects in data analysis	S1 amplitude	S2 amplitude	S2/S1 ratio
	10 schizophrenia patients (medicated), non-REM	1.63 ± 1.27	1.85 ± 2.58	0.93 ± 0.66
	10 schizophrenia patients (medicated), REM	1.40 ± 1.02	1.31 ± 1.36	0.93 ± 0.73
Louchart-de la Chapelle et al. (2005)	88 healthy controls	3.12 ± 2.50	1.17 ± 0.05	0.36 ± 0.20
	26 negative symptom schizophrenia patients (atypical antipsychotic)	3.31 ± 2.70	2.48 ± 1.50	0.97 ± 0.60
	55 no negative symptom schizophrenia patients (atypical antipsychotic)	3.60 ± 2.60	2.78 ± 2.20	0.80 ± 0.40
Martin et al. (2007)	108 healthy controls (common gene)	3.10 ± 1.70	0.60 ± 0.70	0.17 ± 0.15
	41 healthy controls (variant gene)	2.80 ± 1.30	0.80 ± 0.70	0.34 ± 0.39
	26 schizophrenia patients (common gene)	2.10 ± 0.90	1.80 ± 0.90	1.01 ± 0.63
	11 schizophrenia patients (variant gene)	2.20 ± 1.50	2.10 ± 1.50	1.11 ± 0.72
Myles-Worsley (2002)	29 healthy controls	2.96 ± 1.59	0.88 ± 0.74	0.307 ± 0.227
	29 schizophrenia patients (unmedicated)	1.75 ± 1.40	0.98 ± 0.97	0.716 ± 0.598
	56 schizophrenia patients (medicated)	2.04 ± 1.14	1.42 ± 1.14	0.745 ± 0.477
Olincy et al. (2000)	16 healthy controls	2.61 ± 1.57	0.50 ± 0.65	0.1622 ± 0.1210
	16 schizophrenia patients	2.53 ± 1.58	1.53 ± 0.85	0.6701 ± 0.1346
Patterson et al. (2000)	10 healthy controls	4.14 ± 2.69	1.71 ± 1.93	0.36 ± 0.25
	10 schizophrenia patients	2.57 ± 1.80	2.03 ± 1.64	1.18 ± 1.49
Rentzsch et al. (2007)	18 healthy controls	2.80 ± 1.50	1.10 ± 0.80	0.374 ± 0.179
	12 schizophrenia patients without cannabis abuse	3.90 ± 3.10	1.40 ± 0.90	0.366 ± 0.177
	15 schizophrenia patients with cannabis abuse	2.80 ± 1.40	1.30 ± 0.70	0.477 ± 0.194
Sánchez-Morla et al. (2008)	63 healthy controls	3.90 ± 2.10	1.70 ± 1.30	0.41 ± 0.23
	90 schizophrenia patients	4.40 ± 2.80	2.70 ± 1.90	0.67 ± 0.33
Sánchez-Morla et al. (2009)	64 healthy controls	3.91 ± 2.14	1.68 ± 1.26	0.428 ± 0.255
	42 schizophrenia patients (medicated: CLZ)	4.90 ± 2.94	2.75 ± 1.71	0.600 ± 0.258
	47 schizophrenia patients (medicated: FGAs)	4.76 ± 2.48	3.07 ± 1.70	0.700 ± 0.332
	65 schizophrenia patients (medicated: SGAs)	4.18 ± 2.33	2.59 ± 1.78	0.681 ± 0.375
Yee et al. (1998)	11 healthy controls	3.44 ± 2.38	1.36 ± 0.99	0.38 ± 0.18
	22 recent-onset schizophrenia patients (medicated)	3.18 ± 2.26	1.81 ± 1.63	0.59 ± 0.33

Discussion

This meta-analysis specifically addresses the relative importance of measuring S2 amplitude and the ratio measure of sensory gating compared to only measuring S1 amplitude in people with schizophrenia. This meta-analysis builds upon previously published meta-analyses by investigating the differences in the P50 amplitudes and gating ratios between schizophrenia patients and healthy controls by including studies published since the publication of the last meta-analysis (Patterson et al., 2008). The number of new studies was 18 in just 2 years, underscoring the significant interest of investigators in the gating function. The findings clearly show increasing effect size corresponding to additional information. The effect size was small for the S1 amplitude difference, increased to a medium to large effect size of the S2 amplitude difference, and finally a large effect size of the S2/S1 ratio between schizophrenia patients and healthy controls.

Together, these findings suggest that sensory gating deficit of the P50 (S2/S1 ratio) in schizophrenia patients as compared to healthy controls may be more pertinent to the degree of change in brain response from S1 to S2 stimuli between healthy controls and schizophrenia than just measuring the S1 stimuli. However, although the S2/S1 gating ratio is a dominant measure in the literature, it may not be the best approach to summarizing sensory gating deficit in schizophrenia, and exploration of different approaches, such as the S1-S2 amplitude difference, may be worthwhile.

Our estimates of the effect sizes for S1 amplitude and S2/S1 ratio are remarkably similar to previous meta-analyses (Patterson et al., 2008), indicating that, although the number of studies has increased dramatically and the subtypes of patients have narrowed, the finding of a larger effect size for S2 amplitude than that of S1 amplitude appears valid. There is heterogeneity in the effect size, which is partially related to research groups as previously shown (Patterson et al., 2008). Unfortunately for S2/S1 ratio, there appears to be a publication bias with large negative studies not being submitted or accepted for publication.

Difference in the S1 Amplitude

The mean S1 amplitudes of schizophrenia patients and healthy controls exhibited a wide range of values and a high percentage of overlapping, yielding a small combined effect size. In 65.52% of the comparisons, the schizophrenia group had a lower mean S1 amplitude than the control group. These findings were similar to the previous meta-analysis (Patterson et al., 2008) in which they rejected zero difference in the S1 amplitude between schizophrenia patients and normal controls, but 25 of the 37 studies overlapped the zero difference. We thus can conclude that the noted deficit in habituation or gating of the responses to S2 stimuli across studies and comparisons is not predicated on a failure to register the S1 stimuli in schizophrenia patients as the effect size of S2 amplitude and S2/S1 ratio are much larger. However, this conclusion is not in line with Jansen et al. (2004) and Brenner et al. (2009), which proposed that sensory gating deficit in schizophrenia patients is due to the problem in evaluating stimulus in the sensory encoding and, consequently, a failure in responding to and detecting the salient information of the S1.

These summary findings across published articles corroborate the finding at the individual participant level (e.g., Fuerst et al., 2007). Fuerst et al. (2007) demonstrated that the S1 amplitude does not correlate with the gating ratio nor significantly predict the gating ratio in a sample of healthy controls. In addition, data from schizophrenia patients were in fundamental agreement with healthy control data (Boutros et al., 2009). Furthermore, this S1 amplitude finding is in line with the results from Jin et al. (1997) and Clementz et al. (1997). However, whether the P50 S1 amplitude is a candidate for a schizophrenia endophenotype

remains an open question (Patterson et al., 2008). More research, thus, is still needed in order to better elucidate the exact contribution of the S1 in the P50 gating process in schizophrenia.

Difference in the S2 Amplitude—"Gating Out"

The present study was the first to systematically investigate the S2 difference between schizophrenia patients and healthy controls, which the previous meta-analyses did not address. In the current meta-analysis, the medium effect size indicates that the ability to suppress redundant stimuli is deficient consistently in schizophrenia patients as compared to healthy controls and would require fewer patients to detect such a deficiency than using only S1.

When examining the effect sizes of the S2 amplitude and the P50 S2/S1 ratio, we speculate that, across studies, the difference in sensory gating ability between healthy controls and schizophrenia patients may possibly be associated with the difference in brain response to the S2 stimulus, as the effect size of the S2 amplitude was medium to large and the S2/S1 ratio was large. Based on these effect size results, we further conjecture that, at the group level, sensory gating deficit in schizophrenia patients may result from the inability to suppress the S1 response with

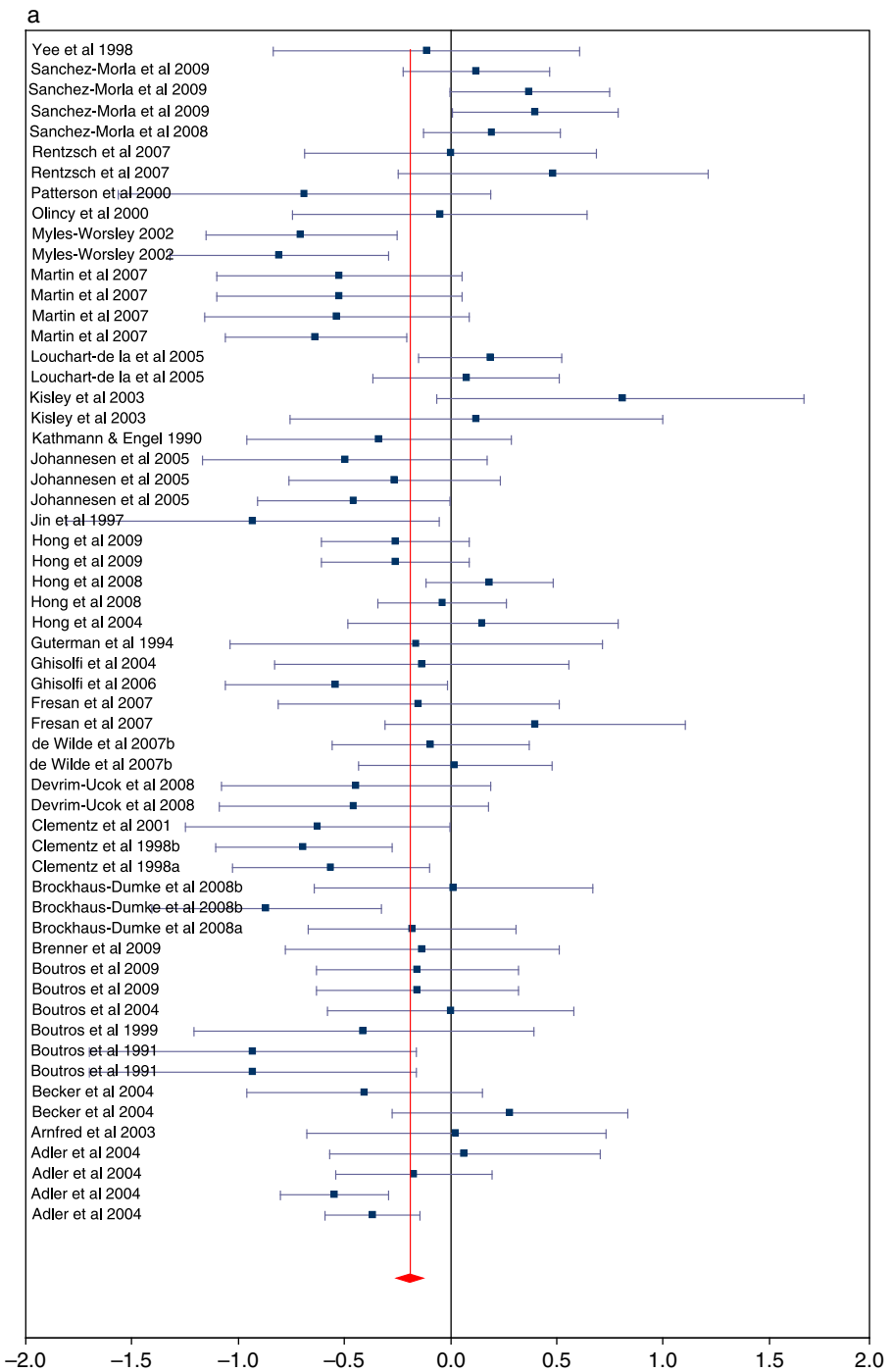

Figure 1a, 1b, and 1c. Forest plots of effect sizes of the S1 amplitude, S2 amplitude, and S2/S1 ratio from weighted random effects model.

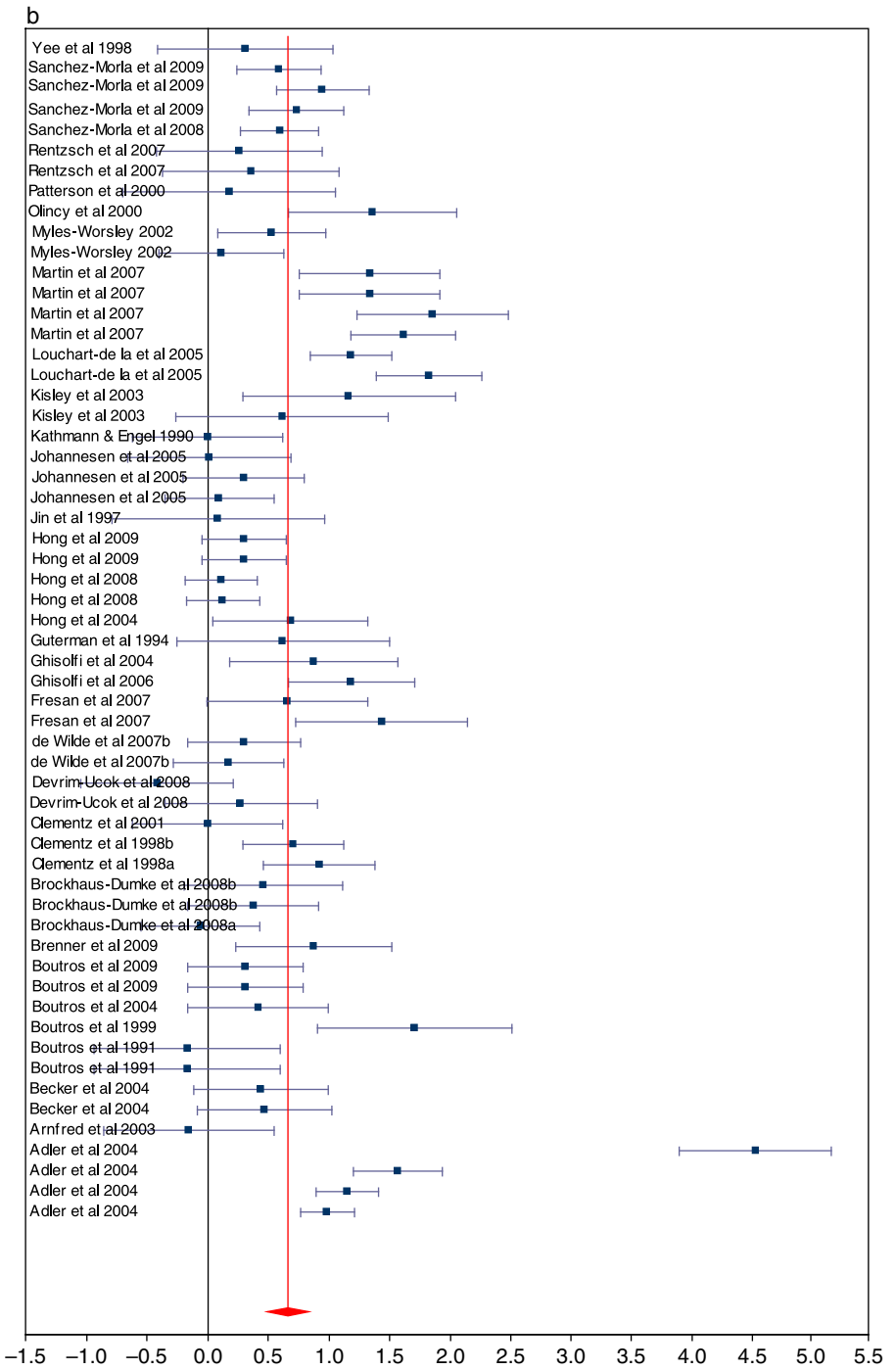

Figure 1. Continued.

repetition as assessed by measuring the S2 response. However, this inference needs further investigation with large individual patient data.

Investigators disagree on the mechanism of the deficient sensory gating. It has been argued that it is due to a neural malfunction of inhibitory mechanism responsible for "gating out" discarded information (Clementz et al., 1997; Freedman et al., 1987). It has also been argued that it is a failure of neural mechanism responsible for registering salient information (Jansen et al., 2004). Finally, it has been argued that it is due to an unusually small S1 response accompanied with an otherwise typical S2 response (Blumenfeld & Clementz, 2001; Johannesen et al., 2005). The findings of the current meta-analysis provide support for the argument that poor sensory gating in schizophrenia patients is a large effect in the published studies and thus "gating out" redundant and irrelevant sensory information.

Difference in the P50 S2/S1 Ratio

The results showed that schizophrenia patients exhibited a larger S2/S1 ratio than healthy controls and the effect size for the S2/S1 ratio was large, which was consistent with the findings from previous three meta-analyses (Bramon et al., 2004; de Wilde et al.,

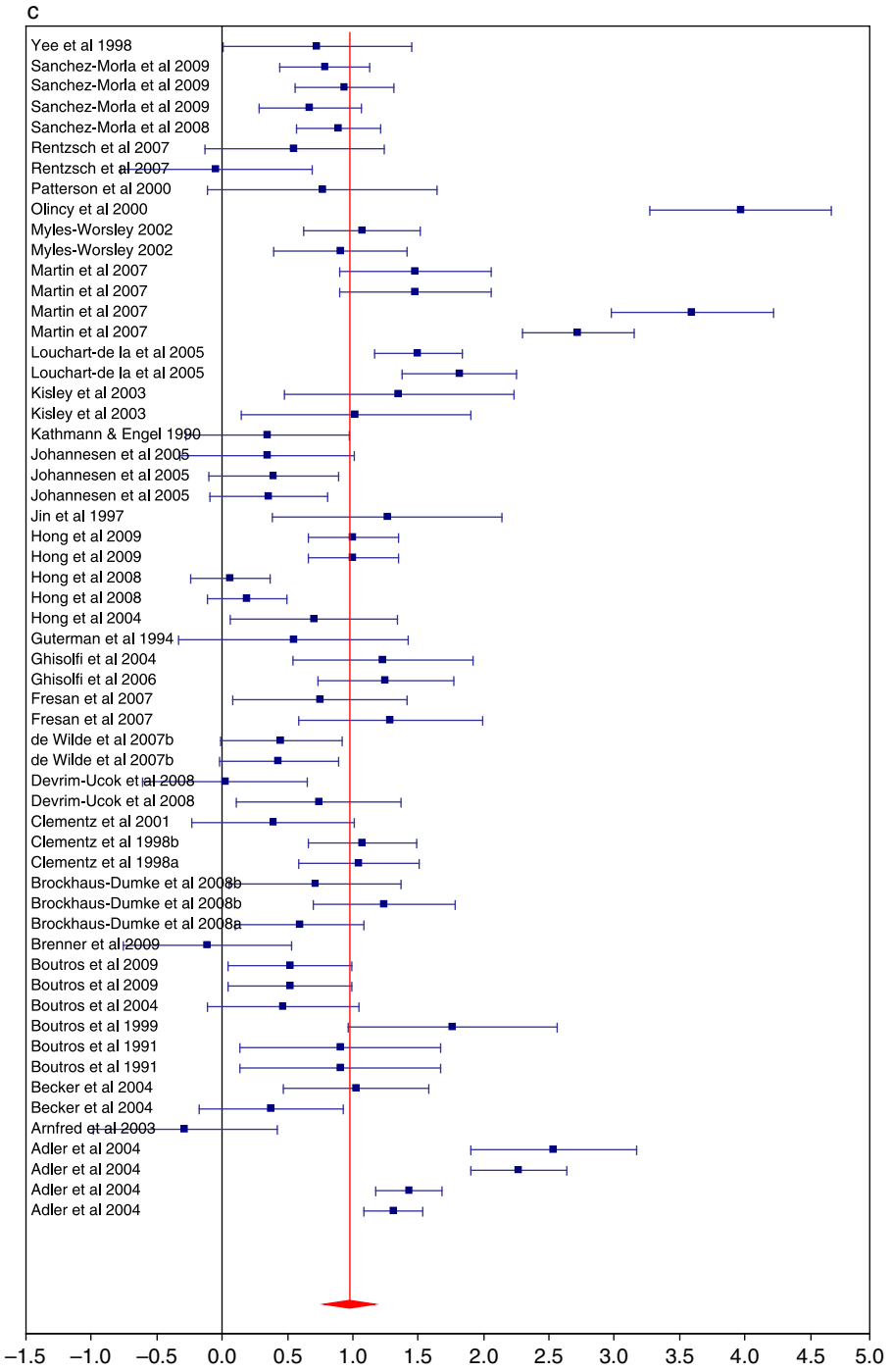

Figure 1. Continued.

2007a; Patterson et al., 2008). In addition, there was an overlap in the P50 S2/S1 ratio between healthy controls and schizophrenia patients, similar to Patterson et al. (2008), and the range of the effect size was similar to the previous three meta-analyses.

To investigate the heterogeneity in the P50 S2/S1 ratio, different moderators have been addressed in the previous meta-analyses (Bramon et al., 2004; de Wilde et al., 2007a; Patterson et al., 2008). For example, Bramon et al. (2004) found that age, gender, and filter setting could not explain the observed variability of the effect size in the P50 ratio and suggested that these parameters contribute similar effects to healthy controls. When other sources of heterogeneity were examined, studies from one research group (i.e., Colorado) displayed a larger effect size than those from other research groups. It is reassuring that the inclusion of 18 more recent studies did not alter this finding, which remains consistent with that of de Wilde et al. (2007a).

Patterson et al. (2008) suggested that methodological issues, such as filter settings, click intensity, and blinding the P50 measurement, need to be considered when analyzing P50 S2/S1 ratio data. When we examined the blinding issue in the S2/S1 ratio, studies using the blinding procedure revealed a medium to large effect size, whereas studies with no blinding procedure showed a

Table 2. *Effect Side (Cohen's d) of S1 Amplitude, S2 Amplitude and P50 S2/S1 Ratio for Each Comparison Among 35 Publications*

Study	Comparison	S1 amplitude (95% Interval)	S2 amplitude (95% Interval)	S2/S1 ratio (95% Interval)
Adler et al. (2004)	132 schizophrenia patients (all) vs. 177 healthy controls	− 0.37 (− 0.60– − 0.14)	0.99 (0.75–1.23)	1.31 (1.07–1.56)
	88 schizophrenia patients (atypical antipsychotic) vs. 177 healthy controls	− 0.55 (− 0.81– − 0.29)	1.16 (0.89–1.43)	1.44 (1.15–1.72)
	34 schizophrenia patients (typical antipsychotic) vs. 177 healthy controls	− 0.18 (− 0.54–0.19)	1.59 (1.19–1.99)	2.30 (1.87–3.24)
	10 schizophrenia patients (no medication) vs. 177 healthy controls	0.07 (− 0.57–0.70)	4.53 (3.89–5.17)	2.55 (2.37–2.58)
Arnfred et al. (2003)	12 schizophrenia patients vs. 22 healthy controls	0.03 (− 0.68–0.73)	− 0.16 (− 0.86–0.55)	− 0.29 (− 1.00–0.41)
Becker et al. (2004)	25 schizophrenia patients (atypical antipsychotic) vs. 25 healthy controls	0.29 (− 0.27–0.84)	0.48 (− 0.09–1.04)	0.38 (− 0.18–0.94)
	25 schizophrenia patients (typical antipsychotic) vs. 25 healthy controls	− 0.41 (− 0.97–0.15)	0.45 (− 0.11–1.01)	1.05 (0.45–1.64)
Boutros et al. (1991)	13 paranoid schizophrenia patients (typical antipsychotic) vs. 13 healthy controls	− 0.69 (− 1.46–0.08)	− 0.35 (− 1.12–0.42)	0.37 (− 0.40–1.14)
	13 undifferentiated schizophrenia patients (typical antipsychotic) vs. 13 healthy controls	− 1.17 (− 1.94–0.40)	0.02 (− 0.75–0.78)	1.44 (0.67–2.21)
Boutros and Belger (1999)	12 schizophrenia patients (typical antipsychotic) vs. 12 healthy controls	− 0.41 (− 1.21–0.39)	1.71 (0.91–2.51)	1.77 (0.97–2.57)
Boutros et al. (2004)	23 schizophrenia patients (atypical antipsychotic) vs. 23 healthy controls	0 (− 0.58–0.58)	0.42 (− 0.16–1.00)	0.47 (− 0.11–1.04)
Boutros et al. (2009)	Mean of all days base-to-peak measure:			
	35 schizophrenia patients (atypical antipsychotic) vs. 31 healthy controls	− 0.35 (− 0.83–0.14)	0.29 (− 0.19–0.77)	0.85 (0.37–1.33)
	Mean of all days peak-to-peak measure:	0.04 (− 0.43–0.50)	0.34 (− 0.13–0.81)	0.19 (− 0.27–0.66)
	35 schizophrenia patients (atypical antipsychotic) vs. 36 healthy controls (for T/C ratio: 35 healthy controls)	− 0.14	0.90	− 0.11
Brenner et al. (2009)	18 schizophrenia patients (medicated) vs. 19 healthy controls	(− 0.78–0.51)	(0.23–1.58)	(− 0.76–0.53)
Brockhaus-Dumke et al. (2008a)	32 schizophrenia patients vs. 32 healthy controls	− 0.18 (− 0.67–0.31)	− 0.06 (− 0.54–0.43)	0.60 (0.10–1.14)
Brockhaus-Dumke et al. (2008b)	14 chronic schizophrenia patients (for S2 amplitude: 13 chronic schizophrenia patients; for T/C ratio: 12 chronic schizophrenia patients) vs. 41 healthy controls (for S2 amplitude and T/C ratio: 35 healthy controls)	− 0.88 (− 1.45– − 0.31)	0.38 (− 0.16–0.93)	1.26 (0.67–1.85)
	29 schizophrenia patients (antipsychotic-naive) (for S2 amplitude and T/C ratio: 21 schizophrenia patients) vs. 41 healthy controls (for S2 amplitude and T/C ratio: 35 healthy controls)	0.01 (− 0.64–0.67)	0.47 (− 0.19–1.13)	0.73 (0.06–1.40)
Clementz et al. (1998a)	36 schizophrenia patients (28 medicated; 8 unmedicated) vs. 36 healthy controls	− 0.70 (− 1.18– − 0.23)	0.92 (0.46–1.39)	1.05 (0.58–1.51)
Clementz et al. (1998b)	44 schizophrenia patients (medicated) vs. 45 healthy controls	− 0.63 (− 1.06– − 0.21)	0.71 (0.29–1.12)	1.07 (0.66–1.49)
Clementz and Blumenfeld (2001)	20 schizophrenia patients (14 atypical, 6 typical antipsychotic) vs. 20 healthy controls	− 0.58 (− 1.21–0.06)	0 (− 0.62–0.62)	0.39 (− 0.23–1.01)
Devrim-Üçok et al. (2008)	16 acute schizophrenia patients (medicated) vs. 24 healthy controls	− 0.47 (− 1.11–0.17)	0.28 (− 0.35–0.92)	0.76 (0.10–1.41)
	16 post-acute schizophrenia patients (medicated) vs. 24 healthy controls	− 0.46 (− 1.10–0.19)	− 0.42 (− 1.07–0.21)	0.02 (− 0.61–0.65)
de Wilde et al. (2007b)	53 inpatient schizophrenia patients (medicated) vs. 28 healthy controls	0.02 (− 0.44–0.48)	0.18 (− 0.28–0.63)	0.44 (− 0.02–0.90)
	53 inpatient schizophrenia patients (medicated) vs. 27 healthy siblings of schizophrenia patients	− 0.09 (− 0.57–0.37)	0.30 (− 0.16–0.77)	0.46 (− 0.01–0.93)
Fresán et al. (2007)	14 violent schizophrenia patients (unmedicated) vs. 17 healthy controls	0.41 (− 0.30–1.13)	1.49 (0.68–2.29)	1.34 (0.55–2.13)
	18 nonviolent schizophrenia patients (unmedicated) vs. 17 healthy controls	− 0.15 (− 0.82–0.51)	0.68 (− 0.01–1.36)	0.77 (0.08–1.46)
Ghisolfi et al. (2004)	12 schizophrenia patients vs. 24 healthy controls	− 0.55 (− 1.08– − 0.01)	0.90 (0.18–1.63)	1.27 (0.52–2.03)
Ghisolfi et al. (2006)	28 schizophrenia patients (medicated) vs. 28 healthy controls	− 0.14 (− 0.83–0.55)	1.21 (0.64–1.78)	1.28 (0.70–1.85)
Guterman and Josiassen (1994)	10 schizophrenia patients vs. 10 healthy controls	− 0.16 (− 1.05–0.71)	0.65 (− 0.25–1.56)	0.58 (− 0.32–1.47)
Hong et al. (2004)	23 schizophrenia patients (medicated) vs. 16 healthy controls	0.19 (− 0.45–0.83)	0.68 (0.05–1.32)	0.70 (0.06–1.34)
Hong et al. (2008)	102 schizophrenia patients (medicated) vs. 70 healthy controls	− 0.04 (− 0.34–0.27)	0.13 (− 0.18–0.43)	0.19 (− 0.11–0.50)
	102 schizophrenia patients (medicated) vs. 74 healthy relatives of schizophrenic patients	0.19 (− 0.11–0.49)	0.12 (− 0.18–0.42)	0.06 (− 0.24–0.36)
Hong et al. (2009)	65 schizophrenia patients (baseline) vs. 62 healthy controls	− 0.16 (− 0.51–0.18)	0.43 (0.09–0.78)	1.06 (0.72–1.41)
	65 schizophrenia patients (atypical antipsychotic after baseline) vs. 62 healthy controls	− 0.35 (− 0.70–0.004)	0.17 (− 0.18–0.52)	0.94 (0.60–1.29)
Jin et al. (1997)	10 schizophrenia patients (medication-free for 5 days) vs. 10 healthy controls	− 0.98 (− 1.91– − 0.05)	0.09 (− 0.79–0.97)	1.33 (0.35–2.31)

Table 2. (Contd.)

Study	Comparison	S1 amplitude (95% Interval)	S2 amplitude (95% Interval)	S2/S1 ratio (95% Interval)
Johannesen et al. (2005)	37 schizophrenia patients (all; medicated) vs. 38 healthy controls	−0.46 (−0.92–−0.002)	0.10 (−0.35–0.55)	0.36 (−0.09–0.82)
	11 nonparanoid schizophrenia patients (medicated) vs. 38 healthy controls	−0.27 (−0.78–0.23)	0.30 (−0.20–0.80)	0.40 (−0.10–0.91)
	26 paranoid schizophrenia patients (medicated) vs. 38 healthy controls	−0.51 (−1.18–0.17)	0.02 (−0.66–0.69	0.35 (−0.32–1.03)
Kathmann and Engel (1990)	18 schizophrenia patients (medicated) vs. 22 healthy controls	−0.34 (−0.97–0.28)	0 (−0.62–0.62)	0.36 (−0.27–0.99)
Kisley et al. (2003)	10 schizophrenia patients (medicated) vs. 10 healthy controls, non-REM	0.13 (−0.75–1.00)	0.65 (−0.25–1.55)	1.08 (0.13–2.02)
	10 schizophrenia patients (medicated) vs. 10 healthy controls, REM	0.86 (−0.06–1.78)	1.23 (0.26–2.19)	1.43 (0.43–2.42)
Louchart-de la Chapelle et al. (2005)	26 negative symptom schizophrenia patients (atypical antipsychotic) vs. 88 healthy controls	0.08 (−0.36–0.51)	1.86 (1.36–2.36)	1.84 (1.34–2.34)
	55 no negative symptom schizophrenia patients (atypical antipsychotic) vs. 88 healthy controls	0.19 (−0.15–0.53)	1.19 (0.83–1.55)	1.51 (1.13–1.89)
Martin et al. (2007)	26 schizophrenia patients (common gene) vs. 108 healthy controls (common gene)	−0.64 (−1.07–−0.20)	1.63 (1.16–2.10)	2.77 (2.23–3.31)
	26 schizophrenia patients (common gene) vs. 41 healthy controls (variant gene)	−0.61 (−1.11–−0.11)	1.30 (0.76–1.84)	1.37 (0.83–1.92)
	11 schizophrenia patients (variant gene) vs. 108 healthy controls (common gene)	−0.54 (−1.16–0.09)	1.89 (1.22–2.56)	3.72 (2.94–4.50)
	11 schizophrenia patients (variant gene) vs. 41 healthy controls (variant gene)	−0.46 (−1.13–0.22)	1.44 (0.72–2.17)	1.65 (0.91–2.39)
Myles-Worsley (2002)	29 schizophrenia patients (unmedicated) vs. 29 healthy controls	−0.82 (−1.36–−0.28)	0.12 (−0.40–0.63)	0.92 (0.38–1.46)
	56 schizophrenia patients (medicated) vs. 29 healthy controls	−0.71 (−1.17–−0.25)	0.53 (0.08–0.99)	1.08 (0.60–1.56)
Olincy et al. (2000)	16 schizophrenia patients vs. 16 healthy controls	−0.05 (−0.75–0.64)	1.41 (0.63–2.18)	3.97 (3.28–4.66)
Patterson et al. (2000)	10 schizophrenia patients vs. 10 healthy controls	−0.72 (−1.63–0.18)	0.19 (−0.69–1.07)	0.81 (−0.11–1.72)
Rentzsch et al. (2007)	12 schizophrenia patients s without cannabis abuse vs. 18 healthy controls	0.50 (−0.24–1.24)	0.37 (−0.37–1.11)	−0.05 (−0.78–0.68)
	15 schizophrenia patients s with cannabis abuse vs. 18 healthy controls	0 (−0.68–0.68)	0.27 (−0.42–0.96)	0.57 (−0.13–1.27)
Sánchez-Morla et al. (2008)	90 schizophrenia patients vs. 63 healthy controls	0.20 (−0.12–0.52)	0.60 (0.27–0.93)	0.89 (0.56–1.23)
Sánchez-Morla et al. (2009)	42 schizophrenia patients (medicated: CLZ) vs. 64 healthy controls	0.40 (0.01–0.80)	.74 (0.35–1.12)	0.68 (0.28–1.08)
	47 schizophrenia patients (medicated: FGAs) vs. 64 healthy controls	0.37 (0.02–0.71)	0.94 (0.57–1.30)	0.93 (0.56–1.29)
	65 schizophrenia patients (medicated: SGAs) vs. 64 healthy controls	0.12 (−0.25–0.50)	0.59 (0.24–0.913	0.79 (0.44–1.13)
Yee et al. (1998)	22 recent-onset schizophrenia patients (medicated) vs. 11 healthy controls	−0.12 (−0.84–1.29)	0.32 (−0.41–1.05)	0.75 (0–1.49)

large effect size. This finding suggests that blinding impacts the P50 measurement. Whether paying specific attention to methodological issues, such as strict blinded evaluation of the P50 component (Boutros, 2008) and increasing the number of averaged trials in order to improve the SNR, will impact the overall effect size of the P50, gating deficit in schizophrenia remains to be seen. Nonetheless, given the large effect size and the results of moderator analysis consistent with the previous studies, the difference in the P50 S2/S1 ratio between schizophrenia patients and healthy controls is plausible, and schizophrenia patients display a problem in sensory gating compared to healthy controls.

In addition to heterogeneity and methodological issues, our results indicated a publication bias in P50 S2/S1 ratio, which was different from both Bramon et al. (2004) and de Wilde et al. (2007a). This inconsistent finding may be due to the addition of recent studies since the publication of those meta-analyses. There may now be a bias to expect significant difference in P50 S2/S1 ratio between schizophrenia and controls. Although this publication bias may be due to our inclusion/exclusion criteria, this is doubtful as it did not impact our estimates for the S1 amplitude.

Implications for Sensory Gating Research in Schizophrenia

The findings of this present meta-analysis have two major implications for sensory gating research in schizophrenia patients. First, this study found a small effect size of the S1 amplitude, a between medium and large effect size of the S2 amplitude, and a large effect size of the P5 S2/S1 ratio. This finding suggests that a large effect size of the P50 S2/S1 ratio and S2 amplitude hold valuable information. In other words, this finding confirms the supposition that, at the group level, when compared to healthy controls sensory gating deficit in schizophrenia patients is potentially caused by an augmentation or a lack of reduction in the S2 response in contrast to healthy controls, suggesting a "gating out" habituation problem. Our findings suggest that the S2 amplitude is necessary to gauge sensory gating when compared to S1 amplitude and that the measurement of S1 amplitude alone is not sufficient to predict or assess the difference in gating function between healthy controls and schizophrenia. Also, the measurement of the S2 amplitude is indispensable to calculate the S1–S2 amplitude difference as another sensory gating index (Smith et al., 1994; de Wilde et al., 2007a).

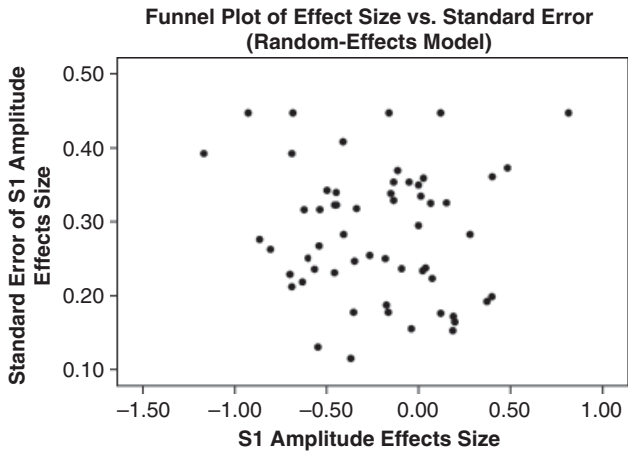

Figure 2. Funnel plot to examine publication bias in the S1 amplitude.

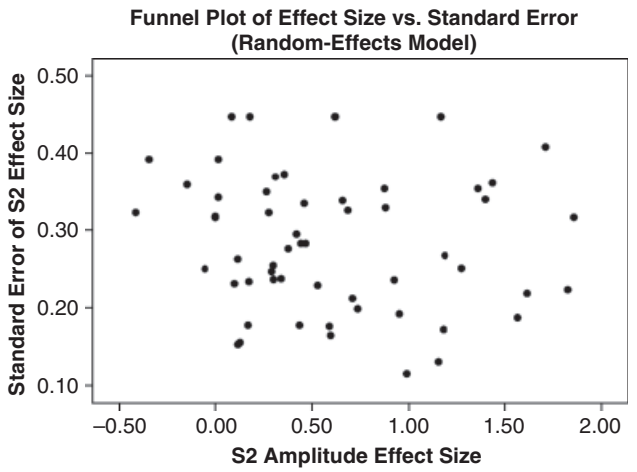

Figure 3. Funnel plot to examine publication bias in the S2 amplitude.

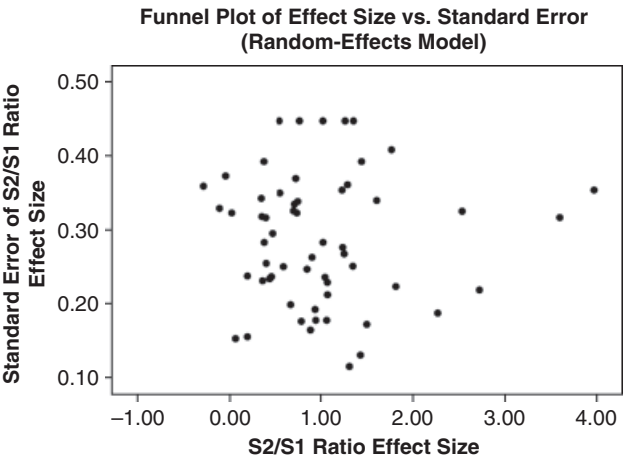

Figure 4. Funnel plot to examine publication bias in the S2/S1 ratio.

The second implication is that the P50 S2/S1 ratio is an operational reflection of the brain's ability to inhibit redundant incoming sensory input, a deficiency of which remains a potential endophenotype for schizophrenia patients. In agreement with both de Wilde et al. (2007a) and Patterson et al. (2008), several concerns need to be addressed. Patterson et al. (2008) indicated that, in order to be an endophenotype, the P50 S2/S1 ratio needs to be a "reliable maker that is state-independent and enduring across different subject characteristics such as diagnostic subtype and symptom status" (p. 243) and questioned the consistency and specificity of this particular P50 measure. In addition, Gould and Gottesman (2006) list five criteria for an endophenotype. Large multicenter studies are necessary to establish the validity of putative endophenotypes or biomarkers (Olincy et al., 2010).

Limitations and Future Direction

This present meta-analysis has two major limitations. The first limitation stems from the P50 S2/S1 ratio itself. The P50 S2/S1 ratio has an inherent bias because it is a mathematical index that the S2 amplitude is divided by the S1 amplitude. As Atchley and

Table 3. *Potential Moderators on Estimates of Effect Sizes of S1, S2, and S2/S1 Ratio*

		Research group		Blinding	
		Colorado group ($N = 13$)	Non-Colorado group ($N = 45$)	Used ($N = 17$)	Not used ($N = 41$)
S1 amplitude	ES	−0.39	−0.15	0.02	−0.32
	95% CI	−0.56–−0.22	−0.26–−0.05	−0.10–0.14	−0.44–−0.21
	SeES	0.087	0.053	0.063	0.057
	Q	20.29	81.14	20.66	73.29
		$p = .062$	$p = .0006$	$p = .19$	$p = .001$
	I^2	40.86%	45.77%	22.54%	45.43%
S2 amplitude	ES	1.39	0.47	0.58	0.71
	95% CI	0.95–1.83	0.33–0.61	0.36–0.81	0.48–0.94
	SeES	0.225	0.070	0.116	0.117
	Q	147.98	141.75	69.05	328.63
		$p < .0001$	$p < .0001$	$p < .0001$	$p < .0001$
	I^2	91.89%	68.96%	76.83%	87.83%
S2/S1 ratio	ES	1.93	0.72	0.79	1.08
	95% CI	1.48–2.37	0.58–0.86	0.57–1.02	0.82–1.33
	SeES	0.228	0.071	0.117	0.130
	Q	151.38	146.63	70.63	406.32
		$p < .0001$	$p < .0001$	$p < .0001$	$p < .0001$
	I^2	92.07%	69.99%	77.35%	90.16%

Note: ES = effect size, 95% CI = 95% confidence interval for effect size, SeES = standard error of effect size.

his colleagues indicated, when a composite score (i.e., ratio score) are used from continuous variables, a pronounced spurious correlation occurs between the ratio score and its numerator and denominator (Atchley, Gaskins, & Anderson, 1976). In addition, Atchley et al. (1976) noticed that the size of the denominator coefficient of variation contributes to the strength of the spurious correlation. Due to this statistical nature, it is not a surprise that the previous meta-analysis (i.e., Patterson et al., 2008) examined the S1 amplitude and other investigators seek other approaches, such as the difference between S1 and S2 amplitude, to better index sensory gating. Nonetheless, we suggest that it is important to not ignore the relative contribution of the S2 amplitude because the S2 amplitude is indispensable for the ratio and difference scores.

The other major limitation is that this meta-analysis only included 35 studies (58 comparisons). Due to a lack of reporting of either the S1 amplitude, S2 amplitude, and/or the P50 S2/S1 ratio, many studies were not included in the present study, and they may systematically differ from those studies included. The analysis did not examine if the sensory gating deficit is specific to schizophrenia patients as the P50 gating deficit has also been reported in individuals with post-traumatic stress disorder (e.g., Ghisolfi et al., 2004), panic disorder (e.g., Ghisolfi et al., 2006), bipolar disorder (e.g., Franks, Adler, Waldo, Alpert, & Freedman, 1983; Sánchez-Morla et al., 2008) and Alzheimer's disease (Jessen et al., 2001). The sizes of these bodies of literature are much smaller than that for schizophrenia. Therefore, it would be important to conduct other meta-analyses that compare the magnitude of differences in the S1 amplitude, S2 amplitude, and P50 S2/S1 ratio between schizophrenia patients and those psychiatric disorders when enough data has accumulated.

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[Correction added after online publication January 7, 2011: In the title, "meta-alysis" should have read "meta-analysis." The corrected version appears here.]