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P50 sensory gating ratios in schizophrenics and controls: A review and data analysis

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Abstract

Many studies have found that the P50 sensory gating ratio in a paired click task is smaller in normal control subjects than in patients with schizophrenia, indicating more effective sensory gating. However, a wide range of gating ratios has been reported in the literature for both groups. The purpose of this study was to compile these findings and to compare reported P50 gating ratios in controls and patients with schizophrenia. Current data collected from individual controls in eight studies from the University of California, Irvine (UCI), Indiana University (IU), and Yale University also are reported. The IU, UCI, and Yale data showed that approximately 40% of controls had P50 ratios within 1 S.D. below the mean of means for patients with schizophrenia. The meta-analysis rejected the null hypothesis that all studies showed no effect. The meta-analysis also showed that the differences were not the same across all studies. The mean ratios in 45 of the 46 group comparisons were smaller for controls than for patients, and the observed difference in means was significant for 35 of those studies. Reported gating ratios for controls from two laboratories whose findings were reported in the literature differed from all the other control groups. Variables affecting the gating ratio included band pass filter setting, rules regarding the inclusion of P30, sex, and age. Standards of P50 collection and measurement would help determine whether the gating ratio can be sufficiently reliable to be labeled an endophenotype, and suggestions are made toward this goal.

Keywords: Sensory gating; P50; Schizophrenia; Controls; Evoked potentials

1. Introduction

A number of theories suggest that schizophrenia is characterized primarily by disordered cognition, and that deficits in perception and attention are basic to the disorder and its symptoms (Geyer and Braff, 1987; Duncan, 1988; Braff and Geyer, 1990; Grillon et al., 1990). A central hypothesis proposed to account for these deficits is that individuals with schizophrenia cannot inhibit, or "gate," irrelevant sensory input, leading to sensory inundation and an overload of information reaching consciousness (McGhie and Chapman, 1961; Shakow, 1963; Venables, 1963). The sensory gating problem observed in schizophrenia may result from neuronal hyperexcitability stemming from a defect in sub-cortical and

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cortical neuronal inhibitory pathways (Adler et al., 1982; Freedman et al., 1987a,b, 1991).

A commonly used physiological procedure to assess inhibitory mechanisms and sensory gating has been the auditory dual-click or conditioning–testing task (Adler et al., 1982; Franks et al., 1983; Nagamoto et al., 1989; Baker et al., 1987, 1990; Freedman et al., 1983, 1987a,b, 1991; Erwin et al., 1991; Boutros et al., 1993; Cullum et al., 1993). In this procedure, paired clicks are presented, separated by an interval of 500 ms, and a positive-polarity brain response occurring approximately 50 ms post-stimulus, the P50 wave of the average auditory evoked brain potential (EP), is measured. The relative decrease of the P50 wave to the second click (S2) compared with the first (S1) has been used as a measure of sensory gating, and quantified as the S2/S1 ratio. It has been hypothesized that the neural response to the second click may be considered a test of the strength of recurrent inhibitory mechanisms, activated by the initial click in the pair (Nagamoto et al., 1989). The abnormal auditory gating observed in schizophrenia (reduced S2/S1 ratio) has been suggested to be a "fixed trait" that is genetically associated (Siegel et al., 1984; Freedman et al., 1997) and that shows potential as a candidate endophenotype (Adler et al., 1999; Freedman et al., 2005). Evidence supporting the P50 sensory ratio as a possible endophenotype is that the deficit has been observed in relatives of patients with schizophrenia who do not show symptoms of schizophrenia (Clementz et al., 1998; Siegel et al., 1984; Waldo et al., 1988, 1995, 2000).

The search for susceptibility genes for psychiatric disorders has been impeded by their clinical and biological complexity and etiological heterogeneity, as well as by the overlap among different disorders in their clinical manifestations as outlined in the current diagnostic classification systems (DSM-IV). An important strategy that has recently emerged in psychiatry is the identification of endophenotypes, less complex processes that are intermediate between genetic predisposition and the clinical and behavioral manifestations of a disorder, and are closer to the underlying pathophysiology (Gottesman and Gould, 2003; de Gues, 2002; Braff et al., 2006). These processes can be neurophysiological, neuropsychological, endocrinological, biochemical, cognitive or neuroanatomical markers. Criteria for a candidate endophenotype include the following: (1) it is associated with the behavior or illness of interest; (2) it is state-independent, that is, does not require that the illness be active; (3) it is reliable and stable; and (4) it shows evidence of heritability and co-segregation of marker and illness within families (Gottesman and Gould, 2003; de Gues, 2002). There is evidence that the P50 sensory gating deficit may satisfy some of these criteria cited as necessary for a candidate endophenotype (Adler et al., 1999; Gottesman and Gould, 2003), but there also is evidence that some of the criteria are not yet met (e.g., Smith et al., 1994; Boutros et al., 1993; Light et al., 2000). Furthermore, multiple factors may confer risk for schizophrenia and each of these may not be present in every case. Neuropsychological deficits, for example, have been found not only in schizophrenia, but in the first degree relatives of patients (Bredgaard and Glenthoj, 2000; Cannon et al., 1994; Sautter et al., 1997; Wolf et al., 2002), also yielding a potential endophenotype.

A number of studies have reported that in healthy control subjects the P50 gating ratio is smaller than in patients with schizophrenia, indicating more effective sensory gating. However, a wide range of gating ratios has been reported in the literature for control subjects as well as individuals with schizophrenia, and several studies have reported abnormal gating in controls (Kathmann and Engel, 1990), and normal gating in patients on atypical anti-psychotics (Light et al., 2000) and even when the patients are not medicated (Arnfred et al., 2003). While P50 sensory gating is promising as an endophenotype, this cannot be confirmed as long as there are significant differences in measured ratios across studies, and until it is well established that deficient sensory gating is widespread in patients with schizophrenia compared with control subjects. The variations among studies may be due to differences in methodology as well as variation in the composition of subject groups, but they may also suggest that there are fundamental differences in the schizophrenia patients that show abnormal gating compared with those that do not (e.g., Boutros et al., 1991a, 1993; Johannesen et al., 2005).

Methodological issues include the effect of high- and low-pass filter selection on P50 measurement, click intensity and duration (Griffith et al., 1995; White and Yee, 2006), loudspeaker vs. headphone use, post-stimulus temporal window used for P50 identification, recognition of P30, use of preceding trough or baseline in P50 peak measurement, rules used to include or exclude P50 measurements, and seated vs. supine (McCallin et al., 1997) or eyes closed vs. open recordings. Some studies, for example, required the presence of P30 to define P50 (Boutros et al., 1991a,b, 1999, 2004; White and Yee, 2006), or looked for the P30–P50 complex (Freedman et al., 1983; Kisley et al., 2001), while other studies considered P30 a possible artifact affected by a startle response (Nagamoto et al., 1989), and eliminated trials with large or prolonged (>10 ms) P30 responses (Adler et al., 1990a,b; Baker et al., 1990; Clementz et al., 1997a,b, 1998). In several

studies, P50 selection windows were used that could include P30, e.g., 25–75 ms (Adler et al., 1982), or 25–65 ms (Judd et al., 1992). Variations in subject characteristics that may affect P50 include sex, age, schizophrenia subtype, symptom profile, nicotine use, duration of illness, stress, and medication type (e.g., Adler et al., 1999). Sex affects P50 amplitudes and the gating ratio (Hetrick et al., 1996), as can schizophrenia subtype (Boutros et al., 1993; Ringer et al., 2004; Johannesen et al., 2005), age (Freedman et al., 1987b; McDowd et al., 1993), nicotine (Adler et al., 1993; Griffith et al., 1998; Leonard et al., 2000), and medication (Freedman et al., 1983; Erwin et al., 1994; Nagamoto et al., 1996, 1999; Light et al., 2000; Myles-Worsley, 2002; Arango et al., 2003; Becker et al., 2004; Brunstein et al., 2005).

The purposes of this study were to characterize the P50 gating ratio in control subjects compared with one another and with schizophrenia patients, and, based on these studies, to identify some critical issues for further research. These goals were achieved by the following means: (1) compiling and summarizing the results and methodologies of studies of P50 sensory gating in schizophrenics and healthy controls reported in the literature in order to compare methods and results across studies; (2) for those literature studies with schizophrenics and controls in the same study, analyzing the difference in within study P50 sensory gating between groups using meta-analysis; (3) comparing P50 sensory gating ratios reported for schizophrenic groups in the literature with gating ratios for controls from four groups of laboratories reported in the literature, and from eight groups of controls for which individual subject data were available; and (4) assessing the degree of overlap in P50 gating ratios across schizophrenic and control groups, using the studies reported in the literature, as well as P50 data from the control groups for which data from individual subjects were available.

2. Methods

2.1. Literature studies reporting mean P50 gating ratios

Table 1 presents P50 sensory gating data from 84 studies of schizophrenic and control groups reported in the literature, going back as far as 1982 and selected using Entrez PubMed, developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM), located at the U.S. National Institutes of Health (NIH). For 48 of these studies, mean P50 ratios were available for both controls and schizophrenic patients in the same study, and 39 of these reported the standard deviations required for the meta-analysis. Twenty-four of the studies presented in Table 1 provided data only from healthy controls, and 11 provided data for schizophrenic patients only. A study was included in the table if numeric mean P50 gating ratios were reported. (Several studies that reported mean P50 ratios only in plot form were included in Table 1 for comparison purposes, but these studies were not included in the statistical analyses or in Fig. 1.) Along with each study citation, the table provides demographic data, including number of subjects studied, age and sex, subject characteristics including diagnosis, and medications taken (typical or atypical, if reported). In order to compare methodologies across studies, the table also provides high- and low-pass filter characteristics used, and click duration and intensity.

The published studies for which only mean P50 gating ratios were available for controls were grouped as follows: (1) three studies from the Yale laboratory, which used 4-ms clicks of 90–95 dB SPL; (2) three studies from UC San Diego (UCSD), which used 83-dB SPL clicks of 0.1, 0.04, or 1-ms duration; (3) 37 other studies from various laboratories (Misc), with click durations ranging from 0.1 to 10 ms, and intensities ranging from 52 to 120 dB; and (4) 23 studies from the Colorado laboratory (Colo), which used clicks with a duration of 0.04 ms, equivalent to a duration of 1 ms at the ear (Freedman et al., 1996), and a peak intensity of 110 dB and a mean intensity of 75 dB.

2.1.1. Subjects

A total of 1445 individuals with schizophrenia, and 1975 controls were evaluated across the studies cited in Table 1. The mean ages (or ranges) of the participants ranged from 28 to 46.8 (19–61) for the schizophrenia groups, and 21.3 to 47.8 (16–57) for the controls. In the majority of studies, diagnoses of schizophrenia were made using DSM criteria and/or SCID ($n=53$). The remaining studies used some combination of the New Haven Schizophrenic Index (NHSI), Brief Psychiatric Rating Scale (BPRS), Schedule for Affective Disorders and Schizophrenia (SADS), Research Diagnostic Criteria (RDC), or International Classification of Diseases (ICD). All of the participants were medicated in 37 of the studies, and none were medicated in five studies. Twenty-three studies identified the medications or whether they were typical or atypical anti-psychotics; the others only indicated whether the patients were medicated or not medicated.

2.1.2. P50 collection

The methods used for each study, including band pass filter, and click duration and intensity, are given in Table 1.

Table 1
P50 sensory gating studies of schizophrenia and control groups cited in the literature[a,b]

Authors, year	Scz *n* male, *n* female	Scz × age (S.D. or range)	Scz S1 amplitude	Scz P50 S2/S1 ratio (S.D.)	Control *n* male, *n* female	Control × age (S.D. or range)	Control S1 amplitude	Control P50 S2/S1 ratio (S.D.)	Band pass filter (Hz)	Click intensity, duration	Scz subtype	Medications typical (Typ) and atypical (Atyp)
Adler et al. (1982)	13 m	30.5 (9.3)	5.3 (0.6)	90 (7.8)	15 (18–60)	33.7 (8.1)	8.9 (0.8)	13.6 (4.1)	1–1000	110 dBA peak, 75 dB mean, 0.04 ms	5 SPT, 8 UD	Unmedicated
Adler et al. (1985)	15 m	32.5 (8.91)	7.0 (2.71)	64.8 (40.2)	16	31.9 (5.6)	9.3 (3.6)	17.2 (17.2)	1–500	110 dBA, 0.04 ms	nr	Psychotropics, nr
Adler et al. (1990a)	6	34.6 all subjects	nr	104 (43)	7	34.6 all subjects	nr	19 (17)	10–250	90 dBA, nr	nr	Unmedicated, 2–12 weeks
Adler et al. (1990b)	12 m, 8 f	40 (15) negative 33 (7) other	6.4 (7.9), 4.5 (4.0)	85 (43), 101 (57)	12, nr	38 (15)	4.7 (2.4)	22 (37)	10–250	110 dB, 0.04 ms	Negative vs. other	Neuroleptics, nr
Adler et al. (1993)	6 m, 4 f	40 (10)	nr	158 (nr)	4 m, 6 f	36 (11)	nr	9 (nr)	10–250	70 dB SPL, 0.04 ms	3 SPT, 7 UD	Medicated, nr
Adler et al. (1994)	na	na	na	na	5 m, 2 f	21–35	4.4 (2.3) baseline 5.1 (3.4) placebo	~24.5 (9.8)[c] baseline, 37.7 (43.2) placebo	10–250	70 dB SPL, 0.04 ms	na	na
Adler et al. (2004)	69 m, 46 f	39.6 (9.9)	2.2 (1.4), 2.7 (2.6), 3.1 (1.7)	70.4 (53.7) 110.1 (87.9) 74.1 (27.8)	40 m, 114 f	37.4 (10.5)	3.0 (1.5)	19.8 (21.0)	10–110	nr, 0.04 ms	nr	88 Atyp vs. 34 typ vs. 10 none
Adler et al. (2005)	4 m, 4 f	41.5 (5.9)	nr	41.4 (39.7), 80.2 (21.3)	na	na	na	na	10–110	nr, 0.04 ms	Stable	Ondansetron vs. placebo
Arango et al. (2003)	24	18–60	nr	61 (29), 60 (27) at baseline	na	na	na	na	10–100	75 dB, nr	Scz or SAD	Olanzapine vs. haloperidol
Arnfred et al. (2001a)	na	na	na	na	10 m	27.6 (23–36)	3.9 (1.6)	29 (24)	0.1–400	104 dB peSPL, 1.6 ms	na	na
Arnfred et al. (2001b)	na	na	na	na	20 m	nr	3.8 (1.8)	33 (26)	0.1–100	104 dB peSPL, 1.6 ms, bkgr	na	na
Arnfred et al. (2003)	12 m	30.7 (scz and control)	2.56 (1.63)	32 (24)	24 m	30.7 (scz and control)	2.52 (1.39)	40 (30)	10–50	104 dB peSPL, 1.6 ms	3 SPT, 5 UD, sczf, SAD, cat, res (all 1)	Unmedicated
Baker et al. (1987)	10 scz	36.5 (9.5)	nr	70.2 (40.3)	21 m, 14 f[d]	nr	nr	18.6 (17.7)	1–300	110 dBA, 0.04 ms	nr	Psychotropics 2/3, nr
Baker et al. (1990)	7 scz	19–55	nr	116 (120)	na	na	na	na	5–250	90 dBA, 0.04 ms	nr	Psychotropics, nr
Becker et al. (2004)	39 m, 11 f	33.9 (9.6), 35.0 (10.6)	4.3 (2.7), 6.4 (4.0)	82 (45), 57 (41)	19 m, 6 f	33.4 (11.1)	5.44 (2.72)	44 (27)	nr	60 dB above SL, 1 ms	nr	Typ vs. clozapine
Boutros et al. (1991a)	26	nr	4.0 (2.3), 2.9 (1.9)	126 (71), 59 (23)	13	nr	5.93 (3.08)	52 (16)	10–300	95 dB, nr	13 UD/dis, 13 SPT	Medicated, nr
Boutros et al. (1991b)	na	na	na	na	6 m, 4 f	28.5 (25–40)	4.8 (2.2), 3.2–4.8, sessions 1–6	73.4 (68.9), 73–144, sessions 1–6	10–300	95 dB peak, nr	na	na
Boutros et al. (1999)	11 m, 1 f	42 (35–46)	2.5 (1.8)	142 (58)	11 m, 1 f	42 (36–52)	3.3 (2.1)	51 (44)	10–50	90 dB SPL, 4 ms	nr	Typ
Boutros et al. (2000)	na	na	na	na	9 m, 4 f	37, 26–46	4.0 (2.4)	52 (31)	10–50	40 dB above HL, nr	na	na

(continued on next page)

Table 1 (*continued*)

Authors, year	Scz *n* male, *n* female	Scz × age (S.D. or range)	Scz S1 amplitude	Scz P50 S2/S1 ratio (S.D.)	Control *n* male, *n* female	Control × age (S.D. or range)	Control S1 amplitude	Control P50 S2/S1 ratio (S.D.)	Band pass filter (Hz)	Click intensity, duration	Scz subtype	Medications typical (Typ) and atypical (Atyp)
Boutros et al. (2004)	20 m, 3 f	38–60	2.6 (1.6)	80 (69)	22 m, 1 f	29–64	2.6 (2.3)	54 (38)	10–50	90 dB SPL, 4 ms	nr	17 Atyp, 4 typ, 2 unmedicated
Brenner et al. (2004)	na	na	na	na	11 m, 20 f	20.4 (18–36)	~5.8[c]	62 (20)	10–50	87 dB SPL peak, 1 ms	na	na
Brunstein et al. (2005)	14 m, 9 f	35.3 (9.1), 42.3 (12.9)	nr	79.8 (36.7), 61.9 (27.0)	na	na	na	na	na	60 dB SPL, 0.1 ms	nr	Typ/atyp vs. typ/atyp + allopurinol
Cardenas et al. (1993)	na	na	na	na	6 m, 6 f	23–29	nr	53.3 (32.2)	10–50	76 dB above SL, 0.05 ms	na	na
Cardenas et al. (1997)	na	na	na	na	9 m, 11 f	27.1 (3.2)	9.82 (6.09)	47 (48)	10–50	55 dB SL	na	na
Clementz et al. (1997a)	10 m	34.9 (7.4)	2.2 (2.9)	80 (47)	8 m, 2 f	36.6 (8.8)	1.8 (1.3)	46 (15)	10–70, 60 notch	83 dB, 0.1 ms, 50 dB, bkgr	nr	6 anti-psychotic, nr, 1 unmedicated
Clementz et al. (1997b)	18 m, 2 f	33.3 (8.5)	1.35 (.51)	~60[c]	10 m, 10 f	31.5 (10.7)	1.66 (0.66)	~35[c]	10–70, 60 notch	83 dB, 1 ms, 60 dB, bkgr	nr	16 anti-psychotics, nr
Clementz et al. (1998)	36 m, 8f	34.2 (9.3)	3.4 (1.1)	59.4 (31.6)	20m, 25f	34.6(14.6)	4.2 (1.2)	29.9 (22.8)	10–250	83 dB, 1 ms, 60 dB, bkgr	nr	31 anti-psychotics, nr
Clementz and Blumenfeld (2001)	13 m, 7 f	36.9 (10.3)	1.8 (0.8)	48 (27)	12 m, 8 f	37.2 (12.2)	2.3 (0.8)	38 (24)	10–50	83 dB SPL, 0.04 ms	nr	14 Atyp, 5 typ, 1 unmedicated
Croft et al. (2004)	na	na	na	na	14 m, 23 f	21.3 (16–33)	4.2 (1.9)	42 (29)	10–49	89 dB, 0.1 ms	na	na
Cullum et al. (1993)	8 m, 6 f	35.4 (6.1)	4.3 (3.5)	91.4 (49.2)	6 m, 9 f	28.8 (7.6)	4.5 (3.6)	30.5 (34.2)	10–250	75 dB SPL mean, 0.04 ms	nr	Neuroleptics, nr
Edgar et al. (2003)	na	na	na	na	10 m, 9 f	43.7 (20–57)	4.77 (3.03)	31.28 (25.69)	1.4–2.3 to 54.5–58.9, stop, pass	35 dB SPL above SL, 3 ms	na	na
Freedman et al. (1983)	29 m[e]	37.5 (3.1)	~7.2[c], ~5.2[c]	~90[c], ~85[c]	17 m	34.0 (1.9)	~8.5[c]	~15[c]	1–1000	110 dB peak 75 mean, 0.04 ms	nr	15 Medicated, nr, 14 unmedicated
Freedman et al. (1987a)	20	nr	nr	84 (49.2)	12	nr	nr	34 (24)	10–200	90 dBA, nr	nr	Medicated, nr
Freedman et al. (1987a)	56	nr	nr	~80[c], ~100[c]	35	nr	nr	~20[c]	10–200	90 dBA, nr	nr	43 Medicated, nr, vs. 13 unmedicated
Freedman et al. (1987b)	na	na	na	na	90 m, 73 f	20.7 (13.7) 18 months–55	8.1 (5.1)	35.8 (33.2)	1–300	110 dB SPL peak, 0.04 ms	na	na
Freedman et al. (1996)	6 m, 4 f	46 (14.2)	nr	80 (nr)	6 m, 4 f	45.8 (14.3)	nr	20 (nr)	10–100	75 dB SPL mean, 0.04 ms, bkgr	4 SPT, 6 mixed	Typ, 1 no medication
Ghisolfi et al. (2002)	16 m, 1 f	36 (9)	~4.6[c]	74 (20.6)	8 m, 5 f	27 (4)	~3.8[c]	28 (10.8)	10–10,000	60 dB above SL, 0.04 ms, 2.5 ms ear	Stable	No atyp
Ghisolfi et al. (2004)	4 m, 8 f	38.8 (10.0)	4.1 (0.5)	88.3 (12.6)	8 m, 16 f	40.7 (11.5)	5.4 (0.6)	44.4 (4.8)	10–10,000	60 dB SPL, 0.1 ms, 1 ms ear	Scz out-patients	All typ

Ghisolfi et al. (2006a)	na	na	na	na	12 f, 13 m	25 (1.7)	4.70 (1.36), 5.93 (2.66) hi vs. lo caffeine	57.1 (12.1)	10–10,000	60 dB above SL, 0.04 ms, 2.5 ms ear	na	na
Ghisolfi et al. (2006b)	12 m, 16 f	37.5 (7.4)	5.6 (2.9)	79.2 (37.3)	10 m, 18 f	39.7 (7.8)	5.2 (3.1)	45.4 (20.9)	1–10,000	60 dB above SL, 0.1 ms, 1 ms ear	nr	All typ
Griffith and Freedman (1995)	9 m, 1 f	41 (8)	5.6 (2.6)	112 (26)	9 m, 1 f	41 (11)	nr	nr	10–250	85 dB SPL mean, 0.04 ms, 1.5 ear	8 SPT, 2 UD	All typ
Griffith et al. (1998)	5 m, 1 f	28 (8)	nr	86 (20)	na	na	na	na	10–50	50 dB above HL, 1 ms	4 SPT, 1 UD, 1 cat	4 Typ, 1 atyp, 1 unmedicated
Guterman et al. (1992)	na	na	na	na	7 f, 3 m	27 (5.4)	5.6 (3.3)	39 (28.2)	50 pass, 60 stop	90 dB SPL, 10 ms	na	na
Guterman and Josiassen (1994)	7 m, 3 f	32 (26–40)	5.35 (4.27)	125 (226) (range 25–760)	7 f, 3 m	27 (20–35)	5.51 (3.18)	37.6 (27.5) (range 5–84)	50 pass, 60 stop	90 dB SPL, 10 ms	3 SPT, 7 UD	Medicated, nr
Hall et al. (2006)	na	na	na	na	14 m, 26 f monozygotic vs. dizygotic twin	34.7, 40.8	2.2 (0.96), 2.12 (0.98)	27.4 (18.8), 39.0 (28.4)	10–100	43 dB SL, 1 ms	na	na
Hetrick et al. (1996)	na	na	na	na	30 m, 30 f	22.4 (4.3), 23.2 (5.6)	4.16 (2.52), 4.95 (3.00)	33.8 (33.6), 51.0 (41.9)	0.8–100	84 dB SPL, 0.1 ms, 62 dB, bkgr	na	na
Hong et al. (2004)	8 m, 8 f	39.3 (9.1)	3.3 (2.2)	65 (39)	14 m, 8 f	40.8 (9.7)	3.0 (1.6)	39 (34)	3–50	52 dB, 1 ms	nr	Anti-psychotics, nr
Hsieh et al. (2004)	5 m, 5 f	35.1 (10.6)	nr	69.5 (44.2)	5 f, 5 m	33.3 (9.9)	nr	36.7 (32.8)	1–30	80–90 dB SPL, 1 ms	nr	Medicated, nr
Jerger et al. (1992)	na	na	na	na	6 m, 6 f	23–29	nr	51.4 (nr)	10–50	65/76 above SL, 0.05 ms	na	na
Jin et al. (1997)	4 f, 6 m	33.1 (7.6)	3.34 (1.74)	73 (35)	6 f, 4 m	26.5 (3.5)	5.60 (2.79)	37 (20)	8–60	100 dB SPL, 0.1 ms	nr	nr
Johannesen et al. (2005)	24 m, 14 f	41.6 (9.6)	1.87 (0.54)	68.99 (30.81)	17 m, 21 f	41.3 (8.8)	2.14 (0.64)	57.57 (33.14)	0–50	81 dB SPL, 3 ms, 58 dB, bkgr	27 SPT vs. 11 non-SPT	26 Atyp, 3 typ, 9 none
Judd et al. (1992)	15 m, 5 f	28.8 (8.49)	10.28 (0.63)	84, calculated	14 m, 6 f	27.9 (5.99)	12.43 (0.77)	46, calculated	0–1500	75 dB, 0.04 ms	nr	Unmedicated
Kathmann and Engel (1990)	14 m, 9 f (4 excluded)	29 (8.3)	2.6 (0.2)	94.7 (84.6)	9 m, 15 f	25.6 (3.6)	3.0 (0.3)	73.0 (40.7)	0.5–100	90 dB, 1.5 ms	8 SPT, 5 DO, 4 res, 2 cat	Neuroleptics, nr
Kisley et al. (2001)	na	na	na	na	5 m, 5 f	31.2, 21–44	1.93 (1.57)	34 (42)	5–100, 60 stop	40 dB above HL, 0.04 ms	na	na
Kisley et al. (2003)	5 m, 5 f	41.6, 20–50	1.63 (1.27)	93 (66)	5 m, 5 f	34.4, 21–47	1.51 (0.62)	39 (35)	5–100	40 dB above HL, 0.04 ms	nr	7 Atyp, 2 typ, 1 typ + atyp (no clozapine)
Kisley et al. (2004)	na	na	na	na	11 m, 41 f	22.1 (4.3)	3.78 (1.93)	40 (25), 0.0–1.17	10–75	60 dB HL, nr	na	na
Koike et al. (2005)	14 m, 8 f	39.8 (14.0)	2.4 (1.31)	84 (55)	11	21–44	nr	36 (30)	0.5–100	70 dB SPL, 1 ms	nr	1 none, 27 atyp, 2 typ
Lamberti et al. (1993)	na	na	na	na	18 m, 10 f	26.7 (19–36)	3.38 (1.74)	74.6 (72.3), 40 block 1, 119 block 4	3–300, 10 pt. smooth	110 dB, 0.04 ms	na	na
Light et al. (2000)	13 m, 13 f	35.4 (9.9)	2.3 (1.6), 2.9 (0.7)	72.8 (85.4), 27.6 (37.5)	nr	32.4 (8.3)	nr	nr	5–50	89 dB, 1 ms	nr	Typ vs. atyp

(continued on next page)

Table 1 (*continued*)

Authors, year	Scz *n* male, *n* female	Scz × age (S.D. or range)	Scz S1 amplitude	Scz P50 S2/S1 ratio (S.D.)	Control *n* male, *n* female	Control × age (S.D. or range)	Control S1 amplitude	Control P50 S2/S1 ratio (S.D.)	Band pass filter (Hz)	Click intensity, duration	Scz subtype	Medications typical (Typ) and atypical (Atyp)
Louchart-de la Chapelle et al. (2005a)	60 m, 21 f	38 (9.1), 40.5 (9.7)	3.3 (2.7), 3.6 (2.6)	97 (60), 80 (40)	42 m, 46 f	29.5 (7.5)	3.12 (2.5)	36 (20)	1–200	Mean 75 dB peSPL, 100 μs for 1 ms at ear, 40 dB, bkgr	26 Negative vs. 55 non-negative, stable	4 Atyp, 77 typ
Louchart-de la Chapelle et al. (2005b)	124	36.3 (10.2) (n=144)	nr	82 (46)	100	31.2 (9.3) (n=113)	nr	38 (20)	1–200	Mean 75 dB peSPL, 100 μs, 1 ms ear	Stable for at least 15 days	25 Atypical, 75 typical
McCallin et al. (1997)	na	na	na	na	6 m, 7 f	23–34	1.62 (0.9) seated, 1.29 (0.41) supine	64 (46) seated, 72 (80) supine	10–50	55 dB SL, 0.05 ms	na	na
Myles-Worsley (2002)	62 m, 23 f	40 (10.4)	2.0 (1.1), 1.8 (1.4)	74.5 (47.7), 71.6 (59.8)	11 m, 18 f	44.1 (17.4)	2.96 (1.59)	30.7 (22.7)	30–100 FFT	50 dB above SL, nr	Scz, SAD	56 Typical vs. 29 unmedicated
Nagamoto et al. (1989)	7 m, 3 f	34 (10)	2.8 (2.3)	~170 (50)[c] trough, 70 (54) pre-stimulus	8 m, 3 f	32 (8)	4.3 (1.7)	~20 (5)[c], 28 (15)	1–300	110 dB SPL peak, 0.04 ms	nr	Medicated, nr, 1 unmedicated
Nagamoto et al. (1991)	13 m, 2 f	33.6 (6.5)	nr	94.7 (60.2)	12 m, 2 f	33.6 (5.5)	nr	28.5 (16.8)	250	110 dB SPL, 0.04 ms	nr	Neuroleptics, nr
Nagamoto et al. (1996)	9 m, 2 f	24–54, 35 (9.9)	1.9 (1.2), 3.4 (1.7)	84.3 (51.6), 56.4 (16.8)	na	na	na	na	10–250	70 dB SPL, 0.04 ms	nr	Typ vs. atyp (clozapine)
Nagamoto et al. (1999)	8 m, 2 f	nr	1.9 (1.0), 3.2 (1.5), 4.1 (2.9)	87.4 (49.7), 59.4 (48.6), 26.8 (43.1)	na	na	na	na	10–250	70 dB SPL ear, 0.04 ms		Typ vs. 1 month & stable on clozapine
Olincy et al. (2006)	8 m, 4 f	20–58	3.52 (1.84)	83 (27)	na	na	na	na	nr	nr	nr	11 Atyp, 1 typ
Oranje et al. (2004)	na	na	na	na	16 m, 17 f	22.8 (3.0), 22.9 (2.0)	2.48 (1.96), 2.09 (1.01)	43 (32), 36 (29)	70 LP	80 dB, 1.5 ms	na	na
Patterson et al. (2000)	4 f, 6 m	33.1 (7.6)	2.57 (0.57)	118 (148)	6 f, 4 m	26.5 (3.5)	4.14 (0.85)	36 (25)	25–62 FFT	100 dB SPL, 0.1 ms	nr	5 days no medication
Price et al. (2006)	53 m, 7 f	33.3 (8.2)	nr	63 (31)	25 m, 19 f	32.3 (9.2)	nr	47 (19)	10–100	100 dB SPL peak, 0.04 ms	Scz, scz spectrum	Stable regimen
Ringer et al. (2004)	4 f, 17 m	42.0 (2.3)	3.7 (1.2), 1.8 (1.8)	56 (21), 96 (11)	7 f, 5 m	28.0 (3.2)	10.1 (4.3)	44 (24)	0.1–70	120 dB, 0.04 ms	11 Unsystematic, vs. 10 Systematic	3 Atyp, 8 typ, 4 atyp, 6 typ
Siegel et al. (1984)	9 m, 6 f, + 29[e]	nr	nr	86.2 (33.4)	21 m, 14 f	36.5 (1.6)	nr	18.6 (17.8)	1–1000	110 dBA SPL peak, 0.04 ms	nr	15 Medicated, nr, 14 unmedicated

Schwarzkopf et al. (1993)	na	na	na	na	12 m, 8 f	26.7 (5.1)	2.48 (3.95)	51.65, 64.4 block 1, 56.2 block 2	3–300	110 dB peak, 0.04 ms	na	na
Thoma et al. (2003)	17 m, 3 f	na	1.79 (0.86)	56 (na)	13 m, 2 f	na	1.61 (0.86)	34 (na)	4 point moving, recursive	30 dB above SL, 3 ms	nr	13 Atyp, 7 typ
Thoma et al. (2005)	16 m, 4 f	46.0 (9.9)	1.72 (0.89)	56 (32)	na	na	na	na	4 point moving, recursive HP A=0.85	nr, 3 ms	12 SPT, 6 UD, 2 DO	13 Atyp, 7 typ
Thoma et al. (2006)	17 m, 1 f	46.78 EtOH+, 36.78 EtOH−	nr	~55 (12)[c], ~83 (18)[c]	13 m, 4 f	47.75 EtOH+, 37.78 EtOH−	nr	~30 (10)[c], ~50 (10)[c]	1–4 to 50–55, stop, pass	30 dB above SL, 3 ms	Stable	13 Atyp, 5 typ
Vinogradov et al. (1996)	7 m, 6 f	40.3, 23–61	nr	56 (31)	8 m, 12 f	38.6, 25–59	nr	42 (na)	nr	nr	nr	Medicated, nr
Waldo and Freedman (1986)	na	na	na	na	13 m	College students	5.6 (2.8)	24.6 (35.4)	1–500	110 dB peak, 0.04 ms	na	na
Waldo et al. (1988)	13 m[5]	36.2 (11.5)	5.1 (2.1)	92 (29)	20 m, 12 f[5]	nr	8.6 (4.2)	18 (18)	1–500	110 dB peak, 75 dB mean, 0.04 ms	nr	Unmedicated
Waldo et al. (1992)	12 f	32.2 (5.6)	nr	102.4 (79.5)	12 f	30.4 (6.7)	nr	39.3 (44.3)	10 Hz, 7 point moving	100–107 dB SPL, 0.04 ms	nr	Neuroleptics, nr
Waldo et al. (1994)	11	31.3 (4.3), 22–43	5.2 (4.4)	98.9 (47)	43	nr	6.4 (3.0)	17.9 (6.4)	10–250	75 dB SPL, 1 ms	nr	10 Medicated, nr
White and Yee (2006)	na	na	na	na	17 m, 17 f	18–35	4.6 (2.3), 3.6–6.0 (1.7–2.8)	38 (29) at 90 dB SPL, 35–42 (24–35)	10–50	80, 90, 100 dBA SPL, 1, 3, 5 ms, 40 dB, bkgr	na	na
Yee and White (2001)	na	na	na	na	11 m, 9 f	18–33	5.61 (2.94)	47 (34)	10–50	90 dB SPL, 3 ms, 40 dB, bkgr	na	na
Mean				79.9 (24.3) (48.2)[f]				39.1 (15.3) (28.7)[f]				

[a] Abbreviations: not applicable (na), not reported (nr), background (bkgr), fast Fourier transform (FFT), schizophrenia (scz), schizophrenia paranoid type (SPT), schizoaffective (SAD), undifferentiated (UD), disorganized (DO), catatonic (cat), schizophreniform (sczf), residual (res).

[b] If HL (Hearing Level), SPL (Sound Pressure Level), peSPL (peak Sound Pressure Level) or SL (Sensation Level) was not specified in a study, it is not included in the table.

[c] Ratio and/or amplitude available from plot only (~).

[d] Control data previously reported in Siegel et al. (1984).

[e] Previously reported in Adler et al. (1982), Freedman et al., (1983), Siegel et al. (1984).

[f] Second number in parenthesis is mean of S.D.s from each study.

Click durations reported ranged from 0.04 to 10 ms with the majority between 0.04 and 4 ms, and click intensities ranged from 70 to 120 dB with the majority of intensities between 75 and 90 dB. High-pass filter settings used for the measurement of P50 ranged from 0 to 10 Hz, and low-pass filters ranged from 50 to 1500 Hz with the majority between 10 and 250 Hz (high and low pass). Forty-one of the studies reported used a high-pass filter setting of 10 Hz (see Table 1). In 19 studies clicks were presented through a speaker placed above the subject's head and parallel to the body (Freedman et al., 1983, 1987a; Siegel et al., 1984; Adler et al., 1982, 1985; Waldo and Freedman, 1986; Baker et al., 1987, 1990; Waldo et al., 1988, 1992, 1994; Cullum et al., 1993; Schwarzkopf et al., 1993; Nagamoto et al., 1989, 1991, 1996, 1999; Price et al., 2006; Hall et al., 2006). Another study presented clicks through a speaker placed in front of the subject (Kathmann and Engel, 1990). Nine studies presented clicks through earphones inserted into the ear canal (Kisley et al., 2001, 2003; Oranje et al., 2004; Johannesen et al., 2005; Edgar et al., 2003, 2005; Thoma et al., 2003, 2005, 2006). The other studies delivered the clicks using headphones.

Most studies measured P50 from the preceding trough, but eight early studies used a baseline period prior to or around P50 (Freedman et al., 1983, 1987b; Adler et al., 1982, 1985; Baker et al., 1987; Waldo and Freedman, 1986; Waldo et al., 1988; Kathmann and Engel, 1990) or used the baseline if P30 and P50 components were merged (Lamberti et al., 1993). Only about one-third of the studies discussed the P30 peak that precedes P50. Five studies eliminated trials with large P30 responses (Adler et al., 1990a,b; Baker et al., 1990; Waldo et al., 1992; Clementz et al., 1997a, 1998), arguing that they could contain myogenic artifact or a startle response (Nagamoto et al., 1989). The myogenic artifact that occurs around 30 ms appears as a very large amplitude negative–positive EEG wave (greater than 50 μV) and over 10 ms long, reflecting activity from the neck muscles (Robinson and Rudge, 1982; Adler et al., 1994). Others looked for P30 (Kisley et al., 2001) or required the presence of P30 to define P50 (Boutros et al., 1991a,b, 1999, 2004). In most studies, the P50 selection window was from 40 to 80 ms, but several studies used windows that started earlier, i.e., 25–75 ms (Judd et al., 1992), and 25–65 ms (Adler et al., 1982), or extended later (40–90 ms) (Schwarzkopf et al., 1993; Nagamoto et al., 1999; Adler et al., 2004; Becker et al., 2004; Oranje et al., 2004; Brunstein et al., 2005; Koike et al., 2005; Ghisolfi et al., 2002, 2004, 2006a,b). Nine studies recorded the EEG with eyes closed (Arnfred et al., 2003; Boutros et al., 1991a,b; Clementz et al., 1997b, 1998; Hetrick et al., 1996; Lamberti et al., 1993; Louchart-de la Chapelle et al., 2005a; Schwarzkopf et al., 1993) and 31 with subjects lying down.

2.1.3. Inclusion criteria for meta-analysis

A subset of 39 of the studies listed in Table 1 met the conventional inclusion criteria for meta-analysis: (1) they included both a schizophrenic and a normal control group; (2) they reported both a mean and a standard deviation for the P50 gating ratio; and (3) they reported a sample size for each group. Studies that reported P50 ratios in plot form only were excluded from the analysis. When a study reported P50 gating for several patient samples (for example, schizophrenic patients on typical vs. atypical medications), each was included since the ratios could be quite different. If a study reported the standard error, it was converted to an S.D. In the case where there is a distribution of effect sizes due to sampling differences and/or the influence of moderator variables, for example, a random effects meta-analysis is recommended and was used here (Sutton et al., 2000; Thompson and Simon, 1998).

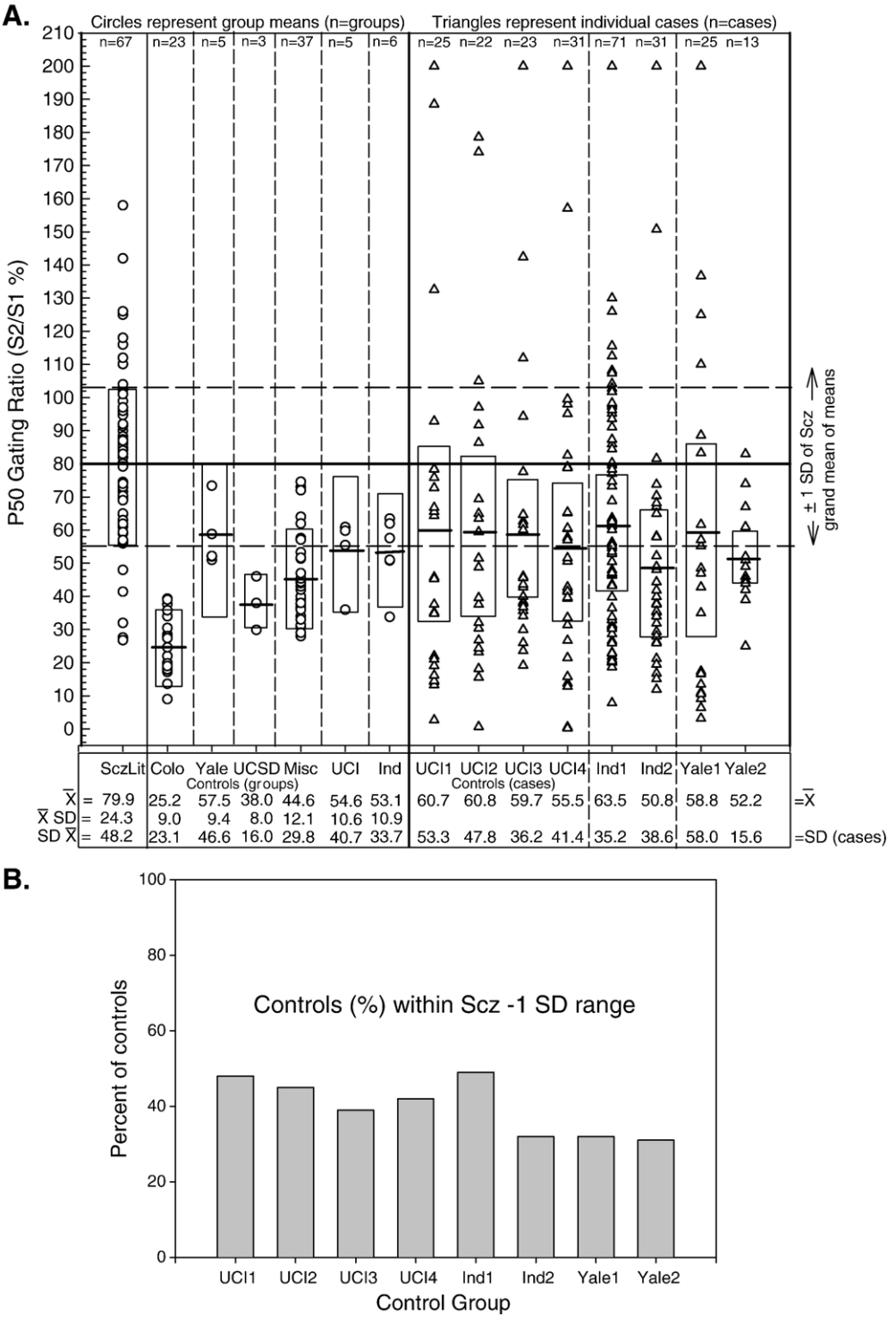
2.2. Control studies with P50 gating ratios for individual subjects

2.2.1. Subjects

Methods for the data collected from four groupings of individual healthy control participants from the

Fig. 1. In A, *mean* P50 gating ratios for schizophrenic and control groups from 84 studies reported in the literature are plotted in circles. The means for the schizophrenia studies are reported in the first column of circles (SczLit). The means for the control studies reported in the literature are separated into 3 from the Yale, 3 from the UC San Diego (UCSD), and 23 from the Colorado (Colo) groups, and 37 others (Misc), and are shown in the next 4 columns of circles. The triangles in the columns 8–15 represent *individual case* P50 gating ratios from the 4 UCI, 2 Indiana (IU), and 2 Yale control samples. The means for the UCI, IU and Yale studies are shown in circles in columns 3, 6, and 7. The dashed lines show the standard deviation of the *grand mean of the means* for the schizophrenic studies. Solid lines show the overall grand mean of the group means for the schizophrenic (SczLit) (long solid line) and control (Colo, UCSD, Yale, Misc) studies from the literature (short solid lines), and the mean over individual cases for each of our control samples (UCI1–4, Ind1–2, Yale1–2) (short solid lines). The boxes surrounding each mean are the mean of the reported standard deviations (literature studies) or the standard deviation over individual cases (UCI, Yale, Ind studies) for each study. The grand mean of the means (literature studies) or the mean of the individual cases ($\bar{X}$) is reported below each column of symbols, along with the standard deviation of the means (literature) or cases (S.D. $\bar{X}$), and the mean of the reported standard deviations for each study (literature) ($\bar{X}$ S.D.). The percentage of subjects in each of our control groups (UCI, Yale, Ind) who fall within the schizophrenic −1 S.D. range is shown in B.

University of California, Irvine (UCI1, UCI2, UCI3, UCI4), two groupings from Indiana University (IU1, IU2), and two groupings from Yale University (Yale1, Yale2) are shown in Table 2. Normal controls were interviewed by a psychiatrist and/or screened by a modified SCID to confirm the absence of a personal or family history of mental illness. None of the controls reported using psychiatric or illicit drugs.



2.2.2. P50 collection

P50 data are reported for the CZ recording site referenced to linked mastoids (UCI1–4), linked ears (Yale1–2), or the tip of the nose (IU1–2), collected using Nihon Koden amplifiers (UCI1, UCI2, UCI4), SA Instrumentation amplifiers (UCI3), Sensorium amplifiers (IU1), Synamp amplifiers, Neuroscan, Inc. (IU2, Yale1), or Grass amplifiers (Yale2).

2.2.3. P50 measurement and analysis

For the control data reported from UCI1, UCI2, UCI3, and UCI4, EEG data were averaged over trials to obtain an average P50 response for each click. In order to compare the effect of band pass filter on the definition and measurement of P50, data were filtered using band pass filters between 0.8–55, 10–55, and 30–55 Hz before being measured. The band pass roll-off settings were 12 dB per octave at 10 Hz and 24 dB per octave at 55 Hz. The P50 evoked potential was defined as the most positive peak between 40 and 80 ms after click onset, and was measured from the peak to the preceding trough. A P30 peak was required to define P50 (Boutros et al., 1991a,b, 1999, 2004). The gating ratio was calculated as the amplitude of the P50 peak to the second click (S2) divided by the P50 peak to the first click (S1). The data from IU1 and IU2, and Yale1 and Yale2, were filtered from 10 to 50 Hz prior to measurement. For all eight groups, subjects with S1 amplitudes below 0.5 μV were excluded from further analysis due to the difficulty in distinguishing a peak from noise, and to replicate the methods of other studies (Nagamoto et al., 1989; Kathmann and Engel, 1990; Griffith et al., 1995; Boutros et al., 2004). Also, to reduce the effect of extreme outliers, and in agreement with previous studies, P50 gating ratios greater than 200% were truncated to 200% (Nagamoto et al., 1991, 1996; Adler et al., 1993; Erwin et al., 1994; Griffith and Freedman, 1995; Ringer et al., 2004).

3. Results

Along with the demographic data and methods, Table 1 presents the mean P50 amplitude at S1, and the mean P50 gating ratio and standard deviation reported from each literature study for schizophrenic patients and normal controls. P50 gating ratios (S2/S1) for the schizophrenic groups range from 56 to 158% (mean = 79.9, S.D. = 24.3), with a range of 9 to 73.4% for the controls (mean = 38.8, S.D. = 15.3).

In Fig. 1, the mean P50 gating ratios (S2/S1) for the schizophrenic (column 1) and normal control groups (columns 2–7) reported in the literature and presented in Table 1 are plotted and compared with P50 gating ratios from individual cases for the eight samples of normal controls from UCI, IU, and Yale (columns 8–15). Each point (circle) plotted for the studies reported from the literature is a mean over the sample of subjects for that study, and the points (triangles) from the controls from UCI, IU, and Yale represent gating ratios from single subjects. The means over individual subjects in the UCI, IU, and Yale samples also are presented (in circles) for comparison with the literature means (columns 3, 6, 7).

3.1. Comparison of schizophrenic and control subjects by meta-analysis

In Fig. 2, a forest plot of the random effects meta-analysis is shown for the P50 gating ratio for the 39 out of the total of 84 studies presented in Table 1 that met the inclusion criteria described in Section 2. This plot presents mean differences and interval estimates for the studies used in the meta-analysis, and also provides a visual representation of the heterogeneity among the results of the studies. The average difference in the P50 gating ratio across these studies was 45.8% and the 95% confidence interval for this mean was 38.2 to 53.4%. The null hypothesis that all studies showed no effect ($x^2_{46} = 2626.0$, $P < 0.0001$) was rejected by the meta-analysis. The meta-analysis also showed that the differences were not the same across all the studies (Cochran's $Q_{45} = 406.9$, $P < 0.001$). The means of the P50 gating ratio in 45 of the 46 group comparisons were larger for schizophrenic than for control subjects, and these differences were significant for 35 of those comparisons. In Fig. 3, the forest plot for P50 S1 amplitudes is shown for the 36 group comparisons from Table 1 that met the inclusion criteria for meta-analysis. The confidence intervals for 25 of the 37 studies overlapped the 0 difference line, and 12 studies did not overlap. The meta-analysis again rejected the null hypothesis of 0 difference for all studies ($x^2_{37} = 499.3$, $P < 0.0001$), and again showed that the differences were heterogeneous and not the same across all the studies (Cochran's $Q_{36} = 298.8$, $P < 0.001$).

3.2. Overlap between schizophrenic and control subjects

The mean P50 gating ratio for the schizophrenic subjects reported in the literature is 79.9 (solid horizontal line intersecting the *y*-axis, Fig. 1,A), and 1 S.D. (24.3) below this mean (dotted horizontal line, Fig. 1,A) is 55.6. The mean P50 gating ratio from each control sample is below or near the 1 S.D. line for the schizophrenics

Table 2
Sample demographics and methodological parameters for studies with individual cases

Group	*n* male, *n* female	Mean age (S.D.), range	Band pass filter, sample rate (Hz)	Click intensity (dB, SPL)	Click duration (ms)	Inter-click/ pair interval	Transducer
UCI1	17 f, 8 m	34.7 (12.6), 21–63	0.56–500, 1379	80	0.1	500 ms, 10 s	Sony headphones
UCI2	15 f, 6 m	34.7 (12.6), 21–63	0.56–500, 1379	100	0.1	500 ms, 10 s	Sony headphones
UCI3	8 f, 16 m	27.4 (8.0), 20–51	0.10–300, 3333	89	0.1 (1.5 ms ear)	500 ms, 10 s	TDH-39 headphones
UCI4	15 f, 14 m	23.2 (6.1), 19–45	0.56–500, 1379 (2756 for $n=10$)	100	0.1	500 ms, 10 s	Sony headphones
Ind1	11 f, 20 m	20.4 (4.2), 18–36	0.01–300, 1000	81 in 58 white noise	3 (insert output)	500 ms, 7–11 s	Tuberphone insert earphones
Ind2	38 f, 35 m	35 (10.3), 18–56	0.05–200, 1000	81 in 58 white noise	3 (insert output)	500 ms, 7–11 s	Tuberphone insert earphones
Yale1	2 f, 24 m	45 (8.7), 26–61	0.05–300, 1000	90 ear	4	500 ms, 10 s	Earphones
Yale2	13	Matched to scz	10–300, 2000	95 peak	4	500 ms, 10 s	Earphones

(columns 2–7). Over the eight control samples containing data from individual subjects (UCI1–4, IU1–2, Yale1–2, columns 8–15), approximately 40% had P50 gating ratios within the "schizophrenic 1 S.D. range" defined here as 1.0 S.D. below the literature mean for patients with schizophrenia (Fig. 1,B). (If the mean of the S.D.s reported in each of the literature studies, 48.2, were used to estimate the S.D. of the literature means reported for the patients with schizophrenia, a larger percentage of controls would fall outside the "schizophrenic 1 S.D. range" as defined for this study.) One-way analysis of variance (ANOVA) ($F_{6,140}=27.32$, $P<0.001$) followed by Fisher's Least Significant Difference (LSD) multiple-comparison test showed that each control group was significantly different from the schizophrenic groups reported in the literature.

3.3. Comparison of control groups

One-way ANOVA comparing P50 gating ratios for the controls with data from individual subjects (UCI, Yale, Ind) yielded no significant differences among the groups ($F_{7,240}<1$, n.s.) at the high-pass filter setting of 10 Hz. When the groups UCI1–UCI4 were compared at each filter setting (group × filter, with repeated measures on the filter factor), no significant main effect for group was found ($F_{2,81}<1$, n.s.). The group by filter interaction also was not significant ($F_{2,278}<1$, n.s.).

The reported means of the control groups from the literature (Colo, Yale, UCSD, and Misc) were compared with the mean of the means from the groups of controls with data from individual subjects (UCI1–4, IU1–2, Yale1–2), using the high-pass filter setting of 10 Hz. One-way ANOVA was significant ($F_{5,754}=14.24$, $P<0.001$). Fisher's LSD multiple-comparison test showed that each control group except UCSD was significantly different from the Colo group. None of the other groups was different from each other except Yale, which differed from the Misc group.

3.4. Effect of high-pass filter setting

Table 3 shows the mean P50 gating ratio for a high-pass filter of 0.8 Hz compared with high-pass filters of 10 Hz and 30 Hz for the controls from UCI1, UCI2, UCI3, and UCI4. A comparison of high-pass filters of 0.01 and 10 Hz is shown for control group IU1. Repeated measures ANOVA (group by filter) was used to test the effects of filter setting on P50 gating ratios for control groups UCI1–UCI4. The main effect of filter setting was significant, $F_{2,219}=6.43$, $P=0.001$. Fisher LSD post-hoc tests showed that, for each group, the P50 ratio for the 10-Hz and 0.8-Hz filters was smaller than the ratio when the filter was 30 Hz. Differences in the P50 ratio between the 10-Hz and 0.8-Hz filters (see Table 3) were not significant. For group IU1 (the other study with gating data for more than one filter), the P50 gating ratio was significantly smaller when the high-pass filter was 0.01 compared with 10 Hz ($t_{60}=3.67$, $P<0.01$).

3.5. Effect of P30

Fig. 4 shows the effect of filter setting on the measurement of P50 for one control subject. As the figure

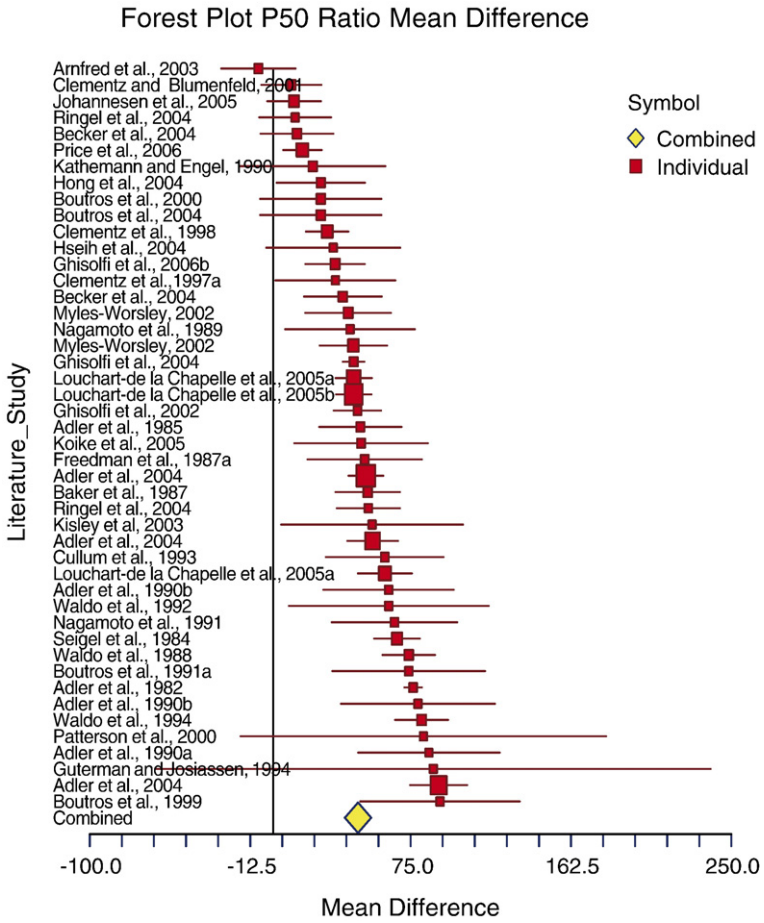


Fig. 2. The forest plot shows the differences in the P50 gating ratio between schizophrenic and control subjects for each study that met the inclusion criteria for meta-analysis. Each square represents the mean difference between schizophrenic and control subjects for that study, with the area of the square reflecting the weight (determined by the sample size) given to that study in the meta-analysis. Each horizontal line represents the 95% confidence interval for the mean difference in that study. The vertical line shows the point of 0 difference. The center of the diamond represents the overall difference across all studies (calculated as the weighted average of the individual differences), and the lines on either side show the 95% confidence interval.

shows, P30 is merged with P50, especially at the 0.8-Hz filter setting. The peak becomes more distinguishable from P50 at the 10-Hz setting, and is completely clear when the filter is set at 30 Hz. With filter settings of 10 and 55 Hz, the amplitude of P50 measures 4.2 μV when P30 is taken into account compared with 8.7 μV when P50 amplitude is measured from the P30 trough.

Twenty-eight normal controls from groups UCI1–UCI4 had P50 peaks that were at least mostly merged with P30 at the high-pass filter settings of 0.8 and 10 Hz, as illustrated in Fig. 3. At the 10-Hz filter setting, measuring the amplitude of P50 from the trough of P30 produced mean P50 ratios that were lower (29.8%) than when P50 was measured using the trough of P50 (45.0%). These differences in the gating ratio measured from the trough of P30 compared with the P50 trough were significant by *t*-test ($t_{27}=5.76$, $P<0.001$).

3.6. Effect of click intensity

The effect of intensity on the P50 gating ratio, as a function of filter setting, was tested by comparing the group of subjects in samples UCI1 and UCI2 who were tested at both the 80- and 100-dB intensities. Repeated measures ANOVA (intensity by filter) showed no significant main effect of intensity in the P50 gating ratio at 80 compared with 100 dB ($F_{1,21}<1$, n.s.). The effect of filter setting was significant ($F_{2,38}=3.21$, $P=0.05$), showing that P50 gating ratios at the 0.8-Hz and 10-Hz filters (50%, 62%) were less than at the 30-Hz filter (72%). An independent groups *t*-test comparing P50 ratios for the groups tested at 80 dB (UCI1, UCI3, IU1, IU2) (60%) with those tested at 100 dB (UCI2, UCI4) (55%) showed no significant effect of intensity ($t_{41}<1$, n.s.) at the 10-Hz filter setting. When the effect

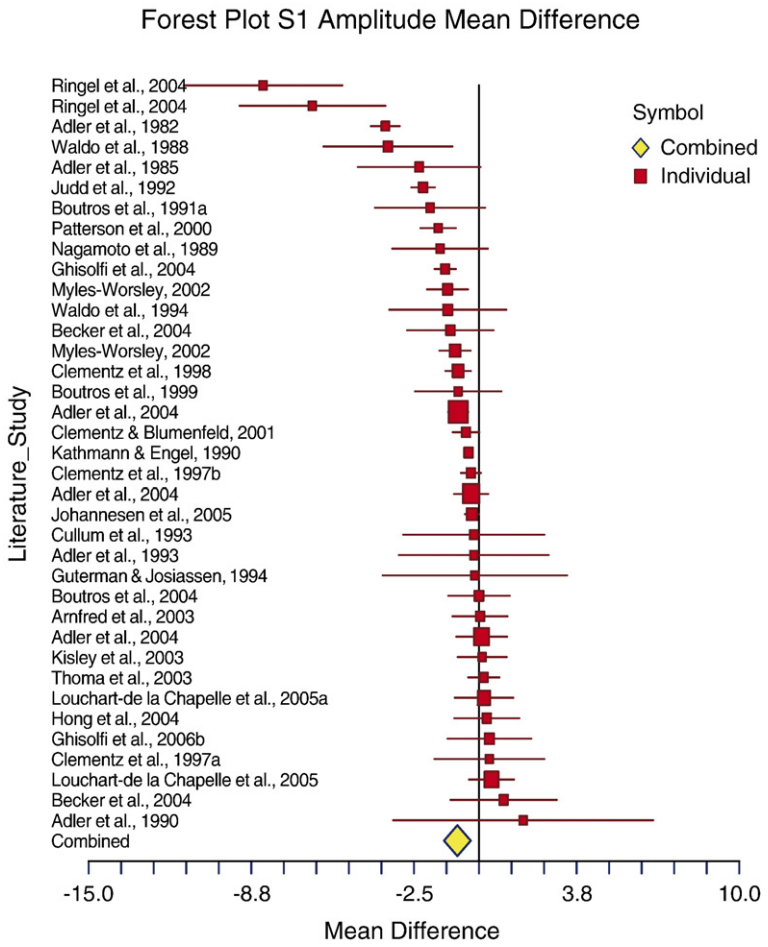


Fig. 3. The forest plot shows the differences in the S1 amplitude between schizophrenic and control subjects for each study that met the inclusion criteria for meta-analysis. Each square represents the mean difference between schizophrenic and control subjects for that study, with the area of the square reflecting the weight (determined using the sample size) given to that study in the meta-analysis. Each horizontal line represents the 95% confidence interval for the mean difference in that study. The vertical line shows the point of 0 difference. The center of the diamond represents the overall difference across all studies (calculated as the weighted average of the individual differences), and the lines on either side show the 95% confidence interval.

of intensity was tested using all three high-pass filter settings, ANOVA with repeated measures combining groups UCI1 and UCI3, and UCI2 and UCI4 (intensity × filter setting) again showed no significant effect of intensity ($F_{1,104}=1.17$, n.s.) (64%, and 57%, respectively).

3.7. Effect of sex

The effect of gender was tested using the control groups with data from individual subjects (UCI1–UCI4, Ind1, Ind2, Yale1, Yale2). (For this analysis, the IU P50 ratios collected using a high-pass filter of 0.01 Hz were

Table 3
P50 gating ratio (percent) (and standard deviation) as a function of filter setting

High-pass filter (Hz)	UCI1	UCI2	UCI3	UCI4	High-pass filter (Hz)	Ind1
0.8	57.4 (55.3)	51.5 (47.3)	61.4 (39.8)	42.2 (40.2)	0.01	49.3 (50.0)
10	60.7 (50.9)	60.8 (46.8)	59.7 (42.5)	55.5 (43.5)	10	63.5 (35.2)
30	79.8 (36.8)	69.8 (31.7)	67.3 (35.4)	64.3 (35.5)		

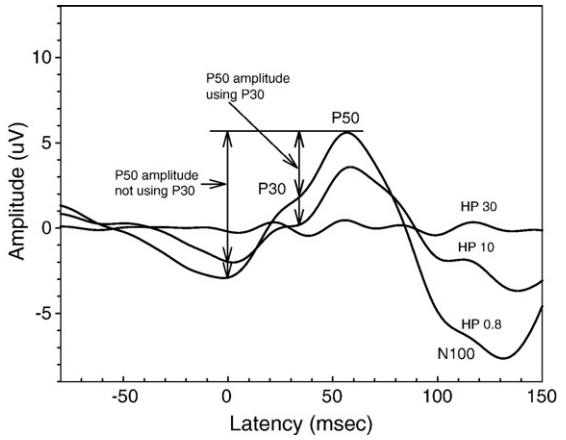


Fig. 4. EP waveforms for one individual control subject are compared with high-pass (HP) filter settings of 0.8, 10, and 30 Hz, and a low pass of 55 Hz. The P30, P50, and N100 peaks at each filter setting are indicated with labels. The P30 and P50 peaks are merged for this individual, especially when the high-pass filter is 0.8 Hz. At 10 Hz, P30 becomes more visible, and at 30 Hz, P30 is clearly distinguished from P50.

combined with the 0.8 filter for UCI.) When the groups were separated by filter setting, females had larger P50 gating ratios than males at the 0.8-Hz high-pass filter (mean=45.4, S.D.=42.2, males mean=57.4, S.D.=46.2, females, $F_{4,148}=4.42$, $P=0.037$) (group×sex ANOVA). (The gender difference also was significant when the IU data were excluded.) The gender difference was not significant at the high-pass filter settings of 10 Hz (mean=55.8, S.D.=39.4, males, mean=62.6, S.D.=42.4, females, $F_{6,215}<1$, n.s.), or 30 Hz (mean=71.4, S.D.=37.5, males, mean=72.4, S.D.=34.8, females, $F_{3,79}<1$, n.s.).

3.8. Effect of age

The correlation between age and the P50 gating ratio was significant ($r_{164}=0.18$, $P<0.05$) when tested across control groups UCI1, UCI3, UCI4, IU1, and IU2 at the 10-Hz high-pass filter setting. When the Yale groups were included, the correlation did not reach significance ($r_{187}=0.12$, n.s.). The correlations for the 0.8- and 30-Hz filter settings, including groups UCI1, UCI3, UCI4, also were not significant ($r_{53}=0.19$, n.s., and $r_{56}=0.14$, n.s., respectively).

3.9. Effect of earphone type and speaker delivery

The P50 gating ratio was not affected by headphone type when UCI1 and UCI4 (Sony headphones), UCI3 (TDH-39), and IU1 and IU2 (ear inserts) were compared (one-way ANOVA, $F_{2,178}<1$, n.s.). Thirteen of the 15 studies from the literature that delivered the clicks through a speaker above the subject's head and parallel to the body were from the Colo laboratory. As shown in Section 3.3, one-way ANOVA on ranks and Fisher's LSD multiple-comparison test showed that each control group except UCSD significantly differed from Colo.

4. Discussion

The results of this study indicate that P50 gating ratios for normal controls can show a wide range of values. For the control data from individual cases reported here from UCI, IU, and Yale, about 40% of the controls had gating ratios that were within 1 S.D. below the mean of means or the schizophrenic subjects reported in the literature. The mean of the gating ratios from the control groups with data from individual subjects ranged from 51 to 63, and these groups did not differ significantly from each other. A number of the literature studies cited in Table 1 also reported P50 gating ratios for controls in this range or higher (51.4–73.4) (Kathmann and Engel, 1990; Jerger et al., 1992; Cardenas et al., 1993; Lamberti et al., 1993; Schwarzkopf et al., 1993; McCallin et al., 1997; Boutros et al., 1991a,b, 1994, 1999, 2004; Johannesen et al., 2005; Ghisolfi et al., 2006a, see Table 1). Also, inspection of the means and S.D.s provided in the literature studies (Fig. 1 and Table 1) suggests some overlap in P50 gating ratios between schizophrenia and control groups in many studies. The overall mean for the literature controls was 38.8 with an average standard deviation across studies of 28.5. The overall mean of the means for the control groups from Colo reported in the literature (25.2) was significantly lower than the mean for all the other control groups except UCSD. In addition, though, the overall mean of the standard deviations reported across the Colo studies was 23.1, showing that at least some of the controls from these studies would have gating ratios comparable to those reported for our data from individual subjects. Despite this variability in P50 ratios across studies, however, all the control groups had P50 ratios that were significantly smaller than the groups with schizophrenia reported in the literature.

Meta-analysis of the studies from the literature that met the inclusion criteria showed a significant difference in the gating ratio between schizophrenic and control subjects, but also significant heterogeneity among studies, in agreement with Bramon et al. (2004). In 45 of 46 group comparisons, the P50 ratio was larger in the schizophrenic groups than controls (see Fig. 2), and the ratio for 35 of these group comparisons did not intersect

the 0 difference line, indicating a significant difference between the control and schizophrenic groups. The meta-analysis for P50 S1 amplitude also rejected the null hypothesis of 0 difference between schizophrenic and control subjects, but 25 of the 37 studies included overlapped the 0 difference line, indicating not only heterogeneity of results, but also suggesting that the ratio may differentiate schizophrenic and control subjects better than S1 amplitude. Importantly, there are factors to consider when evaluating results of meta-analyses, and an important one of these is publication bias, which leads to more studies with positive results being accepted for publication than those with negative results (Thompson and Simon, 1998; Sutton et al., 2000). However, these results do offer support that the P50 gating ratio deficit meets the first of the criteria for a candidate endophenotype (it is present in the illness of interest), especially since the candidate endophenotype may not be present in every case, and there are potentially many risk factors for a complex disorder such as schizophrenia (Braff et al., 2007). There also is accumulating evidence that the gating ratio deficit may satisfy the heritability criterion for an endophenotype (Adler et al., 1999; Waldo et al., 2000).

The P50 ratio measure has inherent reproducibility problems since both the numerator and denominator are affected by signal to noise issues (Smith et al., 1994; Adler et al., 1999). In the few studies that have examined the reliability of the P50 gating ratio, Smith et al. (1994) and Boutros et al. (1991b) observed a lack of reliability over different testing sessions (intraclass correlation coefficients [ICC]=0.0 and 0.15, respectively, for both studies over three testing sessions separated by 1 week), with amplitude measures achieving somewhat higher ICCs (0.68–0.86). Lamberti et al. (1993) observed an ICC=0.47 for the gating ratio over four blocks within a single session. In contrast to these studies, Hall et al. (2006) studied two necessary criteria for an endophenotype (reliability and heritability) in monozygotic and dizygotic twins and concluded that their results for both supported the P50 ratio as a candidate endophenotype. With a stringent trial selection criterion (excluding trials at CZ or eye channels exceeding 20 μV), the ICC for the P50 gating ratio over two occasions from 7 to 56 days apart ranged between 0.40 and 0.82 with a mean of 0.66.

Taken together, our control studies and review of the literature suggest that individual differences are quite large and that, while promising, considering sensory gating as a candidate endophenotype useful for classifying individuals could be problematic until the stability, specificity and consistency of this measure are better established. There are several critical methodological issues that if standardized across studies might aid in the achievement of this goal. These include click intensity, click duration and rise time, band pass-filter settings, earphone characteristics, inclusion of P30 in the definition of P50, and trial rejection criteria. Almost no parametric studies have been conducted to determine how click duration affects P50 measurement. Recently, however, White and Yee (2006) found that neither the P50 gating ratio nor P50 amplitude differed when stimulus durations of 1, 3, and 5 ms were compared. It also has been found that auditory brainstem response thresholds for clicks are not affected by their duration, even though behavioral thresholds are affected (Hecox et al., 1976; Gorga et al., 1982). To enhance comparisons across studies, both the physical click duration and its duration at the output of the transducer should be clearly stated. All of the Colo studies used short click durations of 0.04 ms (reportedly 1 ms at the ear) presented through speakers. While it is not possible to separate these effects, the combination of short click duration and speaker (vs. headphone) presentation may have contributed to the differences between P50 gating ratios for controls reported by Colo and the ratios reported in other studies, since these factors could influence click characteristics at the ear. In the Kathmann and Engel (1990) study, for example, click duration (1.5 ms) has been noted as a possible explanation of the higher gating ratio (73%) found in controls (see Judd et al., 1992) due to duration effects on the power of the click. Evidence regarding this argument is still equivocal, however, since other studies have used click durations from 1.5 to 10 ms and observed mean suppression ratios of 29–50 in controls (Guterman et al., 1992; Guterman and Josiassen, 1994; Yee and White, 2001; Arnfred et al., 2001a,b, 2003; Edgar et al., 2003; Boutros et al., 1999, 2004; Johannesen et al., 2005; Oranje et al., 2004; Thoma et al., 2003, 2005). Two of these same studies found low gating ratios in patients with schizophrenia (32%, Arnfred et al., 2003 and 56%, Thoma et al., 2003, 2005), findings which, even if participants had been unmedicated and/or stable for a long time (Arnfred et al., 2003; Thoma et al., 2003), question a trait definition of the P50 ratio. Kathmann and Engel (1990) also measured P50 relative to baseline as only some of the studies included in Table 1 have done (Adler et al., 1982; Waldo and Freedman, 1986; Waldo et al., 1992; Baker et al., 1987, 1990; Freedman et al., 1987a,b; Kisley et al., 2004), but these studies observed a comparatively lower P50 ratio in controls.

Click intensity can affect the P50 response, perhaps depending on the levels being compared. Griffith et al. (1995) found significant differences in the gating ratio between schizophrenic and control groups when clicks were 30 and 50, but not 70 dB above threshold. White and Yee (2006) reported that the P50 ratio did not differ at click

intensities of 80, 90, or 100 dB SPL, or at background intensities of 0, 40, and 55 dB SPL, but P50 S1 amplitude was significantly affected by the intensity of the click and background. The results reported here also found no difference in the P50 gating ratio when the click intensity was 80 compared with 100 dB. As Table 1 shows, the duration and intensity of the clicks used to elicit the P50 response varied across the studies reported in the literature. Clearly, differences between headphones and speakers also can alter the properties of the stimuli as perceived by the subject, including loudness, duration, frequency and presence or absence of extraneous sounds, and most of the early studies used speakers (Siegel et al., 1984; Waldo and Freedman, 1986; Freedman et al., 1983, 1987b; Adler et al., 1982, 1985, 1990b; Baker et al., 1987, 1990; Kathmann and Engel, 1990; Cullum et al., 1993; Waldo et al., 1988, 1992, 1994; Nagamoto et al., 1989, 1991, 1996, 1999; Price et al., 2006). Nine studies presented the clicks with a white noise background (Hetrick et al., 1996; Clementz et al., 1997a,b, 1998; Yee and White, 2001; Arnfred et al., 2003; Louchart-de la Chapelle et al., 2005a; Johannesen et al., 2005; White and Yee, 2006). Additionally, there are no set standards for the measurement of the intensity of the short duration broadband clicks used in generating the P50 response in sensory gating studies. Measurement of these click transients is difficult since most sound level meters cannot reliably capture such short duration events (Stapells et al., 1982; Gorga et al., 1985; Sininger, 1992). One recommended approach is to route the output of the meter to an oscilloscope so that its amplitude can be measured, and then generate a long-duration sine wave with an equivalent voltage that can be measured with the meter (Gorga et al., 1985). It should be clearly stated in studies whether intensity level has been defined using hearing level (HL), sound pressure level (SPL), or sensation level (SL), and participants should not have significant hearing deficits in the range of frequencies represented by the clicks. Calibration of click intensity using the sensation level for each individual subject would help reduce the effects of hearing differences among subjects, especially when older individuals are being tested. In view of the emphasis on using the P50 gating ratio as an endophenotype, it is surprising that more studies have not been done that specifically test the within-study stability of the P50 ratio and the contribution of these methodological issues. We believe that by comparing different studies with diverse samples and methodologies, the current study contributes to these issues by providing evidence regarding the generalizability and repeatability of P50 ratio findings across studies.

Our results showed that the P50 gating ratio was affected by the selection of the trough used to measure P50 amplitude. In those healthy control subjects whose P30 and P50 peaks were at least mostly merged into one peak, the P50 gating ratio was significantly smaller when the trough preceding P30 was used to measure P50 peak amplitude compared with the trough preceding P50. As mentioned in Section 1, this becomes an issue because some studies have excluded trials with large or prolonged (>10 ms) P30 responses (Nagamoto et al., 1989; Adler et al., 1990a,b; Waldo et al., 1992; Clementz et al., 1997a, b, 1998), due to a presumption that it might represent myogenic artifact (Nagamoto et al., 1989), or used P50 selection windows that could include P30, e.g., 25–75 ms (Judd et al., 1992) or 25–65 ms (Adler et al., 1982), if P30 and P50 were merged. McCallin et al. (1997) showed that P50 gating ratios did not differ significantly when subjects were seated (potentially generating more neck muscle artifact) compared with when they were supine, and a P30 component of neural origin is well known (Deiber et al., 1988; Buchwald et al., 1992; Liegeois-Chauvel et al., 1994). Other investigators have required the presence of P30 to define P50 (Boutros et al., 1991a,b, 1999, 2004), or looked for the P30–P50 complex (Freedman et al., 1983; Kisley et al., 2001). Still others (Jerger et al., 1992; Cardenas et al., 1993; Lamberti et al., 1993; McCallin et al., 1997) measured P50 from the baseline when the preceding negativity was obscured by an overlapping P30. These differences could clearly result in P50 amplitude measurement variability. Our recommendation is that future studies use P30 to define P50.

Several studies already have shown that filter settings are important in P50 measurement and quantification of the gating ratio (Clementz et al., 1997a,b; Freedman et al., 1998; Kanno et al., 2000; Patterson et al., 2000; Yvert et al., 2001; Hong et al., 2004). Our results showed that choice of high-pass filter setting also had a significant effect on the P50 ratio. The gating ratio was smaller at high-pass settings of 0.8 and 10 Hz, than at 30 Hz. Fig. 2 reinforces this point by illustrating the effect of the filter on P50 amplitude. The majority of studies reported in the literature have used a high-pass filter setting of 10 Hz, and this appears to maximize the measurement of P50 by increasing its amplitude. However, there are reports that activity less than 10 Hz contributes to the P50 response (Clementz and Blumenfeld, 2001) and that using a high-pass filter greater than 3.0 Hz might even artificially increase P50 amplitude (Kanno et al., 2000; Yvert et al., 2001). Thus, by affecting P50 amplitude, the choice of filter setting is critical and can significantly influence the ratio measure. Indeed, Clementz and Blumenfeld (2001) observed larger ratio differences between groups at filter settings of 1–20 Hz than 20–50 Hz. Until the effects of band-

pass filter become clear, it is necessary to compare results using both 100 Hz and at least 3-Hz high-pass filters. Also, our results show that the addition of a filter that excludes the low frequency activity (e.g., 30 Hz, as in the current study) is useful for measurement purposes since it can help to distinguish the P30 and P50 peaks (see Fig. 4).

Another methodological issue concerns whether or not the P50 measurements are made blind to clinical diagnosis and disease status. Many of the studies do not discuss this issue, but 10 of the studies cited in Table 1 report that analyses were conducted blind to group membership (Siegel et al., 1984; Adler et al., 1985; Baker et al., 1987; Freedman et al., 1987b; Waldo et al., 1988, 1992; Clementz et al., 1998; Boutros et al., 2000; Becker et al., 2004; Louchart-de la Chapelle et al., 2005a; Ghisolfi et al., 2004, 2006b; Hall et al., 2006), or clinical response to medication or treatment condition (Boutros et al., 1991b; Griffith et al., 1998; Nagamoto et al., 1999; Arango et al., 2003; Oranje et al., 2004; Adler et al., 1994, 2005; Brunstein et al., 2005; Ghisolfi et al., 2006b; Olincy et al., 2006), and this is important to ensure that the P50 measurements are unbiased.

There also are a number of subject factors that could contribute to the variability in P50 gating ratios across controls. For example, our results showed that the P50 gating ratio can be affected by sex as well as age. The P50 gating ratio was larger for females than for males at the high-pass filter setting of 0.8 Hz, in agreement with previous studies (Hetrick et al., 1996). Age was positively correlated with the P50 gating ratio at the 10-Hz high-pass filter setting, indicating that as age increased, sensory gating ability decreased. While the age and sex effects on P50 gating found in the current study were specific to certain filter setting and groups, both of these findings suggest that variations among studies in the composition of subject groups could lead to differences in reported P50 ratios. Subject characteristics and demographics such as sex and age cannot necessarily be controlled across different studies, but they can be carefully specified in each study because P50 is significantly affected by these variables. Especially for the patients, there are a number of other subject factors that could affect the P50 ratio, including clinical sub-diagnosis, symptoms, age of onset of illness, medication status, substance use, and smoking history. For example, paranoid schizophrenia patients may have normal P50 gating ratios (Boutros et al., 1991a; Johannesen et al., 2005). Also, several studies have shown that atypical neuroleptics, especially clozapine, can normalize the P50 gating ratio (Nagamoto et al., 1999; Light et al., 2000; Adler et al., 2004; Becker et al., 2004, see Table 1). More studies are needed to determine the effects of specific psychotropic medications, both typical and atypical, on the P50 gating ratio. Interestingly, for example, Adler et al. (1999) reported that patients on typical neuroleptics had a higher mean ratio with a larger standard deviation (although not significant) than those on no medication.

The P50 gating ratio can be labeled an endophenotype or "trait" deficit in schizophrenia when it is found to be a reliable marker that is state-independent and enduring across different subject characteristics such as diagnostic subtype and symptom status. Our finding that P50 gating ratios for 40% of controls were within the schizophrenic range as defined in this article, as well as the overlap evident in the studies reported in the literature, raises some questions concerning the specificity and stability of this measure. The P50 sensory gating ratio as a clinical measure in psychiatric practice or as an endophenotype will continue to benefit as uniformity is established in methodological procedures and standards of measurement across laboratories.

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