



Review article

Reduced auditory evoked potential component N100 in schizophrenia — A critical review

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Abstract

The role of a reduced N100 (or N1) component of the auditory event related potential as a potential trait marker of schizophrenia is critically discussed in this review. We suggest that the extent of the N100 amplitude reduction in schizophrenia depends on experimental and subject factors, as well as on clinical variables: N100 is more consistently reduced in studies using interstimulus intervals (ISIs) >1 s than in studies using shorter ISIs. An increase of the N100 amplitude by allocation of attention is often lacking in schizophrenia patients. A reduction of the N100 amplitude is nevertheless also observed when such an allocation is not required, proposing that both endogenous and exogenous constituents of the N100 are affected by schizophrenia. N100 is more consistently reduced in medicated than unmedicated patients, but a reduction of the N100 amplitude as a consequence of antipsychotic medication was shown in only two of seven studies. In line with that, the association between the N100 reduction and degree of psychopathology of patients appears to be weak overall. A reduced N100 amplitude is found in first degree relatives of schizophrenia patients, but the risk of developing schizophrenia is not reflected in the N100 amplitude reduction.

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1. Introduction

The amplitude of the N100 (or “N1”) component of the event related potential is often reduced in schizophrenia (initial report by Saletu et al., 1971), and reduced N100 amplitudes have been proposed as markers of functional brain changes related to genetic predisposition to schizophrenia (Ahveninen et al., 2006). However, due to the complexity of factors influencing the N100 amplitude, the significance of a reduced N100 amplitude in schizophrenia has remained somewhat unclear. The overall aim of the current review is to clarify some major issues related to N100 amplitude reduction in schizophrenia and to evaluate critically its potential as a trait marker of schizophrenia.

1.1. Psychophysiology of the N100

N100 is the largest component of the auditory evoked potential (AEP), peaking between 80 and 120 ms after stimulus onset and maximal over fronto-central leads. It is a primarily exogenous component, elicited by any discernible auditory stimulus in absence of task demands. N100 is associated with the onset of auditory stimuli, and its amplitude is strongly dependent on the rise time of stimulus onset (Spreng, 1980). In addition, N100 amplitude is influenced by a number of other factors, such as interstimulus interval (ISI) (Davis et al., 1966), stimulus intensity (Keidel and Spreng, 1965), arousal (Nash and Williams, 1982), and selective attention (Hillyard et al., 1973).

N100 is generated by a complex network of cortical areas, with generators located mainly bilaterally in supratemporal plane and superior temporal gyrus, but also in frontal and motor areas (Näätänen and Picton, 1987). In psychological terms, N100 is associated with percep-

tual processing, as indicated by its frequency specificity (Butler, 1968), being larger the more a stimulus deviates in frequency from the preceding stimulus, or the tonotopic organization of the neuromagnetic N100 (N100m) source in the auditory cortex (Pantev et al., 1988).

1.2. Specific aims of the review

First, we discuss whether the reduction of N100 amplitude in schizophrenia is dependent on experimental factors, especially ISI. A reduction independent of experimental factors would suggest a general deficit in perceptual processing of auditory information in schizophrenia. In contrast, a reduction dependent on experimental factors would suggest a functional deficit beyond simple perception. In this vein, the impact of attention processes on N100 reduction in schizophrenia is discussed.

Second, we evaluate the contribution of antipsychotic medications, as well as the impact of other psychotropic drugs on N100 amplitude reduction in schizophrenia. The impact of drugs is considered to be of interest because the disease related intake of medication (or recreational drugs) represents a serious confound in schizophrenia research.

Third, we attempt to disambiguate whether the whole network of cortical structures generating the N100 is affected by schizophrenia, or just a specific subset. This issue can be addressed by studies applying a detailed topographic analysis or by applying source reconstruction algorithms. A reduced activity of a subset of generators would specify the functional deficit.

Fourth, we discuss the contribution of the clinical state on N100 reduction in patients. An association with the gravity of symptoms would qualify a reduced N100, at least partially, as a state marker. In addition, a reduced

N100 in a subgroup of patients would suggest that N100 reduction is related to a specific syndrome rather than to schizophrenia in general.

Fifth and finally, we review the issue of the heritability of N100 amplitude, as addressed by family and

Table 1
Passive listening experiments

Authors	<i>N</i> total	<i>N</i> med.	ISI [s]	Stimulus duration [ms]	N100 amplitude in patients
Saletu et al. (1971)	19	19	2.0	100	↓
Shagass et al. (1978)	26	0	>3	0.1	↓
Saitoh et al. (1981)	10	9	2	150	↓
Connolly et al. (1985)	10	0	2.5	50	↓
Lifshitz et al. (1986)	51	?	8.5	1000	↓
Kessler und Steinberg (1989)	20	0	1	50	↓ (paranoid sz.)
Roth et al. (1991)	14	14	12–17	50	↓
Todd et al. (2000)	21	21	0.05–1	50	↓ (ISI=0.05 s)
Clunas and Ward (2005)	17	12	1–13	50	↓
Roth et al. (1980)	18	10	6.75–0.75–2.25	50	↓ ∅
Pfefferbaum et al. (1980)	15	8	1.5	464	∅
Roth et al. (1981)	22	14	8	50	∅
Schlör et al. (1985)	20	0	6.8	200	∅
Mukundan (1986)	29	0	3	100	∅
Roth et al. (1991)	17	0	12–17	50	∅
Adler and Gattaz (1993)	14	0	3.3	50	∅
Adler et al. (1990)	10	6	1.6/3.3	50	∅
∑ (all)			1		↑ 9/16 ↓

Findings on N100 amplitude in schizophrenia, as obtained in passive listening experiments; *N* total refers to the number of investigated schizophrenia patients; *N* med. to the number of patients with antipsychotic medication; the ISI [in s] and stimulus duration [in ms] are provided as experimental details; a down-tilted arrow indicates a significantly reduced N100 amplitude; the last line in the table summarizes the proportion of findings of reduced N100 amplitude in the total number of experiments in the table; studies might be cited twice in tables if they contained more than one experiment or reported separate values for medicated and unmedicated patients.

Table 2
Passive oddball experiments

Authors	<i>N</i> total	<i>N</i> medic.	ISI [s]	Stimulus duration [ms]	N100 amplitude in patients
Pfefferbaum et al. (1989)	10	10	1.5	50	↓
Iwanami et al. (1994)	27	27	2	50	↓
O'Donnell et al. (1994)	20	20	1.2	40	↓
Umbricht et al. (2003)	26	24	0.2	100	↓
Ahveninen et al. (2006)	23	22	0.5	50	↓
Shelley et al. (1999)	15	15	1/4 0.25/ 0.5	100	↓ ∅
Pfefferbaum et al. (1989)	13	0	1.5	50	∅
Catts et al. (1995)	22	11	0.51	50/100	∅
Javitt et al. (1995)	31	20	1.3	50	∅
Alain et al. (1998)	15	15	0.45–1.45	100	∅
Umbricht et al. (1998)	17	17	0.7–0.8	50	∅
Umbricht et al. (1999)	10	6	0.7–0.8	50	∅
Javitt et al. (2000)	30	27	0.7–0.8	100	∅
Michie et al. (2000)	14	14	0.46	50	∅
Todd et al. (2000)	21	21	0.51	50	∅
Alain et al. (2002)	17	17	0.07–0.27	126	∅
Kasai et al. (2002)	23	23	0.49–0.53	100	∅
Shinozaki et al. (2002)	13	13	0.45	50	∅
Todd et al. (2003)	20	20	0.45	50	∅
Valkonen-Korhonen et al. (2003)	25	0	1	?	∅
van der Stelt et al. (2004)	22	21	1.3–1.7	100	∅
Matthews et al. (2007)	18	18	0.5	50	∅
∑					6/22 ↓

Findings on N100 amplitude in schizophrenia, as obtained in passive oddball paradigms; the structure is the same as for Table 1.

twin studies, in order to elucidate the role of the N100 amplitude as a potential trait marker of schizophrenia.

2. Methods

We discuss N100s elicited during passive listening and active attention paradigms, by sounds presented in a uniform series (one sound), in an oddball series (frequent and deviant sounds), and in pairs. Although these

Table 3
Active oddball experiments

Authors	N total	N med.	ISI [s]	Stimulus duration [ms]	N100 amplitude in patients
Roth et al. (1980)	18	10	1	50	↓
Roth et al. (1981)	22	14	1/4	50	↓
Saitoh et al. (1981)	10	9	2	150	↓
Baribeau-Braun et al. (1983)	20	20	0.5/1.0	15	↓
Pfefferbaum et al. (1984)	20	11	1	40	↓
Barrett et al. (1986)	20	17	1.8	30	↓
Pfefferbaum et al. (1989)	10	10	1.5	50	↓
Michie et al. (1990)	10	0	0.2–0.5	50	↓
Blackwood et al. (1991)	96	?	0.9	20	↓
Eikmeier et al. (1991)	15	13	1.1–4.1	20	↓
Ogura et al. (1991)	54	0	1.5	90	↓
O'Donnell et al. (1993)	15	15	1.2	40	↓
Ford et al. (1994)	30	0	1.5	50	↓
O'Donnell et al. (1994)	20	20	1.2	40	↓
Oades et al. (1996)	24	24	1.15–1.65	50	↓
Stefansson and Jonsdottir (1996)	20	20	1.1	20	↓
Boutros et al. (1997)	50	50	2	40	↓ (disorg./ undiff. sz.)
Frodl et al. (1998)	35	35	1.5	40	↓
Potts et al. (1998)	24	22	1.2	40	↓
Ford et al. (1999)	57	57	1.5	50	↓
Laurent et al. (1999)	20	0	0.9	90	↓
Karoumi et al. (2000)	21	21	?	?	↓
Alain et al. (2001)	16	16	0.275–0.675	125	↓
Bruder et al. (2001)	14	0	0.9	250	(↓)
Kayser et al. (2001)	66	52	0.9	250	↓
Brown et al. (2002)	80	76	1.3	50	↓
Williams et al. (2003)	40	40	1.3	50	↓
O'Donnell et al. (2004)	12	12	1.2	40	↓
Kogoj et al. (2005)	25	25	2	50	↓
Sumich et al. (2006)	20	15	1	50	↓
Mucci et al. (2007)	40	37	1.5–2	220	↓ (deficit sz.)
Roth and Cannon (1972)	22	20	1	100	∅
Blackwood et al. (1987)	24	0	0.9	20	∅
Pfefferbaum et al. (1989)	13	0	1.5	50	∅
Egan et al. (1994)	16	16	1.5	100	∅
Javitt et al. (1995)	31	20	1.3	50	∅
Kathmann et al. (1995)	20	19	0.58 s	50	∅

Table 3 (continued)

Authors	N total	N med.	ISI [s]	Stimulus duration [ms]	N100 amplitude in patients
Umbricht et al. (1999)	10	6	0.7–0.8	50	∅
Winterer et al. (2001a,b)	42	34	1–1.5	50	∅
Valkonen-Korhonen et al. (2003)	25	0	1	?	∅
Gallinat et al. (2004)	15	0	1.5–4.6	0.1	∅
Σ					29/39 ↓

Findings on N100 amplitude in schizophrenia, as obtained in active oddball paradigms; the structure is the same as for Table 1.

are typically used to elicit mismatch negativities (MMN), P300s and P50 components, respectively, N100s are also elicited by the onset of the sound in each paradigm. To provide the most comprehensive review of N100 reductions in schizophrenia, we describe N100s elicited in all these paradigms. In addition to EEG, findings obtained by magnetoencephalography (MEG) recordings are also described, as N100 and N100m are highly correlated.

PubMed searches using the terms [schizophrenia] and [N1] and [auditory], [MMN] and [schizophrenia], [sensory gating] and [schizophrenia], ([N1m] or [M100] or [N100m]) and [schizophrenia] were conducted. Of note, all literature discussing the issue of a reduced N100 amplitude in schizophrenia was screened for additional references. However, not all studies necessarily provided information on the N100 amplitude in schizophrenia. Furthermore, studies lacking some essential information (as e.g. medication status) or lacking a healthy control group, as well as studies with minor relevance for this review were not included. Publications referring to the same patient sample were only cited once, if no additional information with regard to the N100 was provided in the second publication. Studies, published in other languages than English and German, were not considered for practical reasons. Studies are summarized in Tables 1–5 for different kinds of experiments separately. Studies might be cited twice when different kinds of experiments were conducted within a study or when medicated and unmedicated patients were analyzed as separate samples.

2.1. Experimental and subject factors

2.1.1. Influence of the interstimulus interval (ISI)

2.1.1.1. ISI and N100 amplitude. The dependence of N100 amplitude on the ISI is well documented (first reported by Davis et al., 1966): amplitude increases with

Table 4
Others kinds of experiments

Authors	<i>N</i> total	<i>N</i> med.	ISI [s]	Stimulus duration [ms]	N100 amplitude in patients
Bruder et al. (1999)*	26	18	7.5	250	↓
Mulert et al. (2001)**	18	0	2.5– 7.5	300	↓
Gallinat et al. (2002)**	21	0	2.5– 7.5	300	↓
Σ					3/3 ↓

Findings on N100 amplitude in schizophrenia, as obtained in other kinds of experiments; the structure is the same as for Table 1.

* active dichotic listening task; **active discrimination task.

increasing ISI and plateaus at an ISI of about 8–10 s. That is, it takes about 8–10 s until the neurons generating the N100 are fully responsive again. Such a phenomenon refers to the process of refractoriness or the neural recovery function and is also observed for other ERP components (e.g. P50, Erwin and Buchwald, 1986). The neural recovery function of the N100 is not linear, especially between 0 and 1 s. It is complemented by a short phase of facilitation shortly after a tone presentation: At ISIs less than 0.3 s, N100 is larger than would be predicted from N100 responses at ISIs greater than 0.3 s (Budd and Michie, 1994). Of note, the relation of refractoriness on the level of ERP components and of inhibitory processes on the neuronal level is poorly understood as yet (Wehr and Zador, 2005).

2.1.1.2. ISI and N100 amplitude in schizophrenia patients. Roth et al. (1980) first proposed that a reduction of N100 amplitude in schizophrenia patients depends on ISI. In their experiment, they recorded ERPs at three ISIs: 0.75, 2.25 and 6.75 s in a passive listening paradigm. N100 amplitude was reduced only at the longest ISI. Surprisingly, very few studies tried to replicate that finding. Shelley et al. (1999) used four ISIs: 0.25, 0.5, 1, 4 s and reported N100 reductions in schi-

zophrenia only for the two longest ISIs. In line with that, 12 of 14 passive oddball studies of schizophrenia using ISIs <1 s did not reveal statistically significant deficits in N100 amplitude (Table 2). Also, using an active oddball paradigm and an ISI=1 s, one of the very initial studies failed to show a reduction of the N100 amplitude in patients (Roth and Cannon, 1972).

Most studies applying ISI >1 s were able to reveal a significant reduction of N100 amplitude in medicated patients (Pfefferbaum et al., 1984; Connolly et al., 1985; Ford et al., 1994; O'Donnell et al., 1993, 1994, 2004; Oades et al., 1996; Stefansson and Jonsdottir, 1996; Boutros et al., 1997; Potts et al., 1998; Bruder et al., 1999; Brown et al., 2002; Williams et al., 2003; Kogoj et al., 2005), but also with some exceptions (Pfefferbaum et al., 1980; Roth et al., 1981; Adler et al., 1990; Egan et al., 1994; Javitt et al., 1995; Winterer et al., 2001a,b). Of those, only the study of Adler et al. (1990) reported a significant increase in N100 amplitude in schizophrenia patients.

Two studies with very large samples (Blackwood et al., 1991; Kayser et al., 2001) were able to show a reduced N100 amplitude at an ISI of 0.9 s in active oddball experiments. Thus, one might assume that a deficit in N100 amplitude is also apparent at ISIs <1 s, but less pronounced. Possibly, the deficit gets more pronounced again at very short ISIs: In a range of 0.1 to 1 s, patients did not exhibit a reduced N100, but they did at the shortest ISI of 0.05 s when controls showed an enhancement (Todd et al., 2000). Also Umbricht et al. (2003) reported a reduced N100 amplitude in patients at a very short ISI (0.2 s). Up to now, no study has investigated alterations of the N100 amplitude at longer ISIs (>1 s) and very short ISIs (<0.3 s) in the same patients. However, in sensory gating experiments, we have an opportunity to inspect the effects of ISI on a reduced N100 amplitude in schizophrenia. Sensory gating is studied in experiments in which subjects listen passively to click pairs, separated by 8–12 s and with an

Table 5
Sensory gating experiments

Authors	Recording	<i>N</i> total	<i>N</i> medic.	ISI [s]	Stimulus duration [ms]	N100/N100m amplitude in patients
Blumenfeld and Clementz (2001)	MEG	20	18	9	0.04	↓ (on S1)
Clementz and Blumenfeld (2001)	EEG	20	19	9	0.04	↓ (on S1)
Boutros et al. (2004)	EEG	23	21	8	4	↓ (on S1)
Clementz et al. (1997)	EEG/MEG	10	10	8–10	0.1	∅
Blumenfeld and Clementz (1999)	MEG	12	11	8–10	0.1	∅
Boutros et al. (1999)	EEG	12	12	8	4	∅
Hanlon et al. (2005)	MEG	25	25	7–11	3	∅
Σ (all)						3/7 ↓

Findings on N100/N100m amplitude in schizophrenia, as obtained in sensory gating experiments; the structure is the same as for Table 1, except that it is mentioned in addition whether EEG or MEG was used as recording technique.

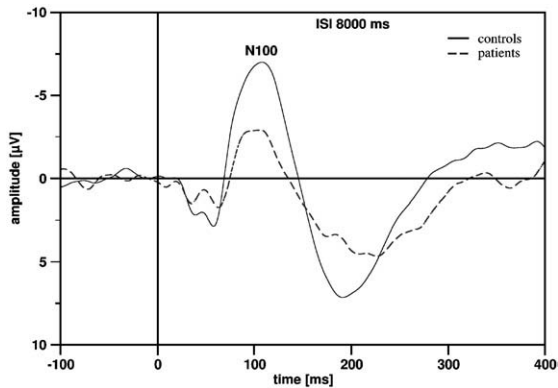


Fig. 1. ERP elicited by the 1st of a pair of clicks recorded at Cz; grand average data of 30 schizophrenia patients and 30 controls (Boutros et al., unpublished data); N100 amplitude is reduced after the long ISI of 8000 ms separating the pairs. In contrast, a number of other sensory gating studies did not reveal such a reduction of the N100 amplitude.

interval of 0.5 s between the two clicks. If the effect of schizophrenia on N100 is greater at longer ISIs, one would expect an amplitude reduction of the N100 elicited by the 1st click in schizophrenia patients (Fig. 1), but no reduction for the N100 elicited by the 2nd click.

Unfortunately, the N100 was not investigated in many sensory gating studies, probably also because an initial study by Freedman et al. (1983) did not reveal deficits in “N100 gating”. Of those studies, which reported amplitude values of the N100 or its neuromagnetic counterpart N100m, none revealed a reduction of the N100/N100m to the 2nd click, but surprisingly 4 of 7 studies did also not show a reduction of the N100/N100m to the 1st click (Table 5). We can only speculate about why N100 was less consistently reduced in sensory gating experiments, as compared to other kinds of experiments. Stimulus features may play a role; in gating experiments, clicks with a maximum of a few milliseconds durations are used as stimuli, while other kinds of AEP studies with very rare exceptions use tones >20 ms duration. N100 amplitude depends on sound duration: The N100 amplitude was found to decrease when the plateau of a tone was shortened from 30 ms to 10, 3, or 0 ms (Onishi and Davis, 1968). This relation might be altered in schizophrenia patients and, therefore, N100 amplitude reduction becomes most apparent when the generating neurons are maximally responsive (long ISIs and >30 ms tone duration). Also the recording technique (preponderance of MEG studies) might have had an influence, as other MEG studies did not show a reduction of the N100m in schizophrenia (Pekkonen et al., 1999; Rockstroh et al., 2001).

In conclusion, patients with schizophrenia exhibit deficits in N100 generation, especially at long ISIs and extremely short ISIs. At ISIs between 0.3 and 1 s, the deficits are much less profound. The relation between deficient response recovery function and deficient response facilitation in schizophrenia patients remains to be elucidated. An N100 amplitude reduction at long ISIs is also apparent in sensory gating experiments, but less consistently than what might be expected from other kinds of studies.

2.1.2. Influence of stimulus intensity

Stimulus intensity is another factor that has been systematically varied in some schizophrenia studies. In healthy subjects, increasing intensities is associated with increasing N100 amplitudes (Keidel and Spreng, 1965). In three studies on schizophrenia patients, tone intensity was varied. In two of the studies, tone intensity did not have a differential effect on N100 amplitude in schizophrenia patients and controls (Pfefferbaum et al., 1980; Adler et al., 1990), perhaps because there was no significant reduction of the N100 amplitude. The third study is difficult to evaluate, as it quantified a N100–P200 composite, instead of the N100 amplitude alone (Juckel et al., 2003). Of note, the loudness dependency of this composite measure has been proposed to be a marker of central serotonergic neurotransmission (Hegerl and Juckel, 1993) and to be a predictor of treatment response to selective serotonin reuptake inhibitors (SSRIs) (Gallinat et al., 2000). With regard to N100 amplitude reduction in schizophrenia, an impact of sound intensity has yet to be shown. This is also true for other stimulus characteristics as e.g. sound complexity, tone frequency, and tone duration.

2.1.3. Influence of attention

2.1.3.1. Attention and N100 amplitude. N100 is modulated to some extent by attention, as e.g. shown by Hillyard et al. (1973). Näätänen et al. (1978) postulated that the increase of N100 amplitudes by attention is due to a separate cortical process (reflected in ERPs as Processing Negativity, PN), while other researchers claimed that the amplitude increase stems from an increased activity of N100 generators (for overview: Hillyard et al., 1995). In healthy subjects, these effects of selective attention were studied primarily by dichotic presentation of auditory stimuli with a high presentation rate, where stimulation differed between left and right ear. Subjects focused on one ear and ignored the other. The effect of selective attention is studied by calculating the difference ERP between the attended and non-attended source.

The degree of attention also differs between active and passive oddball paradigms. In a classical oddball paradigm, two kinds of stimuli are used, one standard stimulus and one (rare) deviant stimulus. In active oddball paradigms, the goal is to elicit a P300 to the deviant (target) stimulus, which requires a behavioral response, such as pressing a button or counting it. The target typically strongly deviates from the standard. Although the N100 is of minor concern, it is often measured. In a typical P300 paradigm, a larger N100 amplitude in response to targets can be due to its status as a target or to its deviance from the preceding sounds (Butler, 1968).

In passive oddball paradigms, the goal is to elicit a MMN to a deviant, but ignored, stimulus. In MMN paradigms, the stimulation rate is typically faster, with the intention of saturating the N100. Typically, the standard and deviant differ minimally from each other in tone frequency, duration, intensity, and location; again, the goal is to minimize the N100 and maximize the MMN (e.g. Sams et al., 1985). Nevertheless, N100 to standards is often measured.

2.1.3.2. Attention and N100 amplitude in schizophrenia patients. Although N100 primarily reflects sensory and perceptual processing, it is also affected by attention, and therefore, its reduction in schizophrenia might be due to deficits in either domain. Although not conclusive, the fact that N100 is reduced to both standards and targets in active attention oddball paradigms (e.g. Roth et al., 1981; Barrett et al., 1986; Pfefferbaum et al., 1989; Ogura et al., 1991), and is also reduced in passive oddball and passive listening paradigms (e.g. Saletu et al., 1971; Connolly et al., 1985; Iwanami et al., 1994) suggests that this reduction is not affected by attention. In all of these paradigms, however, attention cannot be separated from motivation, alertness, arousal, and other non-specific factors.

The best way to assess the specific effect of attention on the N100 reduction seen in schizophrenia is in selective attention tasks, typically involving dichotic listening. Studies applying this kind of stimulation consistently show reduced or missing effects of attention in schizophrenia patients: the attention related increase of the N100 amplitude was found to be missing at slow (0.5–1.5 s), but not at fast stimulation rates (0.25–0.75 s) (Baribeau-Braun et al., 1983). Similarly, N100 amplitude was not affected by attention in patients participating in consonant–vowel tasks (Hiramatsu et al., 1983; Kameyama et al., 1987). More recent studies found a reduced attention effects in patients at fast stimulation rates (Michie et al., 1990; Ward et al., 1991; Iwanami

et al., 1998). Also in one MEG study, a lack of an attention effect was observed for schizophrenia patients (Linnville et al., 1995).

In summary, studies demonstrated that schizophrenia patients have difficulties allocating attention to auditory channels, as reflected in a reduced or missing attention effects on the N100 in dichotic listening experiments. However, a reduced N100 amplitude was also found in experiments not requiring the allocation of attention. Therefore, it appears to be likely that both endogenous and exogenous constituents of the N100 are affected by the disease.

2.2. Drug effects

2.2.1. Effects of antipsychotic medication

The studies mentioned above were conducted mainly in medicated patients. Here, we discuss whether N100 amplitude reduction in schizophrenia could be biased by antipsychotic medication. Such a bias might be introduced by some direct mechanism of the antipsychotic drugs on the neural generators of the N100 or, indirectly, by an amelioration of psychotic symptoms. The influence of medication can be circumvented by studying unmedicated patients. Effects of medication can be studied by comparing medicated and unmedicated patient samples, but without random assignment of patients to groups, data are difficult to interpret. Medication effects can also be studied in dose–response studies, comparing patients on low to those on high doses of antipsychotic agents. Again, without random assignment, conclusions must be drawn cautiously. Finally, the problem of medication might be addressed in longitudinal studies, measuring the psychopathology and ERPs before and after medication. If well-designed, these studies yield useful data on this subject.

2.2.1.1. Between-group comparisons. Evidence for an effect of treatment with antipsychotics on N100 amplitude was obtained first in 1983. Baribeau-Braun et al. (1983) found that patients with high doses of antipsychotics had significantly smaller N100 amplitudes as compared to patients with low doses of antipsychotics. Although the finding was not confirmed a subsequent study (Barrett et al., 1986), it underlined the need for studies in unmedicated patients: Pfefferbaum et al. (1989) found a reduced N100 amplitude in medicated, but not in unmedicated patients. This lack of an N100 amplitude reduction in unmedicated patients was corroborated by other studies (Schlör et al., 1985; Mukundan, 1986; Blackwood et al., 1987; Roth et al., 1991; Gallinat et al., 2004). However, it must be interpreted

Table 6
Effects of treatment with antipsychotic agents

Authors	N	Antipsychotic medication (n)	Experiment	ISI [s]	Effect of medication on N100 amplitude
Blackwood et al. (1987)	14	Flupenthixol (9), chlorpromazine (2), pimozide (1), unmedicated (1)	Active oddball	0.9	↓
Adler and Gattaz (1993)	8	Haloperidole (8)	Passive listening	3.3	↓
Schlör et al. (1985)	16	Haloperidol (16), (+biperiden) (12)	Passive listening	6.8	∅
Ford et al. (1994)	21	Raclopride (17), haloperidole (4)	Active oddball	1.5	∅
Umbricht et al. (1998)	17	Clozapine (11), haloperidole (6)	Passive oddball	0.7–0.8	∅
Umbricht et al. (1999)	10	Risperidone (10)	Active and passive oddball	0.7–0.8	∅
Iwanami et al. (2001)	10	Risperidone (10)	Active oddball	1.5	∅
∑					2/7 ↓

Findings of studies on treatment effects; N refers here the total number of patients re-investigated after treatment with antipsychotic agents; the antipsychotic agents and the number of patients treated with them, the kind of the conducted experiment and the ISI are provided; a down-tilted arrow indicates a significantly reduced N100 amplitude as a result of the antipsychotic treatment.

cautiously, as patients who can be maintained off medications are typically are less severely ill. Furthermore, a reduced N100 amplitude was observed also in unmedicated patients: In their pioneering study, Shagass et al. (1978) compared unmedicated patients with chronic schizophrenia to non-psychotic patients (patients with neuroses and personality disorders) and found a reduced N100 amplitude in schizophrenia patients. A reduction of N100 amplitude in unmedicated patients, as compared to healthy subjects, was revealed by others, too (Ogura et al., 1991; Laurent et al., 1999; Mulert et al., 2001; Gallinat et al., 2002).

Thus, in about half of the studies, a reduced N100 amplitude could be shown in unmedicated patients. The lack of significant differences between unmedicated patients and healthy controls in some of the studies cannot be due to the ISI, as these studies, with exception of Blackwood et al. (1987), applied an ISI of >1.5 s. However, these studies could have confounded clinical status and medication status, as different patients were in the medicated and unmedicated groups, and may have

differed in baseline clinical severity. In fact, symptom severity did not differ between medicated and unmedicated patients in two studies (Pfefferbaum et al., 1989; Roth et al., 1991), suggesting that unmedicated patients had a better baseline status.

2.2.1.2. Within groups comparisons. A number of studies addressed the effects of antipsychotic treatment on the N100 (and other ERP components) within a patient sample (Table 6): One study showed a reduction of the N100 amplitude in patients after being treated for 4 weeks, but not after 1 week, mainly with chlorpromazine and flupenthixol; clinical improvement was also only apparent after 4 weeks (Blackwood et al., 1987). In another study, treatment with 10 mg haloperidole resulted in an N100 amplitude decrease 2 weeks after treatment had started (Adler and Gattaz, 1993). This N100 amplitude decrease was unrelated to the clinical improvement, suggesting a direct effect of neuroleptic treatment on N100 amplitude. Adler and Gattaz (1993) described N100 amplitude changes under neuroleptic treatment as “pattern of a regression to the mean”, as only those patients with highest amplitude values at baseline exhibited decrease. At baseline, no reduction of the N100 amplitude had been apparent in the unmedicated patients, as compared to controls.

In another study, the N100 amplitude was not reduced in unmedicated patients at baseline (Schlör et al., 1985). After medication with ∅ 24 mg haloperidole and remission, no alterations of the N100 amplitude were observed. In line with this study, also a couple of other studies did not show any effects of treatment on the N100 amplitude: in the study of Ford et al. (1994), patients were randomly assigned to different medication groups after 1 week on placebo. Before treatment, the N100 amplitude of patients were significantly reduced, as compared to healthy controls. After 4 weeks on different doses of raclopride or haloperidole, N100 was unchanged in spite of clinical improvement. An effect of treatment on the N100 amplitude was also not apparent in the open-label, uncontrolled studies of Umbricht et al. (1998, 1999) and Iwanami et al. (2001); patients in these studies were mainly treated with the modern antipsychotic drugs clozapine and risperidone. In addition to patient studies, haloperidole had no impact on both the amplitude and latency of the N100/N100m in healthy subjects (Kähkönen et al., 2001; Pekkonen et al., 2002).

Taken together, there is little evidence for a systematic effect of treatment with antipsychotic agents on the N100 amplitude, although it cannot be ruled out completely. Also, more studies are needed to differentiate between the impact of different kinds of antipsychotic drugs.

2.2.2. Effects of other drugs

Findings in schizophrenia patients might not only be biased by antipsychotic medication, but also by the intake of benzodiazepines, anticholinergics and antidepressants. In addition to prescribed medication, the rate of smoking (Kumari and Postma, 2005) and caffeine consumption (Strassnig et al., 2006) is considerably higher in schizophrenia than in healthy controls.

To our knowledge, the effects of benzodiazepines, anticholinergics and anti-depressants on the N100 have never exclusively been tested in schizophrenia patients. For healthy subjects, a reduction of the N100 amplitude after benzodiazepines has consistently been shown in EEG (Rockstroh et al., 1991; Semlitsch et al., 1995) and MEG studies (Sinton et al., 1986; Rosburg et al., 2004). Also the amplitudes of other ERP components were reduced, indicating a general dampening of ERPs by benzodiazepines. In contrast, anticholinergic and anti-serotonergic drugs were reported to decrease P300, but not N100 amplitudes (Meador et al., 1989). Drugs affecting the serotonergic neurotransmission might, however, alter the loudness dependency of the N100–P200 amplitude (Hegerl and Juckel, 1993; Gallinat et al., 2000).

The effects of caffeine and nicotine were not investigated in schizophrenia patients either. In healthy subjects, neither nicotine (Ascioglu et al., 2004; Knott et al., 2006) nor caffeine (EEG: Bruce et al., 1992; MEG: Rosburg et al., 2004) have strong effects on the auditory N100 amplitude. However, amplitudes of other ERP components were increased by caffeine intake (Lorist et al., 1995; Kawamura et al., 1996). Therefore, caffeine effects on auditory N100 warrant further investigation.

Some studies suggest that higher levels of cortical arousal are associated with more negative N100 amplitudes: Ford et al. (1994) found a strong association with N100 amplitude and cortical spinal fluid levels methoxyhydroxyphenylglycol (MPHG), a metabolite of norepinephrine, which is assumed to reflect heightened levels of cortical arousal. In line with that, the N100 amplitude was also found to be correlated with tyrosine concentration, an amino acid functioning as a precursor of norepinephrine (Mochizuki et al., 1998). Both studies also suggest that drugs affecting the level of arousal (as e.g. caffeine) potentially influence the N100 amplitude.

2.3. Hints for a globally affected N100 generating network?

The N100 reflects a complex multigenerator process (Näätänen and Picton, 1987). Here, we discuss whether the whole network of cortical structures generating the

N100 or just a specific subset is affected by schizophrenia. This issue can be addressed by studies applying a detailed topographic analysis or by studies applying source reconstruction algorithms. A reduced activity of a subset of generators could be suggestive for some local structural deficit that can be tested by structural neuroimaging techniques.

2.3.1. Topographical studies

The recorded topography of ERP components is the result of underlying neuronal activity. Any significant shift in the topography of the N100 in schizophrenia would indicate a deficit of a subset of generators, while a general reduction of the N100 would indicate that the whole network, generating the N100, is dysfunctional.

Unfortunately, information about topography is rarely provided in studies on N100 and schizophrenia. A few studies tested for differences in N100 topography between schizophrenia patients and controls, but did not detect any alteration (Potts et al., 1998; Bruder et al., 1999; Shelley et al., 1999; Alain et al., 2002). With the exception of Alain et al. (2002) who used a short ISI, a general N100 amplitude reduction was revealed in these studies. In two of the studies, alterations of the asymmetry were observed for other ERP components: for the P300 in study of Potts et al. (1998) and for the N200 in the study of Bruder et al. (1999), indicating that both studies had sufficient sensitivity to detect topographical changes. Therefore, these studies are suggestive for a general reduction of N100 generators instead of a reduction of a subset of generators.

2.3.2. Source reconstruction studies

Besides the topographical analysis, it is also possible for multichannel recordings to reconstruct the neuronal generators of ERP components by special mathematical algorithms. In that case, the strength of each reconstructed source can be compared directly between patients and controls.

EEG studies of N100 in schizophrenia, applying source reconstruction, are still sparse, although it is probably the most elegant way to tackle the question whether a subset of generators or the whole N100 generating network is affected in schizophrenia. To our knowledge there are three studies on N100 sources and their strengths in schizophrenia: In the study of Frodl et al. (1998), the N100 activity was reconstructed by two distinct sources (dipoles) in the temporal lobe in each hemisphere. N100 sources were generally attenuated in schizophrenia patients, as compared to healthy controls. In the studies of Mulert et al. (2001) and Gallinat et al. (2002), the reconstruction of the N100 component was

performed by a minimum-norm approach (Low Resolution Electromagnetic Tomography LORETA). These studies revealed a comparable strength of activation in the auditory cortex in patients and controls, but schizophrenia patients showed significantly less activation than controls in the anterior cingulate gyrus. The lack of a difference in the primary auditory cortex would be in line with the missing effects with MEG (Section 2.1.1.2), but somewhat contradictory to the previous study (Frodl et al., 1998).

To sum up, findings are conflicting: topographical studies suggest a general down-regulation of N100 related activity, but two of the three source reconstruction studies suggest that the reduced N100 might be related specifically to a down-regulation of activity generated in the anterior cingulate gyrus. As activity of N100 generators is affected differentially by variation of the ISI (Lü et al., 1992) and attention (Hillyard et al., 1995), source reconstruction studies, systematically varying experimental factors, are warranted.

2.3.3. Correlation between N100 amplitude and structural measures

Correlations between structural measures and N100 amplitude would suggest that both are a reflection of a common process and may also suggest how they are related to clinical features (Egan et al., 1994). However, O'Donnell et al. (1993) did not find associations between N100 amplitude and volume of superior temporal gyrus gray-matter, in spite of the suggestion that superior temporal gyrus is the temporal lobe generator of the N100. Egan et al. (1994) revealed some significant correlations between the N100 amplitude and several prefrontal measures, but in this study neither the N100 amplitude nor the frontal structural measures were significantly reduced in schizophrenia patients.

Thus, up to now no association between a reduced N100 amplitude and structural alterations in schizophrenia could be established. It might be noted that a reduced N100 amplitude might not be due to structural deficits of brain areas generating it, but instead to impaired pathways between them (“disconnection syndrome”, Friston 1996) or to neurochemical deficits.

2.4. Relation to psychopathology

Any association between psychopathology and N100 amplitude in schizophrenia patients is of interest, as such associations are indicative of (a) whether N100 amplitude reduction is syndrome or disease related, or (b) whether it represents a state or a trait marker. One way to elucidate the impact of symptoms on the N100 amplitude

is to divide schizophrenia patients into subgroups with specific predominant symptoms. A number of dimensional models have been proposed (Peralta and Cuesta, 2001), the most popular of which has been a three-dimensional model consisting of psychotic, negative and disorganizational symptoms (Bilder et al., 1985). A couple of studies compared the N100 amplitude reduction between different groups of patients, but provided no consistent results (Kessler and Steinberg, 1989; Boutros et al., 1997; Bruder et al., 2001; Mucci et al., 2007) possibly due to different criteria for the patient grouping.

A second approach to elucidate the impact of symptoms on N100 amplitude is to correlate it with the degree of symptoms, as obtained by psychopathological ratings, or to compare patients with severe and less severe symptoms. However, findings are relatively heterogeneous, with most studies revealing no associations between N100 amplitude and psychopathology: Higashima et al. (1998) investigated 73 patients in an active oddball experiment and found that N100 amplitude did not show significant correlations with PANSS (Positive and Negative Symptom Scale) ratings. Similarly, other studies did not detect significant relationships between N100 and psychopathological ratings (Roth et al., 1981; Barrett et al., 1986; Laurent et al., 1999; Karoumi et al., 2000; Alain et al., 2001; Bruder et al., 2001; Boutros et al., 2004; O'Donnell et al., 2004). Furthermore, a comparison between moderately and severely ill schizophrenia patients revealed no significant difference of the N100 amplitude (Ford et al., 1999).

However, some studies have reported modest associations between psychopathological ratings and N100 amplitude (Ford et al., 1999; Gallinat et al., 2002; Valkonen-Korhonen et al., 2003; Sumich et al., 2006), but with a low consistency between studies. At best, N100 might be related to general psychopathology, as reported by two of these studies (Ford et al., 1999; Valkonen-Korhonen et al., 2003), with smaller (i.e., less negative) N1 amplitudes related to more severe psychopathology.

In a third approach, the impact of auditory hallucinations was studied within the same patients. Roth et al. (1980) argued that auditory hallucinations could be regarded as functionally equivalent to exogenous stimulation, thus resulting in a reduced N100. This hypothesis was indeed supported by some recent studies: Comparing patients during phases with or without hallucinations, it was found that active hallucinations resulted in a significant amplitude decrease of the N100 (Hubl et al., 2007). A similar finding had been described in a single case by MEG recordings (Tiuhonen et al., 1992), and comparable effects on the N100m were found in healthy

subjects for auditory stimulation masked with continuous speech (Hari and Makela, 1988).

In summary, there is some evidence that auditory hallucinations affect N100 amplitude in schizophrenia patients, while other associations between N100 and psychopathological ratings appear to be at best weak, as indicated by non-significant or close to non-significant correlation coefficients in a number of studies and inconsistencies between studies. Together with studies indicating a stable N100 though clinical improvement (Eikmeier et al., 1991; Ford et al., 1994; Shinozaki et al., 2002), studies favor the assumption that a reduced N100 amplitude represents primarily a trait marker. In line with this assumption, the duration of illness was reported to have no impact on the N100 amplitude (Mathalon et al., 2000), and a reduced N100 amplitude was found to be apparent already in first episode schizophrenia (Brown et al., 2002).

2.5. Heritability of a reduced N100

Genetic influences in schizophrenia have been widely reported (Harrison and Weinberger, 2005). In this section, we review the issue of the heritability of the N100 amplitude and its reduction in schizophrenia. This issue is of importance as it addresses the question of whether N100 amplitude reduction can serve as a trait marker (or endophenotype) for early detection and intervention. As such, the N100 amplitude should have a high heritability in general and should be reduced in subjects exhibiting an elevated genetic risk for developing schizophrenia.

A high heritability of the N100 amplitude was recently reported in a study on healthy twins (Anokhin et al., 2007). The N100 amplitude was also studied in unaffected 1st degree relatives of schizophrenia patients, including their twin siblings. In two studies, N100 amplitude reduction was revealed in family members of schizophrenia patients (Blackwood et al., 1991; Frangou et al., 1997). More evidence for the heritability of an N100 amplitude reduction in schizophrenia came from a recent combined EEG/MEG study on monozygotic and dizygotic twin pairs discordant for schizophrenia: a reduced N100 amplitude was observed for both schizophrenia patients and their unaffected siblings (Ahveninen et al., 2006). Because of their finding, the authors regarded N100 amplitude reduction as a marker of functional brain changes related to genetic predisposition to schizophrenia.

However, the issue of heritability of N100 amplitude reduction should be interpreted with some caution as none of these studies revealed a difference in N100 amplitude between schizophrenia patients and their non-affected family members. The typical conversion rate is 48% in identical twins, to 13% in children, 9% in siblings and 6%

in parents (Gottesman and Erlenmeyer-Kimling, 2001). Thus, the risk of developing schizophrenia is not reflected in N100 amplitude reduction and, therefore, a reduced N100 amplitude appears not be suited to guide early intervention strategies in high risk population.

In addition, studies have yet to be conducted in order to evaluate the sensitivity and specificity of a reduced N100 amplitude as a potential marker. But there is no reason to be too optimistic. A reduced N100 amplitude was reported also for other psychiatric diseases as e.g. bipolar disorder (Umbricht et al., 2003), perhaps reflecting a vulnerability to psychosis rather than schizophrenia, per se. Studies are further handicapped by the fact that patients with schizophrenia also have an increased risk for other health problems, as compared to non-psychiatric subjects (Carney et al., 2006). The impact of these comorbidities on N100 amplitude is often unknown, but at least hypothyroidism as one comorbidity was recently found to affect the N100 amplitude (Oerbeck et al., 2007).

3. Summary

Since electrodes were attached to the scalps of patients with schizophrenia in the 1960s, scientists and psychiatrists have hoped that EEG-based signals would reveal the biological basis of the illness, be useful in diagnosis, track changes in clinical symptoms, or serve as an endophenotype for early detection and intervention.

Even recently, some authors proposed N100 amplitude reduction as a marker of functional brain changes related to genetic predisposition to schizophrenia (Ahveninen et al., 2006). This proposal is supported by studies on 1st degree relatives and by findings, showing that the N100 amplitude reduction is relatively independent of the gravity of symptoms. However, Ahveninen et al. (2006) observed a deficit of the N100 amplitude at an ISI of 0.5 s, while the vast majority of studies did not show such a deficit in schizophrenia patients at these short ISIs (Table 2). Furthermore, reviewing previous studies revealed that more than half of the studies on unmedicated patients were not able to show N100 amplitude reduction, thus questioning the value of reduced N100 amplitude as an endophenotype even for patients with schizophrenia.

Information contained in the N100 amplitude is not that simple. The N100 cannot be referred to a single cortical process, and its amplitude is influenced by a long list of individual-related variables including but not limited to: attention, arousal, motivation, fatigue, hearing thresholds, street and prescription drugs, smoking, abuse history. Controlling for all of the individual-related factors influencing the N100 amplitude is difficult at best, ruling it out as a simple diagnostic instrument.

However, N100 can be a very useful tool in studies of mechanisms underlying the pathophysiology of schizophrenia. For example, because of its sensitivity to auditory cortical processing, dysfunction of the corollary discharge mechanism in schizophrenia has been studied using N100 amplitude as a reflection of cortical responsiveness to speech sounds as they are being spoken (Ford and Mathalon, 2004; Ford et al., 2007).

Source reconstruction studies of N100 and of its neuromagnetic correlate N100m have revealed some of the functional–anatomical correlates of an N100 amplitude reduction (e.g. Reite et al., 1997; Mulert et al., 2001). In the future, combination of EEG and MEG recordings with other research tools, such as voxel based morphometry (VBM), diffusion tensor imaging (DTI) or magnetic resonance spectroscopy (MRS), might enable further new insights of the structural and chemical deficit underlying an N100 reduction. For example, in a recent combined MEG and MRS study on healthy subjects, the N100m was found to be correlated with *N*-acetylaspartate, a marker of neuronal integrity (Sörös et al., 2006). New insights might also be gained by correlating different electrophysiological markers (e.g. Kisley et al., 2004).

Finally, besides the functional–anatomical basis of N100 reduction, the influence of certain kinds of neurotransmitters and their genetics has to be investigated further. To our knowledge, the genetics of neurotransmitters have not been studied for the N100 as yet, but in other experiments for example the presence of the dopamine D2 Taq1A allele predicted a significant amount of inter-subject variability in the magnitudes of cortical activation (Cohen et al., 2005).

In summary, N100 cannot be used as a simple test of the presence or absence of schizophrenia, or of a symptom, but it can be used as a tool to help us understand abnormalities in basic elemental mechanisms of brain function and structure.

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References

- Adler, G., Gattaz, W.F., 1993. Auditory evoked potentials in schizophrenic patients before and during neuroleptic treatment. Relationship to psychopathological state. *European Archives of Psychiatry and Clinical Neuroscience* 242, 357–361.
- Adler, G., Adler, J., Schneck, M., Armbruster, B., 1990. Influence of stimulation parameters on auditory stimulus processing in schizophrenia and major depression: an auditory evoked potential study. *Acta Psychiatrica Scandinavica* 81, 453–458.
- Ahveninen, J., Jääskeläinen, I.P., Osipova, D., Huttunen, M.O., Ilmoniemi, R.J., Kaprio, J., Lonnqvist, J., Manninen, M., Pakarinen, S., Therman, S., Näätänen, R., Cannon, T.D., 2006. Inherited auditory-cortical dysfunction in twin pairs discordant for schizophrenia. *Biological Psychiatry* 60, 612–620.
- Alain, C., Hargrave, R., Woods, D.L., 1998. Processing of auditory stimuli during visual attention in patients with schizophrenia. *Biological Psychiatry* 44, 1151–1159.
- Alain, C., Cortese, F., Bernstein, L.J., He, Y., Zipursky, R.B., 2001. Auditory feature conjunction in patients with schizophrenia. *Schizophrenia Research* 49, 179–191.
- Alain, C., Bernstein, L.J., Cortese, F., Yu, H., Zipursky, R.B., 2002. Deficits in automatically detecting changes in conjunction of auditory features in patients with schizophrenia. *Psychophysiology* 39, 599–606.
- Anokhin, A.P., Vedeniapin, A.B., Heath, A.C., Korzyukov, O.A., Boutros, N.N., 2007. Genetic and environmental influences on sensory gating of mid-latency auditory evoked responses: a twin study. *Schizophrenia Research* 89 (1–3), 312–319.
- Ascioglu, M., Dolu, N., Golgeli, A., Suer, C., Ozesmi, C., 2004. Effects of cigarette smoking on cognitive processing. *International Journal of Neuroscience* 114, 381–390.
- Baribeau-Braun, J., Picton, T.W., Gosselin, J.Y., 1983. Schizophrenia: a neurophysiological evaluation of abnormal information processing. *Science* 219, 874–876.
- Barrett, K., McCallum, W.C., Pocock, P.V., 1986. Brain indicators of altered attention and information processing in schizophrenic patients. *British Journal of Psychiatry* 148, 414–420.
- Bilder, R.M., Mukherjee, S., Rieder, R.O., Pandurangi, A.K., 1985. Symptomatic and neuropsychological components of defect states. *Schizophrenia Bulletin* 11, 409–419.
- Blackwood, D.H., Whalley, L.J., Christie, J.E., Blackbum, I.M., St Clair, D.M., McInnes, A., 1987. Changes in auditory P3 event-related potential in schizophrenia and depression. *British Journal of Psychiatry* 150, 154–160.
- Blackwood, D.H., St-Clair, D.M., Muir, W.J., Duffy, J.C., 1991. Auditory P300 and eye tracking dysfunction in schizophrenic pedigrees. *Archives of General Psychiatry* 48, 899–909.
- Blumenfeld, L.D., Clementz, B.A., 1999. Hemispheric differences on auditory evoked response suppression in schizophrenia. *Neuroreport* 10, 2587–2591.
- Blumenfeld, L.D., Clementz, B.A., 2001. Response to the first stimulus determines reduced auditory evoked response suppression in schizophrenia: single trials analysis using MEG. *Clinical Neurophysiology* 112, 1650–1659.
- Boutros, N., Nasrallah, H., Leighty, R., Torello, M., Tueting, P., Olson, S., 1997. Auditory evoked potentials, clinical vs. research applications. *Psychiatry Research* 69, 183–195.
- Boutros, N.N., Belger, A., Campbell, D., D'Souza, C., Krystal, J., 1999. Comparison of four components of sensory gating in schizophrenia and normal subjects: a preliminary report. *Psychiatry Research* 88, 119–130.
- Boutros, N.N., Korzyukov, O., Jansen, B., Feingold, A., Bell, M., 2004. Sensory gating deficits during the mid-latency phase of information processing in medicated schizophrenia patients. *Psychiatry Research* 126, 203–215.
- Brown, K.J., Gonsalvez, C.J., Harris, A.W., Williams, L.M., Gordon, E., 2002. Target and non-target ERP disturbances in first episode vs. chronic schizophrenia. *Clinical Neurophysiology* 113, 1754–1763.

- Bruce, M., Scott, N., Shine, P., Lader, M., 1992. Anxiogenic effects of caffeine in patients with anxiety disorders. *Archives of General Psychiatry* 49, 867–869.
- Bruder, G., Kayser, J., Tenke, C., Amador, X., Friedman, M., Sharif, Z., Gorman, J., 1999. Left temporal lobe dysfunction in schizophrenia: event-related potential and behavioral evidence from phonetic and tonal dichotic listening tasks. *Archives of General Psychiatry* 56, 267–276.
- Bruder, G.E., Kayser, J., Tenke, C.E., Friedman, M., Malaspina, D., Gorman, J.M., 2001. Event-related potentials in schizophrenia during tonal and phonetic oddball tasks: relations to diagnostic subtype, symptom features and verbal memory. *Biological Psychiatry* 50, 447–452.
- Budd, T.W., Michie, P.T., 1994. Facilitation of the N1 peak of the auditory ERP at short stimulus intervals. *Neuroreport* 5, 2513–2516.
- Butler, R.A., 1968. Effect of changes in stimulus frequency and intensity on habituation of the human vertex potential. *Journal of the Acoustical Society America* 44, 945–950.
- Carney, C.P., Jones, L., Woolson, R.F., 2006. Medical comorbidity in women and men with schizophrenia: a population-based controlled study. *Journal of General Internal Medicine* 21, 1133–1137.
- Catts, S.V., Shelley, A.M., Ward, P.B., Liebert, B., McConaghy, N., Andrews, S., Michie, P.T., 1995. Brain potential evidence for an auditory sensory memory deficit in schizophrenia. *American Journal of Psychiatry* 152, 213–219.
- Clementz, B.A., Blumenfeld, L.D., 2001. Multichannel electroencephalographic assessment of auditory evoked response suppression in schizophrenia. *Experimental Brain Research* 139, 377–390.
- Clementz, B.A., Blumenfeld, L.D., Cobb, S., 1997. The gamma band response may account for poor P50 suppression in schizophrenia. *Neuroreport* 8, 3889–3893.
- Clunas, N.J., Ward, P.B., 2005. Auditory recovery cycle dysfunction in schizophrenia: a study using event-related potentials. *Psychiatry Research* 136, 17–25.
- Cohen, M.X., Young, J., Baek, J.-M., Kessler, C., Ranganath, C., 2005. Individual differences in extraversion and dopamine genetics predict neural reward responses. *Brain Research/Cognitive Brain Research* 25, 851–861.
- Connolly, J.F., Manchanda, R., Gruzelier, J.H., Hirsch, S.R., 1985. Pathway and hemispheric differences in the event-related potential (ERP) to monaural stimulation: a comparison of schizophrenic patients with normal controls. *Biological Psychiatry* 20, 293–303.
- Davis, H., Mast, T., Yoshie, N., Zerlin, S., 1966. The slow response of the human cortex to auditory stimuli: recovery process. *Electroencephalography and Clinical Neurophysiology* 21, 105–113.
- Egan, M.F., Duncan, C.C., Suddath, R.L., Kirsh, D.G., Mirsky, A.F., Wyatt, R.J., 1994. Event-related potential abnormalities correlate with structural brain alterations and clinical features in patients with chronic schizophrenia. *Schizophrenia Research* 11, 259–271.
- Eikmeier, G., Lodemann, E., Zerbin, D., Gastpar, M., 1991. Event-related potentials in schizophrenic patients in the acute phase and in remission. *EEG-EMG Zeitschrift für Elektroenzephalographie, Elektromyographie und Verwandte Gebiete* 22, 15–20.
- Erwin, R.J., Buchwald, J.S., 1986. Midlatency auditory evoked responses: differential recovery cycle characteristics. *Electroencephalography and Clinical Neurophysiology* 64, 417–423.
- Ford, J.M., Mathalon, D.H., 2004. Electrophysiological evidence of corollary discharge dysfunction in schizophrenia during talking and thinking. *Journal of Psychiatric Research* 38, 37–46.
- Ford, J.M., White, P.M., Csernansky, J.G., Faustman, W.O., Roth, W.T., Pfefferbaum, A., 1994. ERPs in schizophrenia: effects of antipsychotic medication. *Biological Psychiatry* 36, 153–170.
- Ford, J.M., Mathalon, D.H., Marsh, L., Faustman, W.O., Harris, D., Hoff, A.L., Beal, M., Pfefferbaum, A., 1999. P300 amplitude is related to clinical state in severely and moderately ill patients with schizophrenia. *Biological Psychiatry* 46, 94–101.
- Ford, J.M., Roach, B.J., Faustman, W.O., Mathalon, D.H., 2007. Synch before you speak: auditory hallucinations in schizophrenia. *American Journal of Psychiatry* 164, 458–466.
- Frangou, S., Sharma, T., Alarcon, G., Sigmudsson, T., Takei, N., Binnie, C., Murray, R.M., 1997. The Maudsley Family Study, II: Endogenous event-related potentials in familial schizophrenia. *Schizophrenia Research* 23, 45–53.
- Freedman, R., Adler, L.E., Waldo, M.C., Pachtman, E., Franks, R.D., 1983. Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: comparison of medicated and drug-free patients. *Biological Psychiatry* 18, 537–551.
- Friston, K.J., 1996. Theoretical neurobiology and schizophrenia. *British Medical Bulletin* 52, 644–655.
- Frodl, T., Meisenzahl, E.M., Gallinat, J., Hegerl, U., Moller, H.J., 1998. Markers from event-related potential subcomponents and reaction time for information processing dysfunction in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience* 248, 307–313.
- Gallinat, J., Bottlender, R., Juckel, G., Munke-Puchner, A., Stotz, G., Kuss, H.J., Mavrogiorgou, P., Hegerl, U., 2000. The loudness dependency of the auditory evoked N1/P2-component as a predictor of the acute SSRI response in depression. *Psychopharmacology (Berlin)* 148, 404–411.
- Gallinat, J., Mulert, C., Bajbouj, M., Herrmann, W.M., Schunter, J., Senkowski, D., Moukhtieva, R., Kronfeldt, D., Winterer, G., 2002. Frontal and temporal dysfunction of auditory stimulus processing in schizophrenia. *Neuroimage* 17, 110–127.
- Gallinat, J., Winterer, G., Herrmann, C.S., Senkowski, D., 2004. Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing. *Clinical Neurophysiology* 115, 1863–1874.
- Gottesman, I.I., Erlenmeyer-Kimling, L., 2001. Family and twin strategies as a head start in defining prodromes and endophenotypes for hypothetical early-interventions in schizophrenia. *Schizophrenia Research* 51, 93–102.
- Hanlon, F.M., Miller, G.A., Thoma, R.J., Irwin, J., Jones, A., Moses, S.N., Huang, M., Weisend, M.P., Paulson, K.M., Edgar, J.C., Adler, L.E., Canive, J.M., 2005. Distinct M50 and M100 auditory gating deficits in schizophrenia. *Psychophysiology* 42, 417–427.
- Hari, R., Makela, J.P., 1988. Modification of neuromagnetic responses of the human auditory cortex by masking sounds. *Experimental Brain Research* 71, 87–92.
- Harrison, P.J., Weinberger, D.R., 2005. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Molecular Psychiatry* 10, 40–68.
- Hegerl, U., Juckel, G., 1993. Intensity dependence of auditory evoked potentials as an indicator of central serotonergic neurotransmission: a new hypothesis. *Biological Psychiatry* 33, 173–187.
- Higashima, M., Urata, K., Kawasaki, Y., Maeda, Y., Sakai, N., Mizukoshi, C., Nagasawa, T., Kamiya, T., Yamaguchi, N., Koshino, Y., 1998. P300 and the thought disorder factor extracted by factor-analytic procedures in schizophrenia. *Biological Psychiatry* 44, 115–120.
- Hillyard, S.A., Hink, R.F., Schwent, V.L., Picton, T.W., 1973. Electrical signs of selective attention in the human brain. *Science* 182, 177–180.
- Hillyard, S.A., Mangun, G.R., Woldorff, M.G., Luck, S.J., 1995. Neural systems mediating selective attention. In: Gazzaniga, M.S. (Ed.), *The Cognitive Neurosciences*. M.I.T. Press, Cambridge, MA, pp. 665–681.

- Hiramatsu, K., Kameyama, T., Niwa, S., Saitoh, O., Rymar, K., Itoh, K., 1983. Schizophrenic deficits in information processing as reflected in event-related potential abnormalities during syllable discrimination tasks. In: Perris, C., Kemali, D., Koukkou-Lehmann, M. (Eds.), *Neurophysiological Correlates of Normal Cognition and Psychopathology*. Karger, Basel, pp. 63–74.
- Hubl, D., Koenig, T., Strik, W.K., Garcia, L.M., Dierks, T., 2007. Competition for neuronal resources: how hallucinations make themselves heard. *British Journal of Psychiatry* 190, 57–62.
- Iwanami, A., Suga, I., Kanamori, R., 1994. N1 component derived from the temporal region during an auditory passive event-related potential paradigm in schizophrenics. *Clinical Electroencephalography* 25, 50–53.
- Iwanami, A., Isono, H., Okajima, Y., Noda, Y., Kamijima, K., 1998. Event-related potentials during a selective attention task with short interstimulus intervals in patients with schizophrenia. *Journal of Psychiatry and Neuroscience* 23, 45–50.
- Iwanami, A., Okajima, Y., Isono, H., Shinoda, J., Kasai, K., Hata, A., Fukuda, M., Nakagome, K., Kamijima, K., 2001. Effects of risperidone on event-related potentials in schizophrenic patients. *Pharmacopsychiatry* 34, 73–79.
- Javitt, D.C., Doneshka, P., Grochowski, S., Ritter, W., 1995. Impaired mismatch negativity generation reflects widespread dysfunction of working memory in schizophrenia. *Archives of General Psychiatry* 52, 550–558.
- Javitt, D.C., Shelley, A.M., Silipo, G., Lieberman, J.A., 2000. Deficits in auditory and visual context-dependent processing in schizophrenia: defining the pattern. *Archives of General Psychiatry* 57, 1131–1137.
- Juckel, G., Gallinat, J., Riedel, M., Sokullu, S., Schulz, C., Möller, H.-J., Müller, N., Hegerl, U., 2003. Serotonergic dysfunction in schizophrenia assessed by the loudness dependence measure of primary auditory cortex evoked activity. *Schizophrenia Research* 64, 115–124.
- Kähkönen, S., Ahveninen, J., Jääskeläinen, I.P., Kaakkola, S., Näätänen, R., Huttunen, J., Pekkonen, E., 2001. Effects of haloperidol on selective attention: a combined whole-head MEG and high-resolution EEG study. *Neuropsychopharmacology* 25, 498–504.
- Kameyama, T., Niwa, S., Hiramatsu, K., Saitoh, O., Fukuda, M., Nakagome, K., Itoh, K., 1987. Event-related potential correlates of psychotropic drug effects on attentional and hemispheric-dysfunction in schizophrenia. In: Takahashi, R., Flor-Henry, J., Gruzeliar, J., Niwa, S. (Eds.), *Cerebral Dynamics, Laterality and Psychopathology*. Elsevier Science Publisher, Amsterdam, pp. 221–230.
- Karoumi, B., Laurent, A., Rosenfeld, F., Rochet, T., Brunon, A.M., Dalery, J., d'Amato, T., Saoud, M., 2000. Alteration of event related potentials in siblings discordant for schizophrenia. *Schizophrenia Research* 41, 325–334.
- Kasai, K., Nakagome, K., Itoh, K., Koshida, I., Hata, A., Iwanami, A., Fukuda, M., Kato, N., 2002. Impaired cortical network for preattentive detection of change in speech sounds in schizophrenia: a high-resolution event-related potential study. *American Journal of Psychiatry* 159, 546–553.
- Kathmann, N., Wagner, M., Rendtorff, N., Schochlin, C., Engel, R.R., 1995. Information processing during eye tracking as revealed by event-related potentials in schizophrenics, alcoholics, and healthy controls. *Schizophrenia Research* 16, 145–156.
- Kawamura, N., Maeda, H., Nakamura, J., Morita, K., Nakazawa, Y., 1996. Effects of caffeine on event-related potentials: comparison of oddball with single-tone paradigms. *Psychiatry and Clinical Neurosciences* 50, 217–221.
- Kayser, J., Bruder, G.E., Tenke, C.E., Stuart, B.K., Amador, X.F., Gorman, J.M., 2001. Event-related brain potentials (ERPs) in schizophrenia for tonal and phonetic oddball tasks. *Biological Psychiatry* 49, 832–847.
- Keidel, W.D., Spreng, M., 1965. Neurophysiological evidence for the Stevens power function in man. *Journal of the Acoustical Society America* 38, 191–195.
- Kessler, C., Steinberg, A., 1989. Evoked potential variation in schizophrenic subgroups. *Biological Psychiatry* 26, 372–380.
- Kisley, M.A., Noecker, T.L., Guinther, P.M., 2004. Comparison of sensory gating to mismatch negativity and self-reported perceptual phenomena in healthy adults. *Psychophysiology* 41, 604–612.
- Knott, V., Blais, C., Scherling, C., Camarda, J., Millar, A., Fisher, D., McIntosh, J., 2006. Neural effects of nicotine during auditory selective attention in smokers: an event-related potential study. *Neuropsychobiology* 53, 115–126.
- Kogoj, A., Pirtosek, Z., Tomori, M., Vodusek, D.B., 2005. Event-related potentials elicited by distractors in an auditory oddball paradigm in schizophrenia. *Psychiatry Research* 137, 49–59.
- Kumari, V., Postma, P., 2005. Nicotine use in schizophrenia: the self medication hypotheses. *Neuroscience and Biobehavioral Reviews* 29, 1021–1034.
- Laurent, A., Garcia-Larrea, L., d'Amato, T., Bosson, J.L., Saoud, M., Marie-Cardine, M., Maugiere, F., Dalery, J., 1999. Auditory event-related potentials and clinical scores in unmedicated schizophrenic patients. *Psychiatry Research* 86, 229–238.
- Lifshitz, K., Lee, K.L., Avery, J., 1986. The vertex potential: its relation to the EEG and psychiatric diagnosis. In: Shagass, C., Josiassen, R.C., Roemer, R.A. (Eds.), *Brainelectric Potentials and Psychopathology*. Elsevier Science Publishing, New York, pp. 139–150.
- Linnville, S., Teale, P., Scheunemann, D., Reite, M., 1995. Schizophrenia may alter neuromagnetic representations of attention. *Journal of Neuropsychiatry and Clinical Neurosciences* 7, 92–95.
- Lorist, M.M., Snel, J., Mulder, G., Kok, A., 1995. Aging, caffeine, and information processing: an event-related potential analysis. *Electroencephalography and Clinical Neurophysiology* 96, 453–467.
- Lü, Z.L., Williamson, S.J., Kaufman, L., 1992. Behavioral lifetime of human auditory sensory memory predicted by physiological measures. *Science* 258, 1668–1670.
- Mathalon, D.H., Ford, J.M., Rosenbloom, M., Pfefferbaum, A., 2000. P300 reduction and prolongation with illness duration in schizophrenia. *Biological Psychiatry* 47, 413–427.
- Matthews, N., Todd, J., Budd, T.W., Cooper, G., Michie, P.T., 2007. Auditory lateralization in schizophrenia-mismatch negativity and behavioral evidence of a selective impairment in encoding interaural time cues. *Clinical Neurophysiology* 118, 833–844.
- Meador, K.J., Loring, D.W., Davis, H.C., Sethi, K.D., Patel, B.R., Adams, R.J., Hammond, E.J., 1989. Cholinergic and serotonergic effects on the P3 potential and recent memory. *Journal of Clinical and Experimental Neuropsychology* 11, 252–260.
- Michie, P.T., Fox, A.M., Ward, P.B., Catts, V.S., McConaghy, N., 1990. Event-related potential indices of selective attention and cortical lateralization in schizophrenia. *Psychophysiology* 27, 209–227.
- Michie, P.T., Budd, T.W., Todd, J., Rock, D., Wichmann, H., Box, J., Jablensky, A.V., 2000. Duration and frequency mismatch negativity in schizophrenia. *Clinical Neurophysiology* 111, 1054–1065.
- Mochizuki, Y., Oishi, M., Takasu, T., 1998. Correlations between P300 components and neurotransmitters in the cerebrospinal fluid. *Clinical Electroencephalography* 29, 7–9.
- Mucci, A., Galderisi, S., Kirkpatrick, B., Bucci, P., Volpe, U., Merlotti, E., Centanaro, F., Catapano, F., Maj, M., 2007. Double

- dissociation of N1 and P3 abnormalities in deficit and nondeficit schizophrenia. *Schizophrenia Research* 92, 252–261.
- Mukundan, C.R., 1986. Middle latency components of evoked potential responses in schizophrenics. *Biological Psychiatry* 21, 1097–1100.
- Mulert, C., Gallinat, J., Pascual-Marqui, R., Dorn, H., Frick, K., Schlattmann, P., Mientus, S., Herrmann, W.M., Winterer, G., 2001. Reduced event-related current density in the anterior cingulate cortex in schizophrenia. *Neuroimage* 13, 589–600.
- Näätänen, R., Picton, T., 1987. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. *Psychophysiology* 24, 375–425.
- Näätänen, R., Gaillard, A.W., Mantysalo, S., 1978. Early selective-attention effect on evoked potential reinterpreted. *Acta Psychologica Amsterdam* 42, 313–329.
- Nash, A.J., Williams, C.S., 1982. Effects of preparatory set and task demands on auditory event-related potentials. *Biological Psychology* 15, 15–31.
- Oades, R.D., Zerbin, D., Dittmann-Balcar, A., Eggers, C., 1996. Auditory event-related potential (ERP) and difference-wave topography in schizophrenic patients with/without active hallucinations and delusions: a comparison with young obsessive-compulsive disorder (OCD) and healthy subjects. *International Journal of Psychophysiology* 22, 185–214.
- O'Donnell, B.F., Shenton, M.E., McCarley, R.W., Faux, S.F., Smith, R.S., Salisbury, D.F., Nestor, P.G., Pollak, S.D., Kikinis, R., Jolesz, F.A., 1993. The auditory N2 component in schizophrenia: relationship to MRI temporal lobe gray matter and to other ERP abnormalities. *Biological Psychiatry* 34, 26–40.
- O'Donnell, B.F., Hokama, H., McCarley, R.W., Smith, R.S., Salisbury, D.F., Mondrow, E., Nestor, P.G., Shenton, M.E., 1994. Auditory ERPs to non-target stimuli in schizophrenia: relationship to probability, task-demands, and target ERPs. *International Journal of Psychophysiology* 17, 219–231.
- O'Donnell, B.F., Vohs, J.L., Hetrick, W.P., Carroll, C.A., Shekhar, A., 2004. Auditory event-related potential abnormalities in bipolar disorder and schizophrenia. *International Journal of Psychophysiology* 53, 45–55.
- Oerbeck, B., Reinvang, I., Sundet, K., Heyerdahl, S., 2007. Young adults with severe congenital hypothyroidism: cognitive event related potentials (ERPs) and the significance of an early start of thyroxine treatment. *Scandinavian Journal of Psychology* 48, 61–67.
- Ogura, C., Nageishi, Y., Matsubayashi, M., Omura, F., Kishimoto, A., Shimokochi, M., 1991. Abnormalities in event-related potentials, N100, P200, P300 and slow wave in schizophrenia. *Japanese Journal of Psychiatry and Neurology* 45, 57–65.
- Onishi, S., Davis, H., 1968. Effects of duration and rise time of tone bursts on evoked V potentials. *Journal of the Acoustical Society America* 44, 582–591.
- Pantev, C., Hoke, M., Lehnertz, K., Lutkenhoner, B., Anogianakis, G., Wittkowski, W., 1988. Tonotopic organization of the human auditory cortex revealed by transient auditory evoked magnetic fields. *Electroencephalography and Clinical Neurophysiology* 69, 160–170.
- Pekkonen, E., Huottilainen, M., Katila, H., Karhu, J., Näätänen, R., Tiihonen, J., 1999. Altered parallel auditory processing in schizophrenia patients. *Schizophrenia Bulletin* 25, 601–607.
- Pekkonen, E., Hirvonen, J., Ahveninen, J., Kähkönen, S., Kaakkola, S., Huttunen, J., Jääskeläinen, I.P., 2002. Memory-based comparison process not attenuated by haloperidol: a combined MEG and EEG study. *Neuroreport* 13, 177–181.
- Peralta, V., Cuesta, M.J., 2001. How many and which are the psychopathological dimensions in schizophrenia? Issues influencing their ascertainment. *Schizophrenia Research* 49, 269–285.
- Pfefferbaum, A., Horvath, T.B., Roth, W.T., Tinklenberg, J.R., Kopell, B.S., 1980. Auditory brain stem and cortical evoked potentials in schizophrenia. *Biological Psychiatry* 15, 209–223.
- Pfefferbaum, A., Wenegrat, B.G., Ford, J.M., Roth, W.T., Kopell, B.S., 1984. Clinical application of the P3 component of event-related potentials. II. Dementia, depression and schizophrenia. *Electroencephalography and Clinical Neurophysiology* 59, 104–124.
- Pfefferbaum, A., Ford, J.M., White, P.M., Roth, W.T., 1989. P3 in schizophrenia is affected by stimulus modality, response requirements, medication status, and negative symptoms. *Archives of General Psychiatry* 46, 1035–1044.
- Potts, G.F., Hirayasu, Y., O'Donnell, B.F., Shenton, M.E., McCarley, R.W., 1998. High-density recording and topographic analysis of the auditory oddball event-related potential in patients with schizophrenia. *Biological Psychiatry* 44, 982–989.
- Reite, M., Sheeder, J., Teale, P., Adams, M., Richardson, D., Simon, J., Jones, R.H., Rojas, D.C., 1997. Magnetic source imaging evidence of sex differences in cerebral lateralization in schizophrenia. *Archives of General Psychiatry* 54, 433–440.
- Rockstroh, B., Elbert, T., Lutzenberger, W., Altenmüller, E., 1991. Effects of the anticonvulsant benzodiazepine clonazepam on event-related brain potentials in humans. *Electroencephalography and Clinical Neurophysiology* 78, 142–149.
- Rockstroh, B., Kissler, J., Mohr, B., Eulitz, C., Lommen, U., Wienbruch, C., Cohen, R., Elbert, T., 2001. Altered hemispheric asymmetry of auditory magnetic fields to tones and syllables in schizophrenia. *Biological Psychiatry* 49, 694–703.
- Rosburg, T., Marinou, V., Hauelsen, J., Smesny, S., Sauer, H., 2004. Effects of lorazepam on the neuromagnetic mismatch negativity (MMNm) and auditory evoked field component N100m. *Neuropsychopharmacology* 29, 1723–1733.
- Roth, W.T., Cannon, E.H., 1972. Some features of the auditory evoked response in schizophrenics. *Archives of General Psychiatry* 27, 466–471.
- Roth, W.T., Horvath, T.B., Pfefferbaum, A., Kopell, B.S., 1980. Event-related potentials in schizophrenics. *Electroencephalography and Clinical Neurophysiology* 48, 127–139.
- Roth, W.T., Pfefferbaum, A., Kelly, A.F., Berger, P.A., Kopell, B.S., 1981. Auditory event-related potentials in schizophrenia and depression. *Psychiatry Research* 4, 199–212.
- Roth, W.T., Goodale, J., Pfefferbaum, A., 1991. Auditory event-related potentials and electrodermal activity in medicated and unmedicated schizophrenics. *Biological Psychiatry* 29, 585–599.
- Saitoh, O., Kameyama, T., Hiramatsu, K.I., Niwa, S., Itoh, K., 1981. Event-related brain potentials and selective attention in schizophrenia. *Annual Bulletin of the Research Institute of Logopedics and Phoniatrics* 15, 109–127.
- Saletu, B., Itil, T.M., Saletu, M., 1971. Auditory evoked response, EEG, and thought process in schizophrenics. *American Journal of Psychiatry* 128, 336–344.
- Sams, M., Paavilainen, P., Alho, K., Näätänen, R., 1985. Auditory frequency discrimination and event-related potentials. *Electroencephalography and Clinical Neurophysiology* 62, 437–448.
- Schlör, K.H., Moises, H.W., Haas, S., Rieger, H., 1985. Schizophrenia, psychoticism, neuroleptics, and auditory evoked potentials. *Pharmacopsychiatry* 18, 293–296.
- Semlitsch, H.V., Anderer, P., Saletu, B., 1995. Acute effects of the anxiolytics suriclone and alprazolam on cognitive information processing utilizing topographic mapping of event-related brain

- potentials (P300) in healthy subjects. *European Journal of Clinical Pharmacology* 49, 183–191.
- Shagass, C., Roemer, R.A., Straumanis, J.J., Amadeo, M., 1978. Evoked potential correlates of psychosis. *Biological Psychiatry* 13, 163–184.
- Shelley, A.M., Silipo, G., Javitt, D.C., 1999. Diminished responsiveness of ERPs in schizophrenic subjects to changes in auditory stimulation parameters: implications for theories of cortical dysfunction. *Schizophrenia Research* 37, 65–79.
- Shinozaki, N., Yabe, H., Sato, Y., Hiruma, T., Sutoh, T., Nashida, T., Matsuoka, T., Kaneko, S., 2002. The difference in mismatch negativity between the acute and post-acute phase of schizophrenia. *Biological Psychology* 59, 105–119.
- Sinton, C.M., McCullough, J.R., Ilmoniemi, R.J., Etienne, P.E., 1986. Modulation of auditory evoked magnetic fields by benzodiazepines. *Neuropsychobiology* 16, 215–218.
- Sörös, P., Michael, N., Tollkötter, M., Pfeleiderer, B., 2006. The neurochemical basis of human cortical auditory processing: combining proton magnetic resonance spectroscopy and magnetoencephalography. *BMC. Biology* 4, 25.
- Spreng, M., 1980. Influence of impulsive and fluctuating noise upon physiological excitations and short-time readaptation. *Scandinavian Audiology Supplement* 299–306.
- Stefansson, S.B., Jonsdottir, T.J., 1996. Auditory event-related potentials, auditory digit span, and clinical symptoms in chronic schizophrenic men on neuroleptic medication. *Biological Psychiatry* 40, 19–27.
- Strassnig, M., Brar, J.S., Ganguli, R., 2006. Increased caffeine and nicotine consumption in community-dwelling patients with schizophrenia. *Schizophrenia Research* 86, 269–275.
- Sumich, A., Harris, A., Flynn, G., Whitford, T., Tunstall, N., Kumari, V., Brammer, M., Gordon, E., Williams, L.M., 2006. Event-related potential correlates of depression, insight and negative symptoms in males with recent-onset psychosis. *Clinical Neurophysiology* 117, 1715–1727.
- Tiihonen, J., Hari, R., Naukkarinen, H., Rimon, R., Jousmäki, V., Kajola, M., 1992. Modified activity of the human auditory cortex during auditory hallucinations. *American Journal of Psychiatry* 149, 255–257.
- Todd, J., Michie, P.T., Budd, T.W., Rock, D., Jablensky, A.V., 2000. Auditory sensory memory in schizophrenia: inadequate trace formation? *Psychiatry Research* 96, 99–115.
- Todd, J., Michie, P.T., Jablensky, A.V., 2003. Association between reduced duration mismatch negativity (MMN) and raised temporal discrimination thresholds in schizophrenia. *Clinical Neurophysiology* 114, 2061–2070.
- Umbricht, D., Javitt, D., Novak, G., Bates, J., Pollack, S., Lieberman, J., Kane, J., 1998. Effects of clozapine on auditory event-related potentials in schizophrenia. *Biological Psychiatry* 44, 716–725.
- Umbricht, D., Javitt, D., Novak, G., Bates, J., Pollack, S., Lieberman, J., Kane, J., 1999. Effects of risperidone on auditory event-related potentials in schizophrenia. *International Journal of Neuropsychopharmacology* 2 (4), 299–304.
- Umbricht, D., Koller, R., Schmid, L., Skrabo, A., Grubel, C., Huber, T., Stassen, H., 2003. How specific are deficits in mismatch negativity generation to schizophrenia? *Biological Psychiatry* 53, 1120–1131.
- Valkonen-Korhonen, M., Purhonen, M., Tarkka, I.M., Sipila, P., Partanen, J., Karhu, J., Lehtonen, J., 2003. Altered auditory processing in acutely psychotic never-medicated first-episode patients. *Brain Research/Cognitive Brain Research* 17, 747–758.
- van der Stelt, O., Frye, J., Lieberman, J.A., Belger, A., 2004. Impaired P3 generation reflects high-level and progressive neurocognitive dysfunction in schizophrenia. *Archives of General Psychiatry* 61, 237–248.
- Ward, P.B., Catts, S.V., Fox, A.M., Michie, P.T., McConaghy, N., 1991. Auditory selective attention and event-related potentials in schizophrenia. *British Journal of Psychiatry* 158, 534–539.
- Wehr, M., Zador, A.M., 2005. Synaptic mechanisms of forward suppression in rat auditory cortex. *Neuron* 47, 437–445.
- Williams, L.L.M., Bahramali, H., Hemsley, D.R., Harris, A.W.F., Brown, K., Gordon, E., 2003. Electrodermal responsivity distinguishes ERP activity and symptom profile in schizophrenia. *Schizophrenia Research* 59, 115–125.
- Winterer, G., Egan, M.F., Radler, T., Coppola, R., Weinberger, D.R., 2001a. Event-related potentials and genetic risk for schizophrenia. *Biological Psychiatry* 50, 407–417.
- Winterer, G., Mulert, C., Mientus, S., Gallinat, J., Schlattmann, P., Dorn, H., Herrmann, W.M., 2001b. P300 and LORETA: comparison of normal subjects and schizophrenic patients. *Brain Topography* 13, 299–313.