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Auditory event-related potential of subjects with suspected pre-psychotic state and first-episode psychosis

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ABSTRACT

Background: Recent schizophrenia research exploring the complicated pathogenesis of schizophrenia has focused on the subjects with at-risk mental states in order to exclude the influence of confounding factors. This study explores 3 sets of auditory-related event potentials in subjects with different risk levels of psychosis.
Methods: Subjects were recruited from the SOPRES study in Taiwan. P50 and N100 using an auditory paired-click paradigm and duration MMN were assessed on 32 first-episode psychosis (FEP), 30 ultra-high risk (UHR), 37 E-BARS (early/broad at-risk mental states) participants and 56 controls.
Results: MMN was correlated with neither P50 nor N100, whereas many parameters of the latter two were inter-correlated with each other. Compared to healthy controls, MMNs were significantly lower in all 3 clinical groups (E-BARS, UHR and FEP). A gradient of sensory-gating deficits, manifested by increased P50 ratios (S2/S1) and decreased N100 differences, across different levels of clinical severity was suggested by a linear trend. For the UHR subjects, P50 gating ratio, N100 gating ratio, N100 difference, and N100 S2 amplitude might be potential indicators to discriminate converters from non-converters.
Conclusions: By including subjects with E-BARS, our results provide new insight regarding pre-attentive auditory event-related potential in subjects across different risk levels of psychotic disorders. Impaired deviance detection shown by MMNs already exists in people at a pre-psychotic state regardless of clinical severity, while sensory-gating deficits shown by P50/N100 varies depending on the risk levels in prodromal period. Further longitudinal research exploring the relationship between ERPs and subjects with a suspected pre-psychotic state is needed.

1. Introduction

Schizophrenia is a disorder of the brain that involves several levels of deficits (Braff and Light, 2004; Rissling and Light, 2010b). Most neurobiological studies of schizophrenia have been conducted in chronic patients; however, the long duration of illness per se could be a confounder, making the interpretation of neurobiological findings rather difficult (Mathalon et al., 2000; Premkumar et al., 2008; Tanskanen et al., 2010). Also, the long-term use of antipsychotics has profound effects on brain neurochemistry and possibly brain morphology (Breier, 2004). A promising approach to explore the complicated pathogenesis of schizophrenia without being confounded by these factors is to monitor the progression of subjects from a pre-psychotic state to a full-blown psychotic episode (Cornblatt et al., 2003; Keshavan et al., 2011).

In the past decade, researchers worldwide have conducted prospective studies in this regard, but the majority of them focused on the ultra-high risk or late-prodromal state (Breier, 2004; Olsen and Rosenbaum, 2006), while little is known about what happened prior to ultra-high risk state. Keshvan et al. proposed the concept of early/broad at-risk mental states (E-BARS) to suggest needs to explore individuals at an earlier stage and broader range of at-risk mental states (Keshavan et al., 2011). In Taiwan, a study on the psychopathological progress of the pre-psychotic state (the SOPRES study) was initiated in 2006. In addition to including ultra-high risk subjects who demonstrated a significantly higher probability of transition to a full-blown psychotic episode, the SOPRES study also recruited subjects at marginal-risk (subjects presenting with non-specific cognitive and affective symptoms did not

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yet meet any diagnostic category), intermediate risk (subjects with schizotypal-like and some negative symptoms), and first-episode psychosis (Liu et al., 2010; Liu et al., 2011). Thus the SOPRES data allows us to explore individuals putatively at pre-psychotic state while not reaching the severity of ultra-high risk criteria.

Auditory event-related potentials (ERP), including P50, N100, and mismatch negativity (MMN), have been utilized to study normal versus defective information processing in schizophrenia (Adler et al., 1982; Nagamoto et al., 1991; Clementz et al., 1997; Michie, 2001; Keshavan et al., 2008). Sensory-gating methods using paired-click paradigm (Nagamoto et al., 1989; Nagamoto et al., 1991) had provided strong relationship between genes and the pathophysiological aspect of the illness (Freedman et al., 1997). They have also been identified as candidate endophenotypes of schizophrenia in order to reveal possible schizophrenia genes (Turetsky et al., 2007; 2008; Javitt et al., 2008; Rissling and Light, 2010a). Several studies have investigated the relationship of auditory ERP components in high-risk subjects. For example, P300 amplitude reduction has been correlated with an increased vulnerability to psychosis (Bramon et al., 2008; Frommann et al., 2008; Ozgurdal et al., 2008; van Tricht et al., 2010). MMN amplitudes of prodromal subjects were found to be at an intermediate stage between those of the control and schizophrenia subjects, although the difference did not reach statistical significance (Brockhaus-Dumke et al., 2005). P50 and N100 were found with marginal differences between healthy control subjects and high-risk groups in P50 ratio (S2/S1) and N100 difference (S1-S2), while no significant differences in any parameter between converters and non-converters (i.e. at-risk subjects versus truly prodromal patients) (Brockhaus-Dumke et al., 2008).

As compared with other studies that recorded ERPs solely in ultra-high risk subjects or drug-naïve genetically high-risk probands, this study concurrently investigated the auditory ERPs of subjects at different levels of clinical severity, from normal controls to an early/broad at-risk mental state, ultra-high risk state, and first-episode psychosis. Also an addition to previous studies on UHR subjects, we examined the intercorrelation between P50, N100, and MMN, explored the features of P50, N100, and MMN among these clinical subgroups, and compared the baseline ERP findings between the converters and non-converters of our ultra-high risk subjects.

2. Methods

2.1. Participants

Subjects were participants in the SOPRES study who agreed to receive electrophysiological assessments. The rationale and methodology for the SOPRES study have been described elsewhere (Liu et al., 2010; Liu et al., 2011). Briefly, individuals presenting with "non-specific Cognitive deficits, Affective symptoms, Social Isolation, and School failure" (CASIS) (Cornblatt et al., 2003) or having newly developed psychotic-like symptoms were referred for assessment. The SOPRES study was approved by the National Taiwan University Hospital (NTUH) Institute Review Board. All subjects and/or their parents provided signed written informed consent before their participation in this study.

Originally, the levels of clinical severity were categorized into four groups by employing the Thought/Perception Diagnostic Interview Schedule (TP-DIS) (Liu et al., 2011). The group of first-episode psychosis (FEP) included participants with schizophrenia, schizophreniform disorder, brief psychotic disorder, or schizoaffective disorder meeting the DSM-IV criteria in the preceding one year. The ultra-high risk group (UHR) included participants with attenuated psychotic symptoms (APS) or brief limited intermittent psychotic symptoms (BLIPS) (McGorry et al., 2003). The intermediate-risk group (IRG) included participants who presented with odd thinking, feelings, speech, or perceptual experiences, which were not as severe as in the UHR group but met the criteria of schizotypal disorder according to the 10th edition of the International Classification of Diseases (ICD-10) without the duration requirement of two years. The marginal-risk group (MRG) included participants with CASIS symptoms (Cornblatt et al., 2003) without meeting either the threshold for the IRG or other diagnostic category. A group of age- and gender-matched healthy volunteers were also recruited. Of note, in our SOPRES 2-year follow-up, only one third of patients from the UHR group have converted into full-blown psychosis while none of the IRG and MRG subjects converted, and in our preliminary analysis, either from eyeballing the scatter plots or statistically tested, there is no significant distinction between these 2 groups in terms of the results of our interests, thus we combined these two groups to be an analogue of the recently proposed "early/broad at-risk mental states" (E-BARS) in later analyses.

Subjects with an IQ below 70, aged younger than 16 years, with a history of traumatic brain injury, a history of central nervous system illness, a prior psychotic episode lasting for more than one year, or current use of psychoactive stimulants were excluded. The pre-psychotic subjects who developed first-episode psychosis during the 2-year follow-up were defined as converters. In this study all converters came from the UHR group, while none of the E-BARS subjects converted to FEP.

2.2. Experimental procedures

Audiometry testing was used to exclude subjects who could not detect 40-dB sound pressure level tones at 500, 1000, and 6000 Hz presented to either ear. A standard protocol for auditory P50 and MMN paradigm was followed (Lijffijt et al., 2009; Light et al., 2010; Shan et al., 2010). The participants had not smoked for at least 1 h before sessions (Adler et al., 1992; Olincy and Martin, 2005), and were asked to lie down in the supine position in a comfortable recliner in a sound attenuating, electrically shielded booth and instructed to relax with his/her eyes open and to focus on a fixation point (P50 and N100 session) or a cartoon running with no sound on the video monitor (MMN session).

The EEG signals were recorded with a Quik-Cap (Compumedics Neuroscan, El Paso, TX, USA) from 32 scalp locations (10–20 system). The auditory stimuli were generated by a Neuroscan STIM system, and data were recorded on a Neuroscan ACQUIRE system (Compumedics Neuroscan, El Paso, TX, USA). Stimuli were digitized at a rate of 1 kHz and an on-line band-pass filter at 0.5–100 Hz, without 60-Hz notch filter applied. Electrodes placed at the tip of the nose and at Fpz served as the reference and ground, respectively. Four additional electrodes were located above and below the left eye and at the outer canthi of both eyes to monitor blinks and eye movements. Electrode impedances were kept below 5 kΩ prior to recording.

Auditory ERPs were presented to the subjects binaurally via foam insert earphones in two consecutive sessions, i.e. the session of paired-click paradigm for P50/N100 followed by the duration MMN session. On-line averaging was used to monitor the number of trials free from gross artifacts (defined as activities exceeding ±100 μV in the −100–500 ms time window following stimuli). Regarding the pair-click P50/N100 paradigm, paired auditory clicks (1 ms, 85 dB) were presented every 8–12 s through the whole test session (average: 10 s), with a 500-msec inter-stimulus interval (Clementz et al., 1998; de Wilde et al., 2007). The paired-click P50/N100 session was terminated when a minimum of 120 artifact-free trials had been obtained, which took about 30 min. For the duration MMN paradigm, pure tone stimuli (1 kHz, 85 dB SPL, 5 ms rise/fall, Hanning window) were generated by the Neuroscan STIM system. The auditory stimuli consisted of standard stimuli (90%, 50-msec duration) and deviant stimuli (10%, 100-msec duration) delivered in a pseudo-random order with the constraint that deviant stimuli could not be repeated back-to-back. The cartoon soundtrack was turned off and replaced by the experimental auditory stimuli which were presented at a fixed 500-msec

onset-to-onset asynchrony. The MMN session was continued until a minimum of 225 artifact-free deviant trials had been collected on line, which took approximately 30 min.

2.3. Data processing

All data were processed using Neuroscan Edit 4.3 software (Compumedics Neuroscan, El Paso, TX USA) by researchers who were blind to the subject's group (Boutros, 2008). Semi-automated procedures using the Tool Command batch processing Language (TCL), began with EOG artifact reduction through a built-in pattern-recognition algorithm (Semlitsch et al., 1986). For paired-click P50/N100 continuous files, the data were epoched for the time window −100 to 923 ms relative to the first click, in order to cover both S1 and S2 in the same epoch. All epochs containing activities exceeding ±50 μV were excluded and the epochs were then averaged and digitally band-pass filtered (10 to 50 Hz for P50, 1 to 50 Hz for N100) in the frequency domain to prevent temporal aliasing (Boutros et al., 2004). Trials with artifacts were detected manually and rejected from further analysis. Thereafter, all peaks and preceding troughs were detected automatically at the Cz electrode using preset intervals (Clementz et al., 1998; Niznikiewicz et al., 2004; Brockhaus-Dumke et al., 2008; Light et al., 2010). Data from the subjects where the S1 amplitude (P50, N100) was less than 0.5 μV were removed from analysis (Nagamoto et al., 1989; Boutros, 2008). The P50 peak was defined as the largest positive deflection between 45 and 75 ms post-stimulus, and its amplitude was assessed as the difference between this peak and the preceding negative trough (not earlier than 30 ms post-stimulus). The N100 component was identified as the most negative deflection within 80 to 150 ms post-stimulus, and N100 amplitude was defined as the absolute difference between the N100 peak and the preceding positive trough. In addition, if the stimulus 2 (S2) response could not be found within the 10 ms window for P50 or 20 ms for N100 of the latency of the S1 response, the S2 response was scored as 0 (Nagamoto et al., 1989; Boutros et al., 2004). P50 and N100 parameters included the S1 amplitude, S2 amplitude, amplitude difference (S1–S2), and P50/N100 gating ratio (S2/S1). A maximum of 2 for gating ratio was used to prevent outliers from disproportionately affecting the group means (Nagamoto et al., 1989).

For duration MMN analysis, each subject's continuous data files after EOG artifact reduction were then epoched 100 ms pre-stimulus to 500 ms post-stimulus. Following linear detrending and baseline correction to the average pre-stimulus interval, all epochs containing amplitudes exceeding ±50 μV in frontal recording sites (F7, F8, Fp1, Fp2, F3, F4, and Fz) were automatically rejected (Wynn et al., 2010). EEG responses to standard and deviant stimuli were separately averaged to create a standard ERP and a deviant ERP, and both were low-pass filtered at 20 Hz (0-phase shift and 24-dB/octave roll-off) to remove any residual high-frequency artifacts. MMN waveforms were generated by subtracting the standard ERP from the deviant ERP. MMN indices were measured as the mean voltage from 135 to 205 ms from the Fz electrode (Michie et al., 2002; Light et al., 2010; Wynn et al., 2010).

2.4. Statistical analyses

For demographic characteristics, we used analyses of variance and chi-square tests (or Fisher's exact tests if necessary) to compare continuous and categorical variables across different risk groups and normal controls, respectively. The correlations between ERP parameters were examined using the Spearman rank correlation tests. Analyses of variance with post-hoc analyses were used to examine differences in ERP parameters among these four groups. Treating the risk level as a continuous covariate, linear trends of ERP parameters across these four groups were checked by regression models. A subgroup analysis of participants within the UHR group was performed to determine factors associated with converting to full-blown psychosis or not. Demographic characteristics, SOPS symptom dimensions (i.e. positive, negative, disorganized and general symptoms) and ERP parameters were compared between converters and non-converters. Chi-square or Fisher's exact tests were used for categorical variables, while non-parametric Mann–Whitney U tests were used for continuous variables because of the small sample size for converters and non-converters in the UHR group. All tests were 2-sided with $\alpha = 0.05$.

3. Results

In total, we recruited 99 clinical subjects, including 32 FEP, 30 UHR, 37 E-BARS, along with 56 normal controls (Table 1). There were no significant differences in age, gender, education, and smoking status. Only the UHR and FEP subjects were prescribed with antipsychotics.

Regarding the relationship between individual ERP indicators, the Spearman's rank correlation coefficients are outlined in Table 2. The majority of P50 and N100 parameters were mutually correlated, except no correlation existed between N100 ratio and any P50 parameter. MMN was correlated with neither P50 nor N100 parameters.

With respect to the differences in ERPs between these four subgroups (Table 3), only MMN reached statistical significance ($p = 0.019$). In post-hoc analyses, there were significant differences in MMN in the E-BARS ($p = 0.007$), UHR ($p = 0.035$), and FEP ($p = 0.035$) groups as compared to the controls.

Fig. 1 demonstrates linear trends of P50 ratios (S2/S1) and the N100 differences across different risk groups (P50 ratios, $p = 0.060$; N100 differences, $p = 0.018$); that is, these two sensory-gating indicators were largest in the FEP group followed by the UHR group, the E-BARS group and the normal controls in order. Grand average MMN waveforms for the FEP patients (in blue) and control subjects are shown in Fig. 2. The MMN waveform reversed in polarity at the mastoid electrodes.

Further analysis for participants within the UHR group showed no significant differences between converters and non-converters in either demographic profile or any of the four symptom dimensions (Table 4 and Fig. 3). There was some evidence suggesting that the converters had a poorer performance than the non-converters in several P50 and N100 indicators including P50 gating ratio ($p = 0.099$), N100 gating ratio ($p = 0.060$), N100 difference ($p = 0.088$), and N100 S2 amplitude ($p = 0.060$), but not MMN.

4. Discussion

To the best of our knowledge, this study is one of the first to examine auditory ERPs (P50/N100/MMN) in not only subjects with first-episode psychosis (FEP) and ultra-high risk (UHR) subjects, but also in those with presumed early/broad at-risk mental states (E-BARS). In general, MMN was correlated with neither P50 nor N100, whereas many parameters of the latter two were intercorrelated with each other. Specifically, as compared to healthy controls, all three clinical groups, i.e. E-BARS, UHR and FEP had significantly lower MMNs. On the other hand, the differences in P50 and N100 between control and clinical groups were not significant, while a linear trend of more deviance from controls across different levels of clinical severity was noticed in P50 ratios (S2/S1) and N100 differences (Fig. 1). For subjects within the UHR group, certain P50 and N100 indicators might be useful when attempting to discriminate converters from non-converters.

Examining subjects with a gradient of clinical severities spanning from normal control, early at-risk state, ultra-high risk state to first-episode psychosis is helpful to delineate the pathophysiological mechanisms throughout the formation of psychosis. Our results suggest that MMN and P50/N100 represent quite different inferences in the pathological information processing of subjects with at-risk mental status. This is in agreement with current knowledge that MMN reflects deviance detection which might be mediated by glutamate (Korostenskaja et al., 2007; Leung et al., 2007; Javitt et al., 2008; Korostenskaja and Kahkonen, 2009), while P50/N100 refers to sensory gating which is more likely related to

Table 1
Demographic data of the four subgroups.

Variable	NC (n=56)	E-BARS (n=37)	UHR (n=30)	FEP (n=32)	Test statistics[a]	*P*-value[b]
Gender, n (%)					4.40	.222
Male	22 (39.3)	21 (56.8)	17 (56.7)	13 (40.6)		
Female	34 (60.7)	16 (43.2)	13 (43.3)	19 (59.4)		
Age, mean (SD), y	23.64 (6.37)	21.54 (3.45)	22.01 (3.79)	22.63 (4.56)	1.52	.210
Education, mean (SD), y	14.79 (2.85)	13.76 (2.07)	14.33 (2.11)	13.50 (2.48)	2.33	.076
Smoker, n (%)	5 (8.9)	3 (8.1)	5 (16.7)	3 (9.4)	1.649	.648

NC, normal control group; E-BARS, early/broad at-risk mental states; UHR, ultra-high risk group; FEP, first-episode psychosis group.
None of the NC and E-BARS subjects received antipsychotic treatment; in the UHR group, 8 were drug-naïve, 8 used aripiprazole ≤7.5 mg/day, 6 used sulpiride ≤200 mg/day, 4 took amisulpiride 200 mg/day, 3 used risperidone ≤3 mg/day, and 1 used quetiapine 100 mg/day, the majority of them received antipsychotic treatment for less than 3 months; in the FEP group, 6 were drug-naïve, 5 used olanzapine 5–10 mg/day, 10 used aripiprazole 3.75–22.5 mg/day, 4 used amisulpiride 100–400 mg/day, 5 used risperidone 2–4.5 mg/day, 2 used sulpiride 200 mg/day.
[a] ANOVA (analyses of variance) for age and years of education; Chi-square test for gender; Fisher's Exact test for smokers due to the expected number being less than five for at least 1 cell.
[b] *P*-values were 2-sided.

Table 2
The Spearman's correlation coefficients among P50, N100 and MMN Parameters.[a].

	P50 S1	P50 S2	P50 ratio	P50 difference	N100S1	N100S2	N100 ratio	N100 difference	Age
P50 S1									−.089
P50 S2	.235**								−.117
P50 ratio	−.231**	.836**							−.057
P50 difference	.743**	−.405**	−.769**						.007
N100S1	−.573**	−.056	.223**	−.495**					−.059
N100S2	−.157	−.098	−.032	−.082	.192*				.153
N100 ratio	−.044	.073	.098	−.085	.154[c]	−.887**			−.154
N100 difference	.447**	−.019	−.239**	.429**	−.846**	.293**	−.609**		.104
MMN	.007	0.007	.011	.024	.127	.028	.038	−.122	.037

*p-value<.05, 2-sided; **p<.001, 2-sided.
[a] Number of subjects for P50/N100 was 152 and for MMN was 130.

dopamine and other neurotransmitters (Pekkonen et al., 2005; Hall et al., 2006; Price et al., 2006; Turetsky et al., 2007; Javitt et al., 2008; Keshavan et al., 2008; Turetsky et al., 2009). The high correlations between N100 difference and P50 ratio and P50 difference was compatible with previous studies (Fuerst et al., 2007; Brockhaus-Dumke et al., 2008), suggesting "both P50 and N100 reflect stimulus registration in similar ways but gating or habituation to repeated stimulation in different ways" (Brockhaus-Dumke et al., 2008).

Our findings in duration MMN suggest it to be a trait, or a very sensitive marker, for schizophrenia, which means reduced MMN could be detected at subjects presenting with symptoms suggesting a putatively pre-psychotic state (Green et al., 2009; Atkinson et al., 2012), yet such a reduction might not get much worse along with the increase of clinical severity, especially in terms of emergence of attenuated psychotic symptoms. Previous studies have demonstrated impaired duration MMN in nonpsychotic biological first-degree

Table 3
P50, N100 and MMN parameters among the four Subgroups[a].

	NC	E-BARS	UHR	FEP	Test statistics[b]	*P*-value[c]
P50	n=56	n=35	n=29	n=32		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Trials	112.4 (26.2)	111.8 (25.2)	102.83 (30.2)	112.2 (19.9)	1.05	.372
S1 latency (ms)	62.9 (8.1)	63.7 (7.8)	64.2 (6.6)	63.2 (9.0)	0.18	.909
S1 (μV)	2.37 (1.11)	2.49 (1.68)	2.29 (1.22)	2.19 (1.07)	.35	.791
S2 (μV)	.85 (.76)	1.04 (1.12)	1.06 (.73)	1.05 (.83)	0.61	.609
S2/S1 ratio	.40 (.41)	.47 (.48)	.55 (.45)	.58 (.57)	1.20	.313
S1-S2 (μV)	1.52 (1.13)	1.46 (1.22)	1.22 (1.30)	1.14 (1.30)	0.86	.464
N100						
S1 (μV)	−6.96 (3.83)	−6.20 (3.70)	−5.08 (2.58)	−5.36 (3.03)	2.52	.060
S2 (μV)	−1.59 (1.57)	−1.64 (1.88)	−1.10 (1.29)	−1.66 (1.44)	0.89	.447
S2/S1 ratio	.26 (.25)	.34 (.41)	.23 (.27)	.35 (.34)	1.34	.263
S2-S1 (μV)	5.37 (3.80)	4.56 (3.68)	3.99 (2.63)	3.70 (3.24)	1.95	.1244
MMN	n=53	n=30	n=19	n=28		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Fz (μV)	−1.37 (.89)	−.83 (.80)	−.88 (.92)	−.94 (.84)	3.46	.019[d]

NC, normal control group; E-BARS, early/broad at-risk mental states; UHR, ultra-high risk group; FEP, first-episode psychosis group. SD, standard deviation.
[a] Some subjects failed to stay before the ERP session was terminated.
[b] The test statistics were obtained by ANOVA (analyses of variance).
[c] *P*-values were 2-sided.
[d] Post-hoc analyses by independent *t* tests: Control versus E-BARS: p=.007, Control versus UHR: p=.035, Control versus FEP: p=.035.

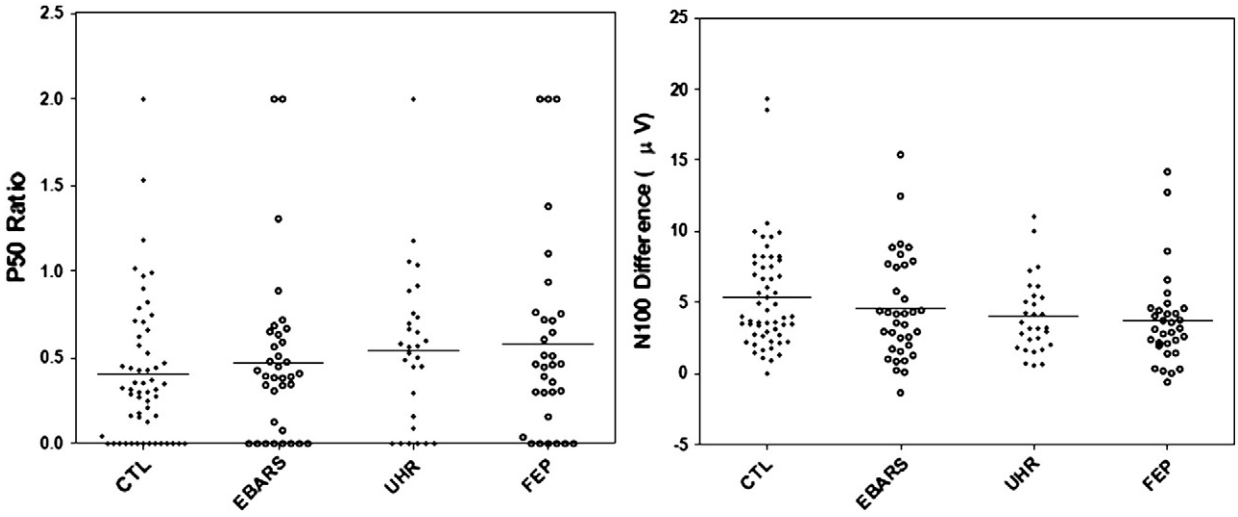

Fig. 1. P50 ratios and N100 differences. The left panel demonstrates P50 ratio (S2 amplitude / S1 amplitude) and the right one N100 difference (μV; S2 amplitude–S1 amplitude) of individual participants. Larger ratio (S2/S1) and smaller difference (S1–S2) indicate poorer gating. The horizontal lines indicate the mean values within each risk group. CTL: control; E-BARS: early/broad at-risk mental states; UHR: ultra-high risk group; FEP: first-episode psychosis.

relatives of patients with schizophrenia (Michie et al., 2002) and reduced MMN in subjects at ultra-high risk state (Michie et al., 2002; Shin et al., 2009; Atkinson et al., 2012), and glutamate system dysfunction has been noted in at-risk mental state subjects (Stone et al., 2009). This study further revealed that even people at early/broad risk states might already demonstrate detectable MMN reduction.

In contrast to MMN, the parallels between the extent of sensory-gating problems manifested by P50 gating ratio and N100 differences and the gradient of clinical severity suggest these two ERP indices might be state-dependent markers for schizophrenia. This might violate the definition of an ideal endophenotype (state-independent or symptom-independent). However, several studies have provided mixed results with regards to the relationship between P50 gating ratio and clinical presentations (Ringel et al., 2004; Louchart-de la Chapelle et al., 2005), between clinical high-risk and genetic high-risk (Myles-Worsley et al., 2004), as well as between different clinical stages (Brockhaus-Dumke et al., 2008). Nonetheless, our findings could provide new insights regarding the interpretation of such inconsistent findings. We conjecture that during pre-psychotic state when sensory-gating deficits are relatively mild, P50/N100 might be state-dependent markers as revealed by our findings; but once frank psychosis occurs and the sensory-gating problems become manifest,

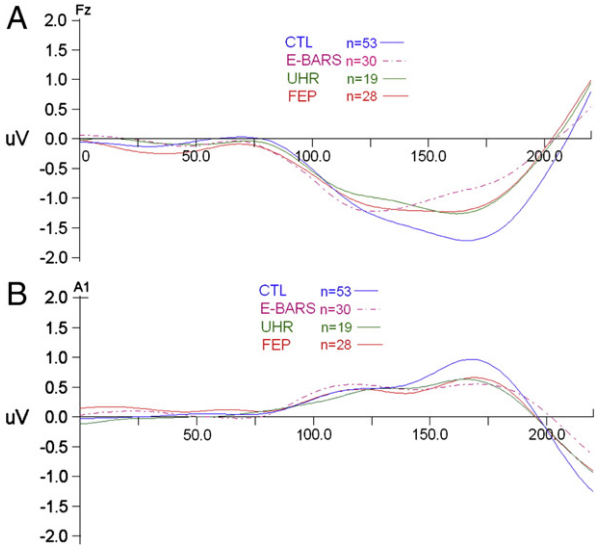

Fig. 2. Grand average mismatch negativity (MMN) waveforms for healthy control subjects (in blue) and (A) MRG, (B) IRG, (C) UHR, (D) FEP subjects (in red). Left and right columns indicates Fz and A1 (mastoid) electrodes. The MMN waveform reversed in polarity at the mastoid electrodes.

Table 4
The comparison of clinical characteristics and ERP parameters in converters versus non-converters among ultra-high risk group (n=30).

	Converter (n=11)	Non-converter (n=19)	Test statistics[a]	*P*-value[b]
Male/Female	7/4	10/9	.344	0.708
Smoker/Non-smoker	1/10	4/15	.718	0.626
	Mean (SD)	Mean (SD)	Test statistics[c]	*P*-value[d]
Age (years)	20.83 (3.07)	22.69 (4.07)	1.140	.254
Education (years)	13.91 (2.12)	14.58 (2.12)	0.881	.379
Symptom dimensions				
Positive	12.55 (3.08)	10.32 (3.97)	−1.596	.111
Negative	12.28 (8.31)	8.95 (6.40)	−1.122	.262
Disorganized	7.45 (4.66)	6.53 (5.22)	−0.691	.490
General	9.73 (4.58)	9.00 (5.13)	−0.497	.619
P50 parameters	Mean (SD) (n=11)	Mean (SD) (n=18)	Test Statistic[c]	*P*-value[d]
Trials	96.1 (37.4)	106.9 (25.1)	0.450	.653
S1 latency (ms)	64.27 (4.63)	64.11 (7.72)	0.315	.753
S1 amplitude (μV)	2.08 (.87)	2.41 (1.39)	0.360	.719
S2 amplitude (μV)	1.20 (.73)	.98 (.74)	−0.339	.735
S2/S1 ratio	.67 (.38)	.47 (.48)	−1.648	.099
P50 difference (μV)	.88 (.99)	1.43 (1.44)	1.348	.178
N100 parameters	Mean (SD) (n=11)	Mean (SD) (n=18)	Test Statistics[c]	*P*-value[d]
S1 amplitude (μV)	−4.60 (1.75)	−5.38 (2.99)	−0.405	.686
S2 amplitude (μV)	−1.67 (1.28)	−.75 (1.21)	1.884	.060
S2/S1 ratio	.35 (.29)	.16 (.23)	−1.884	.060
N100 difference (μV)	2.93 (1.69)	4.63 (2.92)	1.708	.088
MMN	Mean (SD) (n=6)	Mean (SD) (n=13)	Test Statistics[c]	*P*-value[d]
Fz (μV)	−.50 (.49)	−1.06 (1.04)	−1.316	.188

SD, standard deviation.
[a] Chi-square tests.
[b] *P*-values, 2-sided, were obtained by Fisher's exact test due to expected number less than five for at least 1 cell.
[c] Mann–Whitney U tests.
[d] Asymptotic *p*-values, 2-sided.

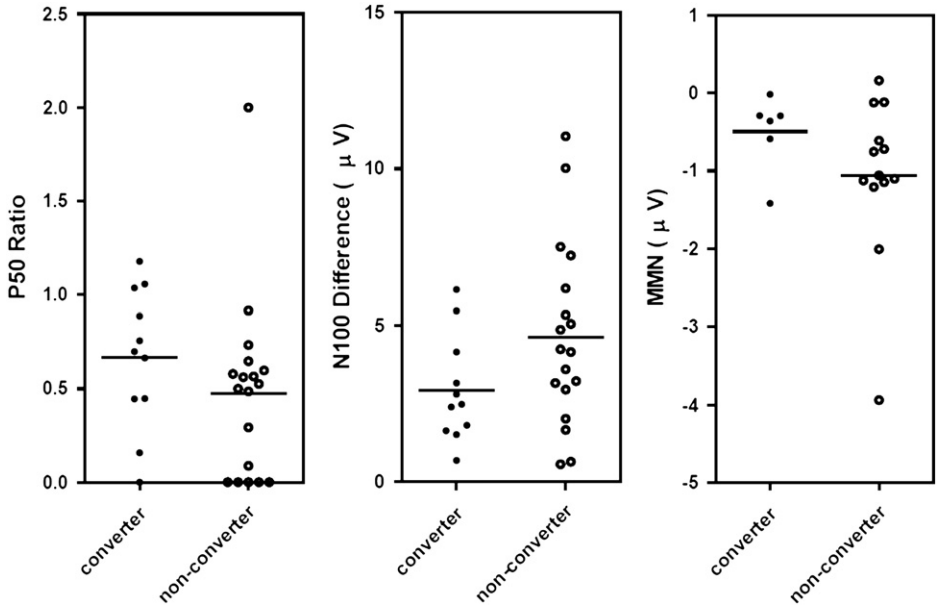

Fig. 3. Three event-related potentials in non-converters versus converters within the ultra-high risk subgroup (UHR). The left panel shows P50 ratio (S2 amplitude/S1 amplitude), the middle one N100 difference (μV; S2 amplitude–S1 amplitude), and the right on MMN (μV) of UHR individuals. The horizontal lines denote the mean values.

the severity of symptoms or duration of psychosis were less likely to have strong correlation with the extent of P50 deficits as revealed by a review of studies (Potter et al., 2006).

Based on our preliminary analysis, P50 and N100, rather than MMN, are potential candidates to differentiate converters and non-converters among subjects at ultra-high risk for schizophrenia, even though a recent study revealed reduced duration MMN associated with a higher risk of converting to first-episode psychosis among at-risk subjects (Bodatsch et al., 2011). Actually, among our UHR subjects, the mean MMN of converters was indeed lower than non-converters (converter versus non-converters = −.50 versus −1.06) but this was not statistically significant. This could merely be an issue of statistical power because of the small sample size in this subgroup analysis (converters, N = 6; non-converters, N = 13). Further research about predicting conversion in UHR subjects by different indices of ERPs will be necessary to clarify this issue.

There are several limitations that are worth noting. The relatively small sample size limits our statistical power to detect smaller between-group differences. The validity of our clinical subgrouping of early/broad at-risk mental states is pending further follow-up and exploration. UHR and FEP subjects were not studied in an antipsychotic-free status; while use of antipsychotic might diminish the magnitude of P50 gating deficit hence masks some potential findings. In addition, we used data collected by midline electrodes to analyze the ERPs for consistency with previous literature and protocols, while the German Research Network on Schizophrenia Group used lateral electrodes to yield positive findings on prodromal studies (Frommann et al., 2008), thus topographic maps and source localization are factors to be considered when studying the ERPs underlying these high-risk subjects.

By employing the concept of E-BARS, this study provides new inferences about pre-attentive auditory event-related potentials, i.e. P50, N100 and MMN, in subjects across different risk levels of psychotic disorders, from early/broad at-risk mental state, ultra-high risk state, and first-episode psychosis. Impaired deviance detection already exists in people at pre-psychotic state, regardless of clinical severity. On the contrary, sensory gating varies depending on different risk levels. A preliminary analysis showed some promising results for predicting conversion to psychosis. Further longitudinal research monitoring neurobiological changes of the same subjects at different levels of clinical severity are necessary to explore the underpinning pathogenesis.

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Contributors

MH Hsieh and CC Liu reviewed literature, designed the study and recruited participants; WL Huang, JC Shan and WJ Cheng did statistical analyses and wrote the first draft of the manuscript; MJ Chiu and FS Jaw contributed to the ERP lab and data analyses; HG Hwu oversaw the project; MH Hsieh, JC Shan and CC Liu finalized the manuscript; all authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare no conflicts of interest regarding the work presented in this paper.

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References

Adler, L.E., Pachtman, E., Franks, R.D., Pecevich, M., Waldo, M.C., Freedman, R., 1982. Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. Biol. Psychiatry 17 (6), 639–654.

Adler, L.E., Hoffer, L.J., Griffith, J., Waldo, M.C., Freedman, R., 1992. Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics. Biol. Psychiatry 32 (7), 607–616.

Atkinson, R.J., Michie, P.T., Schall, U., 2012. Duration mismatch negativity and P3a in first-episode psychosis and individuals at ultra-high risk of psychosis. Biol. Psychiatry 71 (2), 98–104.

Bodatsch, M., Ruhrmann, S., Wagner, M., Muller, R., Schultze-Lutter, F., Frommann, I., Brinkmeyer, J., Gaebel, W., Maier, W., Klosterkotter, J., Brockhaus-Dumke, A., 2011. Prediction of psychosis by mismatch negativity. Biol. Psychiatry 69 (10), 959–966.

Boutros, N., 2008. Lack of blinding in gating studies. Schizophr. Res. 103 (1–3), 336.

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 Res. 126 (3), 203–215.

Braff, D.L., Light, G.A., 2004. Preattentional and attentional cognitive deficits as targets for treating schizophrenia. Psychopharmacology (Berl) 174 (1), 75–85.

Bramon, E., Shaikh, M., Broome, M., Lappin, J., Berge, D., Day, F., Woolley, J., Tabraham, P., Madre, M., Johns, L., Howes, O., Valmaggia, L., Perez, V., Sham, P., Murray, R.M.,

McGuire, P., 2008. Abnormal P300 in people with high risk of developing psychosis. Neuroimage 41 (2), 553–560.
Breier, A., 2004. Diagnostic classification of the psychoses: historical context and implications for neurobiology. In: Charney, D.S., Nestler, E.J. (Eds.), Neurobiology of Mental Illness. Oxford University Press, New York, pp. 237–246.
Brockhaus-Dumke, A., Tendolkar, I., Pukrop, R., Schultzelutter, F., Klosterkotter, J., Ruhrmann, S., 2005. Impaired mismatch negativity generation in prodromal subjects and patients with schizophrenia. Schizophr. Res. 73 (2–3), 297–310.
Brockhaus-Dumke, A., Schultze-Lutter, F., Mueller, R., Tendolkar, I., Bechdolf, A., Pukrop, R., Klosterkoetter, J., Ruhrmann, S., 2008. Sensory gating in schizophrenia: P50 and N100 gating in antipsychotic-free subjects at risk, first-episode, and chronic patients. Biol. Psychiatry 64 (5), 376–384.
Clementz, B.A., Geyer, M.A., Braff, D.L., 1997. P50 suppression among schizophrenia and normal comparison subjects: a methodological analysis. Biol. Psychiatry 41 (10), 1035–1044.
Clementz, B.A., Geyer, M.A., Braff, D.L., 1998. Multiple site evaluation of P50 suppression among schizophrenia and normal comparison subjects. Schizophr. Res. 30 (1), 71–80.
Cornblatt, B.A., Lencz, T., Smith, C.W., Correll, C.U., Auther, A.M., Nakayama, E., 2003. The schizophrenia prodrome revisited: a neurodevelopmental perspective. Schizophr. Bull. 29 (4), 633–651.
de Wilde, O.M., Bour, L.J., Dingemans, P.M., Koelman, J.H.T.M., Linszen, D.H., 2007. Failure to find P50 suppression deficits in young first-episode patients with schizophrenia and clinically unaffected siblings. Schizophr. Bull. 33 (6), 1319–1323.
Freedman, R., Coon, H., Myles-Worsley, M., Orr-Urtreger, A., Olincy, A., Davis, A., Polymeropoulos, M., Holik, J., Hopkins, J., Hoff, M., Rosenthal, J., Waldo, M.C., Reimherr, F., Wender, P., Yaw, J., Young, D.A., Breese, C.R., Adams, C., Patterson, D., Adler, L.E., Kruglyak, L., Leonard, S., Byerley, W., 1997. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. Proc. Natl. Acad. Sci. U. S. A. 94 (2), 587–592.
Frommann, I., Brinkmeyer, J., Ruhrmann, S., Hack, E., Brockhaus-Dumke, A., Bechdolf, A., Wolwer, W., Klosterkotter, J., Maier, W., Wagner, M., 2008. Auditory P300 in individuals clinically at risk for psychosis. Int. J. Psychophysiol. 70 (3), 192–205.
Fuerst, D.R., Gallinat, J., Boutros, N.N., 2007. Range of sensory gating values and test–retest reliability in normal subjects. Psychophysiology 44, 620–626.
Green, M.F., Butler, P.D., Chen, Y., Geyer, M.A., Silverstein, S., Wynn, J.K., Yoon, J.H., Zemon, V., 2009. Perception measurement in clinical trials of schizophrenia: promising paradigms from CNTRICS. Schizophr. Bull. 35 (1), 163–181.
Hall, M.H., Schulze, K., Bramon, E., Murray, R.M., Sham, P., Rijsdijk, F., 2006. Genetic overlap between P300, P50, and duration mismatch negativity. Am. J. Med. Genet. B Neuropsychiatr. Genet. 141B (4), 336–343.
Javitt, D.C., Spencer, K.M., Thaker, G.K., Winterer, G., Hajos, M., 2008. Neurophysiological biomarkers for drug development in schizophrenia. Nat. Rev. Drug Discov. 7 (1), 68–83.
Keshavan, M.S., Tandon, R., Boutros, N.N., Nasrallah, H.A., 2008. Schizophrenia, "just the facts": what we know in 2008 Part 3: neurobiology. Schizophr. Res. 106 (2–3), 89–107.
Keshavan, M.S., Delisi, L.E., Seidman, L.J., 2011. Early and broadly defined psychosis risk mental states. Schizophr. Res. 126 (1–3), 1–10.
Korostenskaja, M., Kahkonen, S., 2009. What do ERPs and ERFs reveal about the effect of antipsychotic treatment on cognition in schizophrenia? Curr. Pharm. Des. 15 (22), 2573–2593.
Korostenskaja, M., Nikulin, V.V., Kicic, D., Nikulina, A.V., Kahkonen, S., 2007. Effects of NMDA receptor antagonist memantine on mismatch negativity. Brain Res. Bull. 72 (4–6), 275–283.
Leung, S., Croft, R.J., Baldeweg, T., Nathan, P.J., 2007. Acute dopamine D(1) and D(2) receptor stimulation does not modulate mismatch negativity (MMN) in healthy human subjects. Psychopharmacology (Berl) 194 (4), 443–451.
Light, G.A., Williams, L.E., Minow, F., Sprock, J., Rissling, A., Sharp, R., Swerdlow, N.R., Braff, D.L., 2010. Electroencephalography (EEG) and event-related potentials (ERPs) with human participants. Curr. Protoc. Neurosci. 25, 21–24 (Chapter 6, Unit 6).
Lijffijt, M., Moeller, F.G., Boutros, N.N., Burroughs, S., Lane, S.D., Steinberg, J.L., Swann, A.C., 2009. The role of age, gender, education, and intelligence in P50, N100, and P200 auditory sensory gating. J. Psychophysiol. 23 (2), 52–62.
Liu, C.C., Hwu, H.G., Chiu, Y.N., Lai, M.C., Tseng, H.H., 2010. Creating a platform to bridge service and research for early psychosis. J. Formos. Med. Assoc. 109 (7), 543–549.
Liu, C.C., Lai, M.C., Liu, C.M., Chiu, Y.N., Hsieh, M.H., Hwang, T.J., Chien, Y.L., Chen, W.J., Hua, M.S., Hsiung, P.C., Huang, Y.C., Hwu, H.G., 2011. Follow-up of subjects with suspected pre-psychotic state in Taiwan. Schizophr. Res. 126 (1–3), 65–70.
Louchart-de la Chapelle, S., Levillain, D., Menard, J.F., Van der Elst, A., Allio, G., Haouzir, S., Dollfus, S., Campion, D., Thibaut, F., 2005. P50 inhibitory gating deficit is correlated with the negative symptomatology of schizophrenia. Psychiatry Res. 136 (1), 27–34.
Mathalon, D.H., Ford, J.M., Rosenbloom, M., Pfefferbaum, A., 2000. P300 reduction and prolongation with illness duration in schizophrenia. Biol. Psychiatry 47 (5), 413–427.
McGorry, P.D., Yung, A.R., Phillips, L.J., 2003. The "close-in" or ultra high-risk model: a safe and effective strategy for research and clinical intervention in prepsychotic mental disorder. Schizophr. Bull. 29 (4), 771–790.
Michie, P.T., 2001. What has MMN revealed about the auditory system in schizophrenia? Int. J. Psychophysiol. 42 (2), 177–194.
Michie, P.T., Innes-Brown, H., Todd, J., Jablensky, A.V., 2002. Duration mismatch negativity in biological relatives of patients with schizophrenia spectrum disorders. Biol. Psychiatry 52 (7), 749–758.
Myles-Worsley, M., Ord, L., Blailes, F., Ngiralmau, H., Freedman, R., 2004. P50 sensory gating in adolescents from a Pacific Island isolate with elevated risk for schizophrenia. Biol. Psychiatry 55 (7), 663–667.
Nagamoto, H.T., Adler, L.E., Waldo, M.C., Freedman, R., 1989. Sensory gating in schizophrenics and normal controls: effects of changing stimulation interval. Biol. Psychiatry 25, 549–561.
Nagamoto, H.T., Adler, L.E., Waldo, M.C., Griffith, J., Freedman, R., 1991. Gating of auditory response in schizophrenics and normal controls. Effects of recording site and stimulation interval on the P50 wave. Schizophr. Res. 4 (1), 31–40.
Niznikiewicz, M.A., Spencer, K.M., Salisbury, D.F., McCarley, R.W., 2004. Event related potentials. In: Lawrie, S., Johnstone, E., Weinberger, D. (Eds.), Schizophrenia: from Neuroimaging to Neuroscience. Oxford University Press, Oxford, pp. 293–330.
Olincy, A., Martin, L., 2005. Diminished suppression of the P50 auditory evoked potential in bipolar disorder subjects with a history of psychosis. Am. J. Psychiatry 162, 43–49.
Olsen, K.A., Rosenbaum, B., 2006. Prospective investigations of the prodromal state of schizophrenia: assessment instruments. Acta Psychiatr. Scand. 113 (4), 273–282.
Ozgurdal, S., Gudlowski, Y., Witthaus, H., Kawohl, W., Uhl, I., Hauser, M., Gorynia, I., Gallinat, J., Heinze, M., Heinz, A., Juckel, G., 2008. Reduction of auditory event-related P300 amplitude in subjects with at-risk mental state for schizophrenia. Schizophr. Res. 105 (1–3), 272–278.
Pekkonen, E., Jaaskelainen, I.P., Kaakkola, S., Ahveninen, J., 2005. Cholinergic modulation of preattentive auditory processing in aging. Neuroimage 27 (2), 387–392.
Potter, D., Summerfelt, A., Gold, J., Buchanan, R.W., 2006. Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia. Schizophr. Bull. 32 (4), 692–700.
Premkumar, P., Fannon, D., Kuipers, E., Cooke, M.A., Simmons, A., Kumari, V., 2008. Association between a longer duration of illness, age and lower frontal lobe grey matter volume in schizophrenia. Behav. Brain Res. 193 (1), 132–139.
Price, G.W., Michie, P.T., Johnston, J., Innes-Brown, H., Kent, A., Clissa, P., Jablensky, A.V., 2006. A multivariate electrophysiological endophenotype, from a unitary cohort, shows greater research utility than any single feature in the Western Australian family study of schizophrenia. Biol. Psychiatry 60 (1), 1–10.
Ringel, T.M., Heidrich, A., Jacob, C.P., Fallgatter, A.J., 2004. Sensory gating deficit in a subtype of chronic schizophrenic patients. Psychiatry Res. 125 (3), 237–245.
Rissling, A.J., Light, G.A., 2010a. Neurophysiological measures of sensory registration, stimulus discrimination, and selection in schizophrenia patients. Curr. Top. Behav. Neurosci. 4, 283–309.
Rissling, A.J., Light, G.A., 2010b. Neurophysiological measures of sensory registration, stimulus discrimination, and selection in schizophrenia patients. In: Swerdlow, N.R. (Ed.), Behavioral Neurobiology of Schizophrenia and Its Treatment. Springer-Verlag, Berlin Heidelberg, pp. 283–310.
Semlitsch, H.V., Anderer, P., Schuster, P., Presslich, O., 1986. A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP. Psychophysiology 23 (6), 695–703.
Shan, J.C., Hsieh, M.H., Liu, C.M., Chiu, M.J., Jaw, F.S., Hwu, H.G., 2010. More evidence to support the role of S2 in P50 studies. Schizophr. Res. 122 (1–3), 270–272.
Shin, K.S., Kim, J.S., Kang, D.H., Koh, Y., Choi, J.S., O'Donnell, B.F., Chung, C.K., Kwon, J.S., 2009. Pre-attentive auditory processing in ultra-high-risk for schizophrenia with magnetoencephalography. Biol. Psychiatry 65 (12), 1071–1078.
Stone, J.M., Day, F., Tsagaraki, H., Valli, I., McLean, M.A., Lythgoe, D.J., O'Gorman, R.L., Barker, G.J., McGuire, P.K., 2009. Glutamate dysfunction in people with prodromal symptoms of psychosis: relationship to gray matter volume. Biol. Psychiatry 66 (6), 533–539.
Tanskanen, P., Ridler, K., Murray, G.K., Haapea, M., Veijola, J.M., Jaaskelainen, E., Miettunen, J., Jones, P.B., Bullmore, E.T., Isohanni, M.K., 2010. Morphometric brain abnormalities in schizophrenia in a population-based sample: relationship to duration of illness. Schizophr. Bull. 36 (4), 766–777.
Turetsky, B.I., Calkins, M.E., Light, G.A., Olincy, A., Radant, A.D., Swerdlow, N.R., 2007. Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures. Schizophr. Bull. 33 (1), 69–94.
Turetsky, B.I., Greenwood, T.A., Olincy, A., Radant, A.D., Braff, D.L., Cadenhead, K.S., Dobie, D.J., Freedman, R., Green, M.F., Gur, R.E., Gur, R.C., Light, G.A., Mintz, J., Nuechterlein, K.H., Schork, N.J., Seidman, L.J., Siever, L.J., Silverman, J.M., Stone, W.S., Swerdlow, N.R., Tsuang, D.W., Tsuang, M.T., Calkins, M.E., 2008. Abnormal auditory N100 amplitude: a heritable endophenotype in first-degree relatives of schizophrenia probands. Biol. Psychiatry 64 (12), 1051–1059.
Turetsky, B.I., Bilker, W.B., Siegel, S.J., Kohler, C.G., Gur, R.E., 2009. Profile of auditory information-processing deficits in schizophrenia. Psychiatry Res. 165 (1–2), 27–37.
van Tricht, M.J., Nieman, D.H., Koelman, J.H.T.M., van der Meer, J.N., Bour, L.J., de Haan, L., Linszen, D.H., 2010. Reduced parietal P300 amplitude is associated with an increased risk for a first psychotic episode. Biol. Psychiatry 68 (7), 642–648.
Wynn, J.K., Sugar, C., Horan, W.P., Kern, R., Green, M.F., 2010. Mismatch negativity, social cognition, and functioning in schizophrenia patients. Biol. Psychiatry 67 (10), 940–947.