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Do schizophrenia patients with low P50-suppression report more perceptual anomalies with the sensory gating inventory?

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ABSTRACT

Background: P50 amplitude changes in dual click *conditioning–testing* procedure might be a neurophysiological marker of deficient sensory gating in schizophrenia. However, the relationship between abnormalities in the neurophysiological and phenomenological dimensions of sensory gating in schizophrenia remains unclear. The aim of the present study was to determine if patients with low P50-suppression (below 50%) report more perceptual anomalies.
Methods: Three groups were compared: twenty-nine schizophrenia patients with high P50-suppression (above 50% amplitude suppression), twenty-three schizophrenia patients with low P50-suppression (below 50%) and twenty-six healthy subjects. The Sensory Gating Inventory (SGI), a four-factor self-report questionnaire, was used to measure perceptual anomalies related to sensory gating. A comparison of demographic and clinical data was also carried out.
Results: Patients with low P50-suppression presented: i) significantly higher scores on the SGI (for the overall SGI score and for each of the 4 factors) and ii) significantly larger P50 amplitude at the second click, than both patients with high P50-suppression and healthy subjects. There were no group differences in the most of demographic and clinical data.
Discussion: The finding offers support for conceptual models wherein abnormal neurophysiologic responses to repetitive stimuli give rise to clinically relevant perceptions of being inundated and overwhelmed by external sensory stimuli. Further studies are needed to explore the contributions of clinical symptoms, medication and neuropsychological functions to the relationship between P50-suppression and the SGI, and the role of sensory "gating in" versus "gating out".

1. Introduction

Schizophrenia is commonly conceptualized as a disorder of attention, cognition, and information processing (McGhie and Chapman, 1961; Uhlhaas and Mishara, 2007). Attention and information processing can be assessed neurophysiologically with auditory event-related potential (ERP) method by measuring P50 amplitude changes in dual click *conditioning–testing* procedure (Freedman et al., 1987). This ERP method is classically used to have a neurophysiological measure of sensory gating in schizophrenia. ERP are measured by means of electroencephalography (EEG). The P50 component is a middle latency positive ERP component occurring around 50 msec after onset of a brief auditory stimulus (Adler et al., 1982). In the conditioning–testing P50 procedure, the P50 amplitude is measured in response to an auditory-paired click stimulus: S1 (conditioning stimulus) and S2 (testing stimulus). It is commonly observed in healthy subjects that the P50 amplitude is smaller after S2 than after S1 (by less than an half of amplitude). It is commonly inferred that the second P50 component is suppressed or "gated". By contrast, it was shown that this P50-suppression or "gating"

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after S2 could be deficient in schizophrenia patients (Adler et al., 1982; Clementz et al., 1997).

Alternatively, the sensory gating deficit in schizophrenia has been explored from a phenomenological point of view through the use of self-reports inspired from the seminal study of McGhie and Chapman (1961). Among the existing exploratory instruments, two perceptual scales were developed to focus attention on the psychophysiological characterization of sensory gating deficits in schizophrenia: the Structured Interview for Assessing Perceptual Anomalies (SIAPA) (Bunney et al., 1999) and the Sensory Gating Inventory (SGI) (Hetrick et al., 2012). The SIAPA is a structured interview administered to the patient that allows the interviewer to score the frequency of reported perceptual anomalies for the five sensory modalities. Bunney et al. (1999) found that patients with schizophrenia reported a significantly greater prevalence of auditory and visual perceptual anomalies compared to healthy subjects. Hetrick et al. (2012) extended the previous work of Bunney et al. (1999) by designing and validating a self-report questionnaire: the SGI. The SGI is composed of 36 items addressing a broad range of sensory gating-like subjective daily perceptual experiences. The psychometric properties of SGI indicate that it provides valuable information on 4 dimensions of perceptual anomalies: Perceptual Modulation PM (linked to 16 items, e.g., "My hearing is so sensitive that ordinary sounds become uncomfortable"), Over-Inclusion OI (7 items, e.g., "I notice background noises more than other people"), Distractibility D (8 items, e.g., "There are times when I can't concentrate with even the slightest sounds going on"), and Fatigue–Stress Modulation FS (5 items, e.g. "It seems that sounds are more intense when I'm stressed").

In attempts to relate the neurophysiological and phenomenological dimensions of sensory gating, it has been suggested to examine the relationship between the perceptual anomalies reported by the two previous phenomenological instruments and the deficient sensory gating in schizophrenia measured with the *conditioning–testing* P50 neurophysiological paradigm (Jin et al., 1998; Light and Braff, 2003). However, this relationship still remains unclear. Actually, the psychophysiological characterization of sensory gating in schizophrenia largely depends on the scale used to measure perceptual anomalies related to sensory gating (Micoulaud-Franchi and Vion-Dury, 2013). In particular, it could be assumed that the lack of relationship between perceptual anomalies scored with the SIAPA and P50-suppression deficits reported by Jin et al. (1998) is related to a limitation of the SIAPA. Indeed, the SIAPA is a structured interview and not a self-report questionnaire, and consequently could prevent the interviewer from accurately reporting patients' experiences (Slevin et al., 1988). Given the potential advantage of subjective assessment of sensory gating deficits compared to interviewer rated abnormalities, the SGI offers the possibility of renewing the psychophysiological investigation to get a better understanding of sensory gating deficit in schizophrenia (Kisley et al., 2004; Johannesen et al., 2008).

In healthy subjects, with a short-form of the SGI (17 items), Kisley et al. (2004) found a significant correlation between Perceptual Modulation factor and P50-suppression: participants with less robust P50-suppression endorsed higher rate of Perceptual Modulation difficulties. With the 36 item SGI, Johannesen et al. (2008) found that a psychometrically defined "perceptually deviant" schizophrenia subgroup had smaller P50 amplitude in response to S1 compared to patients "perceptually normal" and healthy subjects, but no relationship between perceptual anomalies (measured by SGI total score) and P50-suppression deficits were found. However, this study did not analyze scores for each of the 4 factors of the SGI, which could provide valuable psychophysiological information (Kisley et al., 2004; Hetrick et al., 2012).

The present study, therefore, aims to investigate the link between abnormal neurophysiological and phenomenological dimensions of sensory gating in schizophrenia by measuring responses to the conditioning–testing P50 paradigm and the SGI within the same individuals. In particular, we compared the overall SGI score and scores for each of the SGI factors within a sample of schizophrenia patients by differentiating patients with high and low P50-suppression. Note that we used a French version of the 36 items SGI that was previously validated (Micoulaud-Franchi et al., submitted for publication) since we evaluated a group of French schizophrenia patients. A healthy group was also included. We hypothesized: i) that schizophrenia patients with low P50-suppression would report higher SGI scores than both schizophrenia patients with high P50-suppression and healthy subjects, and ii) that schizophrenia patients with high P50-suppresion and healthy subjects would report similar SGI scores on one or more factors of the SGI.

2. Methods and materials

2.1. Participants

Fifty-two out patients with chronic schizophrenia recruited from the Department of Psychiatry, Marseille University Hospital, France, constituted the group of schizophrenia patients (SCZ group). DSM-IV criteria, based on Structured Clinical Interview (SCID) for DSM-IV interviews, confirmed the diagnosis of schizophrenia (First et al., 1997; American Psychiatric Association, 2000). The control group (CTL group) comprised twenty-six psychiatrically healthy subjects who were screened for any current or lifetime history of a DSM-IV axis I disorder, based on the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). We ensured that CTL group and SCZ group were similar in age, gender, and educational level.

Exclusion criteria were reduced capacity to consent, a diagnosis other than schizophrenia on Axis I of the DSM-IV, auditory impairment (no subjective auditory deficit or antecedent of medical advice for auditory impairment), neurological illness, brain injury, severe organic disease and mental retardation.

After receiving a detailed description of the study, participants gave their written informed consent. This study was conducted in accordance with the Declaration of Helsinki and French Good Clinical Practices. The data collection was approved by the *Commission nationale de l'informatique et des libertés* (CNIL number: 1223715).

2.2. Clinical measures

The Positive and Negative Syndrome Scale (PANSS) assessed the SCZ patients' clinical severity of illness (Kay et al., 1987). Scores were computed from the PANSS for a positive symptom factor, for a negative symptom factor, for an excited factor, for a depressive factor and for a cognitive factor (Lancon et al., 1998). The Clinical Global Impression (CGI) assessed the severity of the disorder (Guy, 1976). The Global Assessment of Functioning (GAF) assessed the severity of the handicap (American Psychiatric Association, 2000). The Calgary Depression Scale for Schizophrenia (CDSS) assessed the level of depression in schizophrenia (Lancon et al., 1999). All patients were medicated. The mean chlorpromazine equivalent dose was calculated (Davis, 1976; Woods, 2003). The number of patients medicated by clozapine was collected. Data regarding age of onset, duration of disorder and number of hospitalizations were collected.

2.3. Phenomenological measures

We measured perceptual anomalies related to sensory gating with the Sensory Gating Inventory (SGI). In this questionnaire, participants assign 6-point Likert ratings (from 0 "never true" to 5 "always true") to 36 items (Hetrick et al., 2012). To enable the evaluation of our group of French patients, we used a French version of the SGI that we designed and formally validated (Micoulaud-Franchi et al., submitted for publication). In practice, the algebraic sum of Likert rating for each participant was computed for the overall SGI score and for each of the 4 factors that are similar to the original instrument: Perceptual Modulation, Over-Inclusion, Distractibility and Fatigue–Stress Modulation.

As anxiety appears to be a possible contributor to P50-suppression deficit (White and Yee, 1997; White et al., 2005), the Trait Anxiety Inventory (TAI) was also administered to each participant (Spielberger and Vagg, 1984). The aim, here, was to ensure that individuals' daily experience of neurophysiological sensory gating deficit was, indeed, related to the phenomenological dimensions of SGI and not to anxiety.

2.4. ERP recording and P50 measurement procedure

The ERP recording, the clinical evaluation and the SGI and TAI self-evaluations were performed on the same day for a given participant. Subjects were asked to abstain from cigarette smoking for 1 h before collecting electrophysiological measurements.

The subject, seated in a comfortable recliner in a quiet, well-lit room, wore headphones for auditory stimuli presentation and was instructed to relax and to keep his or her eyes closed. Auditory stimuli were delivered in a *conditioning–testing P50 paradigm* consisting of a click pair presentation (conditioning click, S1, followed by the testing click, S2) in a passive task. The inter-stimulus interval was set to 500 msec and the inter-pair interval to 10 s. Clicks were rectangular pulses of 0.05 msec with an intensity of 100 dB SPL (Baker et al., 1987; Jin et al., 1998). A set of 60 click pairs was delivered (total duration of 12 min). During the recording, the participant was monitoring visually and by EEG for signs of drowsiness or sleep, which if happen, lead the technician neurophysiologist to speak and arouse briefly the participants (Yee et al., 2010).

Electroencephalographic activity (EEG) was monitored on a computer (EB Neuro, Inc.). EEG measurements were recorded from 9 scalp gold disc electrodes according to the International 10/20 convention (Fz, Cz, Pz, Oz, F3, F4, C3, C4, P3, P4). Electrode resistance was less than 10 kΩ. Data were acquired at a 1000 Hz sampling frequency. The ground electrode was on the nose. Two electrodes were placed on left and right earlobes and the EEG was referenced to the average of right and left earlobes and filtered with a band pass filter of 1–200 Hz. Data were segmented into single trials of 1200 msec, beginning 200 msec before the S1 stimulus onset. Electro-oculographic data were recorded, and trials contaminated by ocular movements and movement artifacts were rejected by visual inspection. The proportion of rejected trials did not differ between CTL and SCZ groups. The remaining trials were then averaged for each participant.

The P50 components were measured at the Cz site since it was shown to be the best site for discriminating schizophrenic patients from healthy subjects in our configuration (Clementz et al., 1998). The conditioning P50 component was identified as the positive component presenting the largest peak occurring between 40 and 80 msec after the S1 onset (Nagamoto et al., 1989; Cardenas et al., 1993). The testing P50 component was identified in a similar way after the S2 onset. The amplitudes of these components were actually defined as peak-to-peak amplitudes, i.e. between the peak of the P50 component and the preceding negative peak (Nagamoto et al., 1991; Clementz et al., 1997; Boutros and Belger, 1999). Finally, the percentage of P50 suppression ($P50_{supp}$) was calculated using the following formula: $P50_{supp} = [1-(A_{S2}/A_{S1})]\times 100$, where A_{S1} and A_{S2} are the amplitude of the conditioning and testing P50 component respectively (Clementz et al., 1997). Minimums of 100% suppression or 100% facilitation were used to prevent outliers from disproportionately affecting the group means (Nagamoto et al., 1991; Cadenhead et al., 2000).

2.5. Statistical analyses

Descriptive statistics of the sample included frequencies and percentages of categorical variables, together with means and standard deviations of continuous variables. Neurophysiological data were square root transformed to approximate the normal distributional assumptions required by parametric statistical methods. Data analyses were performed using SPSS software (Version 18, PASW Statistics) and Prism software (Version 6, GraphPad).

We first defined two subsets of patients in the SCZ group according to their amount of P50-suppression. To that end, we fixed a 50% threshold for the $P50_{supp}$ value (Freedman et al., 1983): above 50% was the SCZ group with high P50-suppression (called SCZ1 group composed of 29 patients) while below this threshold was the SCZ group with low P50-suppression (called SCZ2 group composed of 23 patients).

Then, demographic variables (Age, Gender and Educational level), phenomenological variables (SGI and TAI scores) and neurophysiological variables (P50 amplitudes, P50 latencies and $P50_{supp}$) were compared between the 3 groups (CTL, SCZ1 and SCZ2). Clinical variables (PANSS scores, CGI scores, GAF scores, CDSS scores, Chlorpromazine equivalent dose, Age of onset, Duration of disorder, Number of hospitalizations and Number of patients medicated by clozapine) were compared between the two SCZ groups (SCZ1 and SCZ2). Quantitative variables were compared using analysis of variance (single-factor ANOVA with F-test statistics). Tukey's tests were used to correct *post-hoc* multiple comparisons and to determine which groups significantly differed from each other. Qualitative variables were analyzed using χ^2 tests. Finally, a logistic regression analysis was conducted with group membership (SCZ1 or SCZ2 group) as the dependent variable, and SGI scores and clinical variables that significantly differed between SCZ groups as predictor variables. For each analysis, effects were considered as significant when the *p*-value was equal to or less than .05.

3. Results

Results from data analysis are summarized in Table 1 for the 3 groups, and illustrated in Fig. 1. In line with the design of the subgroups within the SCZ group, the SCZ2 group (with low P50-suppression) had a significantly lower percentage of P50-suppression than both the SCZ1 group (with high P50-suppression) and the CTL group. Actually, this effect is mainly attributed to the amplitude differences measured at S2 for the 3 groups: the SCZ2 group presented larger P50 amplitude (2.02 μV) than both CTL group (0.46 μV) and SCZ1 group (0.51 μV). Results also showed that the P50 latency at S2 was significantly longer for the SCZ2 group (67.79 msec) than for the SCZ1 group (55.72 msec). The latency difference was not significant between the SCZ2 group and the CTL group.

Concerning phenomenological data, the TAI scores were significantly lower for the CTL group (27.12) than for both the SCZ1 group (35.52) and the SCZ2 group (41.61). No difference was found between the two SCZ groups. The overall SGI scores were significantly lower for the CTL group (28.46) than for both the SCZ1 group (52.76) and the SCZ2 group (88.91). A significant difference was found between the two SCZ groups: SCZ2 group (with low P50-suppression) had a significantly higher overall SGI scores than the SCZ1 group (with high P50-suppression). Similar significant results were observed for each SGI factor. Interestingly, two factors of the SGI (Over-Inclusion and Fatigue–Stress Modulation) were not significantly different between the SCZ1 group (with high P50-suppression) and the CTL group.

Concerning the demographic and clinical data, we found that the groups did not significantly differ from each other except for the negative symptom factor and the depressive factor of the PANSS. In particular, SCZ2 group presented a significantly higher score for these two factors. SCZ2 group was less medicated by clozapine than SCZ1 group. These clinical factors were included as predictor variables in the logistic regression analysis. The full model significantly predicted the membership in one of the two groups (omnibus chi-square = 19.65, df = 4, p = .001). The model accounted for 42.2% of the variance (Nagelkerke R^2). Overall 75% of predictions were accurate. The SGI score was the most relevant predictor for the SCZ2 group membership (B = .22, Wald = 5.1, p = .02). The absence of clozapine medication trends to also predict the SCZ2 group membership (B = −1.8, Wald = 3.5, p = .06).

Table 1
Demographic, phenomenological and neurophysiological variables for the three groups: control group (CTL), patient group with high P50-suppression (SCZ1, P50 suppression > 50%), and patient group with low P50-suppression (SCZ2, P50 suppression < 50%).

	CTL (N = 26)		SCZ (N = 52)				F-statistics for the main effect of group		Pairwise[b]
			SCZ1 (N = 29) ($P50_{supp}$ > 50%)		SCZ2 (N = 23) ($P50_{supp}$ < 50%)				
	Mean	SD	Mean	SD	Mean	SD	F	p	
Gender (number of subjects)									
Male	16	–	24	–	16	–	–	–	–
Female	10	–	5	–	7	–	–	0.21[c]	–
Age (years)	36.42	10.74	34	9.43	34.78	9.21	0.428	0.654	–
Education level (years)	12.50	3.63	11	3.23	12.83	3.17	2.27	0.11	–
SGI									–
Overall score	28.46	24.04	52.76	34.88	88.91	37.37	21.25	<0.001	SCZ2≫SCZ1>CTL
Perceptual modulation	8.27	10.27	19.72	15.93	35.17	18.82	18.95	<0.001	SCZ2≫SCZ1>CTL
Over-inclusion	5.85	5.93	10.14	6.87	18.70	7.63	22.28	<0.001	SCZ2≫SCZ1,CTL
Distractibility	8.54	6.47	15.10	9.24	22.78	9.40	17.23	<0.001	SCZ2≫SCZ1>CTL
Fatigue–stress modulation	5.81	4.77	7.79	6.44	12.26	5.90	7.93	0.001	SCZ2≫SCZ1,CTL
TAI	27.12	6.06	35.52	12.49	41.61	14.79	9.69	<0.001	SCZ2,SCZ1>CTL
Stimulus S1									
P50 amplitude (μV)	2.12	1.67	2.84	2.04	2.13	1.85	1.31	0.27	–
P50 latency (msec)	63.04	9.26	57.12	14.58	62.27	13.35	1.78	0.18	–
Stimulus S2									
P50 amplitude (μV)	0.46	0.57	0.51	0.55	2.02	1.67	18.51	<0.001	SCZ2≫SCZ1,CTL
P50 latency (msec)	63.30	11.23	55.72	14.36	67.79	14.18	5.49	0.006	SCZ2>SCZ1
P50-suppression[a] (%)	75.51	23.09	80.63	14.94	1.17	40.07	65.97	<0.001	SCZ1,CTL≫SCZ2
PANSS									
Total	–	–	71.38	24.73	81.26	21.50	2.29	0.14	–
Positive	–	–	14.45	7.79	16.91	7.29	1.36	0.25	–
Negative	–	–	19.28	7.47	23.96	8.25	4.58	0.03	–
Excited	–	–	10.93	4.60	10.09	3.59	0.52	0.47	–
Depressive	–	–	9.10	3.49	11.52	3.38	6.31	0.01	–
Cognitive	–	–	16.66	8.01	18.83	6.41	1.12	0.29	–
GAF	–	–	57.41	16.43	58.30	16.16	0.04	0.846	–
CGI	–	–	3.72	1.25	3.91	1.04	0.34	0.56	–
CDSS	–	–	3.90	4.11	5.83	4.01	2.89	0.095	–
Chlorpromazine equivalent dose (mg)	–	–	439.55	329.77	518.43	447.97	0.54	0.49	–
Clozapine (percentage of subjects)			31%	–	8.7%	–		0.05[c]	
Age of onset (years)	–	–	20.21	5.15	22.52	5.41	2.48	0.12	–
Duration of disorder (years)	–	–	13.79	8.72	12.26	7.80	0.43	0.51	–
Number of hospitalizations	–	–	3.69	4.93	4.74	5.59	0,52	0.48	–

[a] The percentage of P50 suppression was calculated as [1−(stimulus 2 amplitude/stimulus 1 amplitude)]×100.
[b] Tukey's *post-hoc* pairwise comparisons: ≫: $p < 0.001$, >: $p < 0.05$.
[c] χ^2 test for qualitative variables.

4. Discussion

These findings confirm our hypotheses. Firstly, the group of patients with low P50-suppression reports SGI scores that are higher to subjects with schizophrenia with high P50-suppression. Secondly, the group of patients with high P50-suppression reports SGI scores on two factors of the SGI (Over-Inclusion and Fatigue–Stress Modulation) that are similar to healthy subjects. Moreover, neurophysiological data were unlikely to be differentially affected by anxiety given the similarity of TAI scores across schizophrenia groups. These results validate the relevance of the SGI, in particular Over-Inclusion and Fatigue–Stress Modulation factors, as a possible self-report proxy of neurophysiological sensory gating abnormalities (Hetrick et al., 2012; Micoulaud-Franchi and Vion-Dury, 2013).

Subjects with schizophrenia with low P50-suppression report SGI scores on the Perceptual Modulation and Distractibility factors that are higher to subjects with schizophrenia with high P50-suppression. However the differences are also significant between subjects with schizophrenia with high P50-suppression and healthy subjects. These results suggest that relatively low-level sensory neurophysiological gating mechanism assessed by the P50 ERP in the conditioning–testing paradigm is probably not the only mechanism related to these phenomenological dimensions. Relatively higher-level and later-stage neurophysiological mechanism (as assessed by the P300 ERP in the oddball paradigm) could be also related to the Perceptual Modulation and Distractibility factors of the SGI (Cermolacce et al., 2011).

To summarize, the results obtained in this current study supports the existence of a relationship between abnormal neurophysiological and phenomenological dimensions of sensory gating in schizophrenia. Within this context, our findings are in line with several previous studies revealing correlations between electrophysiological and phenomenological data. Firstly in Micoulaud-Franchi et al.(2012), we found that the A_{S2}/A_{S1} ratio measured in a similar conditioning–testing P50 paradigm was positively correlated with the Invasiveness scores obtained on a group of 10 schizophrenia patients. In this study, patients assessed the amount of perceived invasiveness during the auditory presentation of calibrated, non-verbal, complex sounds on a continuous, linear scale ranging from 0 (i.e. “not invasive”) to 100 (i.e. “very invasive”). Secondly, in Kisley et al.(2004), a fairly significant correlation between A_{S2}/A_{S1} ratio and the Perceptual Modulation factor of the SGI was found for healthy subjects.

In contrast, the results of the present study are inconsistent with those of Jin et al. (1998) which reported a lack of relationship between abnormal phenomenological sensory gating experiences of SIAPA and P50-suppression deficits, and with those of Johannesen et al. (2008) who showed a relationship solely between P50 amplitude after S1 and abnormal phenomenological sensory gating experiences of the overall score of the SGI. In response to this discrepancy, we present a number of explanations. First, the lack of relationship between phenomenological and neurophysiological measures of sensory gating may be due to limitations of the SIAPA compared to the SGI and suggests that the SGI may be a more accurate and appropriate instrument for measuring

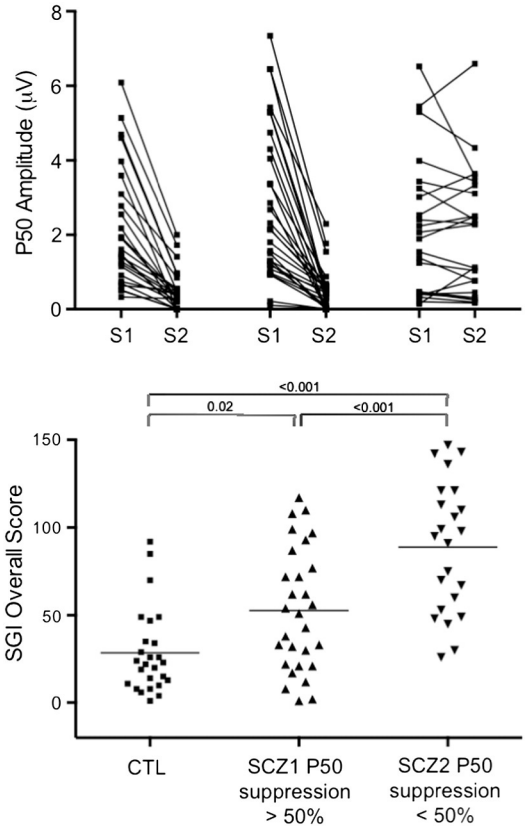

Fig. 1. SGI overall score and P50 amplitude in response to an auditory-paired click stimulus after the stimulus conditioning (S1) and after the stimulus test (S2), in control group (CTL), patient group with high P50-suppression (SCZ1, P50 suppression > 50%), and patient group with low P50-suppression (SCZ2, P50 suppression < 50%). *p*-values of Tukey's tests are indicated.

the phenomenological dimensions of sensory gating. The SGI provides valuable information on the different dimensions of the sensory gating–like experience, which is probably closer to the psychophysiological characterization of the sensory gating construct (Hetrick et al., 2012). Interestingly, the SGI items are mainly based on verbatim accounts of face-to-face interviews, which are a very effective way to construct a questionnaire that assesses self-experience because it is less influenced by the value judgments of the researchers (McKenna, 1997). Note that the SIAPA has not yet been subjected to factor analysis to demonstrate its construct validity whereas this is an advantage of the SGI (Nunnally and Bernstein, 1994). Secondly, patients in the current study were on medication while the Jin et al. (1998) study included only unmedicated patients. Light and Braff highlighted that "we would expect the accuracy of self-reports of deficits or gating experiences to be compromised when patients are unmedicated" (Light and Braff, 2000). Thirdly, the P50-suppression deficit in the Jin et al. (1998) study and in the Johannesen et al. (2008) study were due to a failure to "gate in" sensory information given that the P50-suppression deficit was attributed to an S1 P50 amplitude deficit in schizophrenia. In contrast, in the current study, the P50-suppression deficit constitutes a failure to "gate out" sensory information given that the P50-suppression deficit was attributed to relatively larger S2 P50 amplitude in the schizophrenia group with low P50 suppression. The relationships between sensory "gating out" and sensory "gating in" remain largely unexplored (Clementz et al., 1997; Brenner et al., 2009; Gjini et al., 2010). Further investigations on the link between the different factors of the SGI and other electrophysiological measures of gating in and out (i.e. N100/P200, MMN, P300) could contribute valuable information for psychophysiological significance of sensory gating in schizophrenia (Kisley et al., 2004).

Some limitations in the current study have to be considered. Firstly, the sample size is quite small and could, therefore, lack representativeness. Although the sample size is higher to the Jin et al. (1998) and Johannesen et al. (2008) studies, our results need to be replicated using a larger cohort of patients. In particular, the number of female patients was quite small (23% of the patients). In the study of Hetrick et al. (2012), healthy female scored significantly higher than men on the Distractibility and Fatigue–Stress Modulation factor. Thus, despite no difference of gender in the two groups of patients, effect of gender on the relation between SGI scores and P50 suppression could be additionally investigated in schizophrenia. Secondly, the SCZ2 group (with low P50-suppression) was less medicated by clozapine and had unexpectedly higher scores to SCZ1 group (with high P50-suppression) on two factors of the PANSS: negative symptom factor and depressive factor. No difference in any other demographic or clinical characteristics was shown. In addition, the regression analysis showed that these PANSS factors and clozapine medication did not influence the relationship between the perceptual anomalies reported by the SGI and the deficient sensory gating in schizophrenia. This trend found with clozapine is consistent with the fact that this medication improved P50 suppression in patients with schizophrenia (Nagamoto et al., 1999). The regression model may be validated with another group of patients with schizophrenia in order to further investigate the link between clinical characteristics, medication (in particular clozapine), SGI reports and P50 suppression (Light and Braff, 2000). Thirdly, neuropsychological examinations of attentional end executive functions were not conducted. As the relationship between P50 suppression deficient in schizophrenia and abnormal neuropsychological functions is an important controversial debate (Sanchez-Morla et al., 2013), the impact of neuropsychological function to our psychophysiological results has to be explored. Fourthly, the specificity of our psychophysiological results has to be explored. As patients with bipolar disorders may also report perceptual anomalies (Patterson et al., 2013), comparisons with a bipolar disorder group have to be conducted.

In conclusion, the finding in schizophrenia that decreased P50 suppression was associated with higher rates of self-reported sensory gating phenomenology offers support for conceptual models wherein abnormal neurophysiologic responses to repetitive stimuli give rise to clinically relevant perceptions of being inundated and overwhelmed by external sensory stimuli. According to an approach previously proposed (Micoulaud Franchi et al., 2013), such studies may help us to better define biomarker in psychiatry that are not only based on neurophysiological data, but also on phenomenological data. Further studies are needed to explore the contributions of clinical symptoms, medication, neuropsychological functions and of "low-level" versus "higher-level" and of sensory "gating in" versus "gating out" neurophysiological mechanisms to the relationship between P50-suppression and the SGI.

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Contributors

JAMF, WPH, CL and JVD designed the study and wrote the protocol. JAMF, WPH, AB, AEK, MF, MC, CF, RR and JVD managed the literature searches and analyses. JAMF, LB, MA, SY and RKM undertook the statistical analysis, and JAMF, LB, MA, SY and RKM wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.05.013.

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