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Title:

Are basic auditory processes involved in source-monitoring deficits in patients with schizophrenia?

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Are basic auditory processes involved in source-monitoring deficits in patients with schizophrenia?

ABSTRACT

Patients with schizophrenia (SZ) display deficits in both basic non-verbal auditory processing and source-monitoring of speech. To date, the contributions of basic auditory deficits to higher-order cognitive impairments, such as source-monitoring, and to clinical symptoms have yet to be elucidated. The aim of this study was to investigate the deficits and relationships between basic auditory functions, source-monitoring performances, and clinical symptom severity in SZ.

Auditory processing of 4 psychoacoustic features (pitch, intensity, amplitude, length) and 2 types of source-monitoring (internal and reality monitoring) performances were assessed in 29 SZ and 29 healthy controls. Clinical symptoms were evaluated in patients with the Positive And Negative Syndrome Scale

Compared to the controls, SZ individuals in showed significant reductions in both global basic auditory processing ($p < .0005$, $d = 1.16$) and source-monitoring ($p < .0005$, $d = 1.24$) abilities. Both deficits correlated significantly in patients and across groups (all $p < .05$). Pitch processing skills were negatively correlated with positive symptom severity ($r = -0.4$, $p < .05$). A step-wise regression analysis showed that pitch discrimination was a significant predictor of source-monitoring performance.

These results suggest that cognitive mechanisms associated with the discrimination of basic auditory features are most compromised in patients with source-monitoring disability. Basic auditory processing may index pathophysiological processes that are critical for optimal source-monitoring in schizophrenia and that are involved in positive symptoms.

KEY WORDS: Schizophrenia; Tone-matching; Basic auditory processing; Source-monitoring; Positive symptoms.

1. INTRODUCTION

Schizophrenia is a severe neuropsychiatric disorder that stands as the third leading cause of worldwide morbidity amongst neurological, mental, and substance use disorders (Collins et al., 2011). Schizophrenia is characterized by profound disruption in emotion, cognition and perception abilities, leading to several clinical manifestations. Among them, misperceptions of the self, as described in the RDoC “Agency” subconstruct, are core features of the illness (Ford et al., 2014).

Source-monitoring is a cognitive mechanism that tracks the origin of perceptual materials such as thoughts, speech or motor actions to allow their correct sourcing. Cognitive models suggest that patients with schizophrenia (SZ) are impaired in monitoring the source of their own speech and thoughts, resulting in confusion between externally perceived events and self-generated materials (Frith, 1992; Harvey, 1985; Harvey and Serper, 1990). SZ individuals, particularly those with auditory hallucinations, tend to misattribute internally-generated events to an external source (i.e., externalization bias), which have been hypothesized to be a mechanism from which these symptoms may stem (Waters et al., 2012). Mechanistically, when this externalization bias occurs, subjects become unable to correctly label self-generated material as such. This results in their conclusion that this material came from an external source, which manifests to the clinician as auditory hallucinations (Bentall et al., 1991; Brebion et al., 2000; Brunelin et al., 2006b; Keefe et al., 1999; Stirling et al., 2001; Waters et al., 2012; Woodward et al., 2007). Nevertheless, source-monitoring disturbances have also been demonstrated in schizophrenia participants despite their prominent symptoms (Brebion et al., 2002; Brunelin et al., 2006a; Keefe et al., 1999), highlighting the importance of source-monitoring mechanisms in the pathophysiology of the disease, even if they are not directly related to one single specific clinical dimension. Namely, two types of source-

monitoring processes are impaired in SZ: (i) “reality monitoring”, which enables individuals to discriminate between internally generated and externally perceived events, and (ii) “internal monitoring”, which enables individuals to discriminate between two different internal sources, for instance, one in inner space (i.e., own thoughts) and one in outer space (i.e., self-generated vocal speech).

Additionally, several strands of evidence show that non-verbal basic auditory functions are also impaired in SZ. For instance, patients present with large significant disturbances in tone-matching tasks consisting of discriminating non-verbal sounds according to their psychoacoustic features, such as pitch (Donde et al., 2017; Donde et al., 2018), location (Olsson and Nielzen, 1999), intensity (Holcomb et al., 1995) and dynamic streaming (McLachlan et al., 2013) perception. Critically, such basic perceptual impairments can lead to misinterpretation of the social intent conveyed through speech prosody (Leitman et al., 2010). However, associations between basic auditory processing and clinical symptoms remain heterogeneous. For instance, a recent study have reported poorer basic auditory performances in a group of patients with auditory hallucinations compared with a non-hallucinating group (McLachlan et al., 2013). Other studies have found that these performances were significantly correlated with negative symptoms (Bruder et al., 2004) or with each of the 3 factors of the Positive And Negative Syndrome Scale (Kay et al., 1987)) in SZ (Javitt et al., 2000).

From a hierarchical perspective, source-monitoring can be acknowledged as a “higher order” mechanism than basic auditory processes. Supporting this notion, basic auditory processing impairments have been specifically tied to auditory cortex dysfunction in SZ (Javitt and Sweet, 2015), while source-monitoring has been correlated with broader brain networks involving the temporal superior gyrus, the temporo-parietal junction, the anterior cingular cortex (Mechelli et al., 2007; Vercammen et al., 2010) and the prefrontal cortex (Vinogradov et al., 2008; Wang et al., 2011).

Several strands of evidence suggest that basic sensory features, as perceived during basic sensory processing, are key elements for optimal sourcing of a sensory event (Johnson et al., 1993; Sugimori and Tanno, 2010). In SZ, this contribution has been put forward in the auditory domain by a previous study showing that contrary to healthy controls, SZ individuals with prominent auditory verbal hallucinations did not require the distortion of their feedback to misattribute their own speech to an external source, indicating that basic auditory processes were impaired in these patients (Johns et al., 2001).

However, despite the suggested relationship between basic auditory functions and higher-order source-monitoring, more evidence is required to further establish the link between source-monitoring of speech, basic auditory disturbances and symptom severity in SZ. According to the above-mentioned literature, one can hypothesize that both cognitive processes are involved in the same pathophysiological framework leading to the clinical symptoms of the illness. To explore these linkages, we investigated the relationship between source-monitoring (i.e., internal and reality monitoring) and basic auditory processes among a large range of acoustic features (i.e., pitch, intensity, amplitude and length) in SZ. As prior studies have reported heterogeneous associations between basic auditory processing and clinical symptoms of schizophrenia, we investigated these associations as exploratory to clarify the link between these deficits and different domains of symptoms. We first hypothesized that patients would display lower performances in both source-monitoring tasks and in basic auditory tasks involving all acoustic features perception, compared to control subjects. Second, we predicted that basic auditory and source-monitoring deficits would be positively associated across groups.

2. METHOD

2.1. Design and participants

A between-subjects design compared 30 participants with a diagnosis of schizophrenia according to DSM-5.0 and 30 healthy controls without any current or history of a section-II disorder. Patients were recruited from both inpatient (8/30) and outpatient (22/30) settings associated with the Centre Hospitalier Le Vinatier (Bron, France).

Patient diagnoses were established using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). All controls were examined by a trained psychiatrist to make sure they were free of a current DSM disorder and had no lifetime history of schizophrenia-spectrum disorder. Inclusion criteria were age 18–65 years and fluent spoken French. Exclusion criteria were history of intellectual disability, auditory or neurological impairment, substance use disorder (except for tobacco) and brain neuromodulation procedures in the last 3 months. We also excluded participants who were professional musicians, as musicians display superior ability to discriminate fine auditory changes (Bianchi et al., 2017; Micheyl et al., 2006).

All participants provided written informed consent. The experiment was approved by the local ethics committee (Comité de Protection des Personnes Sud-Est 6, Lyon, France). The study consisted of a single visit. Participants were first informed of the protocol and signed the consent. The absence of severe hearing impairment was confirmed by a simplified audiogram. Then, participants were assessed with the basic auditory and source-monitoring tasks in an isolated room. In the group of patients, the severity of symptoms was assessed using the PANSS. This scale, which is divided in positive, negative and general psychopathology subscores, was administered by trained psychiatrists (authors CD and FH).

2.2. Source-monitoring tasks

Source-monitoring was assessed using two French source memory tasks that were

developed by our group (Brunelin et al., 2006a) from those described by Keefe and colleagues (Keefe et al., 1999) (Fig.1a).

Words presented in the **source-monitoring** tasks were current French words with same neutral emotional valence and length. During **each** task, an instruction was followed by a word that remained on a computer screen for 3 seconds. In the internal monitoring task (Say-Imagine), participants had to distinguish 8 words that they had imagined themselves saying from 8 words they had spoken aloud. In the reality monitoring task (Hear-Imagine), participants had to distinguish 8 words that they had imagined hearing from 8 words they had heard (said by the experimenter). At the end of each task, a response grid including the 16 presented words plus 8 words that were not presented during the task ('new words') was given to the participant. The whole source-monitoring testing procedure lasted approximately 15 minutes.

A variety of information embedded in a memory event at the time it occurs later serves as the basis of judgements about the origin of this event (Johnson et al., 1993). Thus, despite the fact that source-monitoring is an immediate, on-going experience rather than a memory defect, our tasks are suitable for revealing on-going source-monitoring deficits (Waters et al., 2012). Additionally, the 'new word' condition allows eliminating a possible confounding effect of memory functioning on actual source discrimination performances.

2.3. Basic auditory processing tasks

Four basic auditory sensory processing tasks (Length, Pitch, Intensity, and Amplitude) and 1 control task (Length-distractor) were employed. All tasks are based on a behavioural "simple tone-matching paradigm" originally described by (Strous et al., 1995). In this paradigm, participants are presented with series of pairs of short, non-verbal, pure tones. Within each pair, tones are either identical or different in one acoustic feature. Auditory

stimulus presentation was controlled by a laptop computer with the sound volume fixed at 70 dB. Participants listened to tones binaurally through headphones (Sennheiser HD 558 model) connected to the laptop. The task sequence is described in Fig.1b. To avoid learning and fatigability effects, the order of presentation of tasks was randomized across participants. The whole basic auditory testing procedure lasted approximately 30 minutes, with 5-minute breaks between each task.

2.3.1. Sound feature discrimination of pure tones

Length discrimination task: 40 randomized pairs of short, serial, non-verbal tones (300 ms) with a short inter-tone interval (500 ms) were presented. The pairs were divided into six randomized blocks. Within each pair, tones differed in length (i.e., duration) by specified amounts in each block (Δl 15%, Δl 33%, Δl 66%, Δl 133%, Δl 266%, and Δl 533%). Participants had to listen to the pairs of tones and then respond by pressing “first tone was the shortest” or “second tone was the shortest” on a 2-button press.

Pitch discrimination task: 140 randomized pairs of short, serial, non-verbal tones (300 ms) with a short inter-tone interval (500 ms) were presented. The pairs were divided into six randomized blocks. Within each pair, tones were either identical or differed in frequency by specified amounts in each block (Δf 1.5%, Δf 2.5%, Δf 5%, Δf 10%, Δf 20%, and Δf 50%). Tones were derived from three reference base frequencies (2000, 1000 and 500 Hz) to avoid learning effects. Participants had to listen to the pairs of tones and then respond by pressing “the two tones were identical” or “the two tones were different” on a 2-button press.

Intensity discrimination task: 80 randomized pairs of short, serial, non-verbal tones (300 ms) with a short inter-tone interval (500 ms) are presented. The pairs are divided into six randomized blocks. Within each pair, tones differed in intensity by specified amounts in each block (Δi 10%, Δi 20%, Δi 30%, Δi 40%, Δi 50%, and Δi 60%). Participants had to listen to

the pairs of tones and then respond by pressing “first tone had the lowest intensity” or “second tone had the lowest intensity” on a 2-button press.

2.3.2. Modulation discrimination of pure tones

Amplitude task (See (Goswami et al., 2002) for details): 80 randomized pairs of short, serial, non-verbal tones (786 ms) with a short inter-tone interval (500 ms) were presented. All sounds were sinusoidal carriers at 500 Hz, amplitude-modulated at a rate of 0.7 Hz, and had a depth of 50%. The fall time was fixed at 350 ms, and the rise time could be varied from 15 to 300 ms (logarithmically spaced over a continuum of 80 stimuli). Participants had to listen to the pairs of tones and then respond by pressing “first tone had the softest rise” or “second tone had the softest rise” on a 2-button press.

2.3.3. Control for attention functioning

These basic auditory tasks required participants’ sustained attention for several minutes. As attentional processes are known to be impaired in **SZ** (Carter et al., 2010; Fioravanti et al., 2012), we designed a control task called the **Length-distractor** to eliminate a possible confounding effect of these processes on basic auditory performance. This task was exactly the same as the Length task, with the exception of presenting a short (300 ms) white noise as distractor in the intervening period between tones of each pair (i.e., a sequence “tone – white noise – tone”). By disrupting the sustained attention with an irrelevant stimulus, this task would control for attentional functioning during basic auditory performance effort.

2.5. Analyses

All statistical analyses were carried out using R (R Development Core Team, 2008). For all tests, significance was set at $p\text{-value} < .05$. Cohen’s d effect sizes for mean comparisons were

calculated with a d value of 0.2, 0.5 and 0.8 reflecting the cut-off for small, medium and large effect sizes, respectively. Socio-demographic characteristics between groups were compared using independent-sample two-sided Student's t -tests for continuous variables and Fisher's exact F -tests for categorical variables. Illness duration, medication dosage (expressed in chlorpromazine –CPZ– equivalents) and socio-demographic variables revealing group differences were subjected to exploratory correlational analyses to assess their inclusion as covariates in between-group comparisons.

2.5.1. Source-monitoring comparisons

Participants who identified fewer than 4 'new words' in at least one of the two source-monitoring tasks were excluded from the study to eliminate a possible confounding effect of memory capacities or lack of attention towards the task during the encoding phase on source-monitoring performances.

We investigated two variables **source-monitoring outcomes** based on the literature (Brunelin et al., 2006a; Mondino et al., 2016). **In order to separate guessing bias and actual source-monitoring measures, we used analysis of covariance (ANCOVA) with count of false positives (i.e., 'said', 'heard', 'imagined as said' and 'imagined as heard' responses to 'new word')** entered as covariate (Woodward et al., 2007).

1) The percent of correct responses was entered in a three-way analysis of **covariance (ANOVA) ANCOVA** with group (control and patient) as inter-subject factor, and type of task (Say-Imagine and Hear-Imagine), ~~and~~ task condition (internal ('imagined as said' or 'imagined as heard'), external ('heard' or 'said')) as within-subject factors, **and false positive rate as covariate.**

2) The percent of source-inversions between presented source information (i.e., in the Say-Imagine test, misattributing an internal source to an external source (externalization) and

misattributing an external source to an internal event (internalization)) was entered in a three-way ANOVA ANCOVA with group as inter-subject factor, and type of task and type of inversion (internalization, externalization) as within-subject factors, and false positive rate as covariate.

2.5.2. Basic auditory processing comparisons

We measured percentages of correct responses from each basic auditory task (Pitch, Intensity, Length, Amplitude, Length-distractor) according to the literature (Donde et al., 2017). Percentages of correct responses were divided into three conditions for static feature tasks, related to feature differences of tones: 'Difficult' (2 smallest $\Delta\%$), 'Intermediate' (2 intermediate $\Delta\%$) and 'Easy' (2 widest $\Delta\%$). Amplitude scores were isolated in three equal categories according to the level of difficulty of corresponding stimuli. Then, the percentage of correct responses was entered in a two-way ANOVA with group (control and patient) as inter-subject factor and type of task (Pitch, Intensity, Length and Amplitude) as within-subject factor. As a specific control analysis, covariance (ANCOVA) was computed to assess the independence of basic auditory perception (Length) from attention performance (Length-distractor).

2.5.3. Relationships between measures

Pearson correlations were used to compare relationships among variables across groups and within the schizophrenia group. Bonferroni corrections for multiple comparisons were applied, as indicated. In addition, to build a parsimonious model for the prediction of source-monitoring regarding basic auditory performances in SZ, we conducted a backward step-wise regression analysis to condense the variables and thus identify the best predictors of source-monitoring performance among a large number of variables. The candidate predictors were

each basic auditory task score, PANSS dimension scores, illness duration, medication (CPZ) dosage and variables revealing group differences. 'New words' correct recognitions scores in both source-monitoring tasks were excluded from these analyses.

3. RESULTS

One patient with schizophrenia and one healthy participant did not adequately perform the source-monitoring tasks (more than 4 'new words' not recognized in one of the tasks) and were thus excluded from the analyses. The final analysed sample consisted of 29 SZ and 29 healthy controls. A significantly lower level of education was observed in the patient group (Table 1). Mean task scores and comparisons are detailed in S1.

3.1. Source-monitoring comparisons

The three-way ANOVA ANCOVA involving the total numbers of correct responses in source-monitoring tasks revealed a significant main effect of group ($F_{(4,224)}=42.49; p<.0005$). ($F_{(8,223)}=19.0; p<.0005$). No other main effects or interactions were reported.

Post hoc between-group comparisons (Fig.2) revealed that patients showed significantly less correct recognition of imagined ($p<.005$; $d=0.91$) and spoken aloud ($p<.05$; $d=0.53$) words in the internal monitoring task, and less correct recognition of imagined ($p<.005$; $d=0.87$) and heard ($p<.0005$; $d=1.13$) words in the reality monitoring task compared to controls. The total of these correct recognitions was significant within tasks (internal monitoring: $p<.005$, $d=0.87$; reality monitoring: $p<.00005$, $d=1.34$) and across tasks ($p<.00005$, $d=1.24$), with large effect sizes. No significant between-group differences were observed for correct recognition of 'new words' in either source-monitoring task.

3.2. Basic auditory processing comparisons

The two-way ANOVA on the percentage of basic auditory correct responses revealed a significant main effect of group ($F_{(4,227)}=45.5$; $p<.0001$) and type of basic auditory task ($F_{(4,227)}=5.3$; $p<.0001$), but no significant interaction between group and type of basic auditory task.

Post hoc between-group comparisons (Fig.3) revealed that patients were significantly impaired in all auditory tasks, from more to less impaired: Length ($p<.0005$; $d=1.15$), Amplitude ($p<.005$; $d=0.91$), Pitch ($p<.005$; $d=0.90$) and Intensity ($p<.05$; $d=0.78$). We also found a large significant deficit in patients for total correct basic auditory responses ($p<.0005$; $d=1.16$).

The ANCOVA of basic auditory length perception ability controlling for attention performance revealed that patients' basic auditory length perception deficits were significant overall ($F_{(2,55)}=4.8$; $p<.05$), but that there was a significant attention effect between groups ($F_{(4,227)}=30.9$; $p<.0001$). According to this result, we conducted a complementary *post hoc* ANOVA with groups and tasks (Length and Length-distractor) to explore for an additional deficit in one these tasks versus the other. No significant interaction was observed between task and group.

3.3. Relationships between measures

Basic auditory global performance (i.e., the average performance percent of the four basic auditory tasks Length, Pitch, Intensity, and Amplitude –Fig.3e) was significantly correlated with correct recognition in both internal monitoring (across groups: $r_{\text{partial}}=.48$, $p<.0005$, $N=58$; patients group: $r=.48$, $p<.05$, $N=29$; Fig.4a) and reality monitoring tasks (across groups: $r_{\text{partial}}=.43$, $p<.005$, $N=58$; patients group: $r=.40$, $p<.05$, $N=29$; Fig.4b). Across groups,

these correlations remained significant following Bonferroni correction. Within tasks, significant correlations were observed between basic auditory and all word conditions, except for 'said' words.

Within the patient group, a significant negative correlation was observed between performance at the Pitch test (intermediate condition) and PANSS-Positive sub score ($r=-.40$, $p<.05$, $N=29$, but did not survive Bonferroni correction). Examination of relationships with specific PANSS-Positive symptoms showed that delusion and suspiciousness were the most negatively correlated with basic auditory processing (Average performance). However, these correlations lost significance when applying Bonferroni correction.

There was no correlation between global basic auditory performance and PANSS-Negative ($r=.09$, $p>.05$, $N=29$) and PANSS-General psychopathology subscores ($r=-.19$, $p>.05$, $N=29$). In addition, no correlations between source-monitoring tasks and positive, negative, general psychopathology symptom measures were significant (all $p>.05$).

Basic auditory processing and source-monitoring scores did not correlate with illness duration or medication (CPZ) dosage (all $p>.05$). However, there was a significant correlation between education and both sets of task scores. Regression analysis using the same ANOVA models controlling for this covariate revealed that basic auditory and source-monitoring task score differences remained significant between groups.

The step-wise regression analysis studied the influence of candidate predictor variables on the total number of correct recognitions in both source-monitoring tasks: 12 that reflect basic auditory processing (3 levels of Length, Pitch, Intensity and Amplitude percentages of correct responses) and 6 socio-demographic/clinical measures (PANSS subscores, illness duration, CPZ, education). Within the patient group, only Pitch Intermediate ($b=0.20$; $p<.05$) was a significant predictor.

4. DISCUSSION

4.1. Source-monitoring deficits and basic auditory processing in SZ

This exploratory study conducted in 29 SZ and 29 healthy participants corroborated our primary hypothesis by showing that patients displayed lower performances in both basic auditory functions and source-monitoring processes in comparison to controls.

Source-monitoring deficit in patients is consistent with the previous literature regarding internal monitoring (Brebion et al., 2000; Henquet et al., 2005), reality monitoring disruption (Vinogradov et al., 1997), and both (Keefe et al., 1999). Although recent memory retention differences between groups may account for these differences in source-monitoring performance, the absence of group difference in the recognition of ‘new words’ does not support this interpretation. In addition, source-monitoring differences remained significant after regression analysis controlling for the same potential covariates as controlled for basic auditory tasks. An important caveat is that our patient group did not show significant source inversions in source-monitoring tasks in comparison to controls (e.g., misattributing an internal, self-generated item to an external source; S1). Even if one study corroborates this result (Seal et al., 1997), this non-significant difference strongly contrasts with the recent literature (Brunelin et al., 2006b; Waters et al., 2012; Woodward et al., 2007)

Moreover, we observed that patients displayed abnormalities for processing several psychoacoustic parameters, regarding both sound feature (length, pitch, intensity) and modulation discrimination (amplitude). This is consistent with patients’ pitch discrimination impairments reported in our recent meta-analysis (Donde et al., 2017). Additionally, we calculated an increasing magnitude of the effect size between groups as the level of pitch test difficulty decreased (Table 2, S1), supporting the auditory discrimination threshold reduction

related to schizophrenia that was previously underlined in some studies (Kantrowitz et al., 2014; Rabinowicz et al., 2000). The analysis of length perception ability controlled for attention revealed that higher attention performance predicts better auditory processing scores, but that auditory processing cannot be accounted for solely by attention differences between groups. This is important especially since patients usually display large attention deficits (Carter et al., 2010; Fioravanti et al., 2012). Furthermore, patients' basic auditory deficits remained significant after controlling for education, illness duration and CPZ dosages; this outcome was not the case in a basic auditory study of Leitman and colleagues (Leitman et al., 2006). These regression analyses may support the consideration of basic auditory processing deficits as a full-blown dimension of schizophrenia, which would be distinct from the attention domain and likely underpinned by specific pathophysiological neural pathways (Javitt, 2009; Javitt and Sweet, 2015).

4.2. Basic auditory processing correlates with source-monitoring and clinical symptoms

Our results showed significant correlations between basic auditory processing and source-monitoring scores, for both internal ('imagined as said' and 'imagine as heard' words) and external ('heard' words) events across groups. Furthermore, our step-wise regression analysis suggested that pitch processing is a strong predictor of source-monitoring performances, even when socio-demographic and clinical variables are taken into account. These results support the hypothesis of an incorrect identification of the basic auditory cues that are related to a specific auditory source (internal or external) in SZ. Such deficits would lead to an impaired recognition of these events and then to source-monitoring disruption, as each auditory source is related to specific psychoacoustic parameters.

As well as being consistent with previous studies (Bruder et al., 2004; Javitt et al., 2000; McLachlan et al., 2013), the correlation we observed between pitch discrimination and

positive symptoms (as measured by the PANSS scale) suggests that basic auditory deficits are involved in source-monitoring **impairments**, as such deficits were identified as more disrupted in subsamples more prone to positive symptoms (Brebion et al., 2000; Brunelin et al., 2006a; Keefe et al., 1999; Stirling et al., 2001). **However, the association between pitch discrimination and positive symptoms was no longer significant after correction for multiple comparisons and thus should be considered with caution.**

These findings provide new insights into the corollary discharge model (Ford et al., 2010), in that source-monitoring disruption may arise from wrong sensory feedforward of the auditory signal that mismatches with the efference copy, resulting in a loss of the sense of thought agency in patients. However, we must note that consistent with prior studies (Szoke et al., 2009; Vinogradov et al., 1997), no significant correlations were observed between source-monitoring tasks scores and psychometric scales in **SZ**. Likewise, the absence of significant correlation between source inversions and basic auditory processing shows that auditory disruption may rather be involved in decreased accuracy of source recognition than in specific incorrect externalization/internalization of this source.

4.3. Methodological bias and limits

This is the first experiment to explore both basic auditory processing and source-monitoring in **SZ**, as well as clinical symptoms. However, this study has some notable and methodological limitations.

First, the small sample size did not allow performing subgroup comparisons to investigate if both deficits are more pronounced between prominent clinical dimensions. Additionally, hallucinations occurring simultaneously with the tests were not possible to determine, but they may have biased the performances.

Second, indirect measure of self-monitoring through source memory tasks prevents us

from determining if monitoring deficits occur simultaneously with the auditory stimulus encoding or when the information is recalled. Real-time self-monitoring assessments showed deficits in SZ (Allen et al., 2004), but these results were not systematically replicated (Versmissen et al., 2007). Nevertheless, short-term memory recall deficits in patients were eliminated by the absence of differences in ‘new words’ recognition between groups.

Third, several parameters that we did not evaluate in our study may be involved in source-monitoring abilities, such as metacognitive beliefs about own thoughts (Aleman, 2008) and emotional state presented during source-monitoring assessment (Johnson, 2006; Morrison, 1997).

5. CONCLUSION

Our study shows that both basic auditory processing and internal/reality source-monitoring of auditory stimuli are impaired in SZ and cannot be accounted for solely by attention (estimated by auditory performance with distractor noise) or memory deficits (measured with short-term ‘new words’ recall). We hypothesize that primarily auditory disruption at the brain level, as indexed by basic auditory skills, may be involved in larger neural networks underpinning source-monitoring abilities and positive symptoms in patients. Further validation of the present findings is certainly warranted, including studies measuring brain function and general cognitive abilities, controlling for potential bias of both behavioural paradigms. Nevertheless, this study contributes to the literature by demonstrating that early sensory processing may be a key feature of schizophrenia and a potential contributor of cognitive deficits and positive symptoms of the illness.

REFERENCES

- Aleman, A., Larøi, F., 2008. *Hallucinations : the science of idiosyncratic perception*, 1st ed. American Psychological Association, Washington, DC.
- Allen, P.P., Johns, L.C., Fu, C.H., Broome, M.R., Vythelingum, G.N., McGuire, P.K., 2004. Misattribution of external speech in patients with hallucinations and delusions. *Schizophr Res* 69(2-3), 277-287.
- Bentall, R.P., Baker, G.A., Havers, S., 1991. Reality monitoring and psychotic hallucinations. *Br J Clin Psychol* 30 (Pt 3), 213-222.
- Bianchi, F., Hjortkjaer, J., Santurette, S., Zatorre, R.J., Siebner, H.R., Dau, T., 2017. Subcortical and cortical correlates of pitch discrimination: Evidence for two levels of neuroplasticity in musicians. *Neuroimage* 163, 398-412.
- Brebion, G., Amador, X., David, A., Malaspina, D., Sharif, Z., Gorman, J.M., 2000. Positive symptomatology and source-monitoring failure in schizophrenia--an analysis of symptom-specific effects. *Psychiatry Res* 95(2), 119-131.
- Brebion, G., Gorman, J.M., Amador, X., Malaspina, D., Sharif, Z., 2002. Source monitoring impairments in schizophrenia: characterisation and associations with positive and negative symptomatology. *Psychiatry Res* 112(1), 27-39.
- Bruder, G.E., Wexler, B.E., Sage, M.M., Gil, R.B., Gorman, J.M., 2004. Verbal memory in schizophrenia: additional evidence of subtypes having different cognitive deficits. *Schizophr Res* 68(2-3), 137-147.
- Brunelin, J., Combris, M., Poulet, E., Kallel, L., D'Amato, T., Dalery, J., Saoud, M., 2006a. Source monitoring deficits in hallucinating compared to non-hallucinating patients with schizophrenia. *Eur Psychiatry* 21(4), 259-261.
- Brunelin, J., Poulet, E., Bediou, B., Kallel, L., Dalery, J., D'Amato, T., Saoud, M., 2006b. Low frequency repetitive transcranial magnetic stimulation improves source monitoring deficit in hallucinating patients with schizophrenia. *Schizophr Res* 81(1), 41-45.
- Carter, J.D., Bizzell, J., Kim, C., Bellion, C., Carpenter, K.L., Dichter, G., Belger, A., 2010. Attention deficits in schizophrenia--preliminary evidence of dissociable transient and sustained deficits. *Schizophr Res* 122(1-3), 104-112.
- Collins, P.Y., Patel, V., Joestl, S.S., March, D., Insel, T.R., Daar, A.S., Scientific Advisory, B., the Executive Committee of the Grand Challenges on Global Mental, H., Anderson, W., Dhansay, M.A., Phillips, A., Shurin, S., Walport, M., Ewart, W., Savill, S.J., Bordin, I.A., Costello, E.J., Durkin, M., Fairburn, C., Glass, R.I., Hall, W., Huang, Y., Hyman, S.E., Jamison, K., Kaaya, S., Kapur, S., Kleinman, A., Ogunniyi, A., Otero-Ojeda, A., Poo, M.M., Ravindranath, V., Sahakian, B.J., Saxena, S., Singer, P.A., Stein, D.J., 2011. Grand challenges in global mental health. *Nature* 475(7354), 27-30.
- Donde, C., Luck, D., Grot, S., Leitman, D.I., Brunelin, J., Haesebaert, F., 2017. Tone-matching ability in patients with schizophrenia: A systematic review and meta-analysis. *Schizophr Res* 181, 94-99.
- Donde, C., Silipo, G., Dias, E.C., Javitt, D.C., 2018. Hierarchical deficits in auditory information processing in schizophrenia. *Schizophr Res*.
- Fioravanti, M., Bianchi, V., Cinti, M.E., 2012. Cognitive deficits in schizophrenia: an updated metanalysis of the scientific evidence. *BMC Psychiatry* 12, 64.
- Ford, J.M., Morris, S.E., Hoffman, R.E., Sommer, I., Waters, F., McCarthy-Jones, S., Thoma, R.J., Turner, J.A., Keedy, S.K., Badcock, J.C., Cuthbert, B.N., 2014. Studying hallucinations within the NIMH RDoC framework. *Schizophr Bull* 40 Suppl 4, S295-304.

- Ford, J.M., Roach, B.J., Mathalon, D.H., 2010. Assessing corollary discharge in humans using noninvasive neurophysiological methods. *Nat Protoc* 5(6), 1160-1168.
- Frith, C.D., 1992. The cognitive neuropsychology of schizophrenia.
- Goswami, U., Thomson, J., Richardson, U., Stainthorp, R., Hughes, D., Rosen, S., Scott, S.K., 2002. Amplitude envelope onsets and developmental dyslexia: A new hypothesis. *Proc Natl Acad Sci U S A* 99(16), 10911-10916.
- Harvey, P.D., 1985. Reality monitoring in mania and schizophrenia. The association of thought disorder and performance. *J Nerv Ment Dis* 173(2), 67-73.
- Harvey, P.D., Serper, M.R., 1990. Linguistic and cognitive failures in schizophrenia. A multivariate analysis. *J Nerv Ment Dis* 178(8), 487-493.
- Henquet, C., Krabbendam, L., Dautzenberg, J., Jolles, J., Merckelbach, H., 2005. Confusing thoughts and speech: source monitoring and psychosis. *Psychiatry Res* 133(1), 57-63.
- Holcomb, H.H., Ritzl, E.K., Medoff, D.R., Nevitt, J., Gordon, B., Tamminga, C.A., 1995. Tone discrimination performance in schizophrenic patients and normal volunteers: impact of stimulus presentation levels and frequency differences. *Psychiatry Res* 57(1), 75-82.
- Javitt, D.C., 2009. When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. *Annu Rev Clin Psychol* 5, 249-275.
- Javitt, D.C., Shelley, A., Ritter, W., 2000. Associated deficits in mismatch negativity generation and tone matching in schizophrenia. *Clin Neurophysiol* 111(10), 1733-1737.
- Javitt, D.C., Sweet, R.A., 2015. Auditory dysfunction in schizophrenia: integrating clinical and basic features. *Nat Rev Neurosci* 16(9), 535-550.
- Johns, L.C., Rossell, S., Frith, C., Ahmad, F., Hemsley, D., Kuipers, E., McGuire, P.K., 2001. Verbal self-monitoring and auditory verbal hallucinations in patients with schizophrenia. *Psychol Med* 31(4), 705-715.
- Johnson, M.K., 2006. Memory and reality. *Am Psychol* 61(8), 760-771.
- Johnson, M.K., Hashtroudi, S., Lindsay, D.S., 1993. Source monitoring. *Psychol Bull* 114(1), 3-28.
- Kantrowitz, J.T., Hoptman, M.J., Leitman, D.I., Silipo, G., Javitt, D.C., 2014. The 5% difference: early sensory processing predicts sarcasm perception in schizophrenia and schizo-affective disorder. *Psychol Med* 44(1), 25-36.
- Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 13(2), 261-276.
- Keefe, R.S., Arnold, M.C., Bayen, U.J., Harvey, P.D., 1999. Source monitoring deficits in patients with schizophrenia; a multinomial modelling analysis. *Psychol Med* 29(4), 903-914.
- Leitman, D.I., Laukka, P., Juslin, P.N., Saccante, E., Butler, P., Javitt, D.C., 2010. Getting the cue: sensory contributions to auditory emotion recognition impairments in schizophrenia. *Schizophr Bull* 36(3), 545-556.
- Leitman, D.I., Ziwich, R., Pasternak, R., Javitt, D.C., 2006. Theory of Mind (ToM) and counterfactuality deficits in schizophrenia: misperception or misinterpretation? *Psychol Med* 36(8), 1075-1083.
- McLachlan, N.M., Phillips, D.S., Rossell, S.L., Wilson, S.J., 2013. Auditory processing and hallucinations in schizophrenia. *Schizophr Res* 150(2-3), 380-385.
- Mechelli, A., Allen, P., Amaro, E., Jr., Fu, C.H., Williams, S.C., Brammer, M.J., Johns, L.C., McGuire, P.K., 2007. Misattribution of speech and impaired connectivity in patients with auditory verbal hallucinations. *Hum Brain Mapp* 28(11), 1213-1222.

- Micheyl, C., Delhommeau, K., Perrot, X., Oxenham, A.J., 2006. Influence of musical and psychoacoustical training on pitch discrimination. *Hear Res* 219(1-2), 36-47.
- Mondino, M., Poulet, E., Suaud-Chagny, M.F., Brunelin, J., 2016. Anodal tDCS targeting the left temporo-parietal junction disrupts verbal reality-monitoring. *Neuropsychologia* 89, 478-484.
- Morrison, A.P., Haddock, G., 1997. A cognitive model of hallucinations. *Psychological Medicine* 27, 669-679.
- Olsson, O., Nielzen, S., 1999. Contralateral induction by frequency spectrum in hallucinating schizophrenics. *Psychiatry Res* 87(1), 65-75.
- R Development Core Team, 2008. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.
- Rabinowicz, E.F., Silipo, G., Goldman, R., Javitt, D.C., 2000. Auditory sensory dysfunction in schizophrenia: imprecision or distractibility? *Arch Gen Psychiatry* 57(12), 1149-1155.
- Seal, M.L., Crowe, S.F., Cheung, P., 1997. Deficits in Source Monitoring in Subjects with Auditory Hallucinations May be Due to Differences in Verbal Intelligence and Verbal Memory. *Cogn Neuropsychiatry* 2(4), 273-290.
- Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 59 Suppl 20, 22-33;quiz 34-57.
- Stirling, J.D., Hellewell, J.S., Ndlovu, D., 2001. Self-monitoring dysfunction and the positive symptoms of schizophrenia. *Psychopathology* 34(4), 198-202.
- Strous, R.D., Cowan, N., Ritter, W., Javitt, D.C., 1995. Auditory sensory ("echoic") memory dysfunction in schizophrenia. *Am J Psychiatry* 152(10), 1517-1519.
- Sugimori, E., Tanno, Y., 2010. The effects of cognitive activity and perceptual details on speech source monitoring. *Br J Psychol* 101(Pt 4), 777-790.
- Szoke, A., Meary, A., Ferchiou, A., Trandafir, A., Leboyer, M., Schurhoff, F., 2009. Correlations between cognitive performances and psychotic or schizotypal dimensions. *Eur Psychiatry* 24(4), 244-250.
- Vercammen, A., Knegeting, H., Liemburg, E.J., den Boer, J.A., Aleman, A., 2010. Functional connectivity of the temporo-parietal region in schizophrenia: effects of rTMS treatment of auditory hallucinations. *J Psychiatr Res* 44(11), 725-731.
- Versmissen, D., Janssen, I., Johns, L., McGuire, P., Drukker, M., a Campo, J., Myin-Germeys, I., Van Os, J., Krabbendam, L., 2007. Verbal self-monitoring in psychosis: a non-replication. *Psychol Med* 37(4), 569-576.
- Vinogradov, S., Luks, T.L., Schulman, B.J., Simpson, G.V., 2008. Deficit in a neural correlate of reality monitoring in schizophrenia patients. *Cereb Cortex* 18(11), 2532-2539.
- Vinogradov, S., Willis-Shore, J., Poole, J.H., Marten, E., Ober, B.A., Shenaut, G.K., 1997. Clinical and neurocognitive aspects of source monitoring errors in schizophrenia. *Am J Psychiatry* 154(11), 1530-1537.
- Wang, L., Metzak, P.D., Woodward, T.S., 2011. Aberrant connectivity during self-other source monitoring in schizophrenia. *Schizophr Res* 125(2-3), 136-142.
- Waters, F., Woodward, T., Allen, P., Aleman, A., Sommer, I., 2012. Self-recognition deficits in schizophrenia patients with auditory hallucinations: a meta-analysis of the literature. *Schizophr Bull* 38(4), 741-750.
- Woodward, T.S., Menon, M., Whitman, J.C., 2007. Source monitoring biases and auditory hallucinations. *Cogn Neuropsychiatry* 12(6), 477-494.

FIGURES CAPTIONS

Figure 1: Models of behavioural paradigms.

A. Source monitoring assessment. **1:** an instruction is presented on the screen (Internal monitoring: “Say this word aloud” or “Imagine this word”; Reality monitoring: “Listen to this word” – the experimenter say the word – or “Imagine that you are hearing this word”), **2:** a word is presented, and the participant has to apply the instruction to the word, **3:** response grid: for example, in the ‘Internal monitoring’ task, a participant had to note for each word if he said the word, if he imagined saying the word or if the word did not appear on the computer’s screen.

B. Basic auditory processing assessment. **1:** a short visual cue is present on the screen to capture the participant’s attention, **2:** a pair of short tones is presented through headphones, **3:** participant has to respond to the instruction on a 2-button press.

Figure 2: Behavioural assessment of source monitoring.

Bar graph (Mean +/- SD) of % correct for source monitoring tasks. Total scores exclude control task (‘New words’) scores. * $p < .05$, ** $p < .005$, *** $p < .0005$.

Figure 3: Behavioural assessment for basic auditory processing.

Bar graph (Mean +/- SD) of % correct by acoustic feature against level of task difficulty.

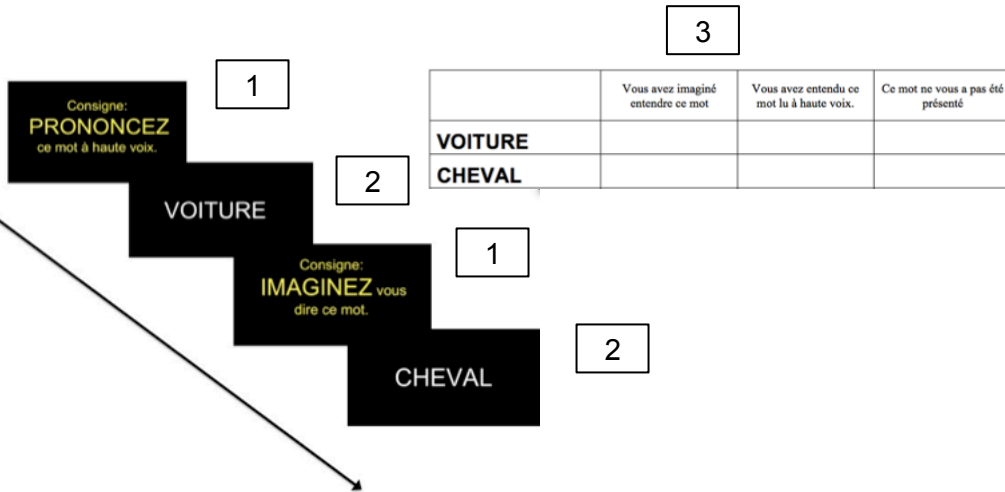
(e) Average refers to the average performance percent of the four basic auditory tasks (Length, Pitch, Intensity, and Amplitude).

* $p < .05$, ** $p < .005$, *** $p < .0005$, **** $p < .00005$.

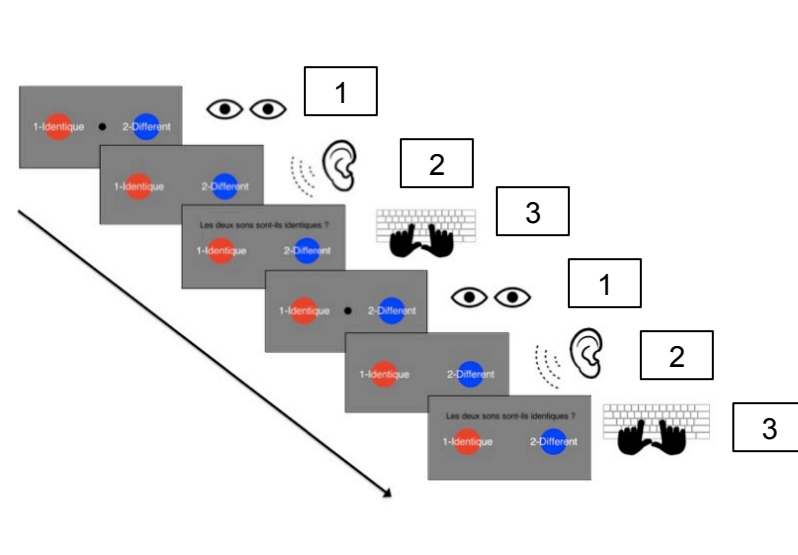
Figure 4: Scatter plots of **A.** % total correct for Internal monitoring and **B.** % total correct for Reality monitoring by basic auditory processing % total correct.

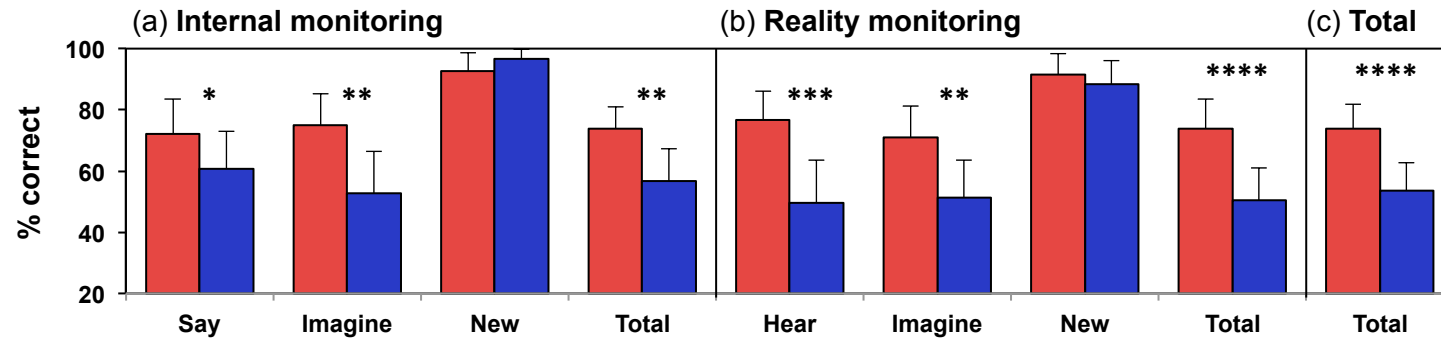
●: Healthy controls (red circles), ▲: Patients with schizophrenia (blue triangles).

A.

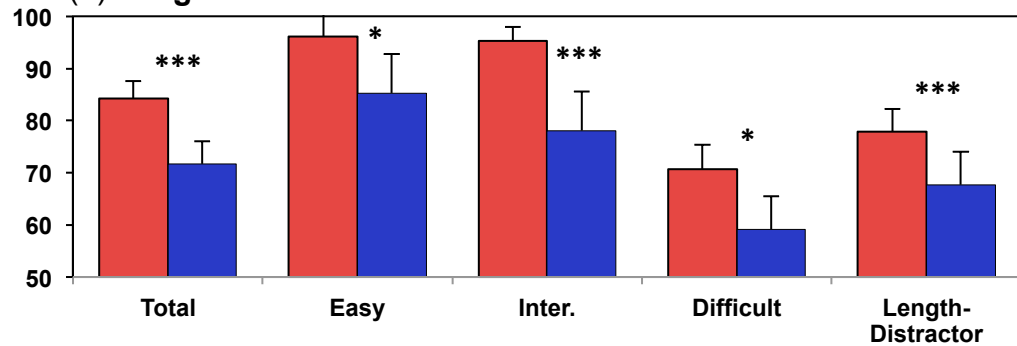


B.

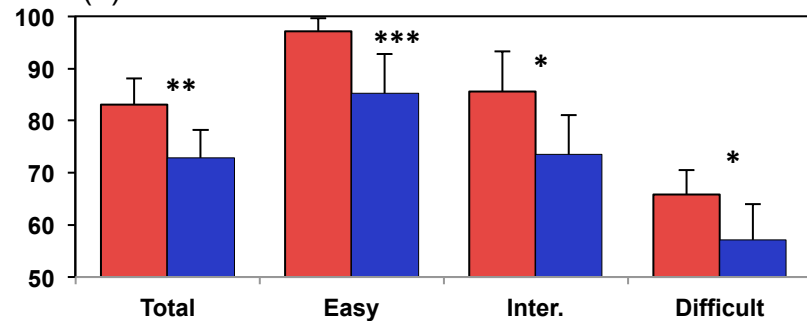




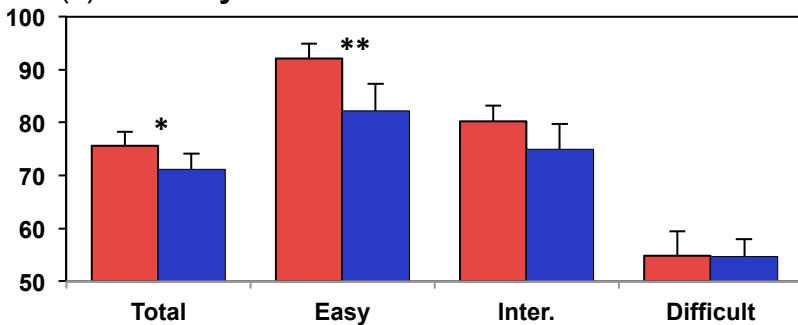
(a) Length



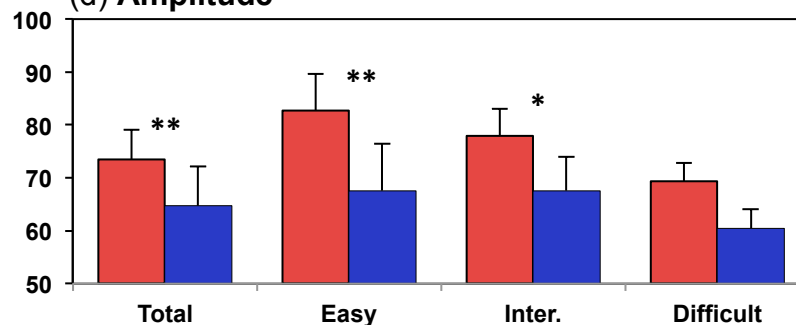
(b) Pitch



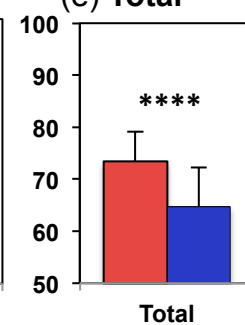
(c) Intensity



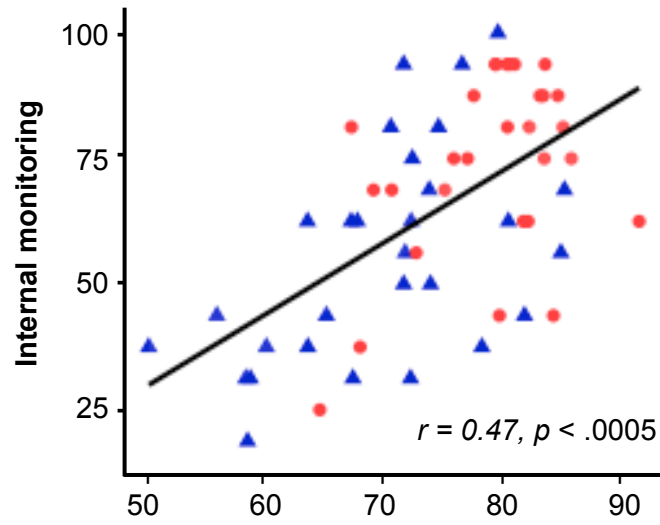
(d) Amplitude



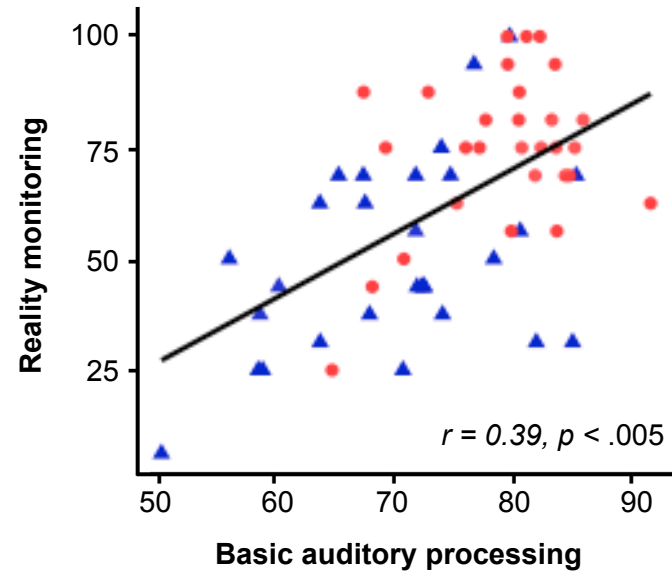
(e) Total



A.



B.



	Patient (N = 29)	Control (N = 29)
Age (years)	37.3 (11.4)	34.4 (12.6)
Sex ratio (M/F)	21/8	23/6
Lateralisation (R/L)	28/1	25/4
Education (years)*	10.9 (3.3)	15.7 (3.6)
Illness duration (years)	14.0 (9.4)	-
CPZ equivalents (mg/d)	1113.6 (997.9)	-
PANSS total	80.9 (18.5)	-
Positive	19.4 (6.2)	-
Negative	23.6 (7.5)	-
General Psychopathology	37.9 (10.2)	-

Table: Socio-demographic and clinical data across groups.
 PANSS: Positive and Negative Syndrome Scale, CPZ: chlorpromazine.
 *: significant difference ($p < .05$) observed between groups.