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► To cite this version:

Jose Eduardo Marques Carneiro da Silva, Julien Krieg, Céline Duval, Thomas Schwitzer, Anne Giersch. Paradoxical Sensitivity to Sub-threshold Asynchronies in Schizophrenia: A Behavioral and EEG Approach. Schizophrenia Bulletin Open, 2021, 2 (1), <10.1093/schizbullopen/sgab011>. <hal-03368753>

HAL Id: hal-03368753

<https://hal.science/hal-03368753v1>

Submitted on 6 Oct 2021

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Paradoxical Sensitivity to Sub-threshold Asynchronies in Schizophrenia: A Behavioral and EEG Approach

José Eduardo Marques-Carneiro^{1,2}, Julien Krieg^{1,2}, Céline Z. Duval¹, Thomas Schwitzer^{1,3,4}, and Anne Giersch^{*.1,2,6}

¹University of Strasbourg, INSERM U1114, Strasbourg, France; ²Department of Psychiatry, University Hospital of Strasbourg, Strasbourg, France; ³Pôle Hospitalo-Universitaire de Psychiatrie d'Adultes et d'addictologie du Grand Nancy, Centre Psychothérapique de Nancy, Laxou, France; ⁴Faculté de Médecine, Université de Lorraine, Vandœuvre-lès-Nancy, France

*To whom correspondence should be addressed; Department of Psychiatry, University Hospital of Strasbourg, 1 place de l'hôpital, 67000 Strasbourg, France; tel: +33-388-116-471, fax: +33 (0)3-88-11-64-46, e-mail: giersch@unistra.fr

The flow of consciousness is disrupted and disorganized in schizophrenia. We explore the hypothesis that this disruption is related to asynchronies not being predicted in advance and standing out instead of being integrated in the flow of events. We recorded EEG continuously during a simultaneity/asynchrony discrimination task, in which subjects decide whether 2 squares are shown simultaneously or with an asynchrony (asynchronies were between 24 and 96 ms). Behavioral data was obtained in 32 patients with schizophrenia and 27 matched controls, and EEG was recorded in a subset of 17 patients vs 15 controls. Two results suggested a lack of asynchrony prediction in patients. Behavioral difficulties at detecting asynchronies increased in patients with schizophrenia relative to controls after a detection of simultaneity, and this effect was correlated with clinical disorganization. Desynchronization of alpha activity observed before the beginning of a trial was larger after asynchronous than simultaneous responses in controls, but not in patients. EEG signals additionally suggested abnormal sensitivity to short asynchronies in patients. The amplitude of early signals around 180 ms after the first square abnormally increased in patients for short asynchronies relative to perfect simultaneity, whereas EEG signals at parietal regions decreased in amplitude in patients relative to controls, in the 400–600 ms interval after the first square. These results reinforce the hypothesis of time prediction and sequencing impairments at the sub-second level and may provide an explanation for the disruption of the patients' consciousness flow.

Key words: schizophrenia/timing/EEG/N2/temporal sequences/millisecond level

Introduction

Phenomenologists have since long argued that the patients' train of thought is fragmented in

time,^{1–5} thus affecting any conscious experience, and possibly participating to the patients' disorganization of thought.^{6–8} Consistent with these hypotheses, we and others showed that patients have difficulties to consciously discriminate successive visual stimuli in time,^{7–14} this difficulty being correlated to clinical disorganization.^{7,8} Additional mechanisms contribute to organize information in time, though, at the millisecond level. Information requires time to be processed,¹⁵ and following information over time efficiently requires information to be predicted in advance, as confirmed by our own data.^{16,17} Our hypothesis is that these prediction mechanisms are impaired in patients with schizophrenia, impeding them from integrating sequences of visual stimuli with short asynchronies in the temporal flow of events.^{11,18,19} Information that is not integrated in the flow of event should stand out and further disorganize the train of thought. Here we explore these hypotheses with behavioral and EEG measures and verify correlations with clinical disorganization. At the conscious level, when 2 visual stimuli are displayed asynchronously in distinct spatial locations, detecting asynchrony requires around 30 to 50 ms of Stimulus Onset Asynchrony (SOA). By definition, these limits mean that for 30 to 50 ms, events are judged to be simultaneous in 50% of the cases, as if time stops. Several models have been proposed to account for the fact that we nonetheless feel that time flows without interruption, not that time stops, even for very short durations.²⁰ Our own data, as well as the literature, suggest that 2 stimuli can be distinguished in time at a non-conscious level (for 17 ms asynchronies), while being judged as being simultaneous at a conscious level.^{11,12,15–17} We proposed that the non-conscious processing of information leads to anticipated attention displacements which help to follow information fluently.^{11,12} For example, if subjects

are exposed to a sequence of 2 consecutive stimuli, this will influence their expectation on the trial that follows,^{9,21} by inducing an attention displacement according to the prior sequence.^{16,17} Our own results confirm that sequences of stimuli are expected from moment to moment and allow for attention displacements at the millisecond level.^{16,17,22} Such non-conscious expectation processes compensate for the time resolution limits at the conscious level by helping to follow events over time in a fluent way. In contrast to controls, patients have been repeatedly suggested to be impaired at planning sequences of information.²³ Instead of displacing their attention towards the last stimulus of a series of 2, they were stuck with the first one. This effect was observed when asynchronies were sub-threshold¹¹ or undetected.^{8,12} The results showed that patients with schizophrenia process sub-threshold asynchronies, but suggested that they are impaired at preparing for the stimulus sequences in advance. Here, this hypothesis is explored by examining trial-to-trial effects and by recording evoked potentials in a task requiring subjects to discriminate between simultaneous and asynchronous stimuli.

In our protocols, 2 stimuli are displayed on a computer screen either simultaneously, or with an asynchrony. Subjects judge on each trial whether the 2 stimuli are simultaneous or asynchronous. In order to explore the hypothesis that subjects expect sequences of stimuli on the basis of the previous trial, we verify to which amount the subjects benefit from perceiving an asynchrony on the trial $t-1$ and improve their rate of asynchrony detection as a consequence. Furthermore, we examine evoked potentials related to each asynchrony. The literature has repeatedly shown that physiological responses to visual stimuli are decreased in patients relative to controls at various delays after the stimuli presentation,²⁴⁻²⁷ especially when the task involves selective attention.²⁸ Importantly, event-related potentials (ERP's) amplitude reductions are largely independent of medication.^{29,30} We thus expected to replicate these effects in the present study, in agreement with the patient impairments at detecting supra-threshold asynchronies.^{7,9-14} Our results also suggest that patients may process the shortest asynchronies as unexpected events, ie, prediction errors, because sequences of events are not properly predicted but nonetheless processed.^{11,12,18,31} If this hypothesis is true it should lead to abnormally large physiological reactions at short asynchronies. Furthermore, if these impairments contribute to thought disorganization in patients, they should be correlated with clinical disorganization.

To the best of our knowledge, we are the first to provide EEG results associated with unimodal asynchrony detection. Investigations have mainly been conducted with multisensory information.^{32,33} In the absence of prior results on patients and in unimodal modality, we performed a first exploratory ERP analysis in Statistical

Parametric Mapping (statistical parametric mapping [SPM]; see [supplementary material](#)), which allowed us to infer relevant within-group modulations of signals.³⁴ We then confirmed the relevance of these first findings with amplitude and root mean squares of evoked potentials³⁵ in between-groups analyses. Finally, we measured alpha desynchronization following asynchronous vs simultaneous responses. Alpha desynchronization is associated with selective attention³⁶ and should occur when participants are preparing for the next event.³⁷ Larger alpha desynchronization following, eg, an asynchronous response would indicate that the preparation is related to the perception of an asynchrony, rather than being nonspecific.

Methods

Subjects

Thirty-two patients with schizophrenia were recruited in the Psychiatry Department of the University Hospital of Strasbourg and 27 controls were recruited through advertisement (posters and announcement on the University Hospital internal website). Among these participants, EEG was recorded in 17 patients and 15 controls (see details in [supplementary material](#)).

The project was approved by the local ethics committee (CPP IV Est), and all subjects gave their informed written consent, in accordance with the recommendations of the Helsinki Declaration ([table 1](#)).

Experimental Task and Procedure

On each trial, a fixation point was first shown in the middle of the screen and was immediately followed by the progressive display of 2 gray rectangles (details on stimuli can be found in [supplementary material](#)). The 2 rectangles appeared simultaneously (SOA = 0 ms) or asynchronously, with 4 levels of Stimuli Onset Asynchrony (SOA), 24, 48, 72, or 96 ms, and remained on the screen until the subject's response. Participants had 2 seconds to answer after the second square, and usually answered in less than 1 second. Participants responded by pressing the left "f" key on the keyboard if they judged the rectangles to be displayed simultaneously, and the right "j" key if they judged the rectangles to be displayed asynchronously, like in preceding studies.^{11,12} There was an additional time interval of 800 to 1000 ms until the next sequence of squares.

Target order and SOA were all tested the same number of times in random order. Subjects had been tested first with the Temporal Order Judgment (TOJ),⁴⁰ but EEG was recorded only during the simultaneity/asynchrony discrimination task that followed, and we report this data here. In order to analyze EEG data as a function of the SOAs, we increased the number of trials in the simultaneity/asynchrony discrimination task relative to what is usually done behaviorally (3×180 trials, ie, 3×36 trials per asynchrony).

Table 1. Demographic and Clinical Data of the Participants, Including PANSS Scores³⁸

	All Patients <i>N</i> = 32 (With EEG Results <i>N</i> = 17)	All Controls <i>N</i> = 27 (With EEG Results <i>N</i> = 15)
Gender (M/F)	21/11 (11/6)	17/8 (11/4)
Age (mean ± SD)	37.1 ± 9 (38.5 ± 8.8)	35.3 ± 10.5 <i>F</i> < 1 (36.4 ± 9.5 <i>F</i> < 1)
Years of education (mean ± SD)	12.9 ± 2.5 (12.9 ± 2.9)	13.3 ± 2.3 <i>F</i> < 1 (13.7 ± 2.5 <i>F</i> < 1)
Medication (typical/atypical/no medication)	7/21/3 (4/12/1)	—
Dose of chlorpromazine equivalents	232 mg/day (205 mg/day)	—
Antiparkinsonian treatment (tropatepine/no medication)	3/29 (2/15)	—
Mean Disease duration	12.9 ± 7.7 (14.5 ± 8.5)	—
Outpatients/Inpatients	32/0	—
PANSS positive symptoms (mean ± SD)	16.7 ± 5.7 (14.9 ± 5.1)	—
PANSS negative symptoms (mean ± SD)	19.9 ± 7.1 (18.5 ± 6.3)	—
PANSS general symptoms (mean ± SD)	35.9 ± 11 (32.1 ± 9.1)	—
PANSS total (mean ± SD)	72.6 ± 20.7 (65.6 ± 17.1)	—
PANSS-positive (5 factors model): Items P1, P3, P5, G9 (mean ± SD)	11.1 ± 3.5 (10.3 ± 3.7)	—
PANSS-negative (5 factors model): Items N1, N2, N3, N4, N5, N6, G7 (mean ± SD)	19.4 ± 7.5 (18.1 ± 6.2)	—
PANSS-disorganized (5 factors model): Items P2, N5, G11 (mean ± SD)	8 ± 3.1 (6.8 ± 2.5)	—
PANSS-excited (5 factors model): Items P4, P7, G8, G14 (mean ± SD)	6.4 ± 3.1 (5.3 ± 1.9)	—
PANSS-depressed (5 factors model): Items G2, G3, G6 (mean ± SD)	7 ± 2.8 (7.1 ± 2.8)	—

Note: PANSS, positive and negative syndrome scale. The 5-factors model was used with the PANSS.³⁹

Details on equipment and EEG preprocessing can be found in [supplementary material](#).

EEG Processing

After preprocessing, data were first segmented into 3 blocks of same size, in order to match the behavioral analysis. Then, we considered blocks 2 and 3 together, because (1) the behavioral analysis showed a stabilization of performance in the 2nd and 3rd block of trials (see the results in [supplementary materials](#)) and (2) we considered that performance was disturbed by the TOJ task that preceded. The 2 tasks are indeed based on the use of exactly the same stimuli but require different types of responses. Subjects had to press to the side of the second stimulus in the TOJ task, whereas in the simultaneity/asynchrony discrimination task, they had to press on different keys in case of a simultaneity vs an asynchrony. Such a procedure may have induced task-switching costs. For these reasons, we discarded the 180 first trials from the analysis in the EEG analysis, yielding a total of 72 trials per SOA. This procedure is similar to the one used in Capa et al.⁴⁰ ERPs were averaged separately for each SOA (0, 24, 48, 72, or 96 ms).

Data was first evaluated with SPM12.⁴¹ This initial SPM analysis allowed us to extract channels or spatial clusters of channels (SPM-clusters) at specific latencies with maximal significant differences between conditions pairs (2 SOAs) within each group ([supplementary figure S3](#)). This data was used to select channels of interest and verify intervals of interest.

ERP Analyses. For each spatial cluster in each group, we averaged the amplitude of ERP signals across channels within the cluster at the time point with maximum statistical differences in the SPM analysis. Equivalent clustering was performed in both groups: if there was a significant effect at least in one group in the SPM analysis, then the amplitude of the evoked potentials was extracted in the same channels at the same latencies in the other group.

Root Mean Square Analysis. We analyzed the EEG results using a second method, ie, by calculating the Root Mean Square (RMS) power of the signal,^{35,42} to confirm ERP analyses (Details and results can be found in [supplementary material](#)).

Event-Related Spectral Power. Event-Related Spectral Power (ERSP, 3–50 Hz) was analyzed on the inter-trial interval, for asynchronous stimuli with asynchronous responses. We explored how ERSP changed as a function of “asynchronous” or “simultaneous” responses on trial *t*–1. Details can be found in the [supplementary material](#).

Results

Behavioral Results

Two patients responded “simultaneous” in more than 90% of the trials, whereas one control responded “asynchronous” in more than 90% of the trials. These 3 participants were excluded from the behavioral results. In all the behavioral analyses, we added the factor EEG

recording (the fact that the participant underwent EEG recording or not) as a between-group factor to verify that sub-groups showed similar behavior. Except otherwise stated, this factor did not interact with the results.

The threshold results can be found in [supplementary material](#). We measured how performance on trial t is influenced by the response on trial $t-1$, which is a proxy for measuring the impact of expectations ([figure 1](#)). If a participant had given an “asynchronous” response on trial $t-1$, it was more likely that an asynchrony would be expected and detected on trial t . The analysis showed a significant interaction between the group and the impact of the response on trial $t-1$ ($F[1, 52] = 5, P < .05$, partial $\eta^2 = 0.09$). The HSD Tukey post-hoc analysis showed that the rate of asynchronous responses was equivalent in both groups when the response on trial $t-1$ had been asynchronous (73.4% in patients vs 78.3% in controls, *n.s.*). The rate of asynchronous responses decreased in both groups when the response had been simultaneous on trial $t-1$, but more so in patients with schizophrenia, resulting in a lower rate of asynchronous responses on trial t in patients than in controls (58% in patients vs 70% in controls, $P < .05$) (see [supplementary material](#) for results discarding an explanation in terms of response bias).

EEG Analysis

We report the data in all patients and controls. The results were still significant without the 3 participants which had been discarded from the behavioral analysis.

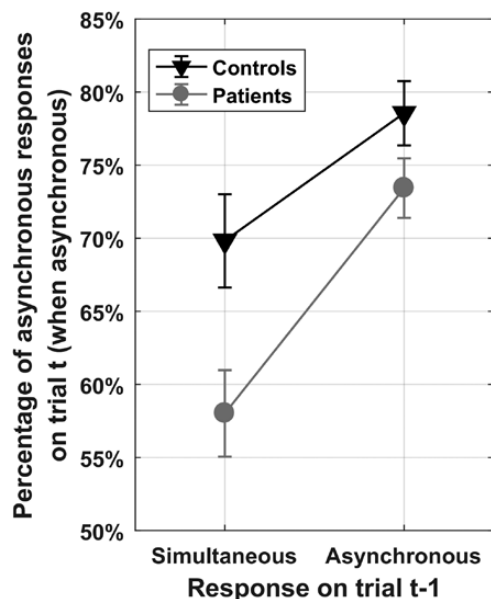


Fig. 1. Illustration of the percentage of “asynchronous” responses in trials with asynchronous stimuli, as a function of the response given by the participant on trial $t-1$ (“simultaneous” vs “asynchronous”), in controls (black triangles) and patients with schizophrenia (gray circles).

Evoked Potentials

The initial ERP analysis with SPM had shown differences for short asynchronies (relative to simultaneous stimuli) at left central (C5, latency 210 ms) and frontal (F5, latency 182 ms) electrodes in early signals (only in patients; [supplementary figure S3](#)), and those were selected for between-group analyses. In addition, the SPM analysis had shown within-group differences between short (24 ms) and long (72 and 96 ms) asynchronies in late signals at parietal electrodes. We selected the electrode clusters that showed differences for both 72 and 96 ms asynchronies at the same latency (P2 CP2 Pz, latency 478 ms).

Signals recorded at one given location and latency were considered as independent within-group variables in the ANOVA, whereas group was a between-group variable. The analysis showed a significant interaction between the electrodes clusters, the SOAs, and the groups ($F[8, 240] = 2.2, P < .05$, partial $\eta^2 = 0.07$). We conducted an HSD Tukey post-hoc analysis to localize the differences. Despite the large number of variables, the post-hoc analysis showed that the amplitude of the signal was significantly more negative for the SOA 24 compared to 0 ms at the location of the F5 electrode at a latency of 182 ms ($0.04 \mu\text{V}$ for SOA 0 ms vs $-1.68 \mu\text{V}$ for SOA 24 ms, $P < .001$), but only in patients ([figure 2D](#)). There was no significant difference for the corresponding signals in controls ($-1.08 \mu\text{V}$ vs $-1.37 \mu\text{V}$, $P > .99$). In addition, the amplitude of later signals at 478 ms at the P2, CP2, and Pz electrodes SPM-cluster were lower in amplitudes for patients relative to controls for the SOA 96 ms ($1.37 \mu\text{V}$ in patients vs $3.7 \mu\text{V}$ in controls, $P < .001$, [figures 2 E and 2F](#), respectively).

We used source localization methods which showed that the source of the early ERP signal observed in the SPM analysis in patients is in the right inferior frontal sulcus (details in the [supplementary material](#)). Besides, we confirmed the analysis performed on ERP signals with an RMS power analysis ([supplementary figure S5](#)).

Event-Related Spectral Power

Power in the 5 to 9 Hz (high theta low alpha) range differed between groups and conditions (response simultaneous vs synchronous on trial $t-1$) in the -550 to 0 ms interval at electrodes F4 and F6. The ANOVA showed a significant interaction between group and conditions ($F[1, 27] = 6.2, P < .05$, partial $\eta^2 = 0.19$). The HSD Tukey post-hoc test showed that there was less power after an asynchronous than after a simultaneous response on trial $t-1$ in controls ($P < .001$ for F4, $P < .001$ for F6). In patients in contrast there was less power after a simultaneous than after an asynchronous response on trial $t-1$, at F4 ($P < .05$) ([supplementary figure S6](#)).

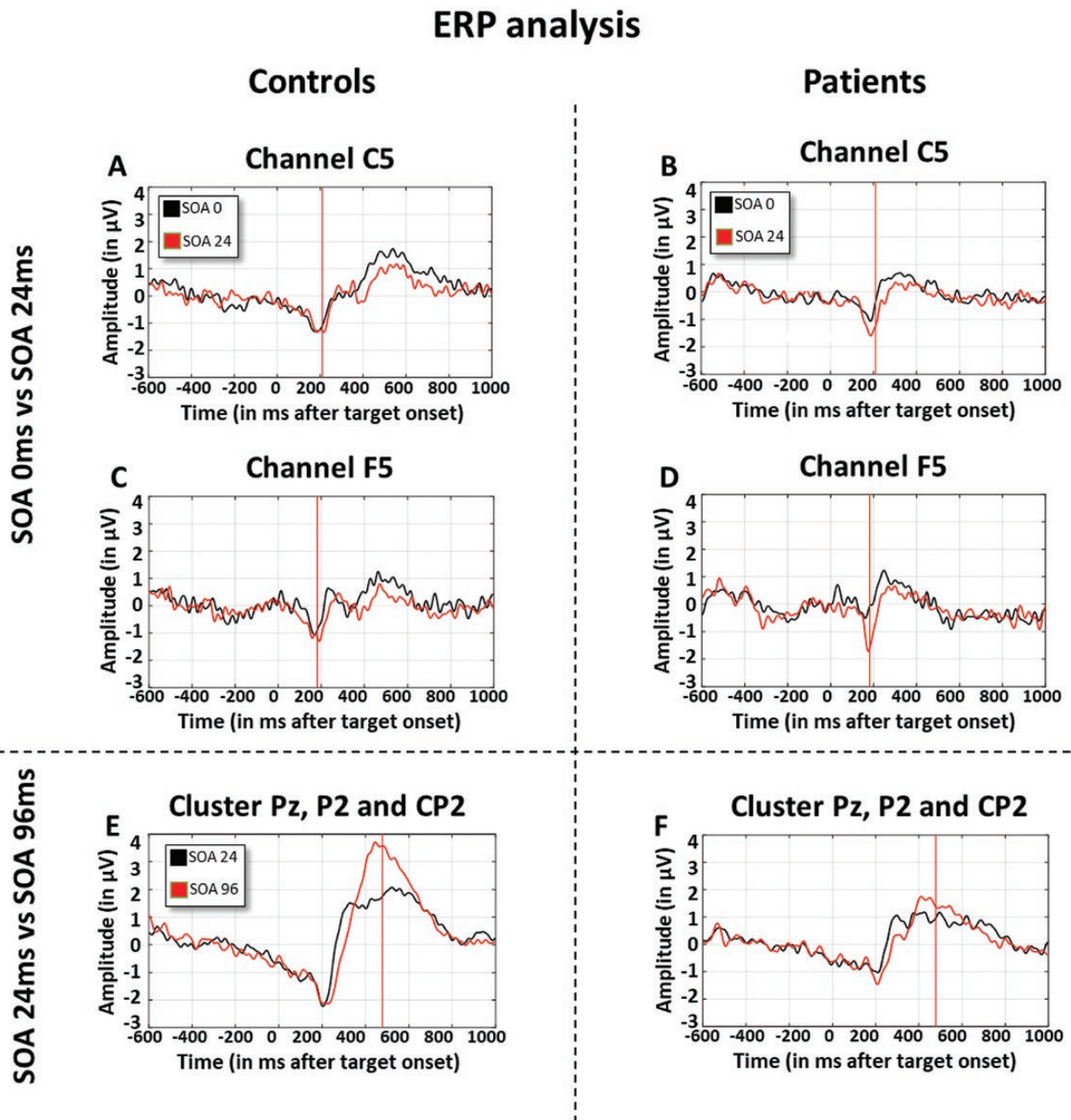


Fig. 2. Evoked related potentials for SOA 0 ms (in black) and 24 ms (in red) are represented in panels A and B for the electrode C5, and C and D for the electrode F5, for healthy controls on left panels (A and C) and patients with schizophrenia on right panels (B and D). Evoked Related Potentials for SOA 24 ms (in black) and 96 ms (in red) at the Pz, P2, and CP2 electrodes cluster are represented in panels E and F for healthy controls and patients with schizophrenia, respectively. Results for SOA 24 vs 72 ms can be found in [supplementary material, supplementary figure S4](#).

Correlations

Behavioral results showed that a simultaneous response on trial $t-1$ decreased “asynchronous” responses on trial t , and more so in patients than in controls when stimuli were asynchronous on trial t . We calculated the difference in the percentage of “asynchronous” responses on asynchronous trials after a simultaneous vs asynchronous response on trial $t-1$. This difference represents a proxy for the impact of the expectation for simultaneous

or asynchronous stimuli and is correlated with the disorganization factor of the positive and negative syndrome scale (PANSS) ($N = 29$, $r = .48$, $P < .01$). The higher the disorganization, the larger the difference in performance on asynchronous trials after a simultaneous vs asynchronous response. This correlation with disorganization symptoms was also found in a subset of 18 patients who were evaluated with the SAPS and SANS scale (details can be found in [supplementary material](#)).

Correlations were also found between behavioral and EEG signals in each group. In the patients' group, correlations were mainly found with EEG signals recorded when stimuli were simultaneous. In controls, it is mainly the RMS power of signals recorded in the parietal electrodes group at the late interval (400–600 ms) that are positively correlated with performance. Details can be found in [supplementary material](#).

Discussion

The results confirm previous data showing that patients have difficulties to discriminate asynchronous from simultaneous stimuli.^{7,9–12} The new result is the reduction of EEG signals amplitude at parietal electrodes for 400–600 ms latencies, as classically observed in visual tasks in patient suffering from schizophrenia.^{24–30} The correlation between these signals and behavior in controls ([supplementary material](#)) supports the idea that late signals may represent a neural correlate of the asynchrony discrimination impairments in patients. The fact that this decrease in amplitude in patients was most evident at parietal electrodes is consistent with the literature showing a role for the parietal cortex in temporal order judgments.^{43–46}

Albeit patients have difficulty to report asynchronies, they also display abnormal physiological reactions for short asynchronies.¹⁸ EEG signals amplitude for 24 ms asynchronies were larger than for perfect simultaneity in patients, contrary to controls ([figure 2](#)). These signals may represent a frontal N2 (180ms), or mismatch negativity, which conveys a conflict signal.^{47–50} The generator of this N2 component appears to be localized in the right inferior frontal sulcus (source localization in [supplementary material](#)). This structure has been suggested to be involved in the mismatch negativity (MMN) for deviant tones,⁵¹ action prediction errors⁵² and more generally temporal updating.^{53–55} The literature thus supports the hypothesis that the N2 component observed in the present study may reflect the coding of a conflict signal in response to a short asynchrony. Such a large signal in patients may appear surprising at first sight. When having to detect a rare signal, patients with schizophrenia are impaired and show decreased rather than increased MMN.^{56–58} This may appear to contradict our findings, which show an increase and not a decrease in the N2 component. It is all the more surprising that prediction impairments in patients have been suggested to impair preparation to regular events and thus reduce the mismatch effect in case of oddballs.^{56–58} Prediction impairments are also apparent in the present results. Patients appear to be more sensitive than controls to the influence of a simultaneous response on trial $t-1$, as if prepared for simultaneous rather than asynchronous stimuli. A preparation for simultaneity is supported by the correlation between EEG signals and performance at 0 ms in patients, whereas correlations are observed with performance on asynchronous trials

in controls ([supplementary material](#)). Moreover, EEG results show a larger desynchronization of theta-alpha activity in anticipation of trial t after asynchronous than after simultaneous responses in controls. This is not the case in patients, who rather show the opposite pattern of results.

In all preparation to asynchrony seems altered in patients. Why this leads to an enlarged N2 component may be due to the fact that there is a mismatch inherent to short asynchronies, unlike oddballs in MMN tasks. The automatic processing of short asynchronies conflicts with the difficulty to consciously report such asynchronies. Previous studies have indeed shown that short asynchronies are automatically processed, even when they are not consciously reported.^{8,11,12} In the present study, the EEG results at 24 ms in patients confirm that short asynchronies are processed, since EEG signals differ between 0 and 24 ms. Such a mismatch is possible because different networks and mechanisms are at work for different aspects of timing.⁵⁹ As suggested by our own work on trial-to-trial effects,^{16,17} prediction at the millisecond level is aimed at following information over time by automatically anticipating events, not at detecting asynchronies consciously. Conscious detection of asynchronies relies on a frontoparietal network⁶⁰ which differs from the cerebellum-related network underlying predictions at the level of milliseconds.⁶¹ One first explanation might be that controls, unlike patients, can use millisecond-level asynchrony predictions to help the detection of asynchronies, thus reducing the mismatch between signals conveyed by the different networks. However, behavioral data shows that patients with schizophrenia can use the perception of asynchronies to improve their detection. An alternative is sensory suppression,⁶² which may help to ignore the subconscious signal of asynchrony. The correspondence between sensory prediction (of asynchronies) and real sensory feedback (the automatic processing of short asynchronies) is known to lead to an attenuation of the sensory feedback.⁶² Such an attenuation would help to lower the conflict between the subconscious processing of asynchrony and the conscious detection of simultaneity. It may be useful in everyday life to ignore short asynchronies, because they may disrupt the conscious train of thought. Attenuation of asynchrony signals may contribute to smooth the succession of transient events into a continuous flow. In patients with schizophrenia, however, attenuation of sensory signals has been shown to be reduced.⁶³ We hypothesize that the N2 signal in patients is explained by a lack of attenuation of the automatic processing of asynchronies.

In summary, patients display both an inability to ignore small asynchronies, whatever its mechanisms, and enlarged temporal windows, as indicated by the difficulty to report asynchronies. As suggested in the literature, the latter may disrupt the sense of self, by impairing

the ability to integrate information over time and to make meaning (like eg, a melody).⁶⁴ Multisensory integration may be especially critical for the sense of bodily self.⁶⁵ We propose that there is a balance between the need to integrate information across time in order to make meaning (the melody) and the need to follow information over time with a high enough time resolution. Prediction at the millisecond level and attenuation of short asynchronies may contribute to preserve integration over time and the sense of time continuity, which is warranted for us to feel ourselves as continuous beings in time.^{18,66} In patients with schizophrenia, in contrast, not-attenuated short asynchronies may interfere with the passage of time, thus contributing to the disorganization of the patients' conscious experience. It might be important to notice that the results in the present study were observed despite the fact that patients first ran a temporal order judgment task. In this task, they had to answer to the side of the last stimulus in a sequence, which we had hoped would encourage them to prepare to process sequences of stimuli. It might be the case that this task was simply too short and that improving asynchrony detection can help to improve the balance between asynchrony detection and integration. Another avenue might be cerebellum stimulation, given its role in sequence planning at the millisecond level (23).

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* Open online.

Funding

The work was supported by the French Ministry of Health (PHRCI 2010-HUS n°4706), the Foundation for Research in Psychiatry and Mental Health (to A.G.), the FondaMental Foundation (www.fondation-fondamental.org, to C.Z.D. and E.M.C.), the APICIL Foundation (to C.Z.D.), the FRM (Fondation pour la Recherche Médicale, DPP20151033957 FRM R16029MM, to E.M.C.), and the FHU (Fédération Hospitalo-Universitaire NeurogenYcs) (to E.M.C.).

Acknowledgments

We thank the French National Institute for Health and Medical Research (INSERM) and the Centre Hospitalier Régional Universitaire of Strasbourg for their logistical support, and Julie Bruckman, Marion Roger, Bichthuy Pham, Bernadette Huth, Cindy Mathis, Christine Zeissloff, Manuel Lutz, Jean-Philippe Lang, Emmanuel Haffen, Marc Hoonakker, and Maxime Curziatti for their help during the testing phases, Dorine Blaison for the initial EEG analysis, and François Foerster for his careful reading of the manuscript. The authors have no

biomedical financial interest and no potential conflict of interest to disclose.

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