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Electrophysiological correlates of visual backward masking in patients with first episode psychosis

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Abstract

Visual backward masking is strongly impaired in patients with schizophrenia. Masking deficits have been proposed as potential endophenotypes of schizophrenia. Masking performance deficits manifest as strongly reduced amplitudes in the electroencephalogram (EEG). In order to fulfill the criteria of an endophenotype, masking deficits should not vary substantially across time and should be present at the first psychotic event. To verify whether these conditions are met for visual backward masking, we tested patients with first episode psychosis (*n*=21) in a longitudinal study. Patients were tested with visual backward masking and EEG three times every six months over a period of one year. We found that the EEG amplitudes of patients with first episode psychosis were higher as compared to those of patients with schizophrenia but lower as compared to those of unaffected controls. More interestingly, we found that the EEG amplitudes of patients with first episode psychosis remained stable over the course of one year. Since chronic schizophrenia patients have strongly reduced amplitudes, we speculate that the neural correlates of masking deficits (EEG amplitudes) continue to decrease as the disease progresses.

Abbreviations:

CogDis: cognitive disorganization, **CTRL**: healthy control participants, **GFP**: global field power, **MMN**: mismatch negativity, **pFEP**: patients with first episode psychosis, **pSZ**: patients with schizophrenia, **SNP**: single-nucleotide polymorphism, **SOA**: stimulus onset asynchrony, **VBM**: visual backward masking, **VD**: vernier duration, **VEP**: visual evoked potential,

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Supplementary material: one pdf file containing 4 tables and 4 figures

1. Introduction

Schizophrenia is strongly influenced by genetic and environmental factors. Even though heritability is about 50%, genome-wide association studies have not found individual single-nucleotide polymorphisms (SNPs) that are strongly associated with the disease. For this reason, endophenotypes - which test for abnormal factors that lie between the genetic underpinnings and the clinical phenotype - are crucial (Gottesman and Gould, 2003). Visual masking performance is deteriorated in patients as compared to controls (Green et al., 2011; Herzog and Brand, 2015; Kéri et al., 2000, 2001; Rund, 1993; Saccuzzo and Braff, 1981, 1986) and is thought to be an endophenotype of psychosis (Chkonia et al., 2010; Green and Nuechterlein, 1999; Nuechterlein et al., 1994). In the last decade, we established a particularly sensitive visual backward masking (VBM) technique, the Shine-Through paradigm, which is both temporally and spatially challenging. In the Shine-Through paradigm, a vernier (two vertical bars separated by a horizontal offset) is presented, followed by a grating mask composed of 25 aligned verniers (Fig.1A). The lower bar of the vernier is offset either to the left or to the right. Participants are asked to indicate the offset direction. Performance is only slightly deteriorated in patients with schizophrenia (pSZ) when the vernier is presented alone, i.e., without the mask (Roinishvili et al., 2008; Schütze et al., 2007). However, performance strongly deteriorates when the vernier is followed by the mask. Performance is measured as the stimulus onset asynchrony (SOA), which is the time between the onset of the vernier and the mask. The SOAs in the pSZ are five times longer as compared to those of unaffected controls (Herzog et al., 2004). The Shine-Through paradigm meets the main criteria of an endophenotype (Gottesman and Gould, 2003). First, the first-order relatives of the patients need longer SOAs than controls but shorter SOAs than patients (Chkonia et al., 2010). Second, masking deficits do not change over the course of one year in chronic patients, indicating that the Shine-Through paradigm is a trait rather than a state marker (Chkonia et al., 2010). Third, patients with functional psychosis, such as schizoaffective patients and bipolar patients, show masking deficits but depressive patients and abstinent alcoholics do not (Chkonia et al., 2012). Fourth, adolescents with psychosis show masking deficits, suggesting that deficits are already present at early stages of the disease (Holzer et al., 2009). Fifth, students scoring high in cognitive disorganization (CogDis), a schizotypal personality trait, are impaired in VBM as compared to those with low CogDis scores, but to a much smaller degree than patients (Cappe et al., 2012). Sixth, we were able to identify a SNP related to the cholinergic nicotinic receptor (α7), which was

correlated with masking performance in patients (Bakanidze et al., 2013). Finally, we could identify neural correlates of masking deficits in schizophrenia: patients have reduced EEG amplitudes in the N1 component, 200 ms after stimulus onset (Plomp et al., 2013) and the same holds true for participants scoring high in CogDis as compared to those with low CogDis scores (Favrod et al., 2017).

As mentioned above, adolescents with psychosis show masking deficits indicating that deficits are present even before the disease fully develops (Holzer et al., 2009). On average, masking deficits are much weaker in adolescents with psychosis than in adult patients. One reason for the weaker deficits is that not all adolescents will develop schizophrenia during their lifetime. Here, we hypothesized that the patients with a first episode of psychosis (pFEP) show similar patterns of deficits as adolescents. We determined performance and neural correlates with the VBM task in pFEP in a longitudinal study. Our main questions were: first, what is the magnitude of masking deficits at the onset of the psychotic breakdown? Second, are the deficits expressed in the EEG correlates? Third, does performance change over the course of one year?

2. Methods and Materials

2.1. Participants

All participants had normal or corrected-to-normal vision with a visual acuity of ≥ 0.8 determined for both eyes with the Freiburg Visual Acuity test (FrAct; Bach, 1996). All participants signed informed consent and were informed that they could quit the experiments at any time. All procedures complied with the Declaration of Helsinki and were approved by the local ethics committee.

2.2. Patients with First Episode Psychosis (pFEP)

Twenty-one pFEP participated in a first session. Out of these 21 patients, 16 participated six months later in a second session. Finally, 11 out of the 16 participants were tested a third time, again six months later. We invited all patients to participate in all three sessions but 5 patients opted to leave the study after the first session and 5 additional patients left the study after the second session.

Patients were recruited either from the Tbilisi Mental Health Hospital or from the Acute Psychiatric Departments of Multiprofile Clinics. General exclusion criteria were drug or alcohol abuse and neurological or other somatic illnesses influencing subjects' mental state. Patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders IV/V by means of an interview based on the Structured Clinical Interview, information of the staff, and the study of the records. Psychopathology of patients was assessed by an experienced psychiatrist (EC) by the Scales for the assessment of negative and positive symptoms (SANS, Andreasen 1984a; SAPS, Andreasen 1984b). At the first contact, patients were diagnosed either as brief psychotic disorder (DSM-IV 298.8) or as schizophreniform disorder (DSM-IV 295.40). At the second contact, patients were diagnosed with schizophrenia except one patient who had a first bipolar I episode. This patient's data is similar to the data of the other patients. In addition, we have previously shown that masking deficits are similar in schizophrenia and bipolar patients (Chkonia et al., 2012). Results that include this patient are almost identical to the results when the patient is omitted (supplementary material Fig.S1).

We prefer to use the term first episode psychosis rather than first episode schizophrenia, because the former term is more heterogeneous, including all types of psychotic disorders. Subtypes of diagnosis are shown in Tab.S1 of the supplementary material for all three sessions. Group characteristics are depicted in Tab.1. All patients were receiving neuroleptic medication before our experiment.

Table 1 | *Demographics for the three groups of participants: controls (CTRL), patients with first episode psychosis (pFEP) for the three EEG sessions and patients with schizophrenia (pSZ). Abbreviations: F=female, M=male, SD=standard deviation, SANS= scales for the assessment of negative symptoms, SAPS= scales for the assessment of positive symptoms, CPZ=chlorpromazine, L=left, R=right, * data collected during the first session, ** during the second session, *** during the third session.*

	CTRL	**pFEP who participated in the 1st session**	**pFEP who participated in the 1st and 2nd sessions**	**pFEP who participated in all three sessions**	**pSZ**
n	20	21	16	11	22
Gender (F/M)	8/12	12/9	10/6	6/5	7/15
Age (years) ± SD	35± 10	30 ± 9*	29± 9*	29± 11*	33± 8

Education (years) ± SD	15 ± 3	13± 2	13 ± 2*	13 ± 2*	13± 2
Illness Duration (months) ± SD		8± 4*	8± 4*	9 ± 4*	98± 76
SANS ± SD		7 ± 5*	8 ± 5*, 9 ± 6**	9 ± 6*, 9 ± 7**, 9 ± 7***	11 ± 6
SAPS ± SD		6 ± 3*	7 ± 3*, 6 ± 3**	7 ± 3*, 6 ± 3**, 7 ± 2***	9 ± 3
CPZ equivalent ± SD		429 ± 334*	452 ± 339*, 258 ± 359**	452 ± 376*, 220 ± 262**, 131 ± 185***	618 ± 408
Handedness (L/R)	2/18	1/20	1/15	0/11	1/21
Visual Acuity ± SD	1.6 ± 0.5	1.4 ± 0.4*	1.5 ± 0.3*	1.5 ± 0.4*	1.4 ± 0.3

2.3. Stimuli and Apparatus

Stimuli were displayed on a Siemens Fujitsu P796-1 monitor with a refresh rate of 100 Hz. The screen resolution was 1024×768 pixels. Patients sat 3.5 m away from the monitor in a weakly illuminated room. The stimuli were white, with a luminance of 100 cd/m^2 on a black background (<1 cd/m^2).

We presented vernier stimuli consisting of two vertical bars separated by a vertical gap of 1' (arc min). The lower bar was slightly offset either to the left or to the right compared to the upper one. The horizontal vernier offset was 1.2'. The mask consisted of either five or twenty-five aligned vernier stimuli. The horizontal spacing between mask elements was 3.33'.

Observers responded by pushing one of the two hand-held buttons. Participants were instructed to be as accurate as possible. Two-way rm-ANOVAs with Greenhouse-Geisser corrections (when necessary) were performed.

2.4. Adaptive procedure

We determined the vernier duration (VD) necessary to reach 75% of correct responses. For each observer, we found the VD, for which the threshold of vernier offset discrimination was below 0.6'. Afterwards, we used the individual VD with a fixed vernier offset of 1.2' and determined the SOA threshold for each participant through an adaptive strategy (Parametric Estimation by Sequential Testing; Taylor, 1967) in order to reach 75% of correct responses. Hence, we did not

determine performance by an examination of a set of SOAs separately but directly determined the masking effect via the psychophysical threshold. The protocol was similar to previous studies (Cappe et al., 2012; Herzog et al., 2004; Shaqiri et al., 2015). We used two types of masks: a 5- and a 25-element grating mask (Fig.1A).

2.5. EEG experiment design

As in previous EEG studies (Favrod et al., 2017; Plomp et al., 2013), we tested four conditions: Vernier Only, Long SOA, Short SOA, and Mask Only (Fig.2A). In the Vernier Only condition, the vernier was presented alone for 30 ms. In the Short and Long SOA conditions, the vernier was presented for 30 ms followed by the 25-element mask for 300 ms with an SOA of either 30 or 150 ms, respectively. The 30 ms SOA is the mean performance level of controls and the 150 ms SOA is that of pSZ. In the Mask Only condition, the mask was presented for 300 ms; there was no vernier.

In each session, 8 blocks of 80 trials (20 trials / condition) were presented. The condition order was randomized within a block. In total, there were 160 trials per condition.

2.6. EEG recordings and pre-processing

We used the EEG BioSemi Active Two system with 64 Ag-AgCl sintered active electrodes distributed across the scalp according to the 10/20 layout system. The sampling frequency was 2048 Hz. EEG data were pre-processed offline in Matlab (R2012a, The MathWorks Inc., Natick, MA) with EEGLAB (Delorme and Makeig, 2004) and using an in-house, automated pre-processing pipeline (The APP; da Cruz et al., 2018.). The signal was down-sampled to 512 Hz, band-passed filtered from 1 to 40 Hz and the 50 Hz line noise was removed using CleanLine (Mullen, 2012). The signal was re-referenced to the biweight estimate of the mean of all electrode-channels (Hoaglin et al., 1983, 1985). Unstable and noisy electrodes were removed and interpolated with a 3D spline function. The proportion of interpolated electrodes was about one channel per EEG recording. EEG epochs were extracted from 100 ms before the stimulus onset (baseline) to 400 ms after stimulus onset. Noisy trials (with artifacts such as eye blinks) were also removed. The rejected trials constituted about 4% of each EEG recording (Tab.S2 in the supplementary material). We did not apply any exclusion criterion based on reaction time. Hit and

miss trials were averaged for each condition and each participant. The individual averages were baseline corrected.

2.7. EEG analysis

The individual visual evoked potentials (VEP) were analyzed in MATLAB (R2010b, The MathWorks Inc., Natick, MA). Signal from one occipital electrode (Oz) was extracted in order to visualize the positive and negative components of the VEPs (supplementary material Fig.S2). The Global Field Power (GFP) is computed as the standard deviation across all electrodes at each time point for each participant and each condition separately (Lehmann and Skrandies, 1980). GFP is an overall measure of brain activity taking into account all EEG sources. Grand averages of GFPs were computed for each condition, each session and each group of participants.

Statistical analysis for the GFPs was performed using the Statistical Toolbox for Electrical Neuroimaging (STEN) developed by Jean-François Knebel (http://www.unil.ch/line/Sten). We performed between- and within-subject rm-ANOVAs for each timeframe with the factor Group and Condition (between-group design) or Session and Condition (within-group design). For the main effects, we considered intervals that yielded significant effects for more than 10 consecutive time frames (about 20 ms and 13 time frames, about 26 ms for post-hoc) in order to remove short significant time intervals in the baseline or unrealistic effects (too early). This approach has been shown to partially control for multiple comparisons and false positives in EEG analyses (Blair and Karniski, 1993; Knebel et al., 2011; Knebel and Murray, 2012). We performed a Bayesian rm-ANOVA for an interval around 200 ms (190-215 ms, arbitrarily chosen to have all grand average peaks included) using JASP (https://jasp-stats.org/, version 0.8.1.1). We used the averaged GFP during this time window to compute the statistics.

2.8.Controls (CTRL) and Patients with Schizophrenia (pSZ)

We compared data of pFEP with data of pSZ and controls that were previously published in (Plomp et al., 2013). The equipment and testing location of the former and the current study were exactly the same. In the past (i.e., Plomp et al., 2013), data were analyzed semi-automatically (i.e., through visual inspection of the data). Recently, we developed an automatic pre-processing pipeline (the APP, da Cruz et al., 2018). Here, we used the APP to analyze the pFEP data set and re-analyzed

the pSZ and controls dataset of (Plomp et al., 2013). Both dataset are pre-processed exactly the same way, avoiding any subjective bias from the EEG expert.

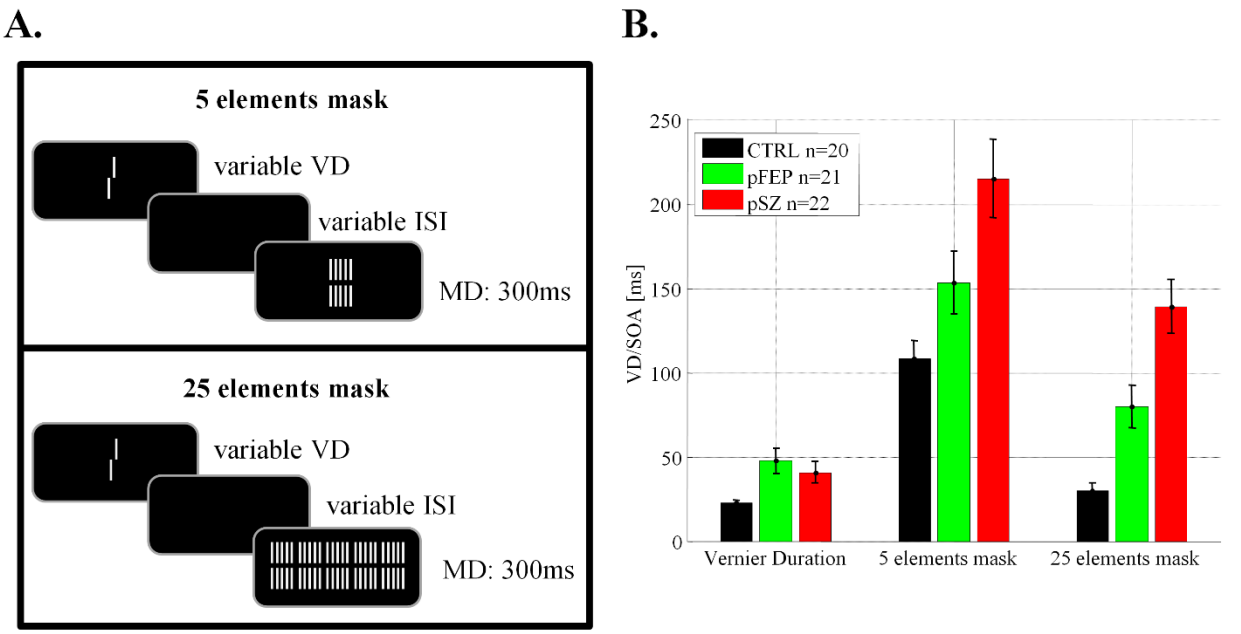
3. Results

3.1. Adaptive procedure

The VD of the controls was significantly lower compared to that of the pFEP (Fig.1B, left). There was no significant difference between the VD of pFEP and pSZ (main effect of Group: $F(2,60)=4.588$, $p=0.014$, $\eta^2=0.133$, post-hoc: CTRL vs pFEP: $t(39)=-2.931$, $p_{tukey}=0.013$, pFEP vs pSZ: $t(41)=0.802$, $p_{tukey}=0.703$ and CTRL vs pSZ: $t(40)=-2.172$, $p_{tukey}=0.084$).

For the masking conditions, the performance of pFEP laid between that of controls and pSZ (significant main effect of Group: $F(2,60)=14.51$, $p<0.001$, $\eta^2=0.326$). Post-hoc tests revealed no significant difference between CTRL and pFEP: $t(80)=-2.343$, $p_{tukey}=0.058$, but significant differences between the performance of pFEP and pSZ: $t(84)=-3.032$, $p_{tukey}=0.010$ and CTRL vs pSZ: $t(82)=-5.363$, $p_{tukey}<0.001$. Masking was stronger with the 5-element as compared to the 25-element mask (significant main effect of Mask: $F(1,60)=100.840$, $p<0.001$, $\eta^2=0.627$). There was no significant Group x Mask interaction: $F(2,60)=0.030$, $p=0.971$, $\eta^2=0.000$ (Fig.1B, right).

Figure 1| *Adaptive procedure:* **A.** *Stimulus display: The vernier duration (VD) was determined for each observer individually. The vernier was then followed by a mask with a variable inter-stimulus interval (ISI). The mask was composed of either 5- or 25-element. The mask duration (MD) was 300ms. Note: SOA=VD+ISI.* **B.** *Behavioral results: vernier duration (VD) and thresholds (SOA) for the two types of mask. Masking performance (SOA threshold) of pFEP is higher as compared to controls (longer SOAs = stronger deficits) but lower as compared to pSZ. VD of pFEP is higher compared to controls. Error bars represent the standard error of the mean. For the VD, a ceiling level was set to 100 ms (5 pFEP had longer duration).*



3.2. EEG experiment

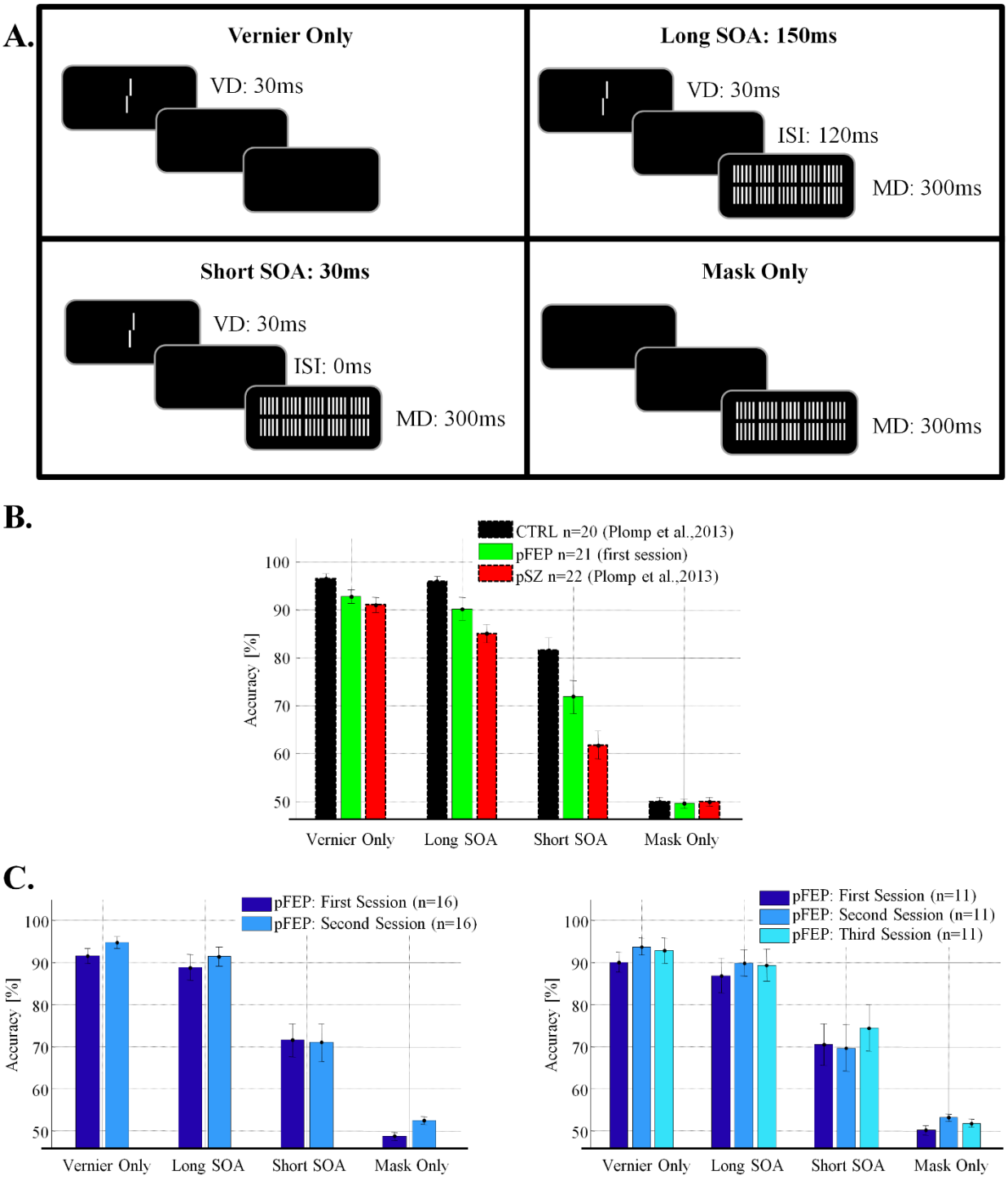
Using the 25-element mask, we first compared the three groups (pSZ, pFEP-1st session and CTRL). Second, we recorded EEG for the pFEP over the course of one year (after 6 months: 2nd session, after 12 months: 3rd session).

The adaptive procedure is very sensitive and allows for the exploration of individual differences. With EEG, we cannot use the adaptive procedure because conditions have to be the same across all observers. For this reasons, we selected the averaged SOA values (30 ms corresponding to the performance of controls and 150 ms for patients) based on previous experiments. The performance of pFEP laid between that of controls and pSZ, especially in the two masking conditions (Long and Short SOAs, Fig.2B). PSZ had the lowest performance. There was a main effect of Group: $F(2,60)=9.884$, $p<0.001$, $\eta^2=0.248$, main effect of Condition: $F(1.729,103.759)=494.508$, $p<0.001$, $\eta^2=0.869$ and interaction Group x Condition: $F(3.459, 103.759)=7.318$, $p<0.001$, $\eta^2=0.026$.

Longitudinally, the performance of pFEP slightly improved for the second session compared to the first session (Fig.2C, left, $n=16$). However, the performance of pFEP did not change over the course of one year when comparing all three sessions (Fig.2C, right, $n=11$). For the sample size of $n=16$: significant main effect of Session: $F(1,15)=4.576$, $p=0.049$, $\eta^2=0.234$ (average statistics in

the supplementary material Tab.S3), significant main effect of Condition: $F(1.529, 22.941)=101.264$, $p<0.001$, $\eta^2=0.871$ and no significant interaction Session x Condition: $F(2.040, 30.597)=1.751$, $p=0.19$, $\eta^2=0.105$. For the sample size of $n=11$: no significant main effect of Session: $F(2,20)=1.517$, $p=0.244$, $\eta^2=0.132$, a significant main effect of Condition: $F(1.433,14.335)=61.946$, $p<0.001$, $\eta^2=0.861$ and no significant interaction Session x Condition: $F(6,60)=1.513$, $p=0.189$, $\eta^2=0.131$.

Figure 2| *EEG experiment:* **A.** *Stimulus display: In the Vernier Only condition, the vernier was presented alone for 30 ms. In the Short and Long SOA conditions, the vernier was followed by a mask with an SOA of either 30 or 150 ms, respectively. In the Mask Only condition, only the mask was presented. VD=vernier duration, ISI=Inter-Stimulus Interval, SOA=Stimulus Onset Asynchrony, MD=mask duration. SOA=VD+ISI.* **B.** *Accuracy for the four conditions (Vernier Only, Long SOA, Short SOA and Mask Only). The performance of pFEP (green, n=21) is lower as compared to controls (black, n=20) but higher as compared to pSZ (red, n=22), in particular for the Long and Short SOA conditions. For the Vernier Only condition, the three groups are at ceiling. For the Mask Only condition, the three groups are at chance level, as expected. Error bars represent the standard error of the mean.* **C.** *Left panel: accuracy across the two sessions for the four conditions and the 16 pFEP. There was a slight improvement between the two sessions. Right panel: accuracy across the three sessions for the four conditions and the 11 pFEP. Performance did not change over the three sessions.*



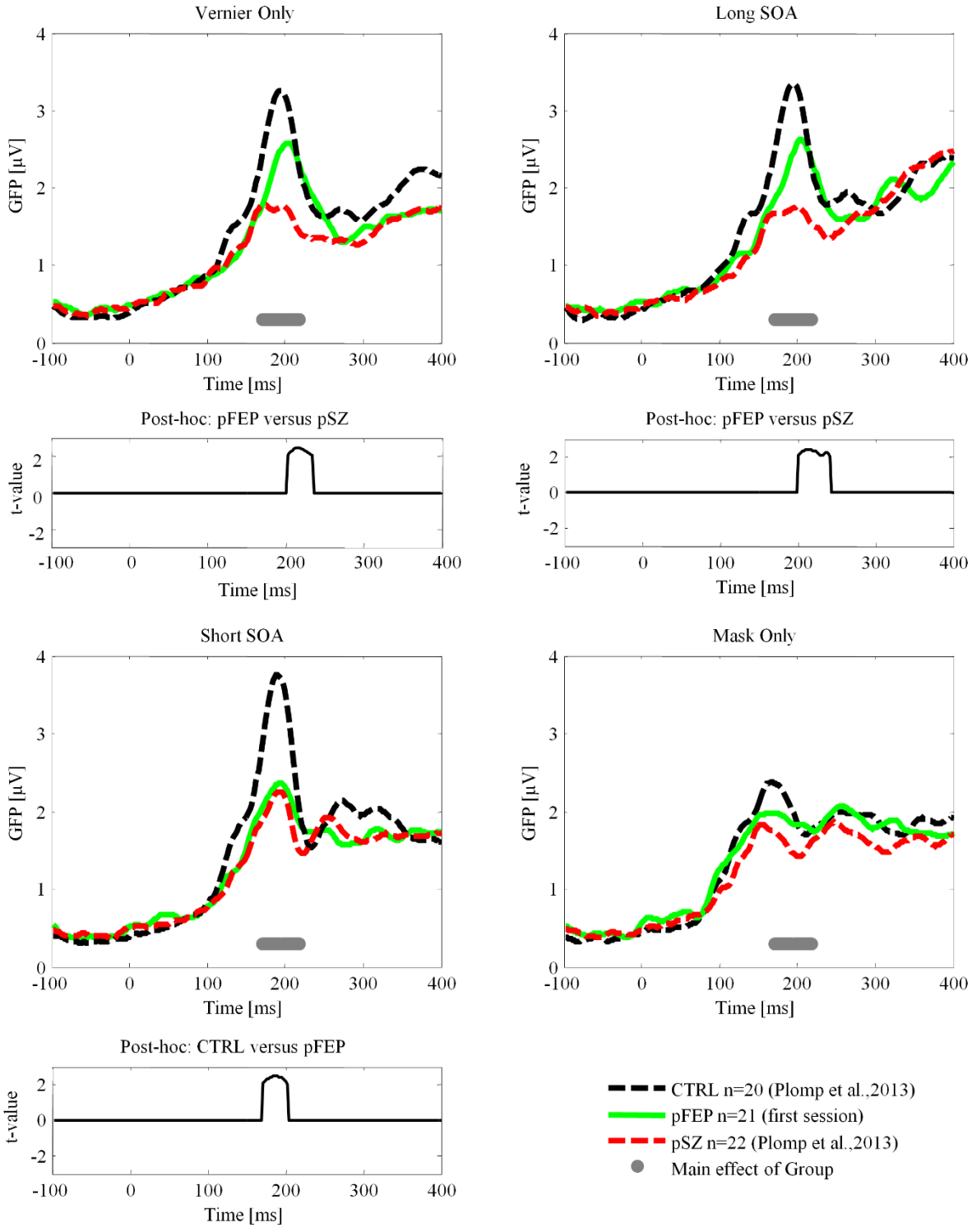
3.2.1. Neural correlates: Group Study

GFP amplitudes of the pFEP were between those of controls and pSZ in the Vernier Only and Mask Only conditions (Fig.3). We found a significant main effect of Group around 200 ms corresponding to the N1 component (for the time interval 170-218 ms with the highest significance

at 192 ms $F(2,60)=5.78$, $p=0.005$). Post-hoc analysis showed that N1 amplitudes of pFEP were significantly lower compared to controls in the Short SOA condition (before 200 ms). PFEP had significantly higher amplitudes compared to pSZ in the Long SOA condition (after 200 ms) and in the Vernier Only condition (Fig.3). F-values and main effects of condition/interaction are shown in the supplementary material (Fig.S3A).

To ensure that the group differences are not restricted to visual areas (but are indeed global) we plotted the topographic maps for the main effect of Group interval in the supplementary material (Fig.S4). The three groups show similar voltage maps around 200 ms which differ only in intensity as reflected by the GFP.

Figure 3| *Global Field Power (GFP) for the three groups: pFEP (green), controls (black) and pSZ (red). The amplitudes at 200 ms are strongly reduced for pSZ but to a lesser degree for pFEP as compared to CTRL. The bottom line shows the results of the timewise rm-ANOVA for the main effect of Group (gray). Post-hoc statistics (t-values) are shown as black lines at the bottom of the panels. There is a significant difference around 200 ms between CTRL and pFEP in the Short SOA condition and between pFEP and pSZ in the Vernier Only and Long SOA conditions. The other comparisons were null.*



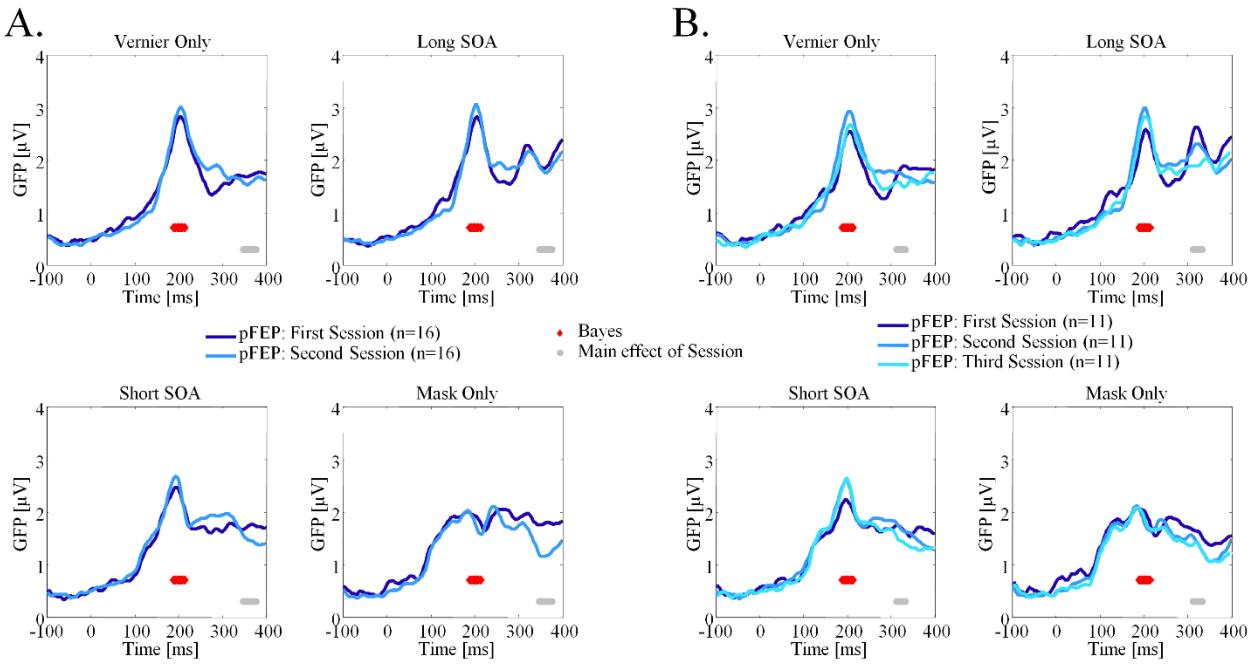
3.2.2. Neural correlates: Longitudinal study

We compared the 16 pFEP who underwent the two first sessions over the course of six months and the 11 pFEP who underwent all of the three sessions over the course of one year.

GFPs traces of the 16 patients who participated in the two sessions are mainly overlapping (Fig.4A). We found a significant main effect of Session after 300 ms (for the time interval 347-377 ms with the highest significance at 356 ms; $F(1,15)=6.72$, $p=0.02$). We did not find any significant effect of Session around 200 ms (GFP peak, N1 component). In order to test whether the GFP amplitude remained stable at 200 ms across the two sessions, we computed a within-subject rm-Bayesian ANOVA for the averaged time window 190-215 ms. We found a Bayesian factor (BF_{10}) for the main effect of Session of 0.220 indicating 4.5 times more evidence in favor of the null hypothesis (no difference across sessions) as compared to the alternative (there was a difference across sessions). F-values for the main effects of condition/interaction are shown in the supplementary material (Fig.S3B).

GFPs traces of the 11 patients who participated in the three sessions are overlapping (Fig.4B). We found a significant main effect of Session after 300 ms (time interval: 312-334 ms with the highest significance at 323 ms $F(2,20)=6.36$, $p=0.007$). We did not find any significant effect of Session around 200 ms. To test whether the GFP amplitude remained stable at 200 ms across the three sessions, we computed a within-subject rm-Bayesian ANOVA for the averaged time window 190-215 ms. We found a BF_{10} for the main effect of Session of 0.204 indicating 4.9 times more evidence in favor of the null hypothesis. F-values for the main effects of condition/interaction are shown in the supplementary material (Fig.S3C).

Figure 4| **A.** *Global Field Power (GFP) for the 16 pFEP who performed the first (dark blue) and second (medium blue) session. The horizontal lines show the results of the timewise rm-ANOVA for the main effect of Session (gray) and the time interval of interest (190-215 ms) selected for the Bayesian rm-ANOVA (red).* **B.** *Similarly, GFP for the 11 pFEP who performed all three sessions: grand average for the first session (dark blue), second session (medium blue) and third session (light blue). The horizontal lines show the results of the timewise rm-ANOVA for the main effect of Session (gray) and the time interval of interest (190-215 ms) selected for the Bayesian rm-ANOVA (red).*



4. Discussion

Schizophrenia is strongly influenced by genetic dispositions. However, genetic studies have found only weak associations between SNPs and the disease (Bernardo et al., 2017; Kavanagh et al., 2015; Kendler, 2015). For this reason, endophenotypes are of crucial interest. VBM is a sensitive endophenotype, in particular the Shine-Through masking paradigm, which has a high sensitivity of 87% and specificity of 89% (Chkonia et al., 2010). Masking deficits are found in the siblings of patients (Chkonia et al., 2010), in students scoring high in CogDis (Cappe et al., 2012; Favrod et al., 2017) and in adolescents with psychosis (Holzer et al., 2009). The latter result shows that deficits are present even before the disease fully develops. In addition, masking deficits are well reflected in the EEG, with GFP amplitudes around 200 ms reduced as compared to controls (Plomp et al., 2013). Here, we asked the question whether adult pFEP show fully blown deficits in the EEG as chronic pSZ and how results change over the course of one year.

First, we conducted a behavioral experiment with an adaptive method and found that the performance levels of pFEP were between those of controls and pSZ with the 5- and 25-element grating mask (Fig.1B). When only the vernier was presented, there were only small differences between the three groups (η^2=0.133). This is in accordance with previous results showing that masking (η^2=0.326), and not vernier acuity, is the sensitive endophenotype. Also, relatives of pSZ

have masking deficits compared to controls but no VD deficits (Chkonia et al., 2010). The same is true for adolescents with psychosis (Holzer et al., 2009). It is the combination of a spatially (fine offset discrimination) and temporally (short SOAs) challenging task that makes the strong differences between patients and controls visible. Importantly, deficits vary greatly from 15 to 141 ms in SOA thresholds with the 25-element mask (Tab.2). VD do not vary as much between the populations from 10 to 55 ms. Interestingly, the masking deficits of pFEP (79.8 ms ± 57.7) were similar to those of adolescents with psychosis (70.6 ms ± 52.4; Holzer et al., 2009, see Tab.2). The slight difference might be explained by the fact that only a subset of the adolescents will develop schizophrenia and that the adolescents were much younger than the pFEP (16 years old vs. 30 years; masking performance deteriorates with age: Plomp et al., 2012; Roinishvili et al., 2011). Hence, deficits in the Shine-Through paradigm are present at the onset of the psychotic event but are not yet fully developed. Similar behavioural results were also true in the EEG experiment (Fig.2B). It remains an open question why deficits further deteriorate when the disease progresses.

Table 2 | *Summary of the behavioral studies using the 25-element mask: vernier durations (VD; mean ± SD) and stimulus onset asynchrony thresholds (SOA; mean ± SD) for each population.*

Group	*n*	age [years]	VD [ms]	SOA threshold [ms]	Study
Schizophrenia	22	33.5 ± 7.9	40.9 ± 30.1	139.1 ± 73.9	Current study
First Episode Psychosis	21	30.0 ± 9.2	47.6 ± 35.7	79.8 ± 57.7	Current study
Controls	20	35.4 ± 10.5	22.5 ± 9.1	29.7 ± 23.0	Current study
Participants scoring high in CogDis	22	21.1 ± 2.0	10.0 ± 0.0	18.6 ± 6.6	Cappe et al., 2012
Participants scoring low in CogDis	18			15.1 ± 3.0	Cappe et al., 2012
Bipolar	22	34.1 ± 10.1	41.8 ± 30.3	124.4 ± 90.6	Chkonia et al., 2012
Schizoaffective	20	35.1 ± 8.9	54.5 ± 33.3	140.7 ± 74.6	Chkonia et al., 2012
Relatives	39	35.0 ± 15.9	27.7 ± 19.0	74.0 ± 62.3	Chkonia et al., 2010
Adolescent with psychosis	15	16.4 ± 1.4	19.9 ± 20.5	70.6 ± 52.4	Holzer et al., 2009
Controls	19	16.0± 1.6	14.4 ± 19.2	22.83 ± 16.7	Holzer et al., 2009

For the EEG results, pFEP exhibited clearly reduced amplitudes in the Short SOA condition compared to controls, showing that masking deficits are present at the first psychotic event. However, in the Vernier Only and Long SOA conditions, amplitudes were intermediate, showing that it is only under the most challenging condition (Short SOA) that deficits are fully visible (Fig.3). These results go hand in hand with the behavioural results.

Interestingly, masking deficits are also present in healthy people scoring high in CogDis, but this again is only true under challenging conditions (Cappe et al., 2012). These masking deficits are also reflected in EEG by lower amplitudes (Favrod et al., 2017). Hence, masking deficits and the corresponding electrophysiological correlates are present in the unmedicated populations of healthy controls with schizotypal traits (Favrod et al., 2017), the unmedicated siblings of pSZ (although EEG correlates are not lower, da Cruz et al., in prep.), medicated pFEP and chronic pSZ (Plomp et al., 2013). The N1 peak is always around 200 ms, independently of the SOAs or the number of elements in the mask (supplementary material Tab.S4). Taken together, these results show that masking deficits are trait markers and that the EEG amplitudes decrease after the beginning of the disease.

In the longitudinal study, we found no evidence that behavioral performance decreases (there is even a slight improvement, which we attribute to learning, Fig.2C) and, respectively, amplitudes of the EEG did not further decrease (there is also a slight increase, if at all, Fig.4). Hence, performance and EEG signals are rather unaffected during the year following a first episode, which is well in line with an endophenotype.

With the Shine-Through paradigm, the amplitude of the N1 component for pFEP is between the ones of the controls and pSZ. There are other endophenotypes of psychosis that show a similar pattern. For example, the Mismatch Negativity (MMN), which is a measure of the brain response to a deviant tone in a sequence of repetitive tones, is deficient in chronic pSZ compared to controls (Salisbury et al., 2018). Interestingly, there was no or only a weak difference in the MMN amplitude between pFEP compared to controls (see also Erickson et al., 2016; Haigh et al., 2017). The MMN has even been proposed to be a measure for disease progression (Umbricht and Krljes, 2005). Similar results were found for the auditory P3, an attention-related component. The P3 amplitude is reduced in all electrodes in chronic pSZ, while the amplitudes are reduced only in the frontal electrodes in pFEP (Demiralp et al., 2002), possibly because the deficits of pFEP are not yet fully developed compared to chronic patients. The P50 suppression (for paired sound stimuli), measuring sensory gating, is also impaired in schizophrenia (no suppression). The mechanisms for the underlying P50 reduction are potentially similar to those observed with the Shine-Through paradigm in the sense that they are both related to the dysfunction of the cholinergic system, in particular the nicotinic receptor α7 (Bakanidze et al., 2013; Turetsky et al., 2012). Deficits in

different sensory modalities may result from a common mechanism. We proposed that masking deficits are the expression of a more general deficit related to target enhancement (Herzog et al., 2013).

There is a long debate as to whether schizophrenia is a neurodevelopmental disorder or whether the brain starts to deteriorate only with the beginning of the disease (Anderson et al., 1998; Knoll et al., 1998; Lewis and Levitt, 2002; Murray et al., 2017; Rapoport et al., 2012). Our results are compatible with both theories, since deficits are already present with the first signs of psychosis (even in unaffected relatives) and deteriorate across the course of the illness. It seems that pFEP are in an in-between state where the neural correlates are not yet fully reduced as in chronic pSZ.

PFEP were medicated. However, masking deficits are unlikely due to medication (Brody et al., 1980; Butler et al., 1996) because healthy high CogDis participants also show masking deficits (Cappe et al., 2012). Furthermore, medication often normalizes performance and/or brain activity, as shown for instance with P50 suppression deficits (Light et al., 2000; Nagamoto et al., 1996).

This work suffers from a few limitations. First, sample sizes are small. Second, patients were followed up only for a short duration (one year). A longer monitoring of patients is needed to determine how deficits evolve over time. Finally, medication was highly heterogeneous, introducing a confounding factor. We could not investigate the effects of atypical versus typical medication, which influence the performance in visual tasks (Fernandes et al., submitted).In conclusion, masking deficits are present when the first psychotic event occurs in pFEP but are not yet fully developed. Performance of pFEP is between the ones of controls and chronic patients. The behavioral results are well reflected in the reduced EEG amplitudes. In addition, pFEP show almost no behavioral or electrophysiological differences compared to controls when the task is easy, while they do show differences when the task is challenging. Importantly, masking performance and neural correlates do not change over the course of one year. These results add further evidence that masking is a sensitive endophenotype for the psychosis spectrum.

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Disclosures

Authors declare no conflict of interest.

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Supplementary Material

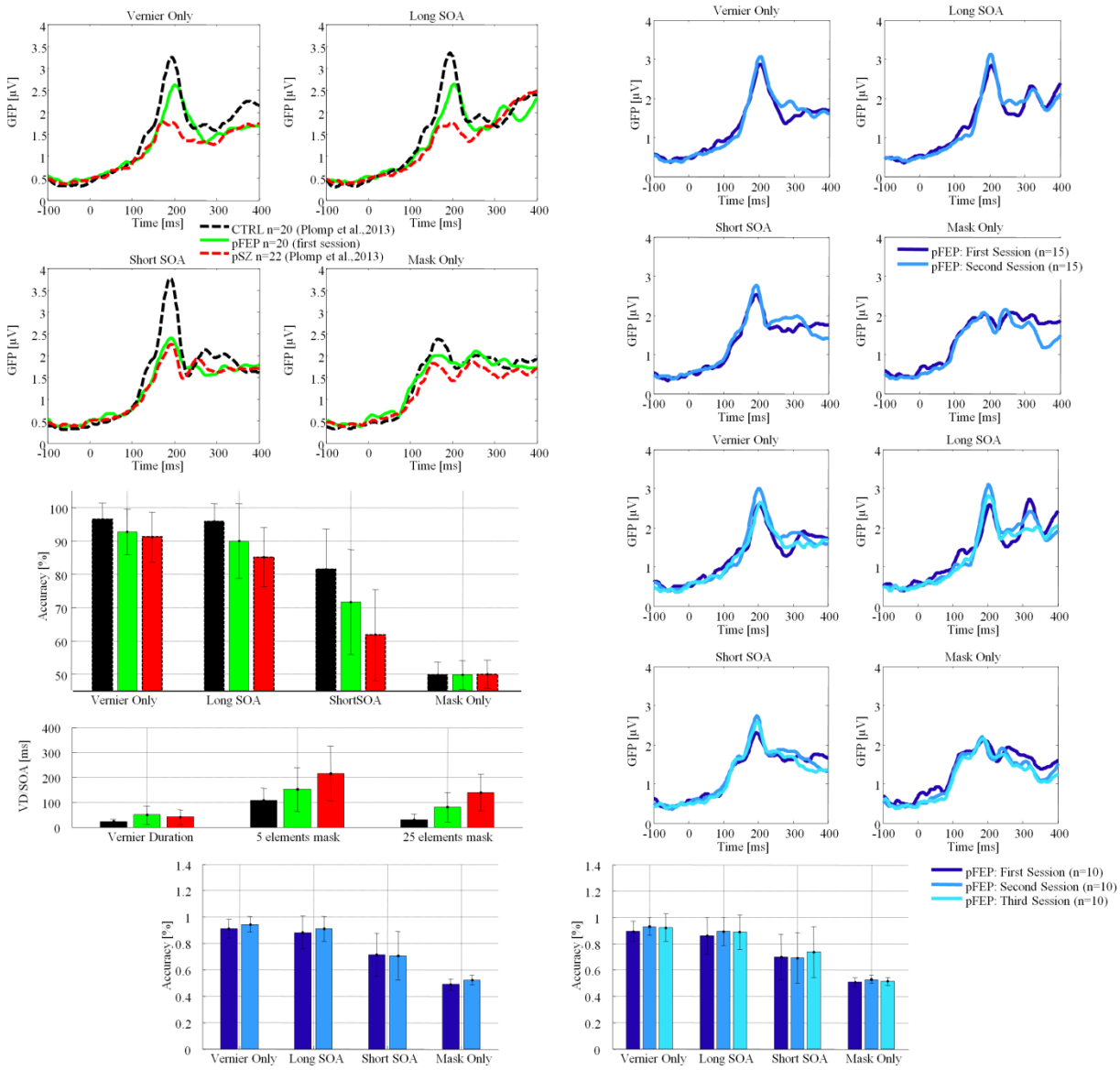

Figure S1| *Replication of the manuscript figures without the bipolar I patient. Patients with FEP sample size: n=20 in the first session, n=15 in the second session and n=10 in the third session.*

Table S1 | *Subtypes of diagnosis according to the DSM-IV for all three sessions.*

n	Diagnosis (DSM-IV)
First Session (n total=21)	
2	Schizophrenia, Disorganized Type (295.1)
15	Schizophrenia, Paranoid Type (295.3)
3	Schizophrenia, Undifferentiated Type (295.9)
1	Bipolar I Disorder, Most Recent Episode Depressed, In Partial Remission (296.55)
Second Session (n total=16)	
1	Schizophrenia, Disorganized Type (295.1)
8	Schizophrenia, Paranoid Type (295.3)
2	Schizoaffective Disorder (295.7)
3	Schizophrenia, Undifferentiated Type (295.9)
1	Bipolar I Disorder, Most Recent Episode Depressed, Mild (296.51)
1	Bipolar I Disorder, Most Recent Episode Depressed, In Partial Remission (296.55)
Third Session (n total=11)	
8	Schizophrenia, Paranoid Type (295.3)
2	Schizophrenia, Undifferentiated Type (295.9)
1	Bipolar I Disorder, Most Recent Episode Depressed, In Partial Remission (296.55)

Table S2 | *EEG pre-processing detailed information: Average per EEG recording for each group, patients with schizophrenia (pSZ), patients with first episode psychosis (pFEP) and controls (CTRL).*

	Number of Bad Channels (64 total)	Excluded Trials [%]	Groups	n
Average	1.09	5.13	pSZ	22
SD	0.68	3.53	pSZ	22
Average	0.58	3.88	pFEP 1st session	21
SD	0.60	2.23	pFEP 1st session	21
Average	0.70	3.75	pFEP 2nd session	16
SD	0.59	2.22	pFEP 2nd session	16
Average	0.82	3.75	pFEP 3rd session	11
SD	0.78	1.55	pFEP 3rd session	11
Average	0.70	3.57	CTRL	20
SD	0.80	2.40	CTRL	20

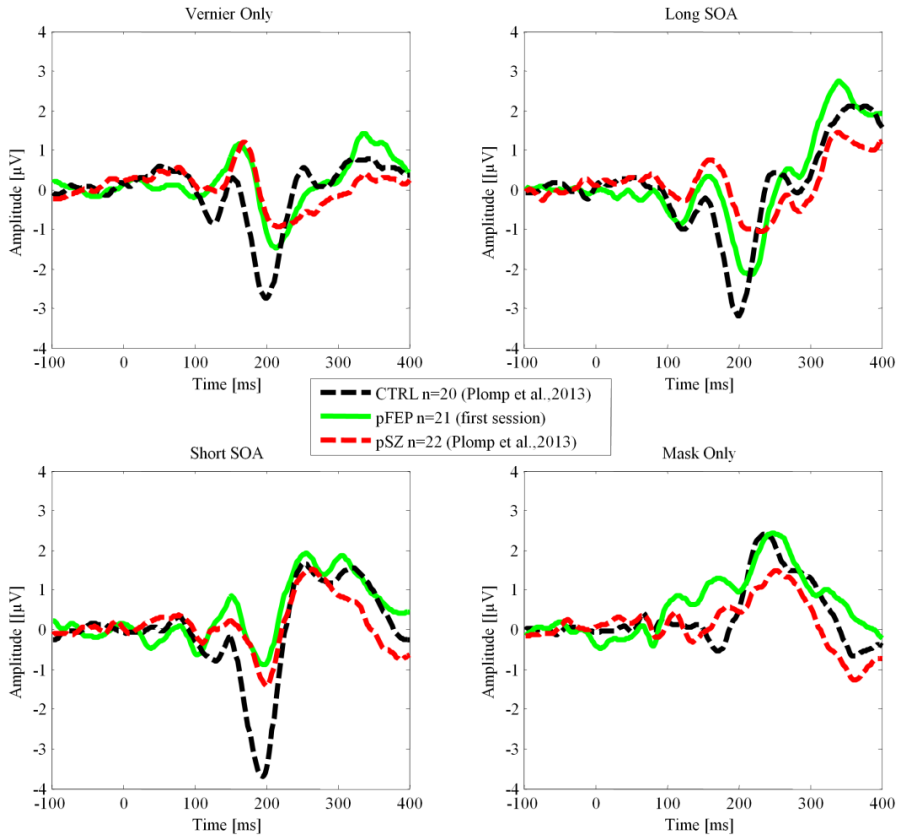

Figure S2| *Visual evoked response of the occipital electrode Oz for the three groups of participant: the controls (CTRL, dashed black), the patients with first episode psychosis (pFEP, solid green) during the first session and the patients with schizophrenia (pSZ, dashed red). A first positive component (P1) appears around 150 ms followed by a strong negative deflection (N1) around 200 ms for each condition with a target vernier.*

Table S3 | *Average statistics for Figure 2C left, n=16*

Condition	Session	Mean	SD
Vernier Only	First	0.916	0.071
	Second	0.947	0.058
Long SOA	First	0.889	0.122
	Second	0.914	0.092
Short SOA	First	0.715	0.159
	Second	0.71	0.179
Mask Only	First	0.487	0.042
	Second	0.524	0.035

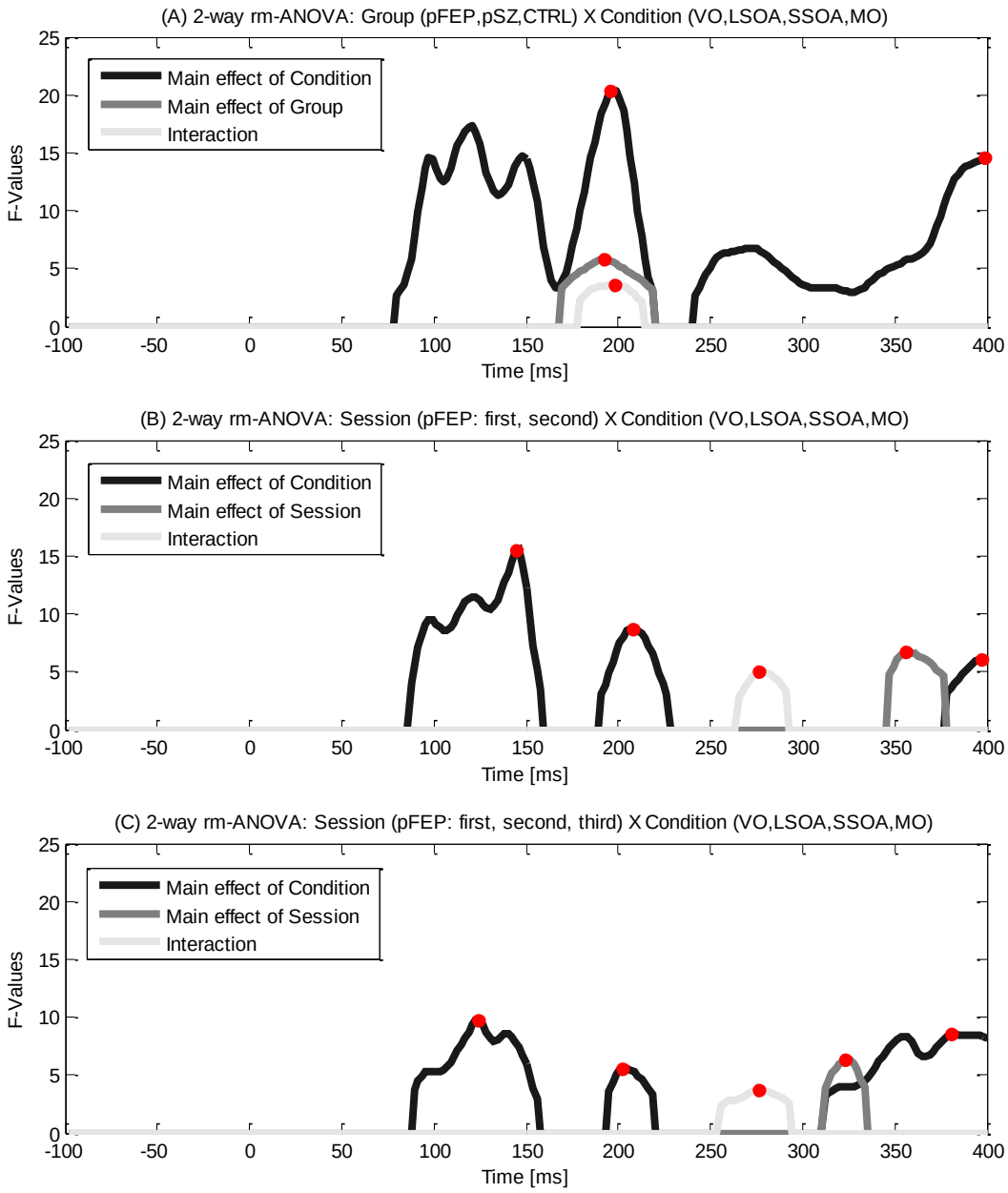

Figure S3| *F-values for the main effects of the rm-ANOVAs. Red dots indicate the highest F-values (for each time interval) which are reported in the main text.* **A.** *The two main effects of Condition lasted for almost the entire epoch (first for the time interval 80-218 ms with the highest significance at 196 ms F(3,180)=20.40, p<0.001 and second for the time interval 242-400 ms with the highest significance at 399 ms F(3,180)=14.65, p<0.001). We also found an interaction Group x*

Condition in an interval around 200 ms (179-212 ms with the highest significance at 198 ms F(6,180)=3.62, p=0.002). **B.** *There were main effects of Condition for three time intervals (the first interval started from 87 to 158 ms with the highest significance at 145 ms F(3,45)=15.51, p<0.001, the second interval started from 191 to 226 ms with the highest significance at 208 ms F(3,45)=8.73, p<0.001 and the last interval started from 379 to 400 ms with the highest significance at 397 ms F(3,45)=6.12, p=0.001). There was an interaction Session x Condition for an interval before 300 ms (265-291 ms with the highest significance at 276 ms F(3,45)=5.06, p=0.004).* **C.** *There were main effects of Condition for three time intervals (the first interval started from 89 to 156 ms with the highest significance at 124 ms F(3,30)=9.76, p<0.001, the second interval started from 195 to 218 ms with the highest significance at 202 ms F(3,30)=5.62, p=0.003 and the last interval started from 312 to 400 ms with the highest significance at 381 ms F(3,30)=8.54, p<0.001). There was an interaction Session x Condition for an interval before 300 ms (255-293 ms with the highest significance at 276 ms F(6,60)=3.72, p=0.003).*

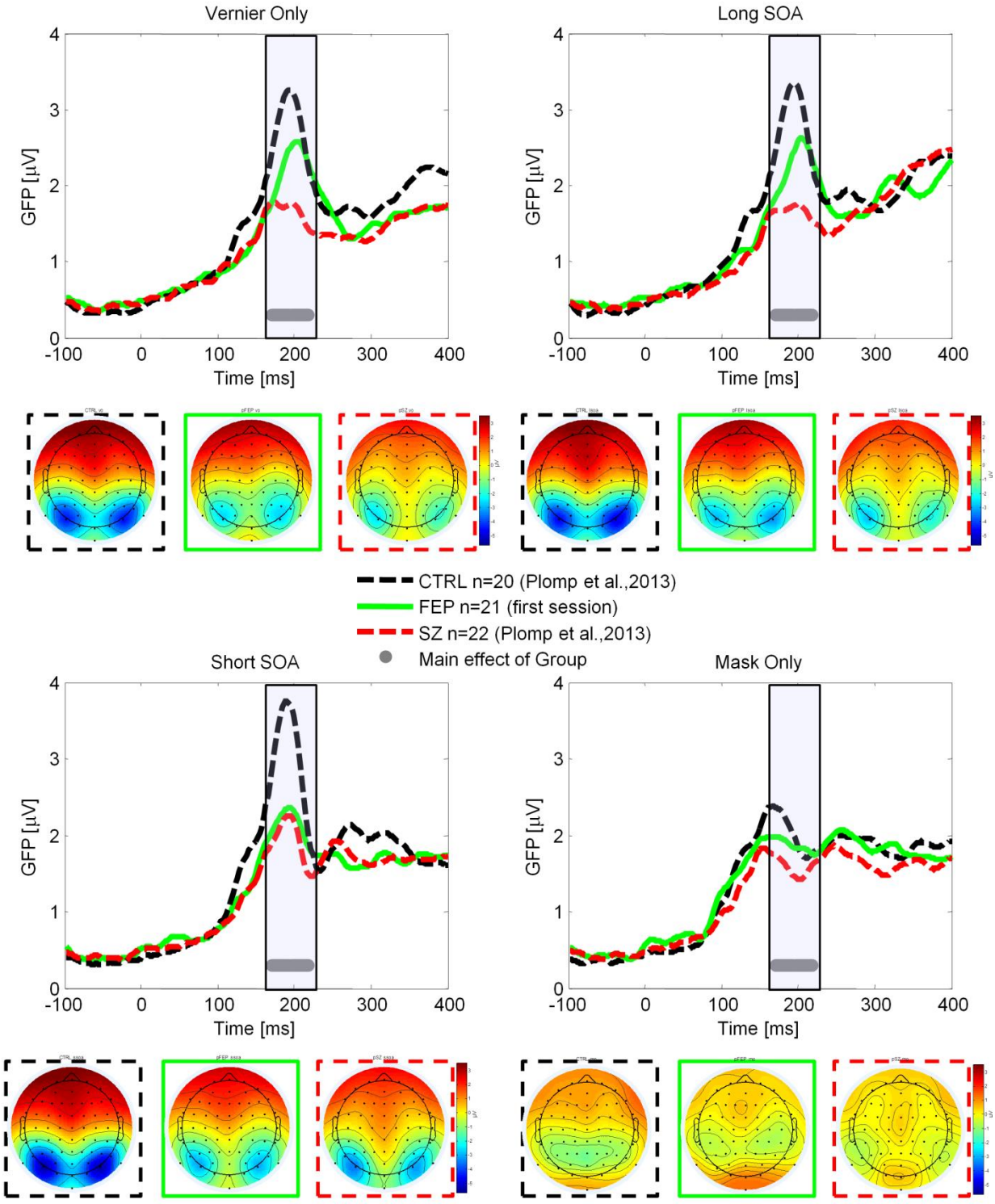

Figure S4| *Voltage maps for the time interval highlighted in gray (main effect of Group). The topographies are similar across groups (except for the Mask Only condition). The maps differ in intensity between groups.*

Table S4 | *EEG studies: Percent correct (mean ± SD), maximal EEG amplitudes (N1; mean ± SD) and the corresponding latencies for the grand average of each population. An EEG condition is defined by the vernier duration (VD) and the SOA duration (SOA). Accuracy does not differ between the current study and the Plomp et al., 2013 study while EEG does since data were re-analyzed with the App (**27**).*

Group	n	VD [ms]	Mask	SOA [ms]	Correct responses [%]	N1 amplitude [ms]	N1 latency [ms]	Study
Schizophrenia	22	30	25 elements	30	61.8 ± 13.6	2.2 ± 1.0	193	Current study
First Episode Psychosis	21	30	25 elements	30	71.9 ± 15.4	2.4 ± 1.6	193	Current study
Controls	20	30	25 elements	30	81.5 ± 12.0	3.8 ± 2.1	191	Current study
Schizophrenia	22	30	25 elements	150	85.1 ± 8.9	1.8 ± 0.8	199	Current study
First Episode Psychosis	21	30	25 elements	150	90.2 ± 11.0	2.6 ± 1.6	205	Current study
Controls	20	30	25 elements	150	95.9 ± 5.3	3.3 ± 1.8	195	Current study
Participants scoring high in CogDis	25	10	5 elements	60	63.4 ± 12.5	1.8 ± 0.7	191	Favrod et al., 2017
Participants scoring low in CogDis	20	10	5 elements	60	64.7 ± 12.1	2.2 ± 0.9	196	Favrod et al., 2017
Participants scoring high in CogDis	25	10	5 elements	80	67.4± 13.6	2.0 ± 0.8	184	Favrod et al., 2017
Participants scoring low in CogDis	20	10	5 elements	80	68.0 ± 13.4	2.4 ± 1.1	195	Favrod et al., 2017
Schizophrenia	10	30	5 elements	110	70.5 ± 12.1	1.6 ± 0.8	218	Favrod et al., 2017
Schizophrenia	10	30	5 elements	230	83.2 ± 13.3	1.7 ± 0.8	216	Favrod et al., 2017
Schizophrenia	22	30	25 elements	30	idem	2.1 ± 0.9	197	Plomp et al., 2013
Controls	20	30	25 elements	30	idem	3.6 ± 2.0	193	Plomp et al., 2013
Schizophrenia	22	30	25 elements	150	idem	1.6 ± 0.7	205	Plomp et al., 2013
Controls	20	30	25 elements	150	idem	3.2 ± 1.7	199	Plomp et al., 2013

Masking is always stronger with the 5-element compared to the 25-element mask. N1 amplitude is the lowest for the chronic patients. Amplitude difference is smaller between the high and low schizotypy healthy populations compared to clinical versus non-clinical populations.