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Neural compensation mechanisms of siblings of schizophrenia patients as revealed by high-density EEG

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Abstract

Visual backward masking (VBM) deficits are candidate endophenotypes of schizophrenia indexing genetic liability of the disorder. In VBM, a target is followed by a mask that deteriorates target perception. Schizophrenia patients and, to a lesser extent, their unaffected relatives show strong and reproducible VBM deficits. In patients, VBM deficits are associated with strongly decreased amplitudes in the evoked-related potentials (ERPs). Here, to unveil the neural mechanisms of VBM in schizophrenia, circumventing illness-specific confounds, we investigated the EEG correlates of VBM in unaffected siblings of schizophrenia patients. We tested 110 schizophrenia patients, 60 siblings, and 83 healthy controls. As in previous studies, patients showed strong behavioral deficits and decreased ERP amplitudes compared to controls. Surprisingly, the ERP amplitudes of siblings were even higher than the ones of controls, while their performance were similar. ERP amplitudes in siblings were found to correlate with performance. These results suggest that VBM is deteriorated in patients and siblings. However, siblings, unlike patients, can partially compensate for the deficits by over-activating a network of brain regions.

Keywords: siblings, schizophrenia, compensation, GFP, EEG, backward masking

1. Introduction

Endophenotypes are trait rather than state markers of a disease supervening on the genetic makeup[1]. Several candidate endophenotypes have been proposed for schizophrenia. Endophenotypes based on visual processing are of great interest because of their good reproducibility, language independence, and contributions to higher cognitive impairments[2–6].

Visual backward masking (VBM) is one of such endophenotypes of schizophrenia[7–11], specially the shine-through paradigm, which has a much higher sensitivity and specificity for schizophrenia than most other cognitive and perceptual paradigms[4,12]. In VBM, a briefly presented target is followed by a mask, which decreases performance in discriminating the target[13]. In the shine-through paradigm, the target is comprised of a vernier stimulus and the mask is comprised of 25 straight verniers making up a grating (sub-section 2.2). If the stimulus-onset asynchrony (SOA) is short enough, the vernier *shines-through* the grating appearing wider and brighter than it really is. The decrement of performance due to the mask is much stronger in schizophrenia patients than in healthy controls[14]. Strong impairments are also found in healthy adolescents with psychosis[15–17] , dismissing the argument that VBM deficits are primarily due to long term medication and social situation. Unaffected first-order relatives (offsprings, siblings, and parents) of schizophrenia patients also show strong VBM deficits, as requested for an endophenotype[4,18,19]. Importantly, relatives are not medicated and thus these deficits add further evidence that masking deficits are trait rather than state markers. Here, in experiment 1, we replicated these results. Moreover, we identified abnormalities in a single nucleotide polymorphism (SNP) related to the cholinergic nicotinic receptor (α7), which correlated well with performance in the shine-through paradigm[20].

The large behavioral deficits in schizophrenia patients are reflected in equally large deficits in electrophysiology correlates as measured by the electroencephalogram (EEG)[21]. Patients have

decreased N1 amplitudes at ~200ms after stimulus presentation, as measured by the Global Field Power (GFP). Similar results were found with a cohort of patients with first episode of psychosis[22] and students scoring high in schizotypal traits[23].

Schizophrenia has a high heritability (70-85%)[24] and siblings of schizophrenia patients have an empirical risk of approximately 10-fold higher to develop schizophrenia than the general population[25,26]. Hence, siblings share a large genetic risk with their affected brothers and sisters. Here, we investigated the neural mechanisms of the shine-through masking paradigm in siblings of schizophrenia patients. As mentioned above, siblings show deteriorated performance in the shine-through paradigm. For this reason, we expected their EEG amplitudes to be in between patients and controls.

2. Methods

2.1. Participants

122 schizophrenia patients, 62 unaffected siblings of schizophrenia patients, and 85 healthy controls joined the experiments. We excluded 6 patients and 1 sibling because their vernier durations were too long as well as 3 other patients because their SOAs were too long (subsection 2.3). 3 patients, 1 sibling, and 2 controls were excluded due to excessive EEG artifacts (subsection 2.4.1). Data from 110 patients, 60 siblings, and 83 controls were kept for further analyses. 97 out of 110 patients were receiving neuroleptic medication. Chlorpromazine equivalents are indicated in **Table 1**. Siblings of patients had no history of psychoses. Controls were recruited from the general population, aiming to match patients and siblings as closely as possible. Refer to Supplementary Material 1.1. for additional information on inclusion/exclusion criteria and clinical assessments.

Group characteristics are presented in **Table 1**. Since patients and controls differ in terms of gender, education and visual acuity, gender was used as a factor while education and visual acuity were used as covariates in subsequent analyses.

45 out of the 60 siblings were siblings of a single patient in the current study (hereinafter referred to as siblings_45 and patients_45). The remaining 15 siblings were siblings of patients that performed a battery of tests but did not participate in the current EEG experiment. Group characteristics of patients_45 and siblings_45 are presented in **Table 1**. In subsequent analyses, for each variable of interest, the score of siblings_45 was subtracted from their patients_45 pair, resulting in a difference score (Δ), which was submitted for statistical analysis.

All procedures complied with the Declaration of Helsinki and were approved by the local ethics committee.

92 **Table 1 -** Group average statistics (±SD) of schizophrenia patients, their siblings, controls, patients_45, and siblings_45.

	Patients	Siblings	Controls	Patients_45	Siblings_45	Statistics		
						Patients vs. Controls	Siblings vs. Controls	Patients_45 vs. Siblings_45
Gender (F/M)	17/93	32/28	39/44	10/35	25/20	$\chi^2(1)=22.838$, $p<.001$	$\chi^2(1)=.561$, $p=.454$	$\chi^2(1)=10.519$, $p=.002$
Age	35.7±8.8	32.1±9.9	34.3±7.8	33.0±8.8	32.3±9.1	$t(191)=1.147$, $p=.506$	$t(141)=1.482$, $p=.423$	$t(44)=.934$, $p=.506$
Education	13.3±2.6	14.1±3.0	15.2±2.8	13.4±2.6	14.6±2.9	$t(191)=4.889$, $p<.001$	$t(141)=2.251$, $p=.052$	$t(44)=2.219$, $p=.052$
Handedness (R/L)	105/5	57/3	78/5	43/2	43/2	$\chi^2(1)=.211$, $p=1.000$	$\chi^2(1)=.069$, $p=1.000$	$\chi^2(1)=.000$, $p=1.000$
Visual acuity	1.4±.4	1.5±.4	1.6±.4	1.4±.4	1.5±.4	$t(191)=2.700$, $p=.024$	$t(141)=.914$, $p=0.724$	$t(44)=.896$, $p=.724$
Vernier duration*	30 [20, 40]	20 [20, 20]	20 [20, 20]	20 [20, 40]	20 [20, 20]	$\chi^2(1)=63.021$, $p<.001$	$\chi^2(1)=.000$, $p=1.000$	$\chi^2(1)=3.533$, $p=.120$
Illness duration	11.7±8.0			8.9±7.5				
SANS	10.4±5.2			10.5±5.6				
SAPS	9.8±7.4			9.2±3.2				
CPZ	560.2±393.5			560.9±398.3				

Abbreviations: SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; CPZ, Chlorpromazine equivalents.

*Median [25th percentile, 75th percentile], Mood's median test

P-values Bonferroni-Holm corrected for multiple comparisons for each pairwise group comparisons within each variable of interest.

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2.2. Stimuli

The apparatus is described in Supplementary Material 1.2. The vernier stimulus consisted of 2 vertical line segments of 10' (arc minutes) length separated by a gap of 1' (**Figure 1A**). The lower line was slightly offset randomly either to left or to the right compared to the upper one, with a fixed offset of about 1.2'. The mask consisted of 25 aligned verniers without horizontal offset, separated by 3.33'. Participants reported the perceived horizontal offset direction by pushing one of two buttons and guessed when they were uncertain. Accuracy was emphasized over speed.

2.3. Experiment 1 – Adaptive Procedure

The paradigm is described in detail in previous work[14]. Briefly, for each participant, we determined the vernier duration (VD) necessary to reach 75% correct responses for a vernier offset of 0.6'. Participants had to reach a VD shorter than 100ms. 6 patients and 1 sibling were excluded at this stage. Next, we presented the vernier with the individual VD for each participant and an offset of 1.2', followed by an inter-stimulus interval (ISI) and the mask with a duration of 300ms (**Figure 1A**). In a staircase procedure, we adaptively determined the target-mask stimulus-onset asynchrony (SOA=VD+ISI) to yield a performance level of 75% correct responses, using Parametric Estimation by Sequential Testing (PEST)[27]. Each participant performed the test twice. First and second testing results were averaged and submitted to statistical analysis. For patients vs. controls, we performed a two-way ANCOVA; for siblings vs. controls, an independent samples *t*-test; for patients_45 vs. siblings_45, a one-sample *t*-test.

Participants with mean SOAs longer than 300ms, twice the mean SOA of patients in previous works[4,14,21,22], were excluded at this stage (3 patients).

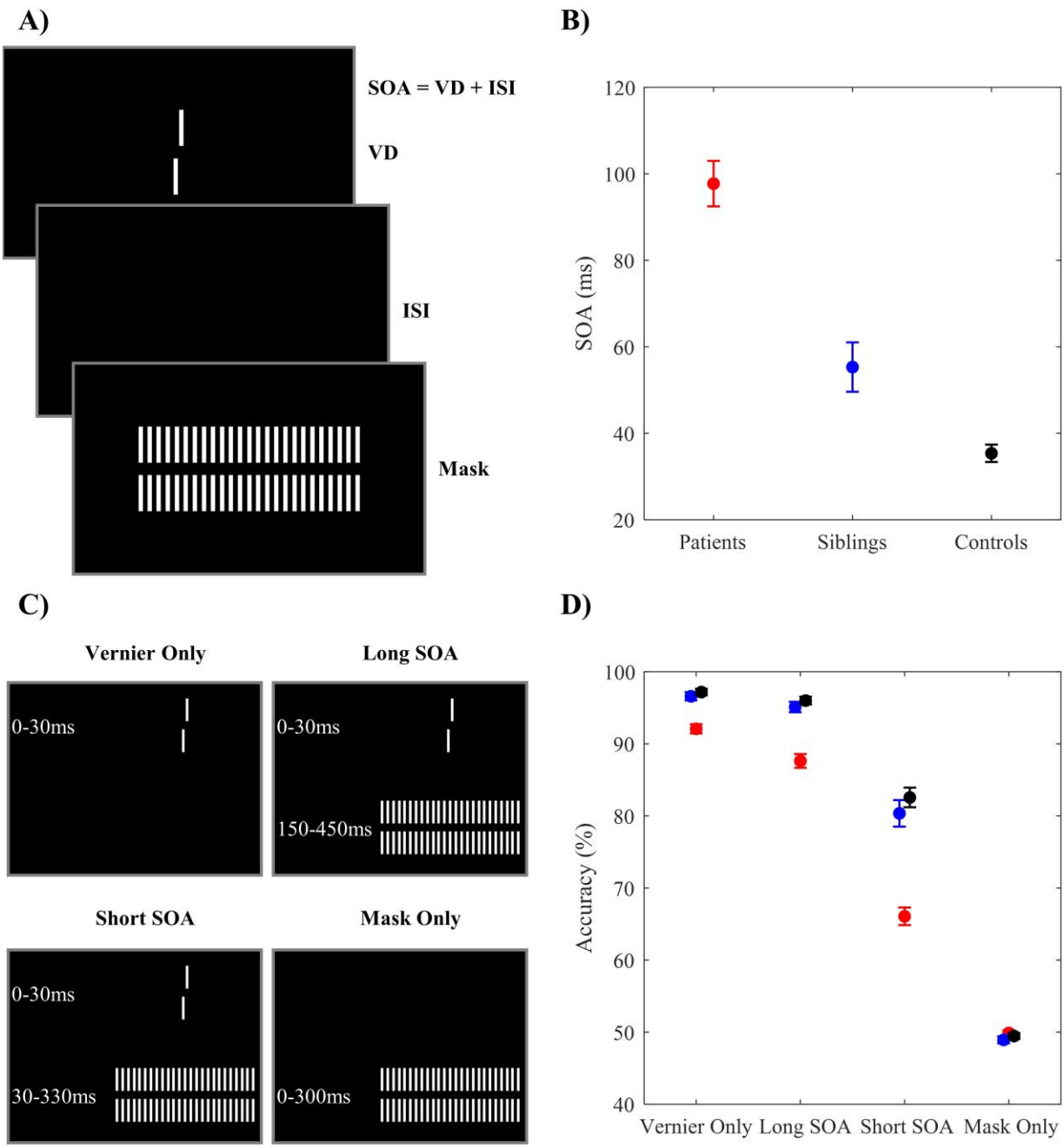


Figure 1 - A) Experiment 1: stimulus display. For each participant, we determined his/hers vernier duration (VD). Then, for each observer, we used his/hers VD and presented a blank screen (ISI) and a mask. We determined the stimulus-onset asynchrony (SOA=VD+ISI), for which 75% correct responses were reached. B) Mean SOA for each group, in experiment 1. Performance of patients and siblings were worse than the one of controls. C) Experiment 2: stimulus conditions. In the Vernier Only condition, the vernier was presented alone for 30ms. In the Short and Long

SOA conditions, the vernier was followed by a mask with an SOA of either 30 or 150ms, respectively. In the Mask Only condition, only the mask was presented. D) Mean accuracy for each group for the 4 conditions, in experiment 2. Patients were less accurate at discriminating the vernier offset compared to both siblings and controls. Siblings and controls performed at the same level. Error bars indicate standard error of the mean (s.e.m.).

2.4. Experiment 2 – EEG

Since the ERPs peak latencies and amplitudes vary with the VD and SOAs, for the EEG experiment, we fixed the VD and SOAs and used the same stimuli for all observers. To ensure that patients could do the task, we set the VD to 30ms (average VD of patients in previous works[4,14]). We had 4 stimulus conditions (**Figure 1C**), as in previous works[21,23,28]. In the Vernier Only condition, only the target vernier was presented. In the Long SOA condition, the mask followed the target vernier with an SOA of 150ms. In the Short SOA condition, the target vernier was followed immediately by the mask (SOA=30ms). The SOAs in the Long and Short SOA conditions were selected according to the mean SOA across schizophrenia patients and controls, respectively, in previous works[4,14,21,22]. We included a control, the Mask Only condition, in which only the mask was presented. In this particular case, accuracy was calculated by comparing the left/right offset response to a randomly chosen notional offset.

For patients vs. controls, a three-way repeated measures (rm)-ANOVA with Greenhouse-Geisser correction ($\hat{\varepsilon}$) was conducted to compare the effect Group, Condition (Vernier Only, Long SOA, and Short SOA), and Gender on performance; for siblings vs. controls, a two-way rm-ANOVA (factors: Group and Condition); for patients_45 vs. siblings_45, a one-way rm-ANOVA (factor: Condition).

2.4.1. EEG Recording and Pre-Processing

EEG was recorded using a BioSemi Active 2 system with 64 Ag-AgCl sintered active electrodes, referenced to the common mode sense (CMS) electrode. The sampling rate was 2048Hz. Offline data were pre-processed using an automatic pre-processing pipeline (APP)[29]

(Supplementary Material 1.4.1 for details) . Data from 3 patients and 1 control were excluded from further analysis due to excessive muscular artifacts or bad electrodes.

2.4.2. GFP Analysis

To avoid the pitfalls of reference-dependency of ERPs and arbitrarily selecting a group of electrodes for analysis, we determined the GFP for each participant and each condition. GFP is a reference-independent measure of neural activity throughout the brain and it is computed as the standard deviation of potentials across all electrodes at a given time point[30]. For each group, we computed a grand-average GFP for each of the 4 stimulus conditions (**Figure 2B**) and identified the peak latencies for each condition. Peak amplitudes differed in each condition because the mask onset latency depended on condition. We statistically compared the GFP peak amplitudes across subjects. For patients vs. controls, we conducted a three-way rm-ANOVA (factors: Group, Condition (Vernier Only, Long SOA, Short SOA, and Mask Only), and Gender); for siblings vs. controls, a two-way rm-ANOVA (factors: Group, and Condition); for patients_45 vs. siblings_45, a one-way rm-ANOVA (factor: Condition).

2.4.3. Electrical Source Imaging (ESI)

To identify the brain areas generating the GFP effects, we compared the estimated current densities (CDs) at GFP peak latencies. Source analysis was performed using CARTOOL[31]. From the individually averaged ERPs, we estimated CDs throughout the brain using a Local Auto-Regressive Average (LAURA) inverse solution[32]. A source space of 4022 points evenly distributed throughout the grey matter of the Montreal Neurological Institute's (MNI) 152 non-linear atlas template brain model was defined, and a model identical to previous works[33–35] was used.

For patients vs. controls and siblings vs. controls, two-way rm-ANOVAs with factors Group, and Condition were computed on the CDs for each solution point. For patients_45-siblings_45, their difference score (Δ) of the CDs for each solution point were submitted to a one-way rm-ANOVA. Multiple comparisons across the 4022 solution points were corrected using Bonferroni-Holm correction. For each cluster of statistically significant solution points, the average position of its solution points, weighted according to their effect sizes, was computed for identification of its center of mass (CoM). CD of the solution point closest to each CoM was used to represent the corresponding brain region.

3. Results

3.1. Experiment 1 – Adaptive Procedure

We first made sure that siblings show VBM deficits as in previous findings[4]. Indeed, mean SOA of patients and siblings were longer than the one of controls (patients vs. controls: p_{holm}=1.624e-14, d=1.226; siblings vs. controls: p_{holm}=3.103e-4, d=0.627; **Figure 1B**). Patients_45 had longer mean SOA than their paired siblings_45 (Δ=-5.78% ± 10.18; p_{holm}=6.098e-7, d=0.899). Detailed statistics in Supplementary Material 2.1.

3.2. Experiment 2 – EEG

3.2.1. Behavior

Performance of patients was inferior to the one of controls in the 3 conditions with the target vernier (Vernier Only: p_{holm}=8.109e-5, d=0.625; Long SOA: p_{holm}=4.577e-6, d=0.739; Short SOA: p_{holm}=1.0325e-9, d=0.975), while siblings and controls achieved similar performances (p_{holm}=0.297, d=0.180; **Figure 1D**). Unlike in experiment 1, where we used an adaptive procedure, in the EEG experiment, we used the same stimuli for all participants and fixed the VD as the mean

VD of patients. Likely for these reasons, the task was not challenging enough to bring out group differences between siblings and controls. Regarding patients_45 vs. siblings_45, patients_45 achieved worse performance than their siblings_45 in all conditions: Vernier Only (Δ=-5.78% ± 10.18; p_{holm}=8.526e-4, d=0.568), Long SOA (Δ=-9.04% ± 12.2; p_{holm}=4.256e-5, d=0.741), and Short SOA (Δ=-16.71% ± 17.28; p_{holm}=3.858e-7, d=0.967). Detailed statistics in Supplementary Material 2.2.1.

3.2.2. GFP

Signals from occipital electrodes PO7 and PO8 were extracted to visualize the negative and positive components of the ERPs (**Figure 2A**). Participants showed strong negative ERPs at ~200ms after stimulus-onset. GFP time course for patients, siblings, and controls in the 4 stimulus conditions are shown in **Figure 2B**. Analysis of the GFP peak amplitudes (**Figure 2C**) showed that patients had decreased GFP peak amplitudes than controls in all target conditions: Vernier Only (p_{holm}=4.466e-5, d=0.663), Long SOA (p_{holm}=1.067e-5, d=0.721), and Short SOA (p_{holm}=1.211e-4, d=0.617). In the Mask Only condition, patients and controls GFP peak amplitudes were comparable (p_{holm}=0.856, d=0.110). Patients_45 showed decreased GFP peak amplitudes compared to their siblings_45 pairs in all conditions: Vernier Only (Δ=-1.64μV ± 1.72; p_{holm}=9.541e-07, d=0.954), Long SOA (Δ=-1.69μV ± 1.67; p_{holm}=2.81e-7, d=1.012), Short SOA (Δ=-1.54μV ± 1.85; p_{holm}=1.364e-5, d=0.828), and Mask Only (Δ=-0.43μV ± 0.96; p_{holm}=0.030, d=0.445). Interestingly, GFP peak amplitudes were higher in siblings compared to controls for the Vernier Only (p_{holm}=0.030, d=0.469) and Long SOA (p_{holm}=0.030, d=0.461) conditions. Siblings and controls had comparable GFP peak amplitudes for Short SOA (p_{holm}=0.543, d=0.228) and Mask Only (p_{holm}=0.857, d=0.031) conditions. For siblings, GFP peak amplitudes were roughly at the same level in all 3 target conditions (one-way rm-ANOVA; F(1.395,82.277)=1.593, P=0.208,

η^2=0.002, $\hat{\varepsilon}$=1.434). For controls and patients, GFP peak amplitudes increased with task difficulty, i.e., from Vernier Only to Long SOA and to Short SOA conditions (one-way rm-ANOVA; controls: F(1.309,107.314)=16.761, P=1.522e-5, η^2=0.021, $\hat{\varepsilon}$=1.528; patients: F(1.395,152.074)=13.834, P=4.415e-5, η^2=0.019, $\hat{\varepsilon}$=1.434). GFP peak amplitudes correlated positively with the performance for all target conditions, when considering all participants. Considering each group separately, this was also the case for siblings for the Vernier Only (r(58)=0.393, p_{holm}=0.018) and Long SOA (r(58)=0.362, p_{holm}=0.040) conditions. Detailed statistics in Supplementary Material 2.2.2.

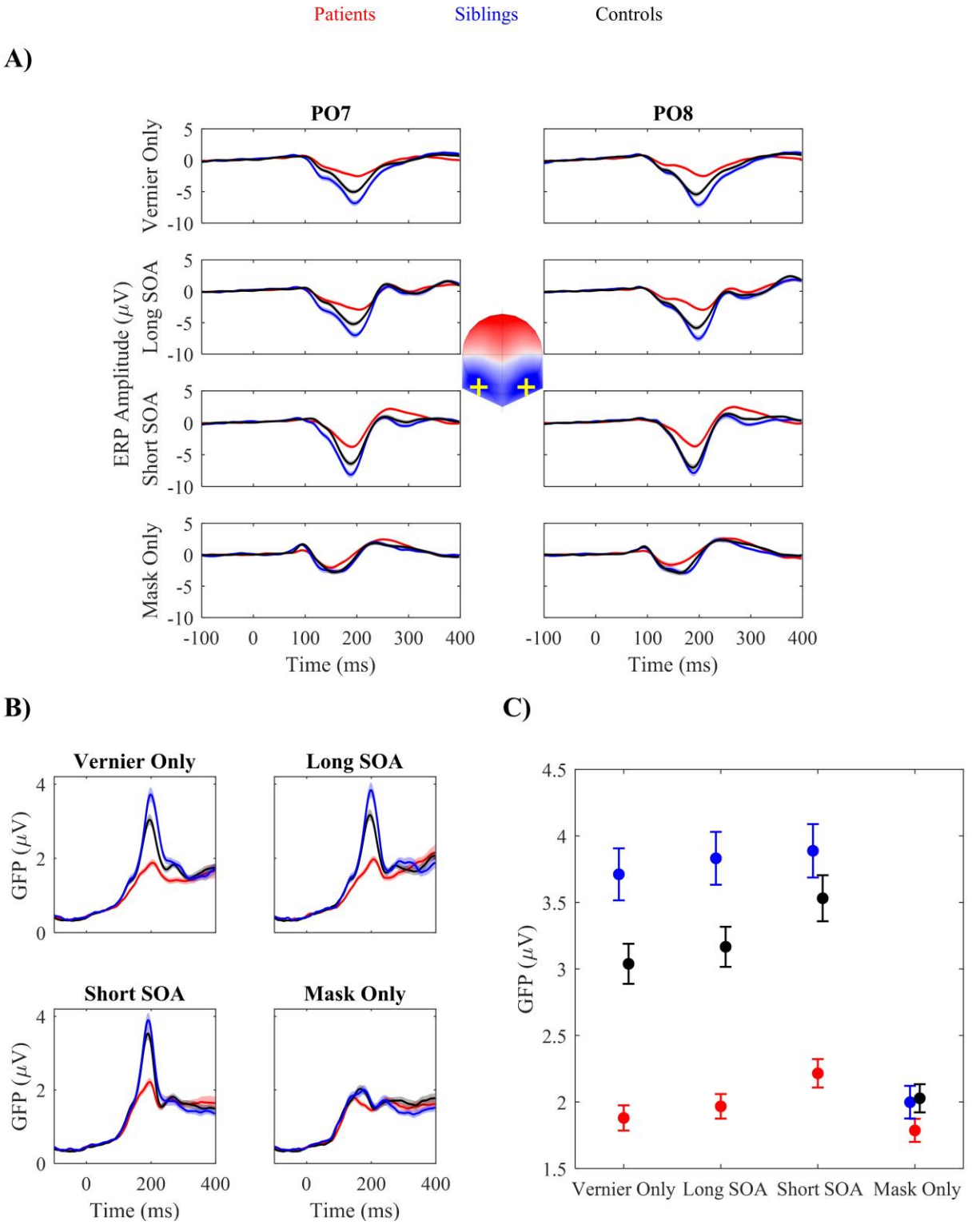
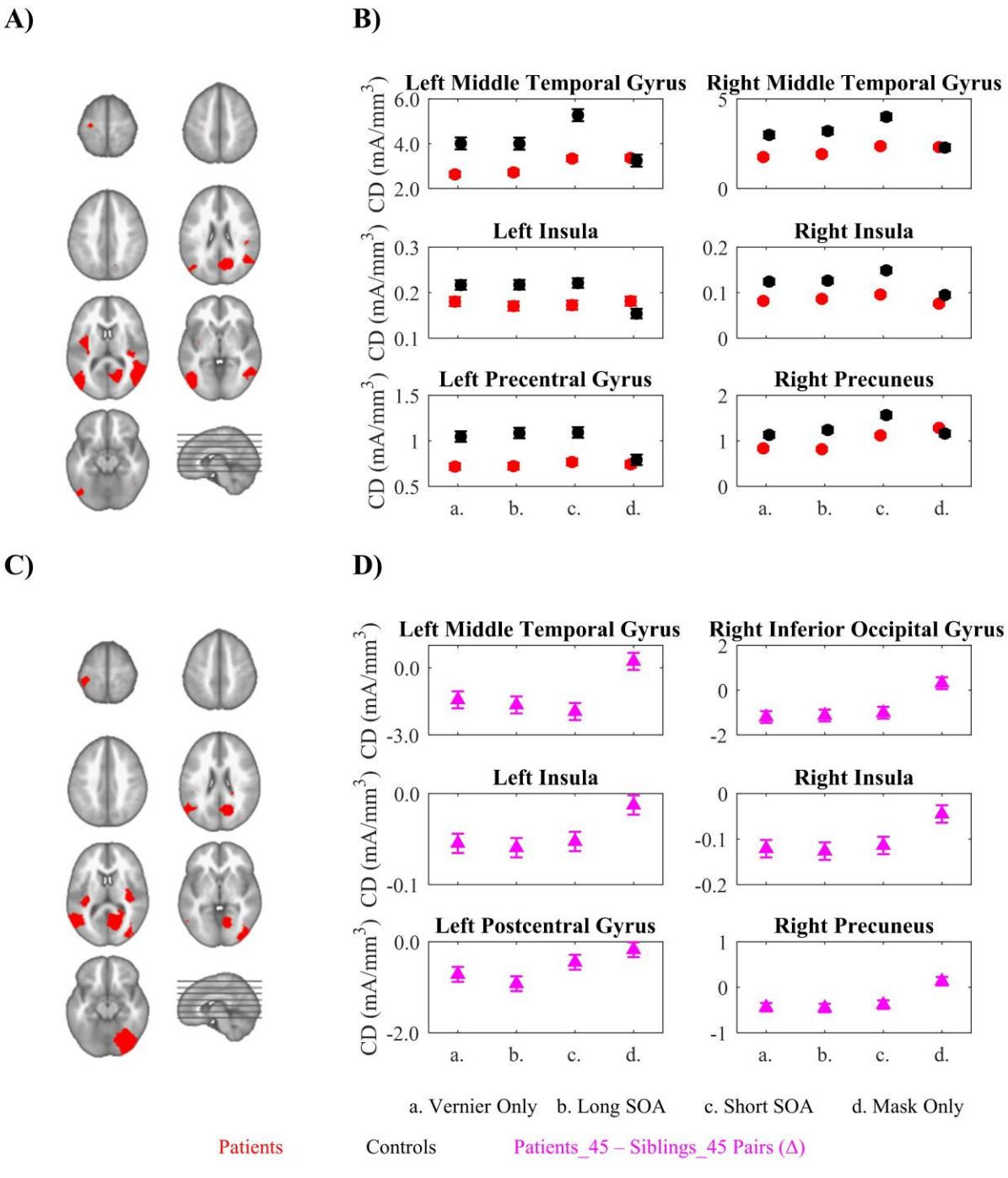


Figure 2 - A) Group grand average ERPs at PO7 and PO8 electrodes, in each condition. Participants showed negative deflections peaking around 200ms, resembling the N1 component.

B) Group average Global Field Power (GFP) time series in each condition. C) Group average peak GFP amplitudes for all conditions. Patients had decreased GFP peak amplitudes in all target conditions. Siblings had higher amplitudes than controls in the Vernier Only and Long SOA conditions. For patients and controls, GFP amplitudes increased with task difficulty. For siblings, GFP amplitudes remained on a high level. Shaded areas and error bars indicate s.e.m.

3.2.3. ESI

Figure 3 shows the EEG source clusters exhibiting statistically significant Group×Condition interaction effects (for patients vs. controls) and Condition effects (for patients_45 vs. siblings_45) after correction for multiple comparisons, as well as the corresponding average CD in each group. No statistically significant interactions effects were found for siblings vs. controls. For patients vs. controls, clusters were located bilaterally in the middle temporal gyrus and insula, as well as in the left precentral gyrus and the right precuneus. For patients_45 vs. siblings_45, clusters were located in the left middle temporal gyrus, right inferior occipital gyrus, right/left insula, left postcentral gyrus and right precuneus. **Table 2** lists the Talairach coordinates of the CoM for these clusters. Detailed statistics in Supplementary Material 2.2.4.



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242 **Figure 3** - Source imaging results. A) Clusters exhibiting significant Group×Condition
243 interaction effects for patients vs. controls are indicated in red. B) Average current density (CD)
244 at the centers of mass (CoM) for the 6 clusters, indicating the direction of the interaction effects.
245 C) Clusters exhibiting significant Condition effects for patients_45 vs. siblings_45. D)
246 Patients_45-siblings_45 difference score at the CoM for the 6 clusters, indicating the direction of

the differences. In general, group differences were larger in target conditions compared to the Mask Only condition. Error bars indicate s.e.m.

Table 2 - Locations of the center of mass of the EEG source clusters showing condition dependent group effects.

Comparison	Label	Talairach Coordinates (x,y,z)
	Left Middle Temporal Gyrus	-43, -68, 6
Patients	Left Insula	-34, -6, 14
vs.	Left Precentral Gyrus	-27, -21, 56
Controls	Right Middle Temporal Gyrus	47, -54, 11
	Right Insula	36, -27, 21
	Right Precuneus	15, -63, 23
	Left Middle Temporal Gyrus	-54, -61, 17
Patients_45	Left Insula	-31, -27, 21
vs.	Left Postcentral Gyrus	-34, -33, 58
Siblings_45	Right Inferior Occipital Gyrus	32, -75, -3
	Right Insula	35, -22, 15
	Right Precuneus	20, -63, 18

Results of multiple linear regressions to predict the accuracy based on the estimated CDs of the CoM of the source clusters revealed that for siblings the activity of the right insula predicted accuracy in all conditions with the target vernier: Vernier Only (β=1.330, SE=0.553, $t(58)=2.410$, $p=0.019$) ; Long SOA (β=1.754, SE=0.701, $t(58)=2.502$, $p=0.015$) ; Short SOA (β=4.026, SE=1.798, $t(58)=2.239$, $p=0.029$). Detailed statistics in Supplementary Materials 2.2.4.

4. Discussion

VBM deficits are candidate endophenotypes for schizophrenia[4,7–11]. Importantly, not only patients show strong VBM deficits but also their unaffected relatives[4,18], a result that we reproduced in experiment 1.

In schizophrenia patients, the large behavioral deficits are associated with strongly decreased ERP amplitudes at ~200ms after stimulus presentation[21]. Similar results were also found in patients with a first episode of psychosis[22] and students with high schizotypal traits[23]. Here, we tested 60 unaffected siblings of schizophrenia patients. These siblings do not have the disease but they share a large genetic risk with their affected brother and sisters. We expected that, since behavioral performance of relatives is in between the ones of patients and controls, their ERP amplitudes would also be in between the ones of patients and controls. Surprisingly, we found that, on the contrary, ERP amplitudes in siblings were even higher than in controls (we found similar results using the area under the curve, Supplementary Material 1.4.2. and 2.2.3.). Interestingly, in siblings, these amplitudes were almost constant across target conditions. While, for patients and controls, ERP amplitudes increased with task difficulty, i.e., from Vernier Only to Long and Short SOA.

We interpret these results as a compensation signal. To process the target vernier, whose neural correlates are indexed by the ERP component at around 200ms[36,37], siblings might need to engage all relevant neural resources in all conditions, independently of task difficulty. Since, in siblings, ERP amplitudes were stable across all target conditions, it suggests that their ERP amplitudes were at ceiling. All observed effects were specific to the target vernier and did not occur when only the mask was presented, suggesting that mainly top-down processes are responsible for these effects.

The lack of behavioral differences between siblings and controls in the EEG experiment suggests that, by over-enhancing neural responses to the target, siblings can partially compensate for their VBM deficits, if the task is not too challenging. In siblings, ERP amplitudes correlated with performance, further supporting a compensation hypothesis. Nevertheless, if the task is extremely challenging, e.g., during the adaptive procedure in experiment 1, this compensation mechanism is not sufficient for normal performance.

To identify the brain regions generating the ERP effects, we conducted an EEG source localization analysis. For patients-controls comparison, we identified 6 brain regions where the groups processed the stimuli differently: left/right middle temporal gyrus, left/right insula, left precentral gyrus, and right precuneus. Our results are similar to the ones reported in previous works[21], which identified 7 regions where patients processed the stimuli differently from controls: left middle occipital gyrus, right middle temporal gyrus, left/right insula, left postcentral gyrus, and left/right precuneus. We attribute the small discrepancies between our studies to the intrinsically low spatial resolution of EEG source localization. For siblings-controls comparison, we did not identify any significant differences. Potentially, the effects were not large enough to survive multiple comparison correction. For patients_45-siblings_45 comparison, we identified 6 brain regions where the groups processed the stimuli differently. The results were similar to the patients-controls comparison: left middle temporal gyrus, right inferior occipital gyrus, left/right insula, left postcentral gyrus and right precuneus. Again, we attribute the discrepancies to the low spatial resolution of the source localization. In general, as shown in Figure 3, group differences were larger in the target conditions than in the Mask Only condition, providing further evidence that mainly top-down processes are responsible for the ERP effects.

Among the identified brain regions, the right insula is of special interest. Multiple regression analysis indicated that activity of the right insula best predicted the behavioral performance, especially for siblings. The insula is associated with several functions. One of special interest is the high-level integration of information from different modalities and brain areas[38]. It has been proposed that the right insula regulates the interaction between selective attention and arousal to keep focused on the target[39]. Too little activity of the right insula, as in patients, may lead to an impairment in collecting evidence for decision making. Too much activity of the right insula, as

in siblings, might indicate that participants need to engage more to achieve a good performance in this challenging task. However, these interpretations should be taken with care since we lacked a specific hypothesis for the source localization and the accuracy of the method is limited. Further studies with better spatial resolution and targeting the right insula might provide more evidence for these claims.

Here, we propose the following hypothesis. When a faint stimulus is presented for a short time, only a weak neural response is elicited and the stimulus goes unnoticed[37]. Only if this stimulus is task-relevant, mechanisms of target enhancement are recruited to avoid overwriting by subsequently presented stimuli. We believe that target enhancement is a general mechanism occurring at all sorts of processing of task-relevant information, from auditory and visual mismatch negativity[40,41] to P50 auditory gating[42] and prepulse inhibition[43], rather than vision specific. Target enhancement is potentially a multi-factorial construct[36], comprised of, but not limited to, recurrent processing[44], attention[45,46], and/or neuromodulation, for example, by the cholinergic nicotinic system[20,47,48], which are important mechanisms to potentiate weak but important information. Attention deficits are core deficits in schizophrenia[49] and the cholinergic nicotinic system might be deficient in patients[20]. In the Mask Only condition, patients and controls showed similar amplitudes but patients showed significantly lower amplitudes than their siblings. This indicates that patients might have some slight bottom-up deficits but deficits only become obvious when there is a target. In patients, amplitudes are low in all target conditions. This suggests that patients cannot translate the briefly presented target into a stable neural representation, making the target more vulnerable to masking[11]. These masking deficits are also present in their unaffected relatives, as corroborated by experiment 1 and previous works[4,18]. We speculate that, to overcome these deficits, siblings are able to recruit more neural resources. Their increased ERP amplitudes

compared to controls support the hypothesis of a compensation mechanism, such that by increasing the activity of a network of brain regions, siblings, unlike patients, can partially compensate for their behavior deficits, if the task is not too challenging (experiment 2). In this network, our results suggest that the right insula, with its extensive connections to many areas of the cortex, might play a key role by integrating high-level sensory as well as perceptual information and subsequent decision-making. Nonetheless, if the task is extremely challenging, as in experiment 1, this compensation mechanism is too weak to fully compensate for the deficits.

Our results suggest that even if there are genetic risks for schizophrenia, the brain is somehow capable of compensating for them. Better understanding of these compensation mechanisms might help to explain why some siblings develop schizophrenia and while others do not, which might open new avenues for characterization of schizophrenia and possible treatments of the disorder.

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