Multisensory processes can compensate for attention deficits in schizophrenia

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Abstract

Previous conflicting findings on multisensory integration in schizophrenia might be related to differences in top-down attention demands across the different studies. We tested this with a visuo-tactile stimulation paradigm and high-density event-related potentials (ERPs) to examine the interplay between multisensory integration and top-down intersensory attention in healthy controls (N=27) and in people with schizophrenia (N=27). Unisensory visual, unisensory tactile or bisensory stimuli were presented while participants attended to either visual or tactile inputs. D-prime values, ERPs, clinical symptomatology, and cognitive performance were examined, comparing the interplay of intersensory attention and multisensory integration between groups. The former was impaired in the schizophrenia group at the behavioral level, but only for unisensory and not for multisensory stimuli. ERPs showed earlier intersensory attention responses (<200ms) were intact in the schizophrenia group, but diminished later (>230ms) over frontal and occipital brain areas. In contrast, multiple phases of multisensory integration, starting around 240ms, were preserved in the schizophrenia group. There was no correlation between ERP response and positive or negative symptoms. Our study provides evidence for long latency intersensory attention deficits in schizophrenia, presumably reflecting aberrant top-down processing. These findings indicate that uncompromised integrative multisensory processes, which elevate and capture attention, may serve as a compensatory mechanism for aberrant top-down processing in schizophrenia. Differences in attentional demands may have contributed to previous conflicting findings.

1. Introduction

Veridical understanding of the physical world requires coordination of information from different sensory modalities. This coordination involves selectively attending to some sensory stimuli and filtering others. To comprehend a multisensory object, sensory input has to be integrated across the different senses and this integration has been shown to capture attention (Talsma et al., 2010). There is some evidence for aberrant multisensory integration (MSI) in SCZ (Stevenson et al., 2017; Williams et al., 2010), but findings are controversial (e.g. Stone et al., 2011; Wynn et al., 2014). It may be that differences in attention demands contribute to the inconsistent findings. Since there is robust evidenceof unisensory attention deficits in SCZ (Berkovitch et al., 2018; Sauer et al., 2017), examining the interplay between intersensory attention (IA) and MSI may shed light on the inconsistency in findings regarding multisensory processing in SCZ.

There is a well-founded dependency between MSI and attention (Talsma et al., 2010). This is visible in early components of event-related potentials (ERPs) measured during IA tasks (Spence & Driver, 1997). In an EEG study, Lange and Röder (2006) found that orienting attention towards visual or tactile sensory stimuli in a bisensory task increases early negative deflections in primary visual and somatosensory cortices, respectively. Similarly, ERPs in a visual-tactile (VT) attention task are greater when stimuli are attended compared to when they are unattended (Keil et al., 2017). Thus, IA has measurable effects on multisensory processing, as reflected in evoked electrical brain activity.

Studies examining MSI in SCZ have revealed mixed results. Stevenson et al., (2017) found deficits in both unisensory and multisensory performance for temporal order judgment tasks. Similarly, in a basic audiovisual target detection task, some studies found deficits in both unisensory and multisensory performance in SCZ, relative to healthy controls (HC) (Williams et al., 2010). However, others found unisensory processing deficits in target detection in SCZ, but comparable MSI in both performance and ERP parameters (Stone et al., 2011; Wynn et al., 2014). Thus, there are consistent findings of unisensory processing deficits in SCZ, but much less consistent findings of deficits in multisensory tasks.

The centrality of attention to MSI is relevant to SCZ, as people with SCZ show deficits in various facets of attention (Gold et al., 2018). Studies have found aberrant top-down processing in SCZ, as reflected in the P300 component (Bramon, 2004). Other studies have shown impairments in top-down visual search (Fuller et al., 2006; Gold et al., 2007) and performance in mismatch negativity tasks in both situations where predicted sounds are

omitted as well as with unpredictable sounds, suggesting weakened top-down predictive coding in SCZ (Sauer et al., 2017). Taken together, top-down attention deficits and their neurobiological correlates are established in SCZ, while findings of MSI deficits in SCZ remain controversial.

In this study we adapted a visual-tactile top-down attention paradigm (Keil et al., 2017; Pomper et al., 2015) to examine the interplay between MSI and IA in healthy control (HC) participants and in people with SCZ. A study from Wood et al., (2006) used an IA approach to examine audiovisual processing, suggesting differences in early and late processing, however the MSI component was not examined. Using a rigorous data-driven analysis approach, we compared the effects of IA and MSI on behavioral data and ERPs between HC and SCZ. We also tested the functional relevance of the outcomes by relating deviances in ERPs to behavioral performance, positive and negative symptoms, as well as a measure of cognitive deficits in SCZ.

2. Methods

2.1. Sample and clinical data

Twenty-nine people diagnosed with SCZ according to the ICD-10, were recruited at the outpatient units of the Charité – Universitätsmedizin, Berlin. After exclusion of outliers, through analysis of behavioral response, or based on preprocessing of EEG data, 27 patients were included in the analysis (see following sections for details of exclusion). Psychiatric assessment was undertaken by an experienced psychiatrist at the recruiting institution. Patients taking the following medications were excluded from the study, in order to minimize distorting effects upon the EEG (Aiyer et al., 2016): benzodiazepines, lithium, valproic acid, and haloperidol (Table 1).

Of 29 Healthy Control (HC) participants recruited from the general population, 27 remained after preprocessing (see following sections for details of exclusion). They were matched for handedness (Oldfield, 1971), education, smoking (Fagerström (Heatherton et al., 1991), age, and gender (Table 1). They were screened for comorbid psychopathology using the German version of the Structured Clinical Interview for DSM-4-TR Non-Patient Edition (SCID). The cognitive capacity of SCZ and HC was assessed with the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004). One psychologist (JKM) tested symptom severity in SCZ using the Positive and Negative Symptom Scale (PANSS; Kay, Fiszbein, & Opfer, 1987) to ensure no biases introduced by interrater variance. Items were grouped according to the 5-factor model: ‘positive’; ‘negative’; ‘depression’; ‘excitement’; and ‘disorganization’ (Wallwork et al., 2012). All participants gave written informed consent, including awareness of EU data protection laws and had normal hearing and normal/corrected to normal vision. People with neurological disorders or previous head injury with loss of consciousness were not included in the study. Furthermore, in the control group, those with immediate family members with a psychiatric disorder or neurological disorder were excluded. All participants underwent a drug screening (Drug-Screen Multi 5 Test, Nal von Minden, Amphetamine, benzodiazepine, cocaine, opioids and cannabis) prior to measurement. The study was carried out in accordance with the 2008 Declaration of Helsinki and was approved by the ethics commission of the Charité – Universitätsmedizin Berlin (Approval number: EA1/169/11).

-- Table 1 --

2.2. Setup and Procedure

Participants were seated in an electrically and acoustically shielded chamber with low lighting. They were presented, in random order, with unisensory-visual, unisensory-tactile, and bisensory visual-tactile stimuli and had to detect occasional target stimuli in either the visual or tactile modality. Visual stimuli (standards and targets) were presented for 150ms against a neutral gray background with a luminance of 30cd/m^2 at the center of a tilted TFT monitor (see Figure 1a). The visual standard stimulus consisted of a Gabor patch in a circular frame, (diameter: 5.75°, spatial frequency = 1 cycle per degree, Gaussian standard deviation = 2°). The target visual stimulus was the same stimulus but flickering at 16.7Hz. The Braille stimulator was attached to the back of the monitor in the center so that visual and tactile stimuli were spatially aligned. Tactile standard and target stimuli were administered by a piezoelectric Braille stimulator (QuaeroSys, St. Johann, Germany), consisting of 16 pins arranged in a square, with 2.5mm spacing between the pins. For the standard tactile stimulus, these were elevated onto the participant's left index finger for 150ms. The target tactile stimulus consisted of multiple high frequency elevations and contractions at 16.7 Hz for 150 ms. An auditory mask of white noise was presented during the experimental blocks to cancel out the sound of the Braille stimulator. The effectiveness of the white noise was verified prior to testing, by asking participants if they could hear anything during presentation of sample tactile stimuli, which was adjusted until the individuals could not hear the stimulator sounds.

The procedure began with presentations of samples of the different stimulus types. Participants performed a speeded response task by pressing a button with their right index finger when a target in the attended modality appeared. There were a total of 1722 trials presented across 14 blocks (i.e. 123 trials per block). Each block lasted about 4 minutes, alternating blockwise between visual and tactile attention tasks. There were 861 of both visual and tactile attention trials, broken down into 235V, 235T and two sets of 235 bisensory VT trials per attention condition. In addition, 52 unisensory V, 52 unisensory T and 52 bisensory VT target trials (where both sensory constituents were targets) were presented. Thus about 18% of trials overall were target stimuli.

The stimuli were presented for 150ms, following this, participants were given 1000ms to respond (or to not respond in case of standards). The interstimulus interval (ISI) was randomized between 600 to 1000ms (average 800ms) between the stimulus presentation and response time. The response interval was indicated by a transformation of the fixation cross into a circle to cue the response (Figure 1b).

-- Figure 1a and 1b --

2.3. Behavior:

To analyse hit-rates vs. false-alarm rates, d-prime values of behavioral responses were calculated (Stanislaw & Todorov, 1999). A successful hit was defined as a response to the correct target stimulus, e.g. in the visual attention condition, the participant pressed a response when a visual target appeared. The false response to this would be when a participant responds instead to a standard stimulus, e.g. for visual attention, the participant presses the button for a standard visual stimulus. Similarly, for the bisensory stimuli, a correct response (visual and tactile target) was contrasted with a false response to bisensory standard stimuli. Median percentage of responses outside of the analysis range of 100ms to 900ms were 0.05% for SCZ [Range: 0-36.7%] and HC [Range: 0-28.01%] (Wilcoxon test, W = 264.5, p-value = 0.356). A three-way ANOVA was conducted with factors (Group [SCZ vs. HC], Attended modality [tactile vs. visual], and Mode [Multisensory vs. Unisensory]).

2.4. EEG Recording

Data were recorded using a 128 channel passive EEG system (EasyCap, Herrsching, Germany), which included two EOG electrodes (online: 1000 Hz sampling rate with a 0.016 – 250 Hz bandpass filter; offline: 49 – 51 Hz, 4th order Butterworth notch filter, 125 Hz 24th order FIR lowpass filter, down sampled to 500 Hz, 1 Hz 1500th order FIR highpass filter). Data was re-referenced to the average of all EEG electrodes. Non-stationary artifacts were identified by visual inspection, and the contaminated trials removed. After this process, there was no significant difference between remaining trials between groups (SCZ: M = 1481.67 [SD = 143.09] trials; HC = 1488 [SD = 173.58] trials; t(50.05) = 0.16, p = 0.870). Independent component (IC) analyses to correct for EOG and ECG artifacts were conducted, (Lee et al., 1999). The median number of components rejected was, 3 [IQR=2] ICs for SCZ and 3 [IQR = 1.5] ICs for HC (W = 408, p = 0.445) (Chaumon et al., 2015). Spherical interpolation was used to interpolate remaining noisy channels. There was no significant difference in the number of channels remaining (SCZ = 118.14 [SD = 5.25] channels; HC = 116.48 [SD=4.50] channels, t(51.18) = -1.27, p = 0.209). One HC was rejected at the preprocessing stage because of excessive eye-blinks, which were not removable by ICA.

2.5. Analysis of evoked brain activity

In line with previous studies on IA (Talsma et al., 2009; Talsma & Woldorff, 2005), for the EEG data analysis, only standard stimuli were included to avoid confounding motor activity.

The primary focus of the analysis was on bisensory VT stimuli, because for these stimuli both IA and MSI effects can be investigated. However, the effects of IA on unisensory stimuli were also examined. To establish regions of interest (ROIs), first data were combined across groups (SCZ and HC) and the difference between within-subjects conditions across all sensors and time-points from 50ms to 400ms post stimulus onset was tested. There were two comparisons that of interest: (i) IA effects, contrasting results for stimuli in visual vs. tactile attention conditions, and (ii) MSI effects using the additive approach, i.e. bisensory VT vs. combined V + T activity. For the analysis of additive effects, a comparison was created by adding evoked responses to bisensory stimuli across both attention conditions and compared these against the addition of ERPs of all four unisensory conditions (i.e. two per attention condition).

The statistical analysis took place in two steps, first using data-driven clustering algorithms and permutation tests to define regions of interest (ROI) and times of interest (TOI) for the within-subjects experimental manipulations. This was applied separately for both the IA effects, and the MSI effects. Afterwards the averaged amplitude of these clusters was analyzed in a two-by-two factorial mixed model ANOVA to test group effects.

2.5.1. ROI & TOI analysis:

Dependent- samples *t*-tests with Monte–Carlo randomization and cluster-based correction for multiple comparisons were used, which enable subsequent data-driven analyses, whilst statistically accounting for multiple comparisons (Maris & Oostenveld, 2007). The experimental cluster test statistic was evaluated against the Monte-Carlo permutation distribution with 1000 permutations, to test the null hypothesis of no differences between conditions (IA effect: visual vs. tactile attention; MSI effect: bisensory vs. additive]). The threshold to control for family-wise error (FWE) was set to $p = 0.025$ (two-sided test) and a cluster-based contrast was performed. The initial cluster-forming threshold was set to $p = 0.005$. The output of this is displayed in weathermap plots in the results, masked for corrected clusters identified in the permutation analysis.

2.5.2. Group Analysis

Data from the above ROIs and TOIs was exported to R and further analysed with a two-by-two mixed factorial ANOVA. For the IA analysis, Group (SCZ vs. HC) and Attended modality (visual vs. tactile), and their interaction, were compared. Similarly, for the MSI analysis, Group (SCZ vs. HC) and Mode (bisensory vs. additive) and their interaction, were

compared. Additional separate analyses for IA effects in the unisensory V and unisensory T conditions, were also performed, which are presented in the Supplementary Material.

2.6. Behavioral correlations with EEG parameters

Correlations between EEG and potential confound measures (Nicotine consumption as measured by the Fägerstrom Test) and antipsychotic medication (Olanzapine equivalent dose) were conducted (Leucht et al., 2016). Additionally, correlations between symptoms of SCZ as (measured by the PANSS and BACS) and EEG values were calculated. Critical significance values were adjusted for multiple comparisons across all EEG values according to Benjamini & Hochberg (1995). Non-parametric Spearman correlations were used where distributions did not meet parametric criteria, defined by Kolmogorov-Smirnov tests.

3. Results

3.1. Behavior

Three outliers (> 3 SD from the mean) were cut based on behavioral analysis of d-primes (2 SCZ, 1 Control), leaving N=27 SCZ and N=27 HC. The three-way ANOVA using the factors Group [SCZ vs. HC], Attended modality [tactile vs. visual], and Mode [bisensory vs. unisensory]) revealed a significant main effect of mode ($F(1,156) = 49.27$, $p < 0.0001$), showing that responses to bisensory stimuli were overall more accurate than those for unisensory stimuli ($\beta = 0.18$). There was also a main effect of Attended modality ($F(1,156) = 13.02$, $p < 0.0001$), showing that attending to tactile stimuli produced more accurate responses than attending to visual stimuli ($\beta = 0.22$). While there was no main effect of Group ($F(1, 52) = 3.74$, $p = 0.059$, $\beta = -0.04$), there was a significant two-way interaction between Group and Mode ($F(1,156) = 4.34$, $p = 0.039$, $\beta = 0.22$). Follow-up simple contrasts of Group within each Mode (uni- and bisensory), averaged over Attended modality (unisensory: HC vs. SCZ, and bisensory: HC vs. SCZ) (Bonferroni adjusted critical $p = 0.025$) showed that responses to unisensory stimuli differed between groups, (HC: adj-m = 4.43 [4.01-4.86], SCZ: adj-m=3.82 [CI:3.39-4.25], $t(69.5) = 2.57$, $p = 0.012$), while responses to bisensory stimuli did not differ between groups (HC: adj-m = 4.87 [CI: 4.43-5.30], SCZ: adj-m=4.63 [CI:4.20-5.06], $t(69.5) = 1.02$, $p = 0.312$). Hence, SCZ showed specific intersensory attention deficits for the processing of unisensory targets, but not for bisensory targets. The ANOVA revealed no other significant interactions (Figure 2).

-- Figure 2 --

3.1. Sensor Level ERPs

3.1.1. Intersensory attention effects: tactile vs. visual attention for multisensory stimuli

The cluster analysis of IA effects (tactile vs. visual) on ERPs revealed 5 clusters differentiating tactile vs. visual attention across combined HC and SCZ groups (Figure 3). The first cluster was right centrally localized (90-108ms). This is followed by two temporally overlapping clusters in occipital (158-216ms) and frontal 168-218ms) regions, and two temporally overlapping later clusters in central (230-320ms) and occipital (282-318ms) regions (Table 2 and Figure 4).

-- Figure 3 --

Follow-up two-by-two mixed ANOVAs (Group*IA Effects) for each of the 5 clusters defined by the analysis, together with topographic plots and ERPs are shown in Figure 4. The first cluster (TOI: 90-108ms), likely driven by the tactile stimuli, was localized over right sensorimotor cortex. In this early cluster there were no group differences present, suggesting that intersensory attention effects were similar for both groups. The following two clusters (TOI: 158-216ms and 168-218ms) cover occipital negative and frontal positive ERP components, respectively. In this stage of processing, there were also no group differences between HC and SCZ. The fourth and fifth clusters (TOI: 230-320ms and 282-318ms) covered central and occipital regions, respectively. Statistical analyses for both clusters revealed that HC had greater deflections for the visual attention condition relative to the tactile attention condition. By contrast, attention effects were much weaker in the SCZ (Table 2). Hence, while IA responses up to 218 ms were found for both groups, SCZ patients lacked on longer latency IA effects that were found in HC. Finally, IA effects were also investigated for unisensory visual and unisensory tactile stimuli. This analysis revealed similar long latency IA deficits in SCZ (Supplementary Material).

-- Table 2 --

-- Figure 4 --

3.1.2. Multisensory integration effects: Bisensory vs. additive conditions

The cluster analysis of MSI of the ERPs showed a series of 4 clusters differentiating bisensory vs. combined unisensory conditions across combined HC and SCZ groups (Figure 6). Specifically, there were two sets of temporally overlapping clusters in occipital (240-280ms) and frontal (246-292ms) scalp regions, and two temporally overlapping clusters in frontal (316-364ms) and occipital (306-354ms) scalp regions.

-- Figure 5 --

Follow-up two-by-two mixed ANOVAs (Group*Multisensory Integration) for each of the 4 clusters defined by the analysis are shown together with topographic plots and ERPs in Figure 7. There were two temporally overlapping frontal negative (246-292ms) and posterior positive (240-280ms) components, and two later temporally overlapping components, one frontal positive (316-364ms) and one posterior negative (306-354ms). Both of these latter components did show group differences, with HC having generally larger ERP amplitudes than SCZ. However, there were no interaction effects for Group and MSI effects. Hence, MSI effects, as expressed through differences between bisensory vs. combined unisensory ERPs, did not differ between HC and people with SCZ.

-- Table 3 --

-- Figure 6 --

3.1.1. Relationships between IA and MSI effects on evoked brain activity and behavioral performance

The ERP amplitudes for bisensory stimuli (i.e. difference between attention conditions for the IA analysis and multisensory integration effects in the MSI analysis) were correlated with bisensory and unisensory d-prime values. This was done separately for the two study groups. First bivariate Pearson correlations were performed for bisensory and unisensory d-prime values and the 5 IA clusters, as well as with the 4 MSI clusters individually for the two groups (HC and SCZ). Where significant correlations were found, the critical p-value was adjusted for multiple comparisons according to Benjamini & Hochberg (1995). Following this, surviving significant results were Fisher-Z transformed to enable a between-group comparison between HC and SCZ.

According to Benjamini & Hochberg (1995) the critical p-value for the IA correlation analysis, which was conducted for five clusters, was adjusted top < 0.005. After this adjustment two correlations remained significant: 230-320ms and 282-318ms (Table 4). Both clusters showed significant correlations between ERP difference waves and unisensory performance, but this correlation was found only in the SCZ group. Fisher-Z transformation revealed that both correlations were significantly stronger for SCZ than for HC (Figure 7). For the 230-320ms cluster, the differences in the central negative deflection in SCZ were stronger for individuals with a better performance. Similarly, the occipital difference waves at 282-318ms were larger in individuals with better performance. The analysis of unisensory ERPs showed similar patterns of diminished long latency IA effects on ERPs in SCZ and correlations between these ERPs effects with behavioral performance (Table 6 and Table 8 in Supplementary Material).

The correlation analysis between d-prime values and MSI effects at four clusters did not reveal any significant relationships (adjusted critical p-value = 0.00625, with all p-values > 0.0135).

Taken together, the correlation analyses suggest that long latency IA effects are behaviorally relevant, but specifically in SCZ patients. Notably, SCZ with relatively intact (compared with the HC group) long latency IA effects in ERPs also showed a relatively normal behavioral performance.

-- Table 4 --

-- Figure 7 –

3.2. Relationships between EEG parameters with cigarette and medication consumption, PANSS and BACS

3.2.1. Cigarette and Medication effects

To test whether the possible confounding variables smoking and medication, the difference of the 5 IA clusters as well as the 4 MSI clusters were regressed against the Fagerström Test and Olanzapine equivalent dose. Critical significance values were adjusted for multiple comparisons according to (Benjamini & Hochberg, 1995) across all EEG clusters. All correlations were non-significant (all adjusted *p*-values> .36).

3.2.2. PANSS

In a further analysis, the IA and MSI clusters were correlated against the five dimensions of the PANSS. Critical significance values were adjusted for multiple comparisons according to Benjamini & Hochberg (1995) with FWE rate defined across all EEG clusters. After adjustment, there were no significant correlations for the dimensions of the PANSS (all adjusted *p* values >.09).

3.2.3. BACS

The relationships between the overall scores on the BACS and EEG scalp level cluster scores for the IA and MSI clusters was tested. Bivariate Pearson correlations for BACS and the 5 IA clusters were performed, as well as for BACS and the 4 MSI clusters individually for the two groups (HC and SCZ). Where significant correlations were found, then the critical p-value as adjusted for multiple comparisons (Benjamini & Hochberg, 1995). Following this, surviving significant results were Fisher-Z transformed to enable a between-group comparison between HC and SCZ.

Comparing BACS against multisensory IA clusters yielded no values above the threshold of significance (all p-values > .171). Thus, they were not further investigated.

Comparing BACS against MSI clusters yielded significant results, after adjustment for multiple comparisons (critical p-value = 0.00625, Benjamini & Hochberg,1995), The Fisher-Z-transform and comparison of the between-group clusters revealed these between group significances to be significant. For the later 306-354ms cluster, higher BACS scores in the HC group are associated with stronger negative difference between unisensory and MSI effects (r = -55, p = 0.0029), but not the SCZ group (p=0.224). The between group difference was

significant when compared using a Fisher-Z transform ($Z = -2.99$, $p < 0.001$). Thus, for HC, a stronger relative deflection from zero in the additive condition, compared to the multisensory condition is associated with higher BACS scores. No such relationship was found for SCZ. Hence, stronger cognitive abilities in HC are related to more pronounced longer latency MSI effects. SCZ had a less pronounced difference in MSI, and their lower BACS scores showed no relationships to these markers.

-- Figure 8 --

4. Discussion

In this study we investigated the interplay between intersensory attention and multisensory integration in HC and in people with SCZ. People with SCZ showed deficits for unisensory target detection, however, they showed normal behavioral performances for multisensory targets. The analyses of evoked electrical brain activity revealed diminished IA effects for people with SCZ over frontal and occipital brain regions at later processing stages. These diminished long-latency ERP effects were correlated with worse behavioral performance. The analysis of MSI revealed multiple phases of integration, but the strength of MSI effects did not significantly differ between groups.

Previous studies of MSI in SCZ are conflicted. Some studies show both impaired unisensory and multisensory processing in SCZ (Stevenson et al., 2017; Williams et al., 2010), whereas others suggest that multisensory processing is relatively intact in patients (Stone et al., 2011; Wynn et al., 2014). The present study aligns with the latter studies, in showing that SCZ have intact MSI but impaired unisensory processing. Unlike any previous studies, our additional manipulation of IA provides some clues as to why the research findings on this are conflicting.

When looking at the processing of multisensory stimuli, as reflected in evoked brain activity, we found comparable attention effects for SCZ and HC up until around 200ms. We observed attention effects over somatosensory regions at around 100ms and over visual regions at around 200ms, which corresponds to previous studies reporting IA effects for the N1 and P1 components (Keil et al., 2017; Lenartowicz et al., 2014; Talsma et al., 2009). Thus, our results suggest intact early effects of IA in SCZ. This is in contrast to an earlier study of IA in SCZ, which showed stronger earlier deficits in N1 components (Wood et al., 2006). However this was specifically for auditory stimuli, thus there may be systematic differences across different combinations of sensory information. Notably, later ERP deflections showed more divergence of IA effects between groups. In the control group later IA effects included a fronto-central negative deflection at around 275ms and a positive occipital deflection at around 300ms. Similar IA effects have been previously described in healthy individuals, and have been interpreted as primarily reflecting top-down processing (Eimer & Forster, 2003; Foxe et al., 2005; Gomez-Ramirez et al., 2016; Keil et al., 2017; Kida et al., 2004). In contrast to the HC group, there were muted long-latency attention effects in the SCZ group. Hence, our results suggest intact IA effects on earlier processing, but aberrant IA effects on later top-down processing in SCZ.

Notably, the impairments in attention processing in SCZ were closely correlated with weakened performance for unisensory stimuli, but not for multisensory stimuli. Hence, although SCZ show deficits in unisensory behavioral performance and aberrant effects of IA on long latency evoked brain activity (for both multisensory and unisensory stimuli), it is possible that the additional information in multisensory stimuli compensates for the reduced long-latency attention deficit in SCZ. In other words, intact multisensory processes, which by themselves elevate and capture attention (Talsma et al., 2010), may boost the processing of multisensory stimuli in people with SCZ in a way that they are sufficiently attended to compensate for longer latency attention deficits. Since no such MSI effects occurred in unisensory stimuli, the long-latency attention deficit in SCZ only becomes behaviorally obvious in unisensory stimuli.

Using the additive approach to investigate multisensory processing, we found multiple phases of MSI. The first phase of MSI effects peaked at around 270ms over occipital (around 260ms) and frontal (around 270 ms) scalp regions, indicative for long-latency integrative processing. The lack of earlier MSI effects was somewhat surprising, since such effects have been reported previous studies in healthy individuals (Molholm et al., 2002; Talsma et al., 2007; Talsma & Woldorff, 2005). It is possible that our rigorous data-driven analysis approach, in which we corrected for multiple testing, has eliminated earlier MSI effects. More importantly, the long-latency MSI effects did not significantly differ between groups, which suggests intact multisensory processing in SCZ. Group deviations in stimulus processing manifested after 300ms, with two temporally overlapping later clusters in frontal (around 340ms) and occipital (around 330ms) scalp regions. In these later clusters, SCZ showed weaker deflections from zero for both multisensory and unisensory conditions. Diminished long latency ERP components in people with SCZ have been described in various previous attention paradigms (Michie et al., 1990; O'donnell et al., 1999; Wood et al., 2007). However, although the amplitudes were generally smaller in SCZ, there were no significant differences in MSI effects between groups. Taken together, our data suggests uncompromised multisensory processing in SCZ.

Our findings could have implications for theories of the aetiology of SCZ symptomology and its relation to sensory processing deficits. Researchers have suggested that the accumulation of processing errors cascades up into higher level distortions, resulting in positive and negative symptoms (Stevenson et al., 2017; Zhou et al., 2018). The observation of preserved MSI in SCZ suggests that perceptual processing deficits are not necessarily cumulative.

Sensory information from a different modality can reduce error processing by providing statistically independent sampling from the environment (Gingras et al., 2009). It appears that SCZ can use this to compensate for top-down attention deficits. Future studies could clarify this by systematically manipulating the reliability of individual cues in multisensory paradigms.

Since SCZ multisensory processes can presumably compensate for top-down deficits in SCZ, we could further examine how patients respond to stimuli with variations in stimulus reliability. If input to one sensory modality was less reliable than input to another, could SCZ successfully assign corresponding weights to the incoming information according to the quality of the signal (Beauchamp et al., 2010)? Another theory of SCZ aetiology holds that distortions in coordination of perception could trigger limits in inner and outer boundaries (Postmes et al., 2014). Our findings suggest that attentional deficits in any failure of integration are an important part of any such model. In sum, the aetiology of SCZ could be related to the interplay between MSI and top-down attention processes.

Our study did not find direct connections between specific SCZ symptomatology and IA deficits or MSI. It is possible that our study sample, though large enough to detect group differences, was not sufficiently large for more fine-grained analysis of the heterogeneous symptomatology present in SCZ. A direct standardized measure of perceptual abnormalities in SCZ, such as the Audio-Visual Abnormalities Scale from Nikitova et al., (2019) may have provided a more informative behavioral correlate for performance and perceptual pathology in SCZ. However, this questionnaire was released after the data for our study were gathered. Another isolated observation in our study was a robust positive correlation ($r = -.55$) between MSI effects at around 330ms and BACS composite performance, but this was only found in the HC group. A previous study showed positive relation between MSI and general intellectual abilities in children (Barutchu et al., 2011), suggesting that improved ability to integrate different sensory processes is a necessary precursor of intellectual performance. If MSI and BACS composite performance both require higher cortical top-down processing (Klemen & Chambers, 2012), it may be that the any relationship between MSI and cognitive performance in SCZ is obscured, as multisensory processes may compensate for the top-down processing deficits in the present study. Nevertheless, future replication of relationships found between cognitive performance and MSI in healthy individuals is necessary.

Due to the multifaceted interplay between attention and multisensory integration, a more complete understanding of our findings would require more detailed modeling approaches,

separating feed-forward and feedback processes and their deficits in SCZ (see e.g. Moran et al., 2008). A dissociation between top-town and bottom-up processing defined in terms of receptor types has also been proposed, with bottom-up processing facilitated by fast AMPA receptors and top-down processing preferentially facilitated by NMDA receptors, the latter of which are particularly disturbed in SCZ (Berkovitch et al., 2017). Examination of MSI with manipulation of these variables, e.g. with low dose Ketamine administration in healthy participants, could provide some evidence of a causal mechanism behind the observed differences in functional brain activity (Berkovitch et al., 2017). Thus, our functional event-related effects in SCZ are presumably related to other biological indices of dysfunction in SCZ.

Our study had some limitations. We sought to minimize the confounding influence of medication by selecting patients with the minimum possible amount of medication and examining follow-up correlations. In these analyses, we did not find relationships between medication and our variables of interest. Nevertheless, an influence of medication on our data cannot be completely ruled out. We also did not explicitly control for the length of time between measurement and onset of the first psychosis, so no relation between the progression of the disorder and IA or MSI could be tested. Schizophrenia is an extremely heterogeneous disorder and affected individuals have a wide range of symptoms and functional capacities. Thus, alternative perspectives with people at early vs. later stages of SCZ, first-degree relatives and/or schizotypal personality disorder would help triangulate results. Taken together, our results provide a solid foundation for further investigation of the interaction between attention and multisensory integration in SCZ.

4.1. Conclusion

Our study sought to clarify ambiguous results in previous studies of MSI in schizophrenia by taking into account attentional aspects of multisensory processing. We found behavioral deficits in SCZ, particularly for unisensory stimuli. At the neural level, we observed aberrant attention effects at longer latency over frontal and occipital brain areas, presumably reflecting feedback top-down processing deficits in SCZ. Our study suggests that multisensory processing, which seems to be intact in SCZ, may compensate for these deficits in longer latency attention processing. This assumption is supported by the normal behavioral performance for multisensory stimuli in patients. It is possible that previous ambiguous findings on multisensory processing in SCZ relate to differences in top-down attentional demands across studies.

5. References

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5.1. Tables:

	SCZ mean (N=27)	SCZ sd	HC mean (N=27)	HC sd	t	p
Age	39.78	9.07	38.63	9.64	-0.45	0.65
Cigarettes	SCZ median (N=15)	SCZ iqr	HC median (N=13)	HC iqr	w	p
(Fagerström score)	6	1.5	2	4	32	0.002**
Gender	SCZ	HC				
female	10	11				
male	17	16				
	SCZ median (N=23)	SCZ iqr	HC median (N=23)	HC iqr	w	p
Education (years)	10	3	13	3	299.5	0.424
	SCZ mean (N=27)	SCZ sd			Count	
Antipsychotic Dose	83%†	57%			Clozapine	8
	†(percentage = of standard daily dose of Olanzapine)				Amisulpride	7
					Quetiapine	3
					Olanzapine	6
					Aripiprazole	7
					Risperidone	6
					Ziprasidone	3
					Paliperidone	1
BACS Z scores	SCZ median (N=27)	SCZ iqr	HC median (N=27)	HC iqr	w	p
BACS Z Verbal	-0.94	1.55	0.30	2.02	541	0.002**
BACS Z Digit	-0.26	1.14	-0.05	1.13	460	0.100
BACS Z Token	0.12	1.57	0.43	1.68	444.5	0.169
BACS Z Fluency	-0.62	1.09	0.08	1.26	516	0.009**
BACS Z Symbol	-1.18	1.53	0.26	1.33	555.5	0.001***
BACS Z Tower	0.34	0.61	0.19	0.50	374	0.876
BACS Composite Z-Score	-0.79	1.69	0.21	0.95	553	0.001***
PANSS	SCZ mean (N=27)	SCZ sd				
Positive 5	7.67	4.12				
Negative 5	12.30	5.78				
Disorganized 5	6.19	2.48				
Excitement 5	12.15	3.83				
Depression 5	7.15	3.57				

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 1: Demographics for participants. Differences between groups were calculated by either parametric independent t-tests (t) or non-parametric Wilcoxon tests (w), where data did not fulfil assumptions of parametric tests, iqr = inter-quartile ratio. Antipsychotic dose is calculated as the percentage of standard daily dose of Olanzapine, which is 10mg. BACS raw scores were converted to z-scores normalized for age and gender.

	Multisensory			
TOI	Cluster	β	F(1,52)	p
90-118ms	Group	0.032	0.14	0.711
	attention	0.18	48.43	<.0001***
	Group*Attention	0.03	0.40	0.530
158-216ms	Group	0.16	1.10	0.299
	attention	0.19	47.45	<.0001***
	Group*Attention	-0.04	0.904	0.346
168-218ms	Group	-0.19	1.65	0.204
	attention	-0.23	42.94	<.0001***
	Group*Attention	0.04	0.48	0.493
230-320ms	Group	0.27	1.72	0.196
	attention	0.40	34.31	<.0001***
	Group*Attention	-0.19	5.29	0.025*
282-318ms	Group	-0.08	0.085	0.772
	attention	-0.34	38.60	<.0001***
	Group*Attention	0.21	11.60	0.002**

*p values: *** 0.001 ** 0.01 * 0.05*

Table 2: Intersensory Attention effects on ERPs to bisensory stimuli. Results for the main effects of t-test for each time-point and electrode of the full time-course of stimulus-evoked activity. Time windows were identified post-hoc by clustering analysis in order to structure the results. Amplitudes(μV) within the cluster-algorithm defined TOI and ROI were then averaged. These averages were tested against Group and Attention in a follow-up linear mixed-model ANOVA to determine whether there were Group effects or Group*Attention interaction effects.

	Multisensory vs. combined unisensory			
	Cluster	β	F(1,52)	p
246-292ms	Group	-0.06	0.27	0.60
	Modality	0.21	50.69	<.0001***
	Group*Modality	-0.01	0.03	0.86
184-236ms	Group	0.22	2.51	0.12
	Modality	-0.18	47.40	<.0001***
	Group* Modality	-0.03	0.32	0.57
316-364ms	Group	0.21	4.54	0.04*
	Modality	-0.35	44.34	<.0001***
	Group* Modality	0.08	1.00	0.32
306-354ms	Group	-0.24	6.27	0.02*
	Modality	0.38	53.49	<.0001***
	Group* Modality	-0.10	1.58	0.21

p-values: *** 0.001 ** 0.01 * 0.05

Table 3: Multisensory integration effects on ERPs to bisensory vs. combined unisensory stimuli. Results for the main effects of t-test for each time-point and electrode of the full time-course of stimulus-evoked activity. Time windows were identified by clustering analysis in order to structure the results. Amplitudes (µV) within the cluster-algorithm defined TOI and ROI were then averaged. These averages were tested against Group and Modality (Multisensory vs. Combined Unisensory) in a follow-up linear mixed-model ANOVA to determine whether there were group effects or group*modality effects. MSI effects were found for both groups. The magnitude of the MSI effects did not significantly differ between groups, as shown by the absence of Group*Modality interactions.

Multisensory correlations		r		
TOI	d-prime	HC	SCZ	Fisher Transform HC vs. SCZ
090-118ms	multisensory average	-0.32	-0.1	
	unisensory average	-0.38	-0.06	
158-216ms	multisensory average	-0.33	-0.19	
	unisensory average	-0.26	-0.33	
168-218ms	multisensory average	0.33	0.16	
	unisensory average	0.27	0.39	
230-320ms	multisensory average	0.01	-0.5	
	unisensory average	-0.02	***-0.7****	Z = 2.94*, p = 0.002
282-318ms	multisensory average	-0.08	0.29	
	unisensory average	-0.19	***0.55****	Z = 2.21*, p = 0.014

Critical alpha for correlations p < 0.005

Table 4: Correlation matrix of d-prime performance and IA. Spearman correlations are presented, critical p value, adjusted for number of comparisons was 0.005. To test whether the there was a difference in the r values between groups, a Fisher transform was carried out, significant results highlighted in grey.

5.2. Figure Legends:

Figure 1 a) Illustration of the stimulus setup, monitor tilted on an angle, participant's hand behind the screen to where the tactile stimulator was located. Tactile stimulation was for the left hand, right hand index finger made the behavioral responses. Left hand was held in place with cushioning to avoid muscle movement or fatigue. **1b) Illustration of the timeline of a single trial**.

Figure 2 Behavioral outcome for HC and people with SZ. Mode represents the difference between conditions with combined multisensory stimuli and unisensory stimuli. The attended modality condition represents the instruction to either attend to visual or tactile stimuli. Patients with SCZ were worse that HC in the processing of unisensory visual and tactile targets (red dots). Notably, no such difference was found for multisensory targets (turquoise dots). Points represent individuals, large dots with error bars represent mean and ±1 SD. The significant main effects and interactions are represented with asterisks (* $p < 0.05$, ** $p < 0.01$, ***$p < 0.001$).

Figure 3 Data-driven tests of IA effects on bisensory VT stimuli. defined ROIs and TOIs for the contrast between visual and tactile attention for combined SCZ and HC groups. Positive and negative clusters are masked for cluster-based significance, each row corresponds to a time window where a significant cluster was found in the contrast between visual and tactile attention for the combined SCZ and HC groups. The grey bars indicate the TOIs of the clusters, of which there are 5 in total. The TOIs overlap for both the 158-216ms and 168-218ms clusters, as well as the 230-320ms and 282-318ms clusters, the darker grey bars represent this overlap.

Figure 4 Intersensory attention effects on ERPs to bisensory stimuli. Left column: Topographic plots of ERPs with the attend-visual, attend-tactile condition, as well as their difference**.** Clusters of significant sensors are highlighted by black dots in the difference plot. Middle column: ERP traces for the significant clusters and their difference waves (in black). Right column: Point and density plots of repeated measures ANOVA of group*attention effects upon amplitudes in defined clusters. Large points represent mean, and confidence intervals represent ±1 SD. While earlier (< 220 ms) IA effects were comparable between HC and SCZ, people with SCZ lacked on longer latency (> 230 MS) effects of IA, which were specifically found in the HC group. Only group related significance (either main effect or interaction) is marked with * in the graphs, p values: ** 0.01 * 0.05.

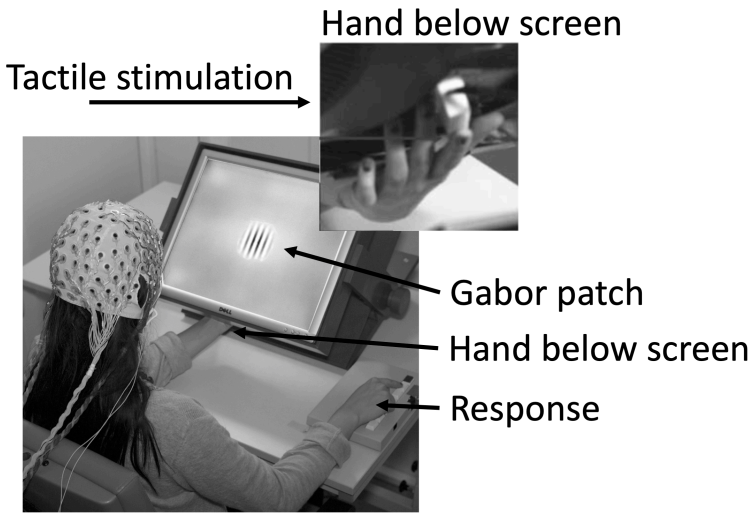
Figure 5 Data-driven tests of additive effects defined ROIs and TOIs for the contrast between bisensory and combined unisensory stimuli for combined SCZ and HC groups. Positive and negative clusters are masked for cluster-based significance, each row corresponds to a time window where a significant cluster was found in the contrast between bisensory and combined unisensory responses for the combined SCZ and HC groups. The grey bars indicate the TOIs of the clusters, of which there are 4 in total. The TOIs overlap for both the 246-292ms and 240-280ms clusters, as well as the 316-364ms and 306-354ms clusters, the darker grey bars represent this overlap.

Figure 6: Multisensory integration effects on ERPs. Left column: Topographies of ERPs for bisensory ('bisens') and additive condition, as well as their difference, with the cluster of significant sensors marked in the latter. Middle column: ERPs for the significant clusters and their difference waves (black line). Right column: Point and density plots of repeated measures ANOVA of group*MSI effects upon amplitudes in predefined clusters. Large points represent mean, and confidence intervals represent ±1 SD. The overall ERPs amplitudes at later processing stages were larger in HC compared with SCZ but the MSI effects did not differ between groups. Only group related significance (either main effect or interaction) is marked with * in the graphs, p values: ** 0.01 * 0.05.

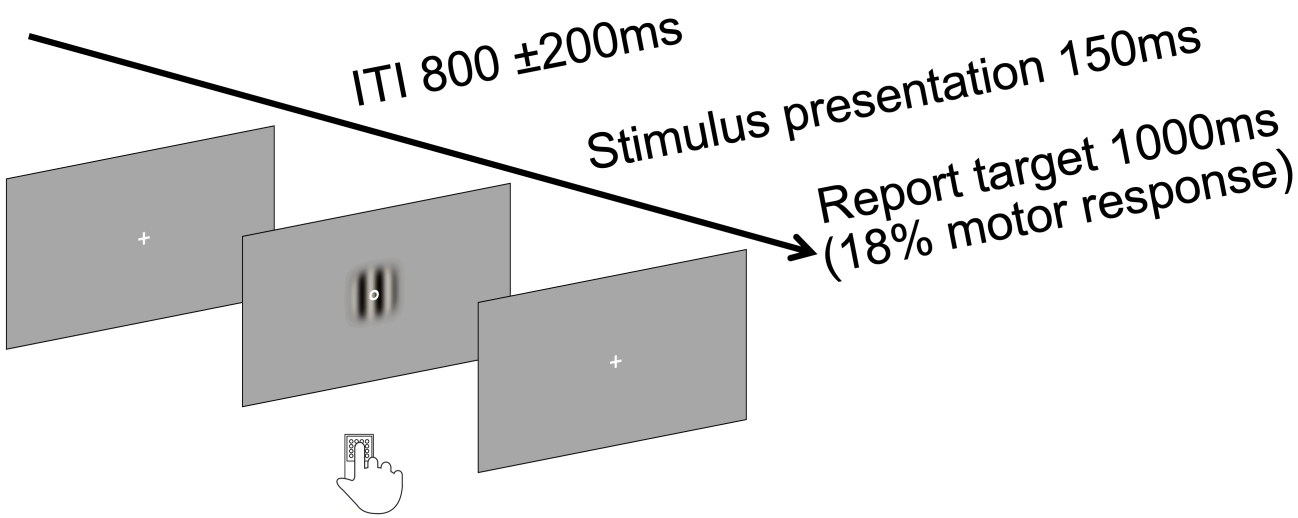
Figure 7. Relationships between behavioral performance and IA effects on ERPs. Scatterplot contrasting d-prime values of unisensory responses with average differences amplitudes in the bisensory condition. Above is the central cluster defined at 230-320ms and below the occipital cluster defined at 282-318ms. The y-axis measures the difference between Visual Attention and Tactile Attention.

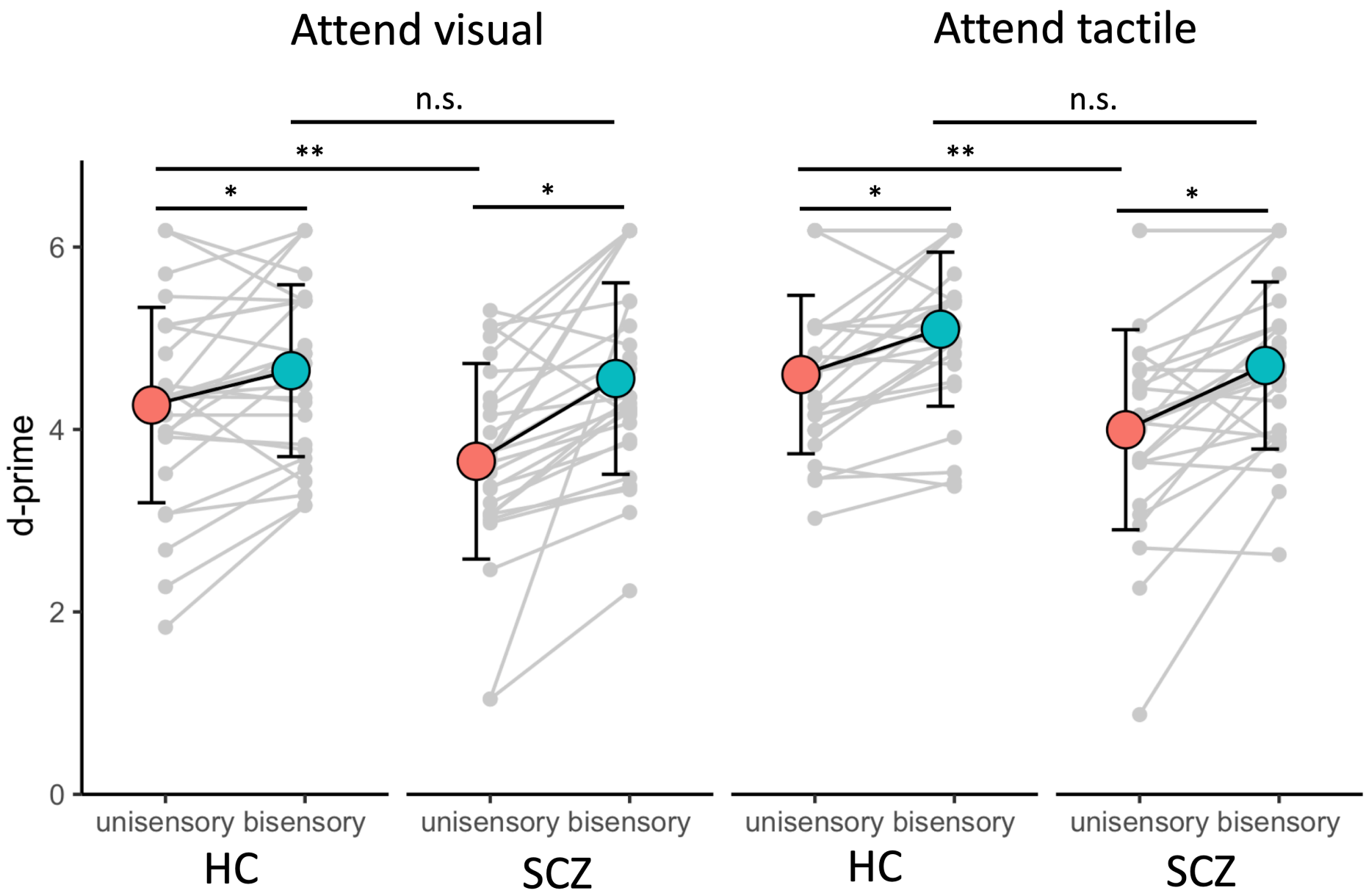
Figure 8 Scatterplots of BACS Composite Z-scores and amplitude in posterior multisensory integration cluster at 306-354ms for HC and SCZ separately. Z-scores are the raw scores adjusted for population norms, according to gender and age group, thus they do not centre around 0.

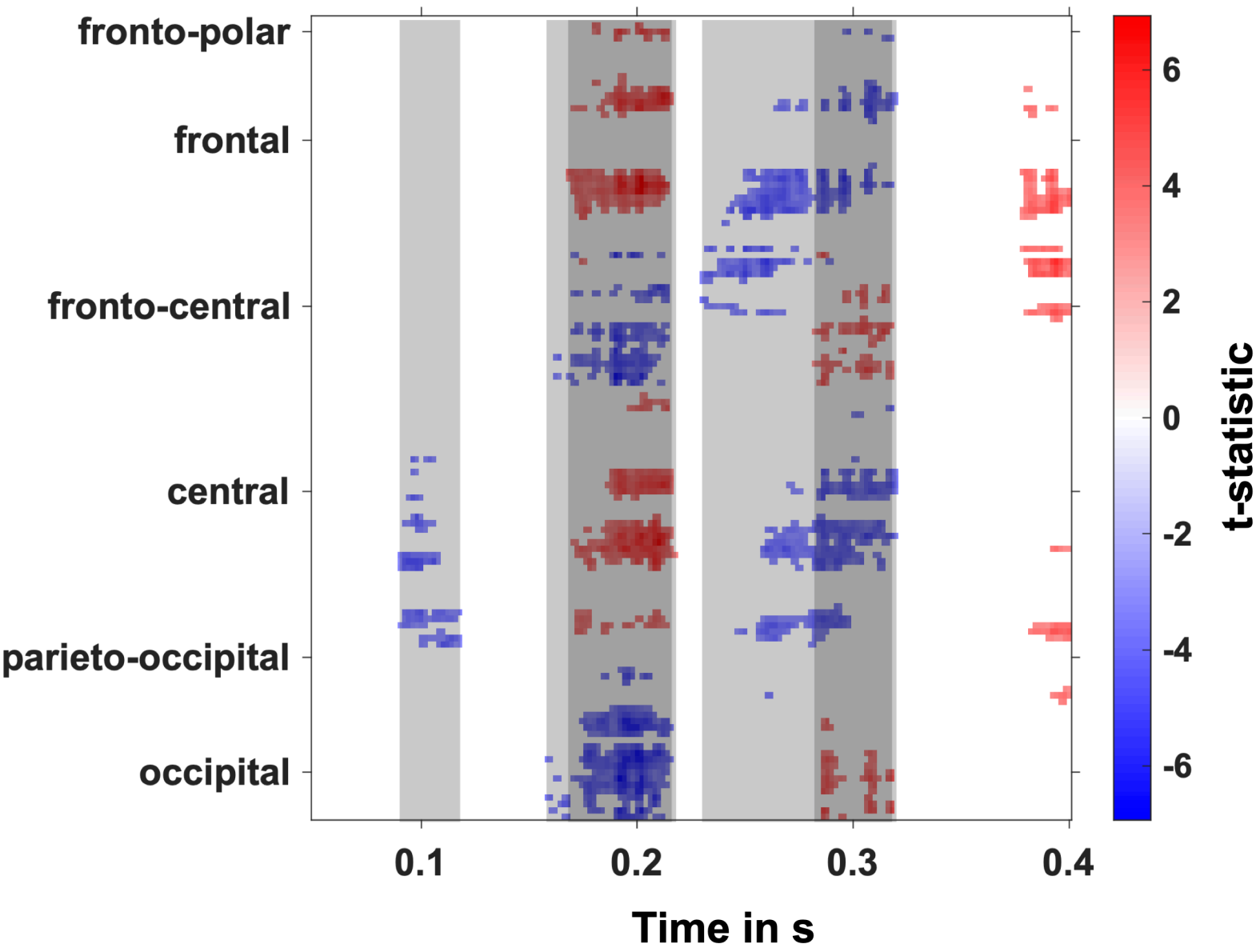
a) Setup Gabor Patches and Braille Stimuli

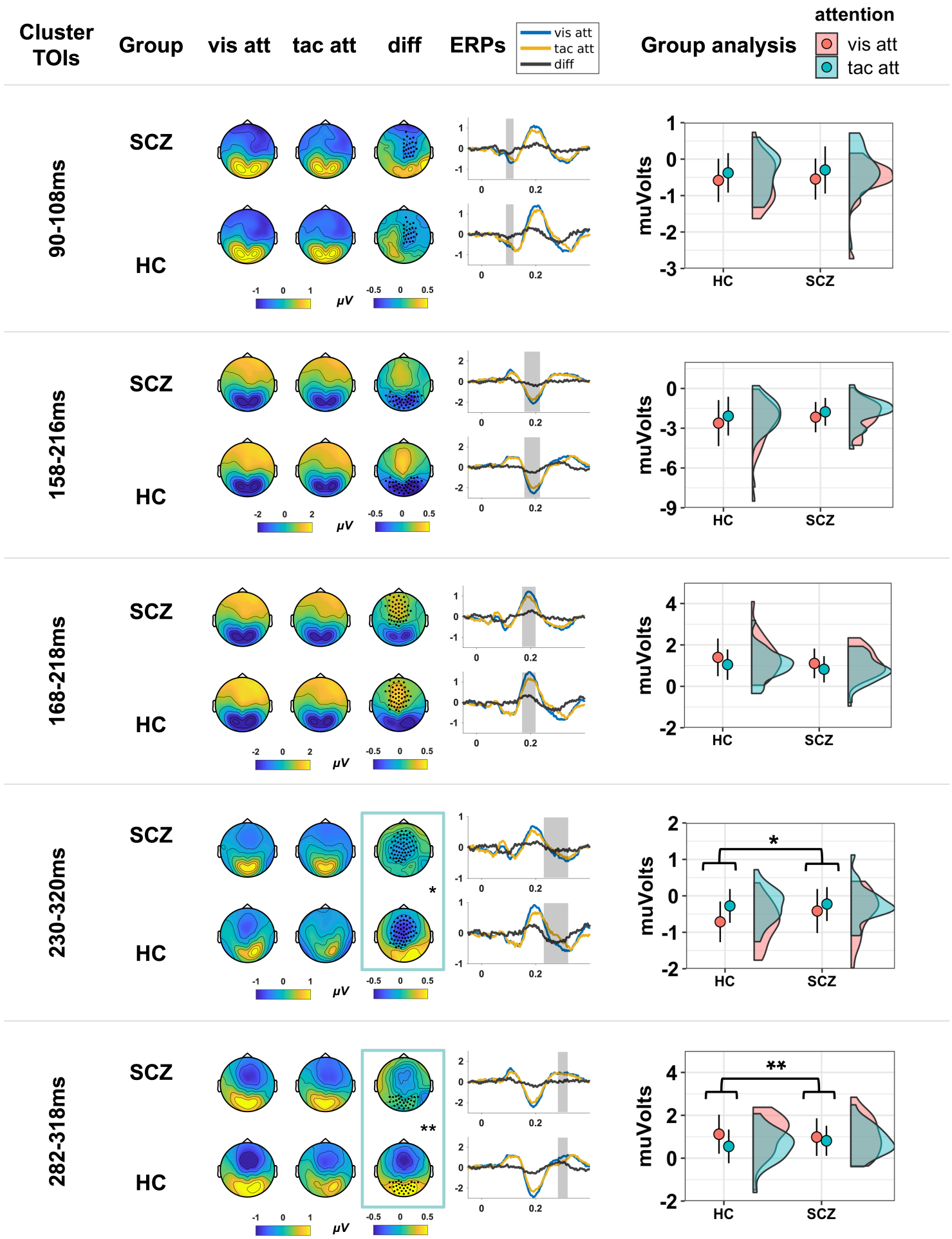


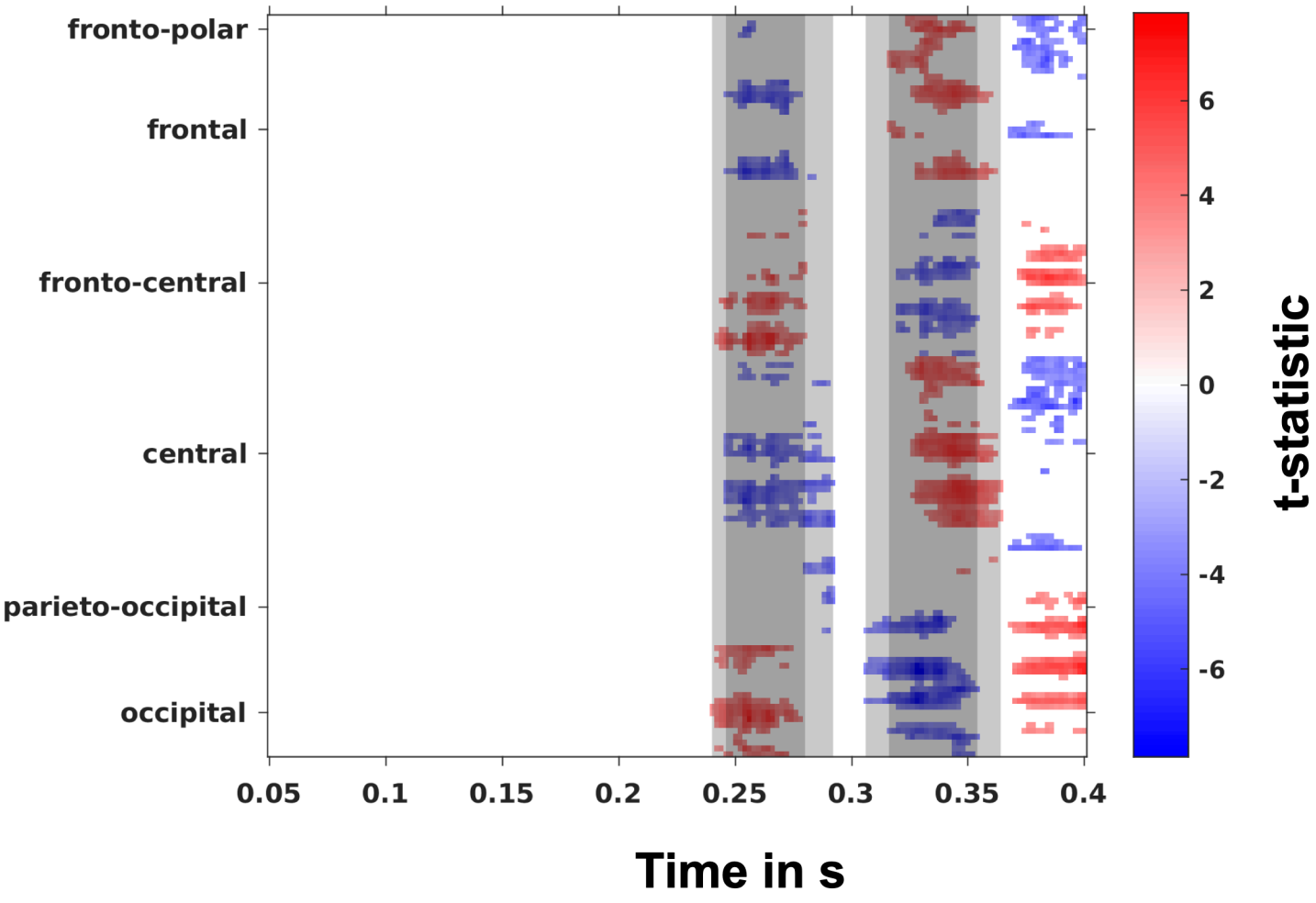
b) Single trial timeline

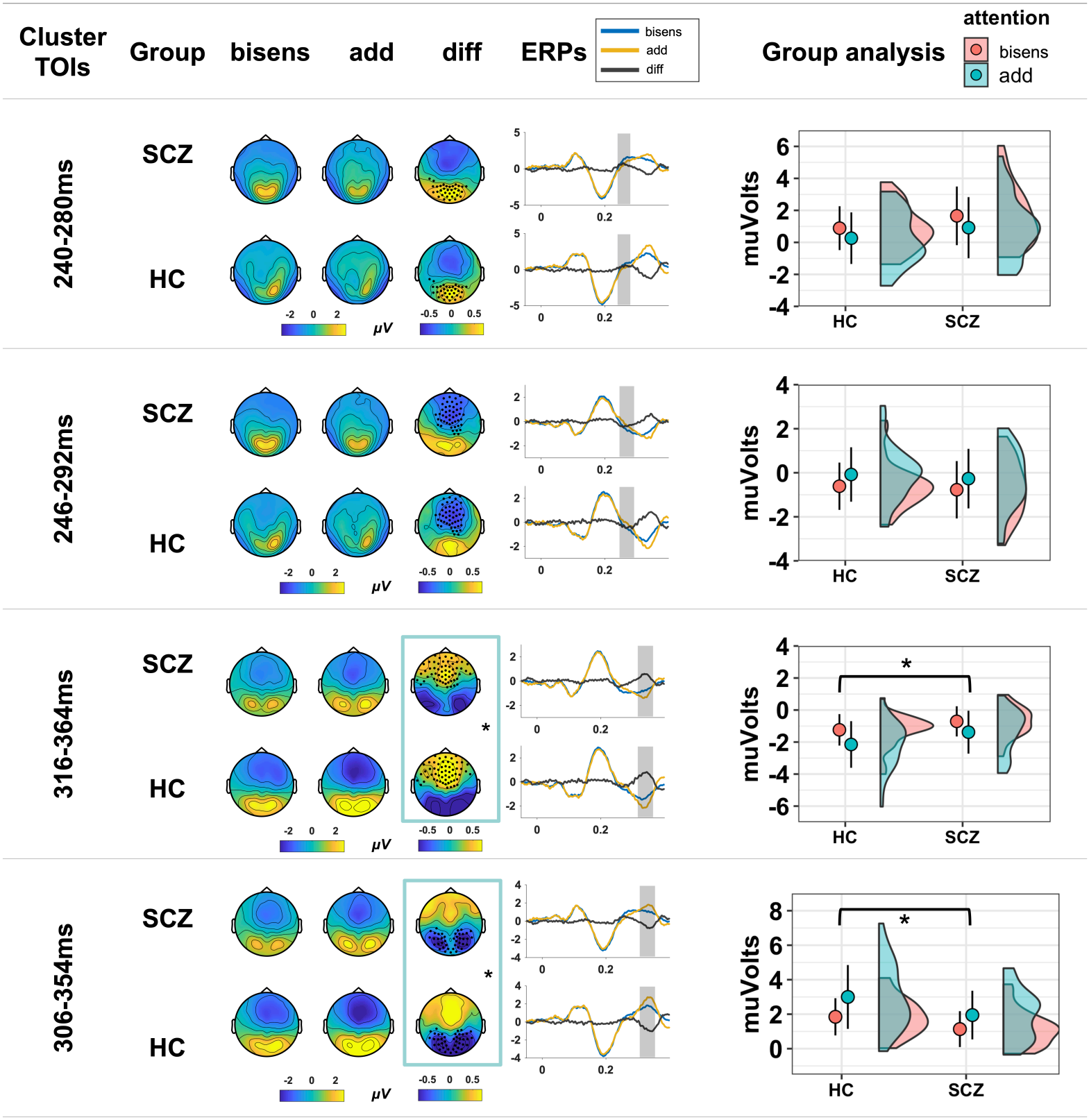



Attend visual
Attend tactile
n.s.
**
*
d-prime
0
2
4
6
unisensory bisensory
HC
SCZ

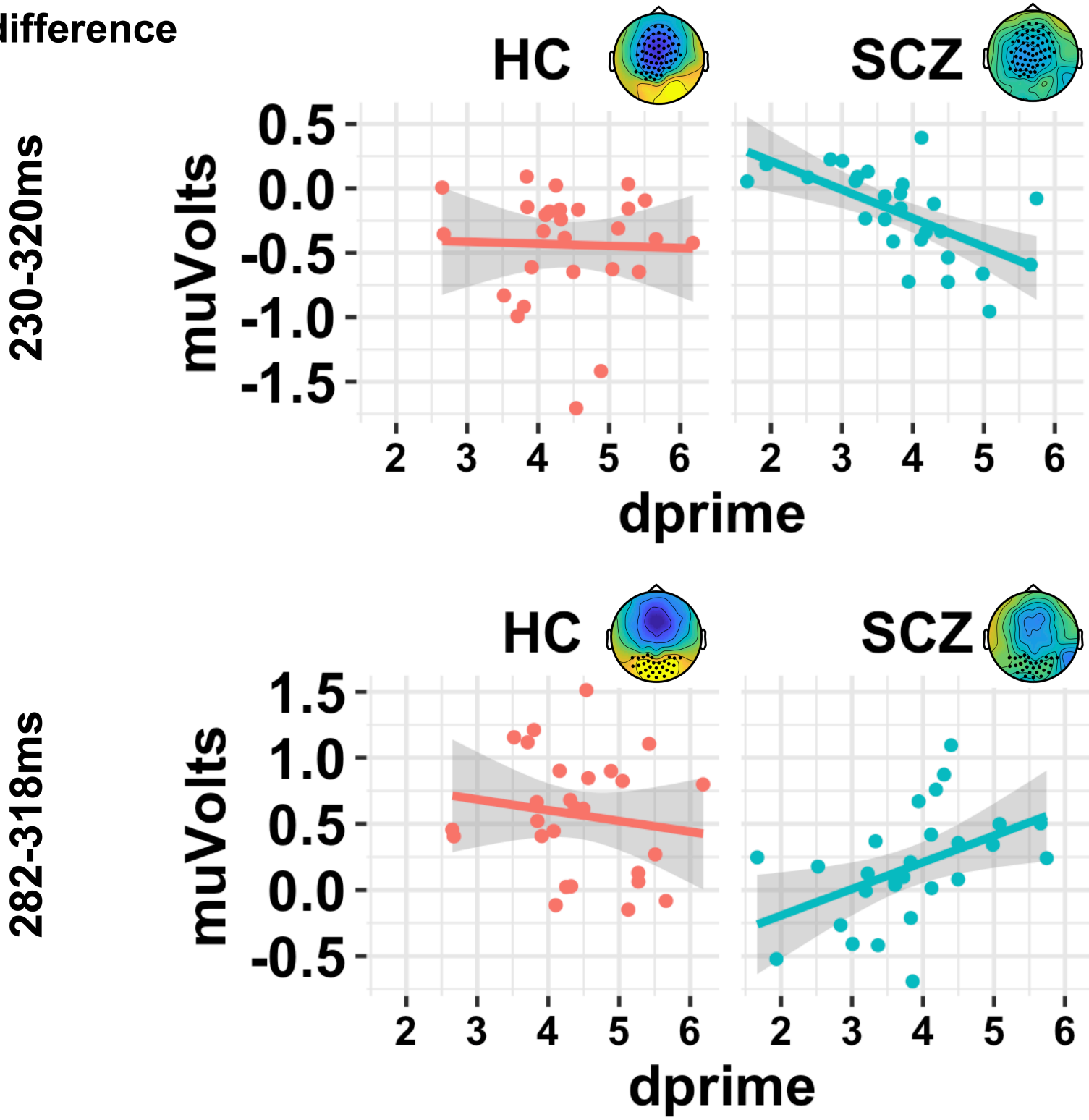

fronto-polar
frontal
fronto-central
central
parieto-occipital
occipital
0.1
0.2
0.3
0.4
Time in s
6
4
2
0
-2
-4
-6
t-statistic

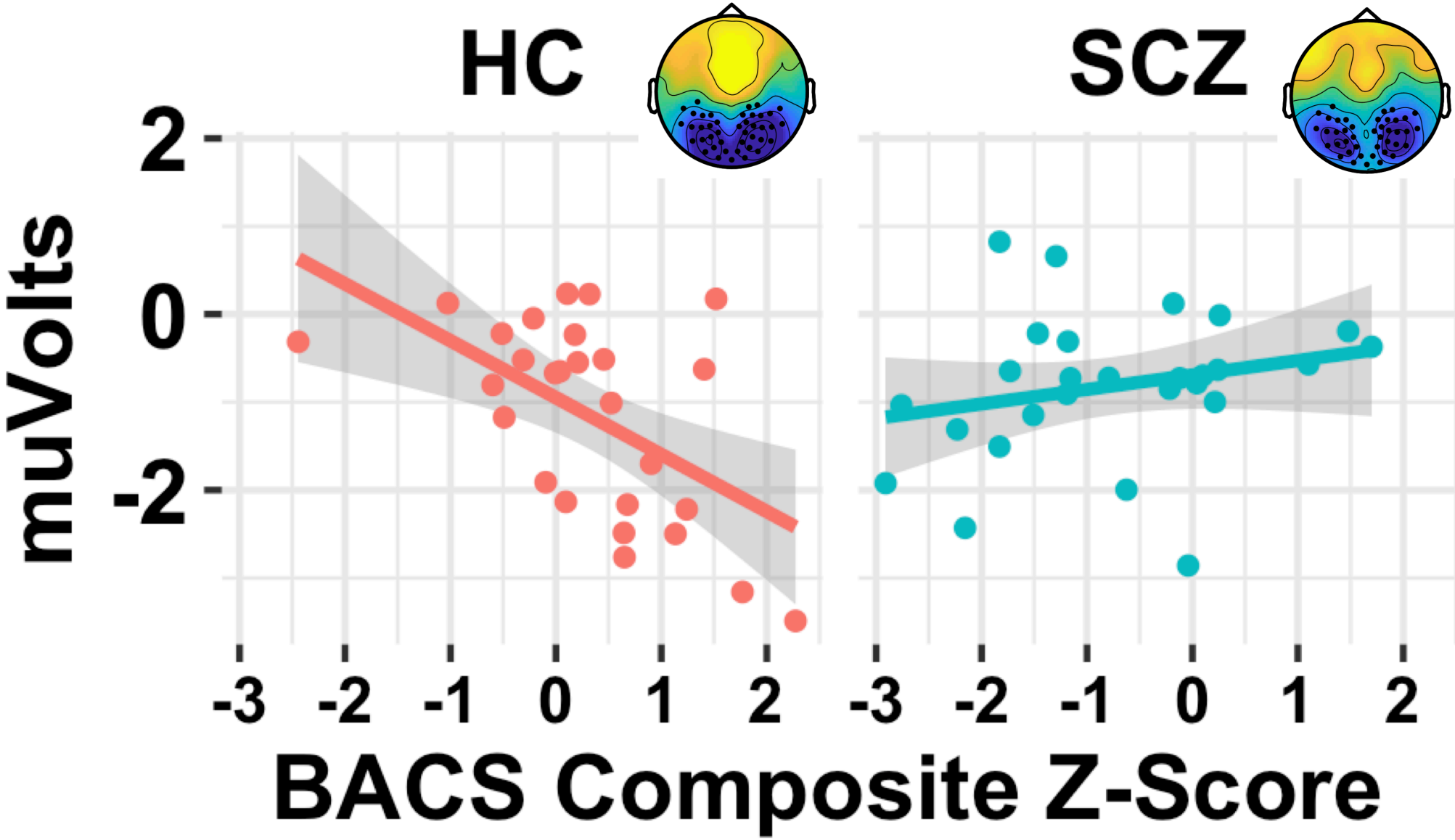

Cluster TOIs
Group
vis att
tac att
diff
ERPs
vis att
tac att
diff
Group analysis
attention
vis att
tac att
90-108ms
158-216ms
168-218ms
230-320ms
282-318ms
SCZ
HC
μV
muVolts
HC
SCZ
*
**


fronto-polar
frontal
fronto-central
central
parieto-occipital
occipital
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
Time in s
6
4
2
0
-2
-4
-6
t-statistic


Cluster TOIs
Group
bisens
add
diff
ERPs
bisens
add
diff
Group analysis
attention
bisens
add
240-280ms
246-292ms
316-364ms
306-354ms
SCZ
HC
-2 0 2
μV
-0.5 0 0.5
0
0.2
muVolts
HC
SCZ
*

Cluster TOI difference




HC
SCZ
muVolts
2
0
-2
-3
-2
-1
0
1
2
-3
-2
-1
0
1
2
BACS Composite Z-Score