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**The temporal sensitivity to the tactile-induced Double Flash Illusion mediates
the impact of beta oscillations on schizotypal personality traits**

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Abstract

The coherent experience of the self and the world depends on the ability to integrate vs. segregate sensory information. Optimal temporal integration between the senses is mediated by oscillatory properties of neural activity. Previous research showed reduced temporal sensitivity to multisensory events in schizotypy, a personality trait linked to schizophrenia. Here we used the tactile-induced Double-Flash-Illusion (tDFI) to investigate the tactile-to-visual temporal sensitivity in schizotypy, as indexed by the temporal window of illusion (TWI) and its neural underpinnings. We measured EEG oscillations within the beta band, recently shown to correlate with the tDFI. We found individuals with higher schizotypal traits to have wider TWI and slower beta waves accounting for the temporal window within which they perceive the illusion. Our results indicate reduced tactile-to-visual temporal sensitivity to mediate the effect of slowed oscillatory beta activity on schizotypal personality traits. We conclude that slowed oscillatory patterns might constitute an early marker for psychosis proneness.

Keywords

Multisensory Integration; Schizotypy; Temporal Sensitivity; Beta Oscillations

1. Introduction

Identifying biomarkers for the early diagnosis of schizophrenia has become a crucial goal of current research. Schizophrenia is a highly invalidating and debilitating disorder which affects about 0.5% of the worldwide global population (Sukanta et al., 2005). Schizophrenia often-emerges in late adolescence or early adulthood and its symptoms are non-remitting. Interestingly, the emergence of the disorder is typically preceded by a 3-4-year prodromal phase in 75% of patients (Hafner et al., 2003; Sorensen et al., 2009). During this phase, subtle behavioural changes, cognitive impairments and sub-threshold psychotic symptoms usually emerge (Klosterkötter et al., 2001). As such, recent research has increasingly focused on identifying those individuals at a higher risk of developing schizophrenia, and has strived to identify appropriate strategies for risk prediction and early intervention (Fusar-Poli et al., 2013, McGorry et al., 2009). Researchers have identified a series of cognitive and behavioural variations of schizophrenic traits which, while of reduced severity, share salient characteristics similar in form. These variations are thought to form a single personality trait: schizotypy (Lenzenweger 2018; Stotz-Ingenlath 2000). Schizotypy seemingly shares a factor-structure with schizophrenic symptoms; namely the positive, negative and disorganised subscale. It has been hypothesised that elevated levels of schizotypy represent a vulnerability to psychosis (Kwapil et al., 2013). As such, it could be argued that schizotypy and schizophrenia are *qualitatively* close but *quantitatively* distant. Areas of overlap between schizotypy and schizophrenia have indeed been shown both at the behavioural and neural levels (Koychev et al., 2011; Ettinger, U. et al. 2015) in several domains.

At the behavioural level, for example, both schizophrenia and schizotypy have been associated with altered responses to somatosensory stimuli (Lenzenweger et al.,

2000; Chang et al., 2005; Benson et al., 2019; Michael & Park, 2016). Proprioception and touch allow for the proper discrimination between the outer environment and the sense of one's bodily boundaries. As such, a distorted haptic or proprioceptive sense could invalidate proper self-other boundary recognition. Related to this, Ferri et al., (2016) investigated the role of touch remapping in people with high and low schizotypy. They demonstrated altered remapping of environmental stimuli in the bodily space in the high- relative to the low-schizotypy group. Dysfunctions in somatosensory processing and its integration with other senses seemingly lead to a more malleable body representation and an increased proneness to multisensory bodily illusions both in schizophrenia and schizotypy (Thakkar et al., 2011; Ferri et al., 2014; Michael & Park, 2016). This increased/heightened proneness to multisensory illusions might also be accounted for by another perceptual dysfunction seemingly shared by both schizophrenia and schizotypy, namely a dysfunction in the temporal profile of multisensory integration. Researchers have indeed observed that both schizophrenic patients (Foucher et al., 2007; Stevenson et al., 2017; Haß et al., 2017) and high-schizotypy individuals (Ferri et al., 2017; Ferri et al. 2018) often experience stimuli that are further apart in time and in space as co-occurring, possibly leading to higher proneness to multisensory perceptual illusions (Haß et al., Ferri et al., 2018).

At the neural level, neurophysiological evidence suggests that schizophrenia is associated with abnormalities in oscillatory activity and functional connectivity, especially in the beta- and gamma- band frequencies and that these impairments are linked to both perceptual and cognitive deficits (Uhlhaas et al, 2008). Moreover, such observations, already described in schizophrenia, have been extended to schizotypy (Koychev et al., 2011). Interestingly, evidence is now emerging linking neural oscillations in distinct frequency bands to different mechanisms of multisensory

processing (Senkowski et al., 2008; Ronconi et al., 2017). An investigation conducted by Cecere, Rees, and Romei (2015) using the audio-visual Double Flash Illusion task (aDFI) in healthy individuals, found a relationship between individual's alpha band oscillations in the visual cortex and the Temporal Window of Illusion (TWI). In a typical aDFI, a participant is presented with a single flash as the visual stimulus paired with two auditory beeps presented in quick succession. The pairing of the two auditory stimuli often results in the perception of a second illusory flash, even if only one flash is ever presented (Shams et al., 2000). In particular, Shams et al., (2002) adopted a version of the illusion which uses a wide range of inter-beep intervals, well-suited to determine the size of the TWI (Shams et al., 2002; Cecere et al., 2015). Using electroencephalography (EEG) to measure brain activity, the researchers found a link between the TWI and the individual alpha frequency. More specifically, they found that slower (and faster) alpha frequencies were associated with longer (and shorter) TWIs. The authors interpreted these findings as a sampling mechanism gating sensory information into temporal units. These findings have been recently replicated (see Cooke et al., 2019; Keil and Senkowski, 2017). Moreover, Cooke et al., (2019) investigated the neural dynamics related to the tactile version of the DFI, that is the tactile-induced DFI (tDFI) where the two auditory stimuli are replaced by two tactile stimuli as in Violentyev et al., (2005). The researchers found that the TWI induced by the tDFI does not relate to the individual alpha frequency but to the individual beta frequency instead. More specifically, they found that slower (and faster) beta frequencies are associated with longer (and shorter) TWIs.

Taken together, these results suggest that prolonged periods of temporal integration between different sensory modalities, which have been observed in schizophrenia (Stevenson et al., 2017) and characterize also schizophrenic-like subclinical

conditions (Haß et al., 2017) may at least partially originate from a slowing-down of those oscillatory frequency patterns associated with the temporal dynamics of multisensory integration processes. In other words, prolonged periods of temporal integration between different sensory modalities would mediate the impact of specific oscillatory pattern changes on individual levels of schizotypy. The overarching goal of our work is to test this model with the final aim of providing a neuro-behavioral early marker for schizophrenia risk. This goal will be achieved through the validation of the following empirical points:

- (i) extending the findings of Ferri et al., (2018), who showed enlarged TWI in high schizotypes using the aDFI, to the somatosensory domain, hence using the tDFI;
- (ii) replicating the findings of Cooke et al., (2019), who showed that the individual TWI for the tDFI positively correlates with the individual beta frequency (IBF) in the occipital cortex;
- (iii) investigating the potential association between schizotypy and IBF.

We expect people with high schizotypy to show an enlarged TWI for the tDFI, in turn predicted by a slower individual beta frequency. Most importantly, the association between the individual beta frequency and the individual scores in a self-report measure of schizotypy, should be mediated by the size of the TWI.

2. Material and Methods

2.1. Participants

An a-priori sensitivity power analysis (G*Power) was performed to determine the sample size that would provide $\geq 80\%$ power to find correlations between behavioural and EEG data corresponding to an effect size $r = 0.50$. The analysis returned a sample of 26 participants. This effect size estimate was chosen based

on a recent study showing that both the speed of individual alpha oscillations predicts the temporal window of the auditory-induced illusion, and that the speed of individual beta oscillations predicts the temporal window the tactile-induced double flash illusion with an effect size $r > 0.50$. Studies reporting correlations between auditory- or tactile- induced illusions and SPQ scores were not available. A total sample of 55 participants (33 females, mean age 25) volunteered to take part in the study after having been screened with respect to their schizotypal traits using the Schizotypal Personality Questionnaire (SPQ; (Raine, 1991)). The questionnaire was administered through Qualtrics, a web-based data collection system. None of the participants reported any history of substance abuse or other neuropsychiatric disorders. Furthermore, they reported normal or corrected-to-normal vision. Participants gave written consent before taking part in the experiment. They were all naïve to the purpose of the study.

2.2. Apparatus and procedure

All visual stimuli were presented on a 17.5" cathode ray tube monitor via a Dell Optiplex 960 computer (Windows XP, resolution: 1280x1024) with a refresh rate of 85Hz. The tactile stimulation was provided by a Heijo Research Electronics tactile stimulator taped onto the participant's left index finger. The stimulator would produce a suprathreshold tap by pushing a plastic tip against the participant's skin whenever a current was passed through the solenoid. White-noise (approximately 50db) was continuously played to participants through speakers during the tactile stimulation, to cover the mechanic noise produced by the tactile stimulator (Experimental stimuli were presented via E-prime (version 2.0; Psychology Software Tools, Pittsburgh, PA).

The electroencephalogram (EEG) was recorded at 500Hz from 64 Ag/AgCl electrodes mounted on an elastic cap (Easycap, Herrsching, Germany) alongside the ground electrode (position: AFz) and the reference electrode (placed upon the right mastoid bone). The EEG signals were amplified using BrainVision Recorder (BrainProducts GmbH, Gilching, Germany). All the electrodes were set at an impedance of a maximum of 10k Ω .

In all trials, participants were presented with a flashing disc of a diameter of 2 cm displayed against a grey background. The disc always flashed once for 12 ms and was located below a small fixation cross continuously present at the centre of the screen. During the task, the disc presentation was always paired with a double tactile stimulation (double tap) to the left finger. Each participant was told to fixate the central cross at all times and to verbally report the number of flashes they saw on the screen, regardless of what was felt under the finger. The experimenter responded according to the participants' report (1 or 2 flashes) by pressing "1" or "2" (respectively) on the keyboard. Following the experimenter inputting the participant's response, a varying time interval between 500 and 1500 ms passed before the following visuo-tactile stimulus pair was presented. The second tactile stimulus always followed the first visuo-tactile pair.

The two tactile stimulations were delivered one after the other at varying Stimulus Onset Asynchronies (SOAs) ranging between 36 and 204 ms with increments of 12ms. Each block of trials had 15 different time intervals between taps (repeated 10 times) with a total of 150 randomly ordered trials per task. This range of SOAs appears to be well-suited to define the time frame within which the illusion is perceived (Cecere et al., 2015; Cooke et al., 2019).

2.3. Experimental Design

Each participant was instructed to fixate the central cross and report the number of flashes they saw on the screen, while ignoring the tactile stimulations (taps). The participants were seated 57 cm away from the computer screen with their visual angle aligned with the centre of the screen. They were asked to place their left index finger below the presentation of the flashing disc to maximise spatial co-occurrence of the visual and tactile stimuli processing. Each visual stimulus flashed for 12 milliseconds and always occurred with a seven-milliseconds tap aligned with the onset of the flash. The second tap was randomly presented in one of the 15 inter-tap intervals. The double taps were intended to produce an illusory effect and trick the participants into seeing two flashing discs while there was only ever one presented. In particular, the quicker the taps, the stronger the illusion was expected to be. The responses were indicated by participants saying '1', if one flash was perceived, or '2', if two flashes were perceived. The experimenter then pressed the corresponding key on the keyboard (See Figure 1).

3. Behavioural data analysis

The temporal window within which the visual illusion was maximally perceived was calculated using the participants' perceived illusory flashes across the different SOAs. The percentage of trials in which the tactile-induced Double Flash Illusion (tDFI) was perceived (total "two" responses out of 10) was plotted for each participant's inter-tap interval to obtain the TWI induced by the tDFI (i.e. the point in time after which the illusion starts to degrade). In order to calculate the TWI, a psychometric sigmoid function [$y = a + b / (1 + \exp(-(x - c)/d))$]; a = lower asymptote at high values of x ; b =

amplitude of the psychometric curve (together $a+b$ forms the upper asymptote at low values of x); c = inflection point; d = slope] was fitted to the data, which gave us an estimate of the average number of trials in which the participants perceived the illusion in each inter-tap interval. The inflection point was of particular interest as it corresponds to the point of the fitted curve dividing those trials in which the participant maximally perceived the illusions from those trials within which the illusion tended not to be perceived, thus representing the most representative measure of the TWI for each participant. A total of 22 participants were excluded. We have based our exclusion criteria on fitting procedures (i.e. whenever data could not be fitted, participants were excluded, leading to the exclusion of 18 participants) and on R-square values (whenever individual fitting R-scores values were lower than 0.6), leading to the exclusion of another 4 participants. Importantly, we explored whether participants whose performance could not be fitted (because of noisy data in reporting the illusion over time, or because never experiencing the illusion or because instead always perceiving the illusion independently of SOAs) were clustered towards one extreme of the SPQ scores distribution. However, our excluded participants' SPQ scores were equally distributed on a continuum (data not shown) and cannot be dependent on personality traits that might have affected the perception of the illusion. It has to be noted that such rejection rate is relatively high (corresponding to 40% of all the original participants) when compared to the one observed in previous reports (corresponding to 20% of all the original participants) (Cecere et al., 2015; Cooke et al., 2019). However, both in Cecere et al., (2015) and in Cooke et al., (2019), participants were pre-screened with a practice trial to ensure, as a prerequisite to take part in the study, that they could reliably perceive the illusion. Those participants who could not perceive the illusion from the start, were thus not included in the study, which

resulted in a reduced rejection rate, mostly corresponding to the participants included in the study whose perception of the illusion did not fit a sigmoid function. When applying the same criteria to the current study, again around 20% of the participants would have been excluded because of fitting and the other 20% because of lack of illusion, thus consistent with previous reports by our group. Thus, in agreement with the sample size estimated by the power analysis, the total number of participants included in the study was $n = 33$ (18 females, mean age 25).

4. EEG data analysis

EEG scans were performed during all trials to investigate pre-stimulus oscillatory activity both in the alpha and beta bands (see Cooke et al., 2019). For each participant, 64 channels EEG was recorded at a sampling rate of 500Hz. The EEG signal was re-referenced offline to the average of all scalp electrodes. EEG data was subsequently segmented into 2000ms stimulus-free and artifact-free epochs time-locked to and preceding the visual stimulus onset. 2000ms prior to visual stimulation never includes the previous stimulation due to a variable time of the participant vocal response followed by a variable time of the experimenter inputting the participant vocal response on the keyboard followed by a variable time of 500-1500ms between the keyboard input and the next visuo-tactile stimulus pair. Given that a total of 150 stimulus trials were presented, this resulted in 150 epochs of pre-stimulus oscillatory activity. Each single epoch was inspected to determine the data and reject any artefacts created by involuntary movements (minor muscle contractions or eye blinks) or interference. A total of 41.45% ($\pm 3.88\%$) of the epochs were rejected due the presence of eye movements and muscle artifacts. This relatively high number of rejected epochs contaminated by eye movements and muscle artefacts may be due to residual artifact

induced by the verbal response provided by the participants. The individual alpha and beta peak frequencies were calculated across all electrodes on each 2 sec epochs with spectral analysis based on Fast Fourier Transform (FFT) with no overlapping windows and nominal resolution of 0.1, subsequently averaged. For each frequency peak calculation, signal was band pass filtered within the frequency of interest before undergoing FFT using infinite Impulse Response (IIR) filter applied to separate individual wave bands in the visual cortex. This allowed filtering out frequencies that may contaminate calculation of the frequency of interest. Thus, peak frequency was determined as the frequency having the largest spectral values in the ranges 7-13 for alpha and 12-25 for beta (as measured at channel Oz). Once the frequency peak was calculated for each individual, the same value of cycles per seconds (e.g., 20Hz) was transformed in the corresponding duration of one single cycle (e.g. 50ms).

Figure 2 shows the procedure through which we have extracted peak frequency in the alpha and beta band. In order to ensure that extracted peaks in alpha and beta oscillatory bands represent independent components in our EEG analysis we performed a correlation analysis between alpha and beta frequency peaks which returned a nonsignificant correlation between individual alpha and beta peaks ($r=-0.02$ $p=n.s.$).

5. Statistical analyses

5.1. Relationship between schizotypal personality trait (SPQ) and temporal window of illusion (TWI)

To test for the possible association between the individual schizotypal traits and the individual TWI measured during the tDFI task, we ran Pearson's correlation analyses between SPQ total scores and TWI, as well as between the SPQ subscales (i.e. perceptual cognitive, interpersonal and disorganized) scores and TWI. Moreover, to test for their robustness we computed skipped parametric (Pearson) correlations (Wilcox, 2004) using the Robust Correlation toolbox (Pernet et al., 2013) and conducted null hypothesis statistical significance testing using the nonparametric percentile bootstrap test (2000 resamples; 95% confidence interval, corresponding to an alpha level of 0.05), which is more robust against heteroscedasticity compared to the traditional t-test (Pernet et al., 2013). Finally, we corrected for multiple comparisons whenever appropriate.

5.2. Relationship between temporal window of illusion (TWI) and individual frequency peaks (IBF, IAF).

To confirm the beta frequency-specificity accounting for the TWI measured during the tDFI (Cooke et al., 2019) in our participant sample, we ran Pearson's correlation analysis between IBF and individual TWI as well as between IAF and TWI. Moreover, as above, to test for their robustness we computed skipped parametric (Pearson) correlations (Wilcox, 2004) using the Robust Correlation toolbox (Pernet et al., 2013) and conducted null hypothesis statistical significance testing using the nonparametric percentile bootstrap test (2000 resamples; 95% confidence interval, corresponding to an alpha level of 0.05).

5.3. Relationship between schizotypal personality trait (SPQ) and individual beta frequency peak (IBF).

Given the existing evidence of abnormal neural oscillations in the schizophrenia spectrum since its early stages (Uhlhaas et al, 2008), we tested the association between IBF and SPQ total scores, as well as between IBF and the SPQ subscales (i.e. perceptual cognitive, interpersonal and disorganized) scores, using Pearson's correlations. As above, to test for the robustness of the correlation, we computed skipped parametric (Pearson) correlations (Wilcox, 2004) using the Robust Correlation toolbox (Pernet et al., 2013) and conducted null hypothesis statistical significance testing using the nonparametric percentile bootstrap test (2000 resamples; 95% confidence interval, corresponding to an alpha level of 0.05).

5.4. Mediation analysis

A mediation analysis (model 4 in the SPSS PROCESS macro80) was performed to probe any effects of IBF on individual schizotypal personality traits, mediated by its effects on tTWI. All the analyses were carried out with standardized values for all the variables. Consistent with published guidelines (Memon et al., 2018), we report 95% confidence interval (CI) based on 5000 bootstrap iterations (bias-corrected) for all major effects.

5.5. Median split analysis

Since participants have been enrolled in the experiment independently of their SPQ scores, we have used a median split approach according to the individual SPQ score to test whether low and high SPQ scores show significant differences both in the TWI and beta peaks.

6. Results

6.1. The individual SPQ score accounts for the size of the TWI

Recent work (Haß et al., 2017) has found a significantly enlarged temporal window within which schizophrenic patients (relative to a healthy control group) experience the auditory version of the DFI. This observation was extended to a schizotypal sample (Ferri et al., 2018). Here we tested whether the individual SPQ score could predict the size of the tactile-induced TWI. To this aim, a two-tailed correlation analysis between the individual SPQ scores and the individual TWI was conducted. We found a significant positive correlation between the size of TWI and the individual SPQ score ($r=.56$, $p=.001$, two-tailed), which also survived the robust skipped correlations method ($r = 0.48$, $CI = [0.13, 0.76]$) (See Figure 3.D), indicating that the wider the TWI, the higher the SPQ score. In other words, individuals with higher schizotypal personality traits show wider TWIs. Moreover, in order to understand whether specific characteristics associated with the schizotypal traits do preferentially account for the size of the TWI, we investigated the relationship between the different SPQ subscales and the individual TWI. Results of these analyses showed that each of the three SPQ subscales significantly and positively correlate with the individual TWI, also surviving the skipped correlation method and the p-value correction for multiple correlations: cognitive-perceptual subscale ($r=.43$, $p=.01$, two-tailed; skipped $r = .44$, $CI = [.12 .69]$), disorganised subscale ($r=.44$, $p=.01$, two-tailed; skipped $r = .44$, $CI = [.13 .68]$), interpersonal subscale ($r=.50$, $p=.01$, two-tailed; skipped $r = .23$, $CI = [.12 .55]$) (see Figure 4). As there was no preferential contribution from any subscale, we used the total SPQ score in the subsequent analyses.

6.2. Individual beta peak frequency accounts for the size of the TWI

Recent research has shown a significant relationship between the size of TWI induced

by the tDFI and the individual beta frequency (Cooke et al., 2019). We expected here to reproduce this relationship selectively for the beta but not alpha frequency. To this aim, individual oscillatory frequencies were converted from cycle units (Hz) into millisecond units ($\text{period} = 1000/\text{frequency}$) so as to correlate TWI and oscillatory activity on the same measure scale (of time) and the same unit (ms). We found a significant positive correlation between the TWI and the duration of an individual beta frequency ($r=0.37$, $p=0.035$, one-tailed, based on an a priori hypothesis, see Cooke et al., 2019), which survived the skipped correlation method ($r=0.42$, $CI = [.16 .65]$) (See Figure 3.C), replicating previous findings by Cooke et al., (2019). This result indicates that participants with wider TWIs (i.e. more prone to perceive the illusion) have also a slower beta cycle. As expected, no significant correlation was found between the TWI and the peak alpha frequency (IAF; see Figure 3.B) ($r = 0.16$, $p = 0.37$ two-tailed).

6.3. Individual beta peak frequency accounts for the individual SPQ score

So far, we have observed that larger tactile-induced TWIs relate both to higher SPQ scores and slower IBF. However, before testing the mediation role of the tactile-induced TWI for the impact of IBF on SPQ, another association needs to be tested, that is the one between IBF and individual SPQ scores. To this aim, a two-tailed Pearson's correlation analysis between IBF and the SPQ total score was performed, which revealed a significant positive correlation ($r = .35$; $p=0.04$, two-tailed), which survived the skipped correlation method ($r = .36$, $CI = [.06 .61]$). Specifically, results of this correlation indicate that people with slower beta oscillations also have a higher SPQ total score (See Figure 3.I). Again, as expected, no significant relationship was found between the IAF and the SPQ score ($r = .19$, $p = .28$; Figure 3.H).

6.4. Mediation Analysis

To better understand the relation between SPQ, TWI and IBF, we used a mediation model to examine a possible mediation role of the TWI for the effect of IBF on SPQ. We found a significant mediation effect (0.291, 95% CI: 0.0633 – 0.715), whereby relatively enlarged TWI mediated a positive association between IBF and SPQ (i.e. slower IBF in individuals with higher SPQ scores). Results of this analysis showed that there was no significant residual direct effect of IBF on SPQ (0.192, 95% CI: -0.322 – 0.708) suggesting that the impact of IBF on SPQ are fully mediated by the TWI. Standardized parameter estimates (bootstrapped standard errors in parentheses) are reported in Figure 5.

6.5. Median split analysis

These findings highlight the relevant role played by oscillatory activity in accounting for individual differences in multisensory interactions, which are in turn able to predict SPQ scores, and in principle able to differentiate people with low and high-schizotypy scores. To test this directly we applied a median split analysis to contrast people with low and high SPQ scores on their IBF and TWI measures.

In line with our expectation we found that the average TWI (103.6 ms) for the lower end of the median split (approximating the profile of a low-schizotypy group) was significantly shorter than the average TWI (123.0 ms) for the upper end of the median split (approximating the profile of a high-schizotypy group) ($t(32) = 2.04$; $p = 0.03$, $d = -3.21$). Finally, we measured whether the median split could also significantly differentiate groups according to their beta frequency. Indeed, we found that the IBF for the lower end SPQ score group was significantly faster (57.8) than the IBF for the upper end SPQ score group (65.5) ($t(32) = 2.04$; $p = 0.02$, $d = -0.86$). Interestingly, when looking at frequency specificity, our control analysis did not show any significant

difference for the IAF between the lower end (101.5) and upper end (102.4) of SPQ score group ($t(32) = 2.04$; $p = 0.83$).

7. Discussion

In the current study, we aimed to describe the temporal profile and the oscillatory dynamics of the tactile-induced DFI in relation to schizotypal personality traits and their interplay.

We had previously shown a tight relationship between the auditory version of the DFI and the SPQ scores (Ferri et al., 2018), such that individuals with higher SPQ scores showed larger TWIs. Here, we were able to extend this observation to the tactile version of the DFI. Indeed, we found a positive correlation between the TWI, as measured with the tDFI, and the SPQ scores, thus confirming that the higher the SPQ score the larger the TWI. Establishing this relationship by extending previous observation on crossmodal audio-visual interactions to somatosensory-visual interactions is of particular interest to the ongoing search for early biomarkers of schizophrenia (Ferri et al., 2018). Indeed, alterations in the somatosensory and proprioceptive domains have been reported as early symptoms of schizophrenia (Chang & Lenzenweger., 2001; 2005) and therefore potentially prodromal to the insurgence of the first psychotic episode.

This first characterization of the temporal profile of the tDFI accounting for low- and high-schizotypal profiles was followed by an investigation of their potential neural underpinnings. Relevant to this initiative, is the recent work by our group (Cooke et al., 2019), which demonstrated a relationship between the TWI for the tDFI and the

IBF; namely, larger (and shorter) TWIs were associated to slower (and faster) IBFs. In the present study, we replicated the findings from Cooke et al., (2019) and crucially assessed, for the first time, whether IBF could account for the different size of the TWI as a function of the individual SPQ score. Our results confirmed the presence of a significant relationship between the size of the TWI and the SPQ score which was also associated with the IBF values. Specifically, slower IBFs were associated with larger TWIs, characterizing participants with the high-schizotypal profile, while faster IBFs were associated to shorter TWIs, characterising participants with the low-schizotypal profile. Moreover, we confirmed that IBF significantly correlated with the SPQ scores such that the slower the IBF, the higher the SPQ score. These results are in line with the notion that slower oscillatory activity is associated with prolonged periods of integration of information across the senses, as indicated by an enlarged TWI accounting for high schizotypal traits.

In Cecere et al., (2015), we observed that an average temporal window of integration for the auditory-induced DFI about 100 ms - corresponds to the duration of an alpha cycle. We tested this hypothesis by parametrically modulating the temporal distance between the two beeps presented together with the one flash (i.e. temporal window of illusion), and found that the individual alpha peak frequency correlates with the temporal window of illusion, such that the slower the alpha frequency, the larger the temporal window of illusion. This finding is in line with the idea that alpha frequency may represent a sampling unit of sensory information over time. We (and others) have replicated this finding but also extended our observations to the tactile version of the crossmodal illusion. Interestingly, we found that beta, a typical oscillation of the sensorimotor system, but not alpha, best accounts for this phenomenon. As discussed

in Cooke et al., (2019), a possible mechanism linking temporal integration across the senses with specific cross-sensory oscillatory patterns is that communication between sensory areas follows a cyclical gating mechanism allowing for efficient cross-sensory coordination at the specific temporal loop of the cross-sensory feedback network. This observation is in line with extensive research reporting slower oscillatory activity (Fuggetta, Bennett, Duke, & Young, 2014; Nagase, Okubo, & Toru, 1996; Omori et al., 1995) as well as larger temporal windows of integration across the senses in schizophrenia spectrum disorders (Haß et al., 2017). In a previous research, we explored whether such effect was already present in schizotypy, confirming larger temporal windows of integration for the sound-induced flash illusions in participants with high schizotypy relative to participants with low schizotypy (Ferri et al., 2018). In the present study, we provided further confirmation for this picture by testing the oscillatory correlates of these effects.

The hypotheses tested specifically revolved around the neural underpinning of the temporal dynamics of the illusion. Previous research looking at the relationship between this illusion and oscillatory activity has generally tested for the incidence of oscillatory activity on the individual report of the illusion rather than on its temporal dynamics, linking the incidence of the illusion occurrence to modulation of alpha (e.g. Lange et al., 2013; Cecere et al. 2015) and gamma power (e.g. Balz et al., 2016). Indeed, there is evidence for a role of both alpha and gamma power in schizophrenia (Uhlhaas et al., 2008; 2011), also shown to be linked to the aberrant incidence of the sound induced illusion in schizophrenia (Balz et al., 2016). However, our group was the first to look at the relationship between temporal dynamics of the illusion - namely the temporal window within which an individual perceives the illusion - and oscillatory

activity, a finding which has been replicated by independent groups (Keil and Senkowski 2017) and extended here to the study of schizotypal individuals.

These findings provide novel, compelling evidence on the functional role played by oscillatory activity in neural code efficiency. They add to the body of evidence (Cecere et al., 2015; Cooke et al., 2019) supporting the notion that oscillatory activity in different frequency bands may play a crucial role in orchestrating sensory binding within critical windows of integration. A general view here is that a tendency towards slower oscillatory activity within a given frequency band is symptomatic of a general loss of neural code efficiency (see Ferri et al., 2018; Cecere et al., 2015; Cooke et al., 2019). Specifically, we found that individual beta frequency, previously associated with somatosensory-to-visual functional connectivity (Cooke et al., 2019) accounts for the individual TWI which in turns predict the individual SPQ score. Thus, oscillatory indices, as the IBF, measured during a multisensory task, as in the present study, may represent an important biomarker in the development of schizophrenic symptoms and represents a prodromal early biomarker of schizotypy.

A possible caveat in the interpretation of our results is that the effects observed may be alternatively explained as the result of a response bias. In our study, we did not use any unimodal condition or any other multisensory condition (e.g., two actual flashes presented). Thus, one may argue that enlarged TWIs may reflect simple response bias rather than an effective change in cross-sensory binding mechanisms. However, based on previous research by our group (Ferri et al., 2018; see also Di Luzio et al., 2020/ in press) we can, at least indirectly, discard this alternative explanation. In Ferri et al (2018), we showed that when analysing overall proneness, participants with high levels of schizotypy were more prone to the illusion relative to participants with low

levels of schizotypy. Importantly, we found that the between group differences in the proneness to perceive the illusion were abolished when correcting for the individual TWI. In other words, the effect of proneness could be explained by the temporal window within which high schizotypy individuals perceived the illusion. A decision bias account would have been better described by a general shift in the illusion report independently of SOA (i.e., it should have been still present when accounting for the TWI), but this was not the case. Instead, our findings from Ferri et al., (2018) favour the interpretation that the effect is specifically determined by the temporal characteristics of the multisensory integration process rather than by a response bias. In the current study, we could not conduct a similar analysis as our participants were distributed across a continuum of SPQ scores rather than clustered in either low and high scores. We have nevertheless attempted to use a median split approach to divide participants in lower and higher schizotypy scores and check whether overall proneness was different across groups. The analysis performed did not show any significant difference in the proneness to perceive the illusion ($t(32) = 2.042, p=0.65$). This suggests that SPQ scores do not account for the overall proneness to the illusion, independently of SOAs, while they can account for individual differences in the SOA at which their perception of the illusion decays. Thus, we are confident in interpreting that these analyses support the notion that the effect found in the current study, akin to Ferri et al., (2018), is specifically determined by the temporal characteristics of the multisensory integration process rather than by a response bias.

Investigating the pattern of neural alterations in high schizotypy is fundamental to elucidate the possible existence and nature of a continuum between schizotypy and

schizophrenia. Research has now emerged suggesting that the abnormalities in oscillatory activities and functional connectivity found in schizophrenia, may also extend to schizotypy. A study from Koychev et al., (2011) found abnormalities in a measure of network synchronisation, the “phase-locking factor”, and a deficient modulation of the sensory processing by higher-order structures in schizotypy. A study from Ferri et al., (2017) found that people with high schizotypy display abnormal long-range temporal correlation patterns that are similar to those observed in patients with schizophrenia (Nikulin et al, Neuroimage 2012). In our study, individuals with high schizotypy showed a general reduction in the speed of beta frequency (i.e. lengthening of the beta wave time) in the visual cortex, which effectively lengthened their temporal window of integration for the tDFI. This pattern could contribute to the multisensory impairments often observed in schizotypy and schizophrenia. Moreover, it could be associated to abnormalities in the neural dynamics that coordinate brain activity in large-scale networks. Indeed, as observed in Cooke et al., (2019), the tDFI phenomenon, rather than being dependent on local network rules (i.e. local occipital oscillatory resonance activity), is determined by long-range communication networks (i.e. functional connections between somatosensory and visual cortices) which influence visual cortical processing. As such, the tDFI’s TWI would be mediated by beta oscillations as somatosensory processing (pre-synaptic), which is typically linked with beta activity, phase-align beta oscillations in the visual cortex (post-synaptic), defining the temporal resolution of interregional synchronization within which the TWI phenomenon arises. This pattern has previously been observed in the auditory-to visual network by Romei et al., (2012) who demonstrated that a simple auditory stimulus could phase align oscillatory alpha activity within the visual cortex. These observations have been interpreted (Cooke et al., 2019) within the Communication

Through Coherence” framework (Fries, 2005; 2015) as a means of communication between the senses for optimal multisensory binding. Such an interpretation would be in line both with reports of abnormal oscillatory activity and abnormalities in network synchronisation as measured by the “phase-locking factor” from Koychev et al., (2011), in turn leading to a deficient modulation of the sensory processing in schizotypy as observed in the present study.

Finally, the current data provide support to the hypothesis that the disruption of neural dynamics that coordinate brain activity in large-scale networks could be one of the possible causes for the emergence of psychosis. In particular, abnormal brain dynamics could impact the multisensory experiences in schizotypy and in schizophrenia. Brain stimulation could represent an emerging approach to target and intervene on abnormal neural dynamics and abnormal multisensory integration. Evidence has now emerged that different brain areas can be entrained at specific frequencies (Romei et al., 2016). Furthermore, tACS or transcranial magnetic stimulation (TMS) could be implemented to modulate the TWI of both schizophrenic and schizotypal individuals. At the network level, further research could adopt a novel cortico-cortical paired associative stimulation (ccPAS) TMS paradigm based on the Hebbian principle of cortical plasticity (Hebb, 1949; Romei et al., 2016; Veniero et al., 2013 Chiappini et al., 2018). This protocol adopts a repeated stimulation of pre- and post-synaptic relevant neural population over specific brain networks aimed at enhancing functional connectivity between different brain areas and thus enhance effective multisensory integration.

6. Conclusion

Research in schizotypy represents a valuable target for the definition of endophenotypes in schizophrenia spectrum disorders. Indeed, it allows researchers to further investigate the early biomarkers of psychosis risk without the confounding variables of a major condition, such as the neural changes occurrent after the emergence of the disorder, and the neural adaptations secondary to pharmacological treatment. As such, our study provides a valuable advance in the understanding of early biomarkers of schizophrenia which are associated with a high profile of schizotypy. These findings put the basis for a systematic evaluation of the identified neurophysiological biomarkers of schizophrenia across different sensory domains and brain networks. From this perspective, future research combining advanced EEG and neurostimulation approaches using an information-based approach (Romei et al., 2016) will be vital for developing efficient and cost-effective early intervention and treatment strategies.

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Figures.

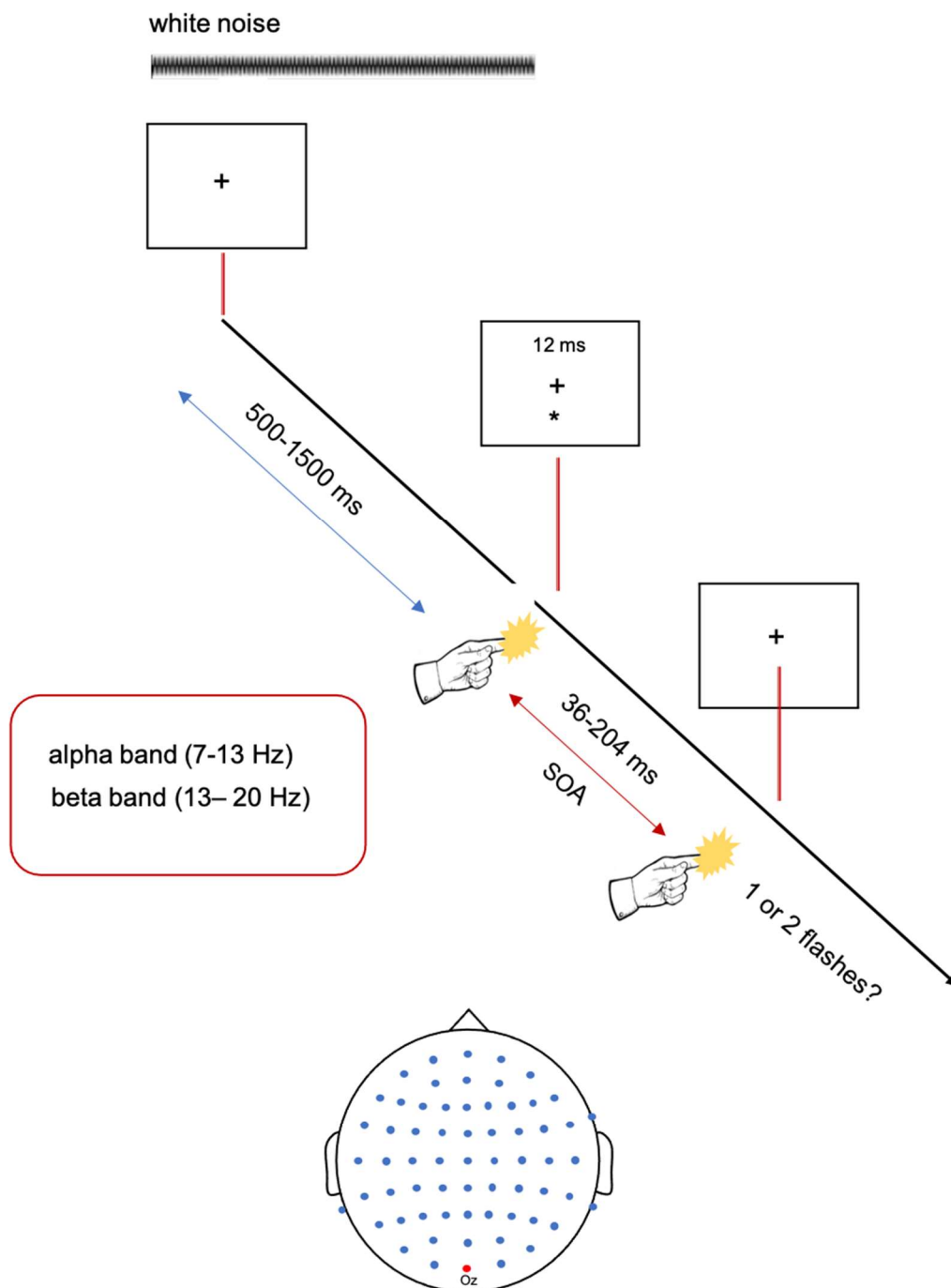


Figure 1. Paradigm. A Schematics of the experimental paradigm. In each trial,

participants were told to fix a central cross for a period randomly ranging between 500 and 1500 ms. Thereafter, they were presented with one visual white disc (flashing for 12 ms) accompanied by two brief tactile stimuli (7 ms each). The first tactile stimulus (tap) was aligned with the onset of the flash, whereas the second tap was randomly presented at 15 different delays (randomly ranging between 36 and 204 ms). Participants were required to verbally report whether they perceived one or two flashes. The verbal report was then input by the examiner via the “1” and “2” key on the keyboard which prompted the new trial to start after a variable inter-trial interval. During the tactile stimulation, white-noise (approximately 50db) was played to participants through speakers to mask the mechanic noise produced by the tactile stimulator. During the experiment, EEG was continuously recorded.

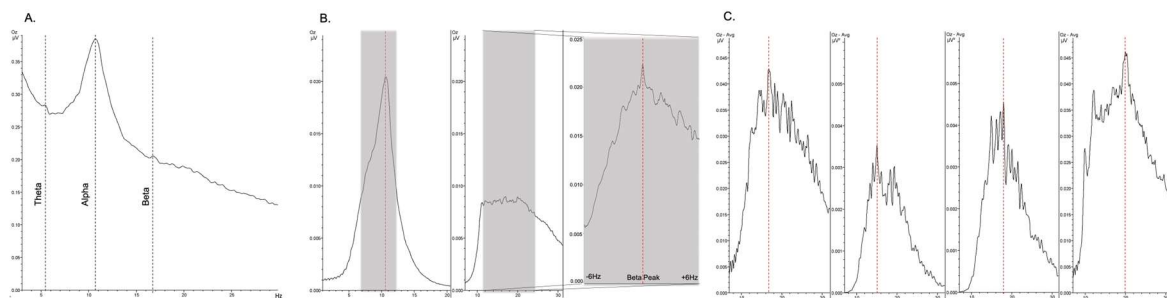


Figure 2. FFT analysis procedure. **A.** Mean FFT analysis performed on the entire spectrum between 0.5 Hz and 40Hz. As can be appreciated, there is a clear and prominent peak in the alpha band while less clear peaks can be observed in surrounding theta and beta bands. **B.** In order to avoid smearing of alpha signal into beta oscillations, we have bandpass filtered the signal to exclusively include the oscillatory signal within the frequency band of interest. This has provided clear signal calculation both in alpha and beta band. Due to the lower signal to noise ratio and higher frequency range, the mean signal in the beta band can be best appreciated

after averaging individual signals around the individual peak rather than as a function of the absolute frequency (right inset). **C.** A few exemplar individual beta peaks measured with the adopted analysis strategy. Please note the lower signal to noise ratio, compared to the alpha frequency and the wide range of peaking frequencies.

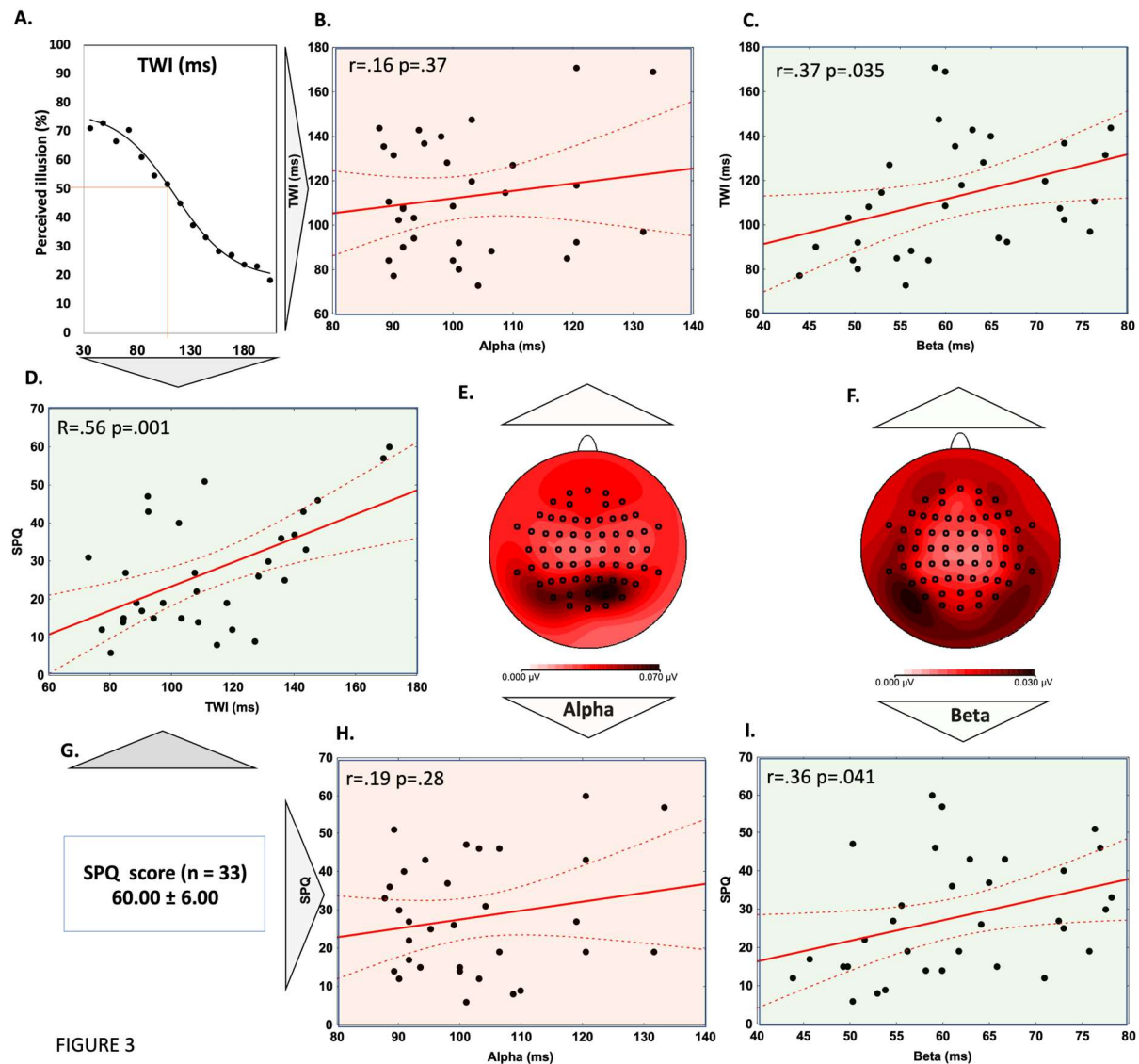


FIGURE 3

Figure 3. Correlation analyses.

A. The sigmoid curve represents the best fit of the average probability of perceiving the illusion plotted as a function of inter-tap delays. The sigmoid fit determines the

temporal window of illusion (TWI), i.e. the temporal window within which the illusion is maximally perceived, corresponding to the inflection point of the sigmoid.

B. Correlation plot depicting the relationship between the TWI for the tactile DFI and the individual peak frequencies in alpha and **C.** beta oscillatory bands.

D. Correlation plot between the individual SPQ's score and the width of the TWI.

E. Oscillatory activity at individual peak signal averaged across participants in the alpha and **F.** beta oscillatory bands.

G. Correlation plots depicting the relationship between individual SPQ's scores and individual peak frequencies in the alpha and **H.** beta oscillatory bands.

Significant correlations are reported on green background together with r values and corresponding significant level p . Non significant correlations are reported on salmon color background.

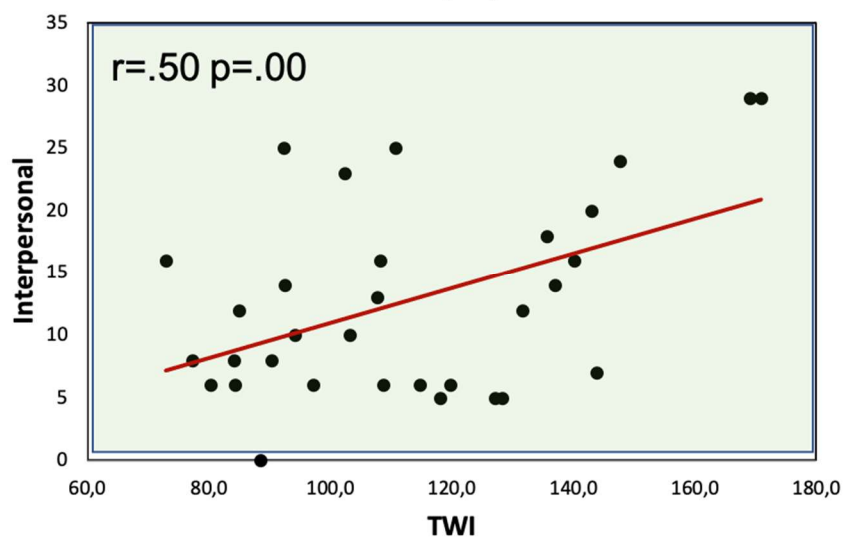
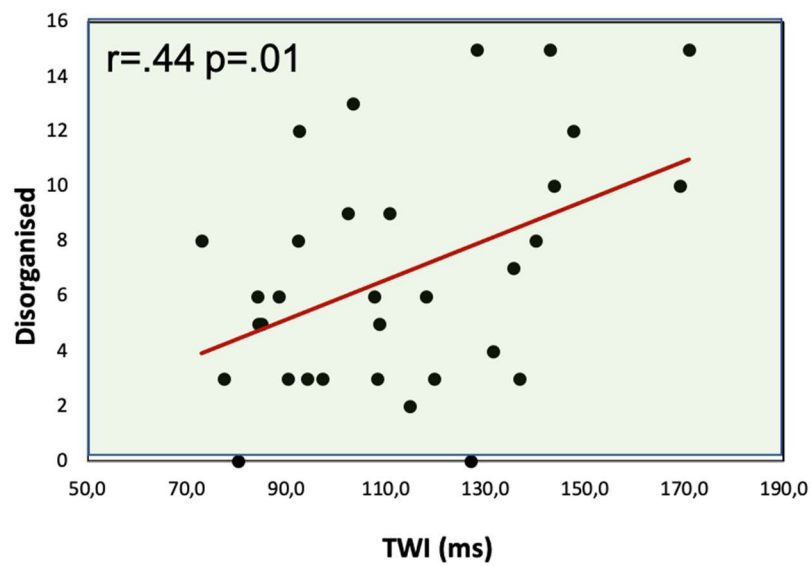
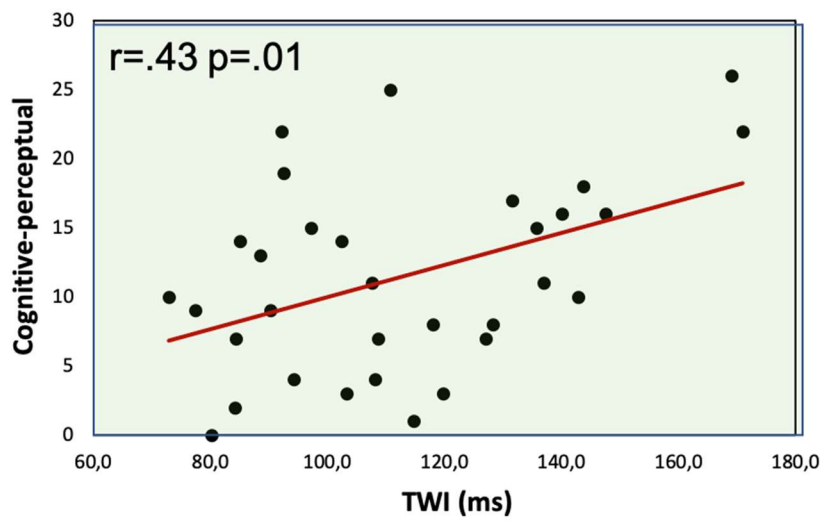


Figure 4. Factor specific correlations

Correlation plots depicting the relationship between the TWI for the tactile DFI and the individual scores in each of the three subscales for the SPQ.

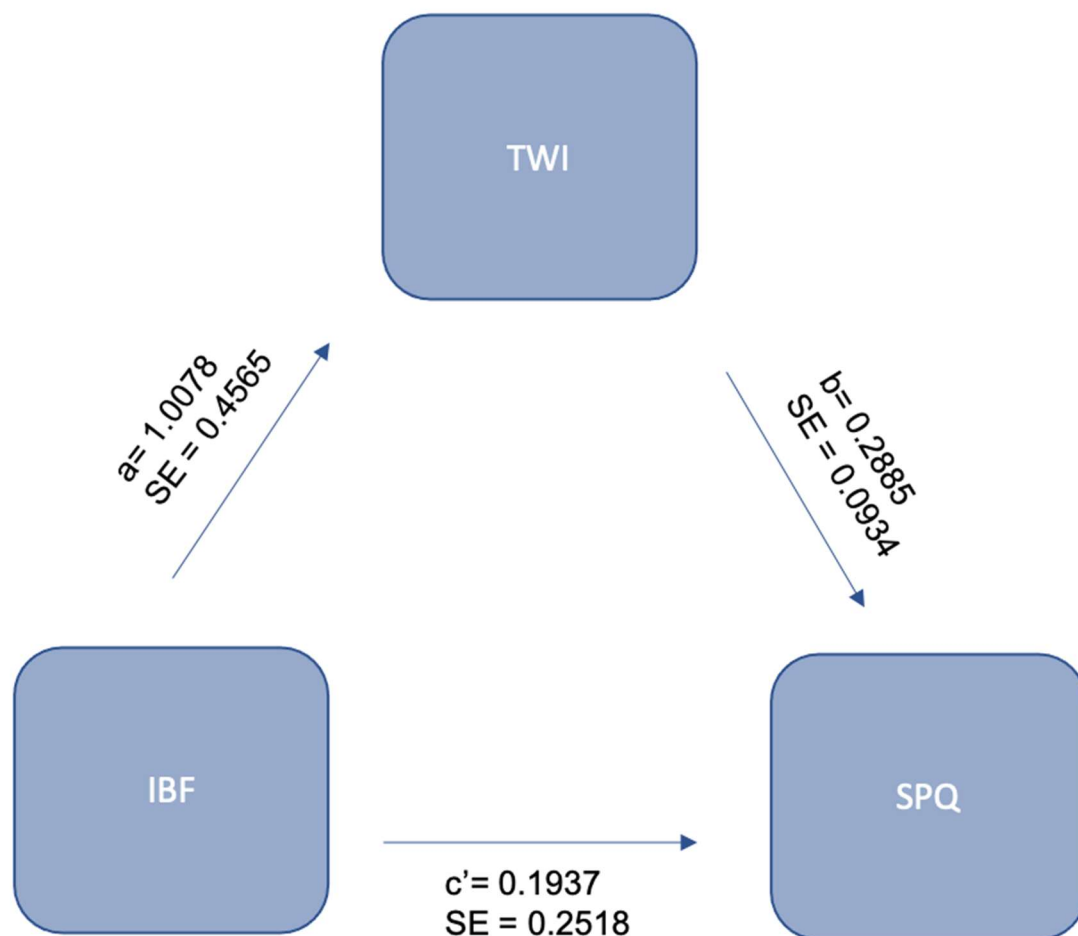


Figure 5. Mediation model. Standardized parameter estimates and standard errors are reported. No significant direct effect of IBF on SPQ was found, suggesting that the impact of IBF on individual schizotypal personality traits is fully mediated by the TWI.