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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - SHORT COMMUNICATION

Frequency-specific coupling between trial-to-trial fluctuations of neural responses and response-time variability

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Abstract We assessed intra-individual variability of response times (RT) and single-trial P3 amplitudes following targets in healthy adults during a Flanker/NO-GO task. RT variability and variability of the neural responses coupled at the faster frequencies examined (0.07–0.17 Hz) at Pz, the target-P3 maxima, despite non-significant associations for overall variability (standard deviation, SD). Frequency-specific patterns of variability in the single-trial P3 may help to understand the neurophysiology of RT variability and its explanatory models of attention allocation deficits beyond intra-individual variability summary indices such as SD.

Keywords Intra-individual response-time variability · Event-related potential · Cognitive control · Attention deficit

Introduction

Elevated intra-individual response-time variability (RTV), reflecting inconsistent behavioral responses in cognitive performance, has been reported in individuals with psychiatric conditions, most commonly, attention-deficit/hyperactivity disorder (ADHD) (Kofler et al. 2013), as well as in healthy aging, neurological and neurodegenerative disorders (MacDonald et al. 2006). Research investigating RTV has yet to clarify the underlying construct and neural underpinnings of this cognitive measure.

Studies examining the RT distribution have shown that high RTV is largely determined by a few slow responses and may reflect periodic lapses in attention (Leth-Steensen et al. 2000; West et al. 2002). Consistent with models of impaired regulation of 'top-down' attentional

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control underlying RTV (Stuss et al. 2003), these data supported the hypothesis that RTV reflects deficient attention allocation to meet task demands. Accordingly, studies have used the excellent temporal resolution of electroencephalography (EEG) to test the association between RTV and event-related potentials, particularly the parietal P3 following target stimuli (target-P3) thought to reflect attention allocation. Specifically, reduced target-P3 mean amplitude has been observed in healthy adults (Saville et al. 2011) and individuals with ADHD (Banaschewski et al. 2004; Kratz et al. 2011) exhibiting high RTV. An inverse relationship between RTV and target-P3 amplitude has also been reported in healthy adults (Nakata et al. 2012) and individuals with traumatic brain injury (Segalowitz et al. 1997).

Electrophysiological studies have also begun using single-trial information to examine the underlying neurophysiology of RTV. One early study related higher target-P3 amplitude variability, measured as the standard deviation of the mean (SD), to greater SD of RT (SD-RT), commonly used to measure RTV (Lazzaro et al. 1997). In contrast, recent work indicated less variable target-P3 amplitudes in individuals with high RTV and no correlation between SD of target-P3 and SD-RT (Saville et al. 2011). Therefore, the relationship between RTV and variability of the target-P3 amplitude remains unclear.

However, SD-RT alone does not measure characteristic periodic dynamics of RTV (Castellanos et al. 2005). Frequency analyses indicate that RTV occurs at slow cycle lengths (Castellanos et al. 2005; Feige et al. 2013), suggesting that frequency-specific RT fluctuations may help link RTV to its underlying neurophysiological mechanisms (Sonuga-Barke and Castellanos 2007). Accordingly, we tested whether overall and frequency-specific fluctuations of target-P3 amplitudes relate to RT fluctuations.

Methods

Participants

We collected RT data during simultaneous EEG recording and functional magnetic resonance imaging (fMRI) in a Flanker/NO-GO task from 23 healthy participants (12 males) aged 20–35 years ($M = 24.70 \pm 4.29$). Here, analyses on RT and EEG variability are presented; EEG-fMRI results have been reported previously (Baumeister et al. 2014). Due to insufficient EEG data quality, six participants were excluded from subsequent analyses, leaving a final sample of 17 participants (9 males; $M = 24.7 \pm 4.1$ years) who attained above 90 % accuracy. All subjects gave written informed consent prior to their participation. The study was approved by the Ethics Committee of the Ruprecht-Karls-University Heidelberg Medical Faculty.

Experimental paradigm

All participants performed a 10-min, 19-s long Flanker/NO-GO task (Baumeister et al. 2014; Blasi et al. 2006). Briefly, 145 stimuli, with three "GO" (neutral, congruent, incongruent) and one "NO-GO" conditions, were pseudorandomly presented for 800 ms interleaved with a fixation cross. Participants were instructed to press a button as fast and accurately as possible according to the direction of the target arrow while ignoring the two flankers on each side during "GO" conditions (e.g., >><>> or □□>□□), but inhibit their response for "NO-GOs" (XX>XX). For 109 trials the inter-stimulus interval (ISI) was 3-s. To introduce variable 3–12-s ISI, the remaining trials were followed by up to three 3-s null events presented in pseudorandom order, during which the fixation cross continued.

Electrophysiological recording and analysis

The signals were recorded from 60 EEG electrodes (Plichta et al. 2013), 2 electrooculogram and 2 electrocardiogram electrodes using MR-compatible caps and amplifiers (Brain Products, Gilching, Germany) and a 0.01–250 Hz recording bandpass. Standard fMRI gradient, ballistocardiogram and eye movement correction, plus 30 Hz low-pass filtering and re-referencing to the average reference are described in Baumeister et al. (2014). The target-P3 analysis segment was 1500 ms including a 250-ms pre-stimulus period. Baseline-corrected, artifact-free epochs were averaged for each target condition. For the single-trial analysis, we exported the mean voltage of the 300–600-ms post-stimulus window for each epoch at Pz and Cz (similar to the single-trial P3 analyses in Baumeister et al. 2014 but focusing on the GO-P3, and consistent with Lazzaro et al. 1997; Nakata et al. 2012).

Variability measures

We computed the intra-individual SD-RT and SD from single-trial target-P3 amplitudes (target-P3 SD) for correct responses after excluding the task's first 30 s to avoid potential adjustment effects. To obtain continuous RT and target-P3 time series, we replaced missing responses, NO-GO and null events using linear interpolation between adjacent observations. Expected trial-type effects on mean RT (data not shown) and mean target-P3 amplitude (Fig. 1a) were removed by linear regression yielding residual time series. We applied the Morlet-wavelet transform to each participant's RT and target-P3 time series as

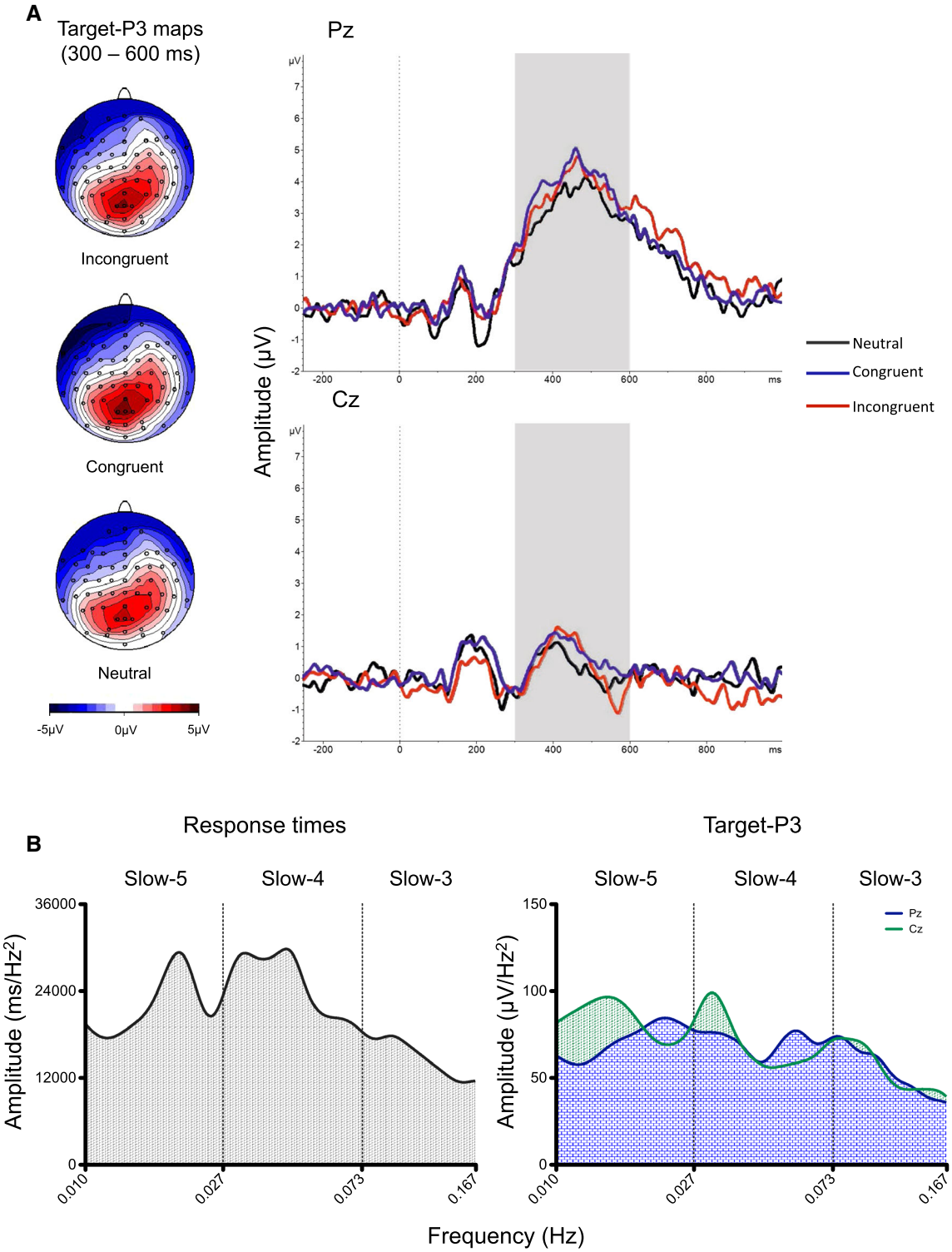

Fig. 1 **a** Maps of the grand mean in the selected post-stimulus window and stimulus-locked waveforms of the target-P3 for the "GO" conditions; congruent > neutral, $t = 3.6$, $p < 0.01$. **b** Average amplitude of the sampled frequency spectrum (0.006–0.167 Hz) across participants for RT fluctuations (*left panel*) and target-P3 fluctuations at Pz and Cz (*right panel*)

described previously for RT data (Adamo et al. 2012; Di Martino et al. 2008). Lastly, we estimated the average amplitude of three frequency bands based on physiological models of slow brain oscillations (Penttonen and Buzsaki 2003): Slow-5 (0.010–0.027 Hz), Slow-4 (0.027–0.073 Hz) and Slow-3 (0.073–0.167 Hz).

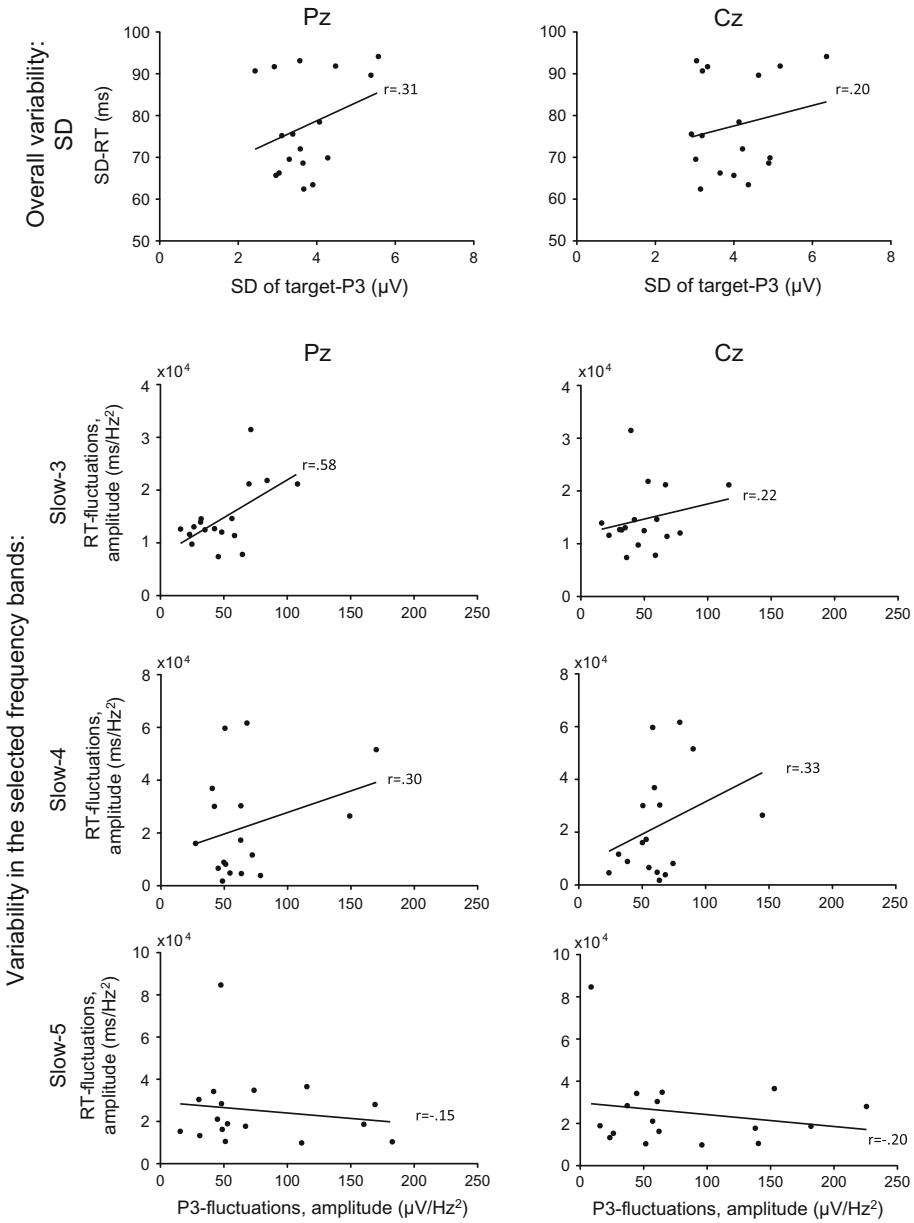

Fig. 2 Correlations between RTV and target-P3 amplitude variability. *RT* response time, *SD* standard deviation. *Upper* and *lower boxes* display the correlations between SD-RT (*y*-axis) and target-P3 SD (*x*-axis), and between wavelet transform-based amplitudes for RT fluctuations (*y*-axis) and target-P3 fluctuations (*x*-axis), respectively

Statistical analyses

We conducted Pearson's correlations to measure the relationship between all variability measures (SD and frequency amplitudes) of RT performance and the corresponding indices for the target-P3 amplitude at both Pz and Cz.

Results

The relationships between RTV and target-P3 variability indices are depicted in Fig. 2. SD-RT did not correlate with the target-P3 SD at Pz and Cz. The RT fluctuations positively correlated with target-P3 fluctuations in the frequencies 0.073–0.17 Hz (Slow-3) at Pz ($r = 0.58$, $p = 0.014$, $p < 0.05$ after Bonferroni correction for three bands), but not at Cz. At both sites, we did not find significant correlations between behavioral and neural responses for frequencies in the Slow-4 and Slow-5 bands. Still, these slower frequency bands contributed at least as much to the absolute variability in RT and target-P3 as the Slow-3 band (Fig. 1b), indicating that the correlation in the Slow-3 band did not simply follow the main sources of variability.

Discussion

Our aim was to determine whether trial-to-trial variability of target-P3 amplitude reflects RTV and if their

correlations occur at specific frequencies. While RTV and target-P3 variability did not correlate when measured with the SD, we observed a frequency-specific coupling between behavior and neural responses in the Slow-3 frequency band (0.073–0.17 Hz) at the electrode Pz.

Our findings parallel those of a study showing a decoupling between SD-RT and SD of target-P3 amplitude (Saville et al. 2011), but contrast a recent report of a positive association between SD-RT and target-P3 SD at Pz (Moore et al. 2013). Specifically, Moore and colleagues found that SD-RT and target-P3 SD correlated in a flanker-incompatible condition (i.e., participants must respond to the opposite direction of the target stimulus) but not in the compatible condition in children. Here, we neither found significant correlations between modalities for the SD across congruent, incongruent and neutral stimuli (details in "Results") nor for each condition separately (data not shown). Beyond possible reduced power in our small sample, the uncoupling between SD indices of behavioral and target-P3 responses might result from lower cognitive control demand in our paradigm with flanker-compatible conditions only and better cognitive control in our age group.

Increasing evidence has indicated that RTV occurs at slow frequencies (e.g., <0.25 Hz). As RT fluctuation patterns resemble the spontaneous hemodynamic fluctuations at brain areas implicated in attention impairments (Fox and Raichle 2007; Zuo et al. 2010), hypotheses suggest that frequency-specific measures may help understand the underlying pathophysiology of RTV and the associated attention deficits (Sonuga-Barke and Castellanos 2007). Accordingly, we extended the study of the association between RTV and target-P3 variability to their underlying trial-to-trial fluctuations. Supporting the hypothesis that greater target-P3 variability reflects higher RTV (Lazzaro et al. 1997; Moore et al. 2013), our findings indicate that slow periodic variability patterns may identify such an association regardless of the correlation with SD.

Our study has a number of limitations. To conduct frequency analyses, interpolation of nearly half of the time series and interspersed gaps of ≥3-s might potentially enhance frequencies in the Slow-3 range. However, data manipulation would have affected the results for Pz- and Cz-derived fluctuations equally. Replications in larger sample sizes are needed to confirm these preliminary findings. Yet, prior evidence suggesting that neural fluctuations in relatively fast frequencies can be estimated with better accuracy supports our findings of neurophysiological oscillations at similar frequencies (Fornito et al. 2011). Finally, future analyses are warranted to assess further potential accounts of RTV, including variability of target-P3 latency (Saville et al. 2011) and prestimulus state as measured with EEG spectral power (Reinhart et al. 2011).

In conclusion, we found that RTV relates to target-P3 variability in specific frequencies, and confirmed the association between RTV and slow fluctuations in attention allocation measured with the target-P3, despite non-significant associations for overall variability (SD). We suggest that frequency-specific trial-to-trial fluctuations are important to detect and understand the relationship between neural and behavioral variability.

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