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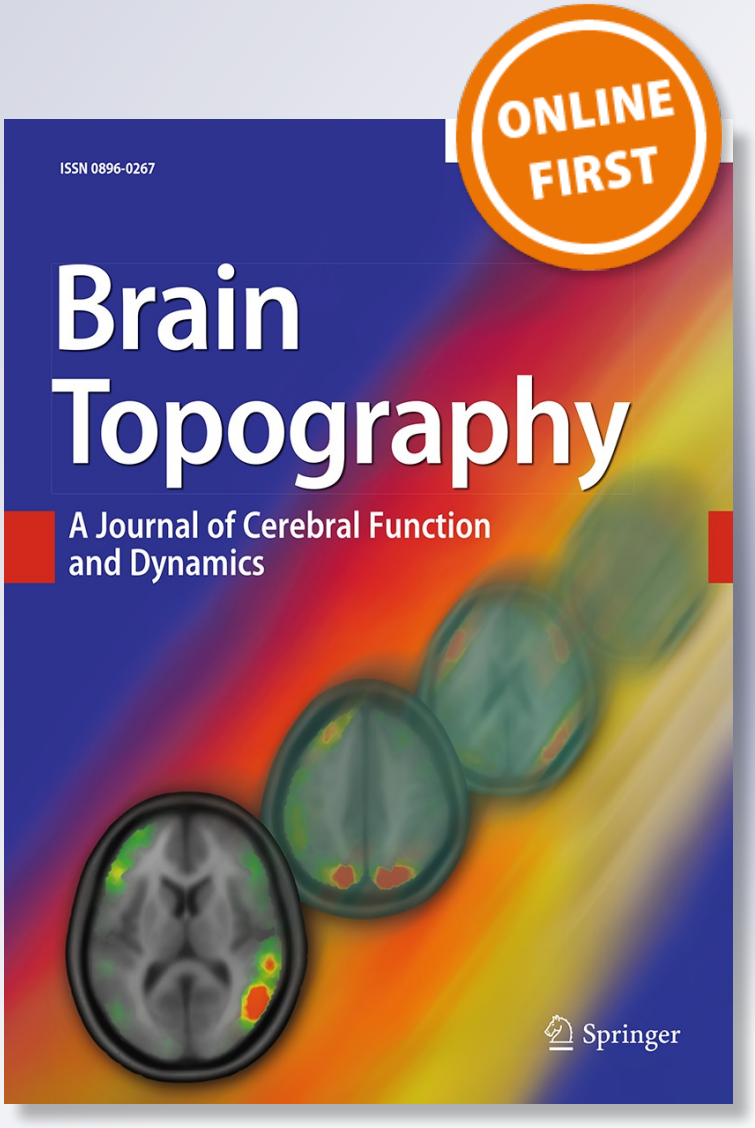

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ORIGINAL PAPER

Reaction Time in a Visual 4-Choice Reaction Time Task: ERP Effects of Motor Preparation and Hemispheric Involvement

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Abstract Reaction time (RT), the most common measure of CNS efficiency, shows intra- and inter-individual variability. This may be accounted for by hemispheric specialization, individual neuroanatomy, and transient functional fluctuations between trials. To explore RT on these three levels, ERPs were measured in a visual 4-choice RT task with lateralized stimuli (left lateral, left middle, right middle, and right lateral) in 28 healthy right-handed subjects. We analyzed behavioral data, ERP microstates (MS), N1 and P3 components, and trial-by-trial variance. Across subjects, the N1 component was contralateral to the stimulation side. N1-MSs were stronger over the left hemisphere, and middle stimulation evoked stronger activation than lateral stimulation in both hemispheres. The P3 was larger for the right visual field stimulation. RTs were shorter for the right visual hemifield stimulation/right hand responses. Within subjects, covariance analysis of single trial ERPs with RTs showed consistent lateralized predictors of RT over the motor cortex (MC) in the 112–248 ms interval. Decreased RTs were related to negativity over the MC contralateral to the stimulation side, an effect that could be interpreted as the lateralized readiness potential (LRP), and which was strongest for right side stimulation. The covariance analysis linking individual mean RTs and individual mean ERPs showed a frontal negativity and an occipital positivity correlating with decreased RTs in the 212–232 ms interval. We concluded that a particular RT is a composite measure that depends on the appropriateness of the motor preparation to a particular response and on stimulus lateralization that selectively involves a particular hemisphere.

Keywords Visuospatial processing · Choice reaction time task · N1 · P3 · Lateralization · Interindividual and intraindividual variance

Introduction

Hemispheric specialization is an important mechanism to enhance processing of particular information. Traditionally, hemispheric asymmetry has been observed and defined as neuroanatomical differences between homotopic regions of the two hemispheres (Amunts et al. 2000; Büchel et al. 2004; Jenner et al. 1999; Penhune et al. 1996; Toga and Thompson 2003), as local functional properties differing between the left and right sides of the brain (Gazzaniga 2000; Han et al. 2002; Nielsen et al. 2013; Stephan et al. 2003), and as behavioral lateralization (Amunts et al. 2000; Corballis 2014; Tommasi 2008). An alteration or reduction of normal hemispheric asymmetry has been observed in disorders such as schizophrenia (Crow et al. 2013; Løberg et al. 1999; Sharma et al. 1999), autism (Herbert et al. 2002, 2005; Lo et al. 2011), and dyslexia (Heim et al. 2003a, b; Jenner et al. 1999; Spironelli et al. 2008). These findings suggest that brain asymmetry is essential for normal brain functioning.

In the visual system, lateralization has been demonstrated to affect spatial information processing. The right and left visual hemifields are represented in different cerebral hemispheres and processing of visual information takes place in the contralateral hemisphere. Visual areas in

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both hemispheres are bound together by the splenium of the corpus callosum (Bocci et al. 2014; Catani et al. 2003; Gazzaniga 2000). The splenium enables a transmission of visual information between hemispheres after visual information reaches the contralateral hemisphere. Poffenberger (1912) proposed a tool to estimate interhemispheric information transfer by applying a simple reaction time (SRT) task with lateralized visual stimuli and both uncrossed and crossed responses (see Poffenberger 1912, and a review by Marzi 1999). Since then, many studies have used the Poffenberger paradigm to evaluate interhemispheric information transmission in normal subjects (Ipata et al. 1997; Mooshagian et al. 2008; Saron and Davidson 1989; Westerhausen et al. 2006) and in patients with agenesis or commissurotomy of the corpus callosum (Aglioti et al. 1993; Iacoboni et al. 1994; Iacoboni and Zaidel 1995; Mooshagian et al. 2009). Diffusion tensor imaging (DTI) findings showed that interhemispheric transfer time correlates with structural properties of the corpus callosum (Westerhausen et al. 2006). Due to the interhemispheric transfer, the splenium allows one hemisphere to compensate for the deficits of the other, and alterations to the splenium itself can contribute to visual deficits (Bocci et al. 2014). However, the interhemispheric information transfer was found to be asymmetric, as exemplified by the advantage of the left visual field over the right due to a superiority of the right hemisphere for visual stimuli detection and the advantage of the right hand over the left due to a superiority of the left hemisphere for movement planning (see the meta-analysis of Marzi et al. 1991). Moreover, numerous studies on healthy subjects and patients with brain lesions have shown that the right hemisphere is dominant in spatial information processing and is capable of attending and representing both hemifields, while the left hemisphere is concerned mainly with the contralateral hemifield (Fink et al. 1997; Nobre et al. 1997; Sack et al. 2005; Sheremata et al. 2010; Stephan et al. 2003; Tuch et al. 2005; Weintraub and Mesulam 1987; Whitford et al. 2011).

An important index of the efficiency of information processing is reaction time (RT) to particular stimuli. Results of transcranial magnetic stimulation (TMS) during SRT and choice reaction time (CRT) tasks showed that the left hemisphere is dominant for movement selection in both right- and left-handed subjects, because TMS stimulation of the left premotor cortex delayed both right and left hand responses (Schluter et al. 1998). Similarly, in left-handed subjects, TMS increased RT only after left primary motor cortex (MC) stimulation. However, in right-handers, RT was slower after TMS over both left and right primary motor cortices (Basso et al. 2006). Numerous studies investigated hand dominance in SRT or CRT task performance and hemispheric asymmetry regarding handedness. Significantly faster right (for right-handers) hand responses were observed during SRT (Kalyanshetti and Vastrad 2013) and CRT task (Steel et al. 2002). In contrast, Annett and Annett (1979) observed faster left hand responses to lateralized visual stimuli in 2-CRT tasks in the majority of subjects, and only a minority of participants exhibited the reversed RT pattern, but this was not related to the dominant hand. Another CRT study also reported faster left hand responses to lateralized visual stimuli (Barthelemy and Boulinguez 2001). In cued CRT tasks, faster left hand responses supported right hemisphere dominance (Bestelmeyer and Carey 2004; Frecska et al. 2004), but this left hand superiority could be accounted for by the cueing effect and an activation of visuospatial attentional networks lateralized to the right hemisphere, which is dominant in visual spatial information processing and visual attention (Gitelman et al. 1999; Kim et al. 1999; Konrad et al. 2009, Thiebaut de Schotten et al. 2011; Tuch et al. 2005).

Apart from those effects accounted for by lateralization, RT shows intraindividual trial-by-trial and interindividual variability. The underlying neural mechanisms for this variability are not yet fully clear. Several studies have suggested that interindividual RT variability is systematically related to variability in white matter and its properties (Kolev et al. 2006; Madsen et al. 2011; Tuch et al. 2005). In addition, the variance in individual RT increased with white matter and cortical gray matter volume decreases (Walhovd and Fjell 2007). Numerous studies investigating information processing speed used DTI techniques to describe white matter pathways and their asymmetry according to their diffusion parameters (Konrad et al. 2009; Madden et al. 2004; Madsen et al. 2011; Tuch et al. 2005; Walhovd and Fjell 2007) to account for variance in RT during visual task performance. Correlations between RT and measured white matter structural properties were observed for white matter tracts of attentional brain networks such as the parieto-frontal network, predominantly in the right hemisphere (Konrad et al. 2009, Thiebaut de Schotten et al. 2011).

The neural correlates of CRT tasks and visual stimulus lateralization can be explored by DTI techniques, but also EEG techniques and ERP responses to laterally presented stimuli. There are several possibilities for investigation of visuospatial processing and RT with regard to stimulus lateralization. Some ERP studies investigating visual spatial attention and RT used Posner-type cueing paradigms to shift spatial attention to one side of the screen by presenting a cue before stimulus presentation. This cue can be valid or invalid and may be presented centrally (a so-called endogenous cue) (Frecska et al. 2004; Mangun and Hillyard 1991; Nobre et al. 1997) or peripherally (exogenous cue) (e.g. Fu et al. 2010). Even cross-modal cueing can be applied (Störmer et al. 2009). In other studies, no cues were

used, but participants were instructed to focus attention to either the left or the right side (Heinze et al. 1990; Johannes et al. 1995; Luck et al. 1990). In the third type of studies, subjects were given no cue and no directional attention instructions (e.g. Ramchurn et al. 2014).

Despite differences in paradigms, based on the findings of ERP studies, visual P1, N1, and P3 components may be the most informative. The early ERP components—P1 and N1—reflect sensory processing of incoming information. The P1 component is usually observed 80–130 ms after stimulus onset, is evoked by stimulus appearance, and can be modulated by selective spatial attention (Fu et al. 2010; Heinze et al. 1990; Hillyard and Anllo-Vento 1998; Johannes et al. 1995; Luck et al. 1990; Mangun and Hillyard 1991; Störmer et al. 2009). The N1 usually has a peak at 140–200 ms after the stimulus onset. Moreover, its amplitude is enhanced in CRT tasks compared to SRT tasks, and thus the N1 is strongly modulated by selective attention (Hillyard and Anllo-Vento 1998; Johannes et al. 1995; Luck et al. 1990; Mangun and Hillyard 1991; Störmer et al. 2009; Vogel and Luck 2000). Importantly, both P1 and N1 show increased amplitudes contralaterally to the stimulation side (Hillyard and Anllo-Vento 1998; Liu et al. 2009; Mangun and Hillyard 1991; Wascher et al. 2009). The P3 component is later in time (250–500 ms) and is considered to reflect cognitive processing and the process of decision-making (Hillyard and Kutas 1983; Kelly and O'Connell 2013; O'Connell et al. 2012). Furthermore, Verleger et al. (2005) suggested that the P3 component reflects a process that mediates between perceptual analysis and response initiation and that possibly monitors whether the classification of a stimulus is appropriately transformed into action. The P3 component reflects the activation of established stimulus–response links during a task performance (Verleger et al. 2005, 2014a, b), and increased difficulty of decision in an oddball task leads to decreased P3 amplitude and increased RT (Verleger et al. 2014a).

Larger average P3 amplitudes and earlier P3 latencies were associated with faster RTs in auditory oddball task studies (Friedman 1984; Roth et al. 1978). In addition, recent RT studies with lateralized visual stimulation reported results pointing to the P3 as one possible ERP correlate of RTs. For example, a recent 2-CRT study (Ramchurn et al. 2014) showed that the P3 amplitude was significantly greater for faster compared to slower behavioral responses, but the P3 peak latencies did not differ according to the speed of the behavioral RT. Furthermore, investigation of intraindividual variability of RTs revealed that the P3 amplitudes were reduced in the average ERPs of subjects with high intraindividual variability. These subjects also responded significantly more slowly than subjects with low variability (Saville et al. 2011). In contrast, in the previously mentioned choice response task study (Verleger et al. 2005), the P3 amplitudes were similar, but latencies varied with response speed in the both stimulus- and response-locked average ERPs. Findings were similar for auditory and visual stimulation. The authors accordingly proposed that the P3 represents a process intermediate between stimulus processing and response planning. In his review, Verleger (1997) summarized different variables of stimuli and stimulation procedures that affect P3 latency and may delay response times.

Summing up, the P3 can be a target for ERP analysis in lateralized 4-CRT tasks investigating correlations with RT. Regarding other possible targets, Murray et al. (2001) observed different brain activation patterns related to visual field stimulation by different lateralized stimuli but failed to find a systematic relationship between peak P1 latency and SRT. However, the body of literature on different ERP correlates of RT for tasks using lateralized visual stimuli is still small, and other features of early visual ERP components may be systematically related to RT.

Sternberg (1969) proposed the Additive Factor Model to study processing stages with regard to RT. The Additive Factor Model decomposes stimulus processing into a set of stages, for instance, stimulus encoding, translation, and response organization, appearing from stimulus onset to response in a particular experiment. Each stage may be particularly sensitive to specific experimental variables or factors, and RT is affected by different stages of stimulus processing and the interactions of these stages. In particular, the duration of a stage is thought to have an impact on RT. Based on this description of processing stages in the Additive Factor Model, these processing stages could be linked to particular ERP components; the stimulus encoding stage could be represented by the P1 and the N1, as these components are known to be modulated by selective spatial attention (Hillyard and Anllo-Vento 1998; Johannes et al. 1995; Luck et al. 1990; Mangun and Hillyard 1991; Störmer et al. 2009). A translation state and perhaps a response organization stage might be assigned to the P3, as the P3 reflects a process in between stimulus processing and response planning (Verleger et al. 2005). A recent study (Hackley et al. 2007) supported the assumption that stages of the Additive Factor Model could be assigned to ERP components but proposed the trisection approach to investigate mental chronometry. The trisection method divides mean RT into three time segments based on the onsets of ERPs, and results of this study showed that latencies of the N1 and the N2pc are related to RT.

We applied a simple 4-CRT task with lateralized stimuli to investigate hemispheric asymmetry and visuospatial processing using ERPs. In order to link our study to the existing DTI literature, the CRT task was identical to a task used in the DTI study of Tuch et al. (2005), who reported significant correlations between RT and white matter

properties in projections supporting visuospatial processing. In order to isolate and compare the different components of the ERP in a comprehensive way, microstates (MS) analysis was applied (Murray et al. 2008). MS analysis is a topographic ERP analysis that allows evaluation and statistical comparison of latency, strength, and topography between and within experimental conditions. This time-based approach is particularly interesting when investigating time-based behavior correlates such as RT. Additionally, to identify the scalp electric field topography of processes that affect RTs on a trial-by-trial basis, we used multichannel regression analyses (covariance mapping) (Koenig et al. 2008).

We expected that P3 or other ERP components could predict RT in simple 4-CRT task. Moreover, we expected to observe lateralized brain activation in response to visual stimulation of the left or right visual hemifields.

Materials and Methods

Participants and Paradigm

Twenty-eight healthy controls (17 females, mean age 35.6 ± 10.5 years) performed a simple 4-CRT task. All participants were right-handed with a mean laterality quotient (LQ) of 97.0 ± 7.3, according to a short version of the Edinburgh handedness inventory (Oldfield 1971) and had normal or corrected to normal vision. Participants were recruited from volunteering friends and hospital staff and received no remuneration. The investigation was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the canton Bern. All subjects gave their prior written informed consent.

Stimuli and task (see Fig. 1 for stimuli and stimulation procedure) were based on the study by Tuch et al. (2005). During the experiment, four empty squares were continuously presented on a computer monitor placed 120 cm in front the subject. These squares were horizontally aligned, with two on the left and two on the right side of the center of the screen. All squares were presented as white outlines of squares on a black background and altogether extended a visual angle of about 6.6°, about 1.3° each. Horizontally, the middle squares extended from 0.14° to 1.54°, and the lateral squares from 1.82° to 3.12°. In each trial, one of the four squares was briefly (100 ms) filled with white, indicating the target. The interstimulus interval was 2000 ms. Thus, depending on location, targets were assigned to four conditions depending on whether they stimulated the left lateral (LL), left middle (ML), right middle (MR), or right lateral (RR) visual field. Participants fixed their gaze on the center of the screen at a white fixation cross between the two middle squares. The target positions were selected in a strictly random order and were not prevented from reappearance at the same position, the only difference from Tuch et al.'s (2005) study. Participants were asked to respond to targets by pressing the corresponding key on a four-key response board. For this purpose, participants rested their index and middle fingers of both hands on four keys of the response board. The corresponding keys were assigned to fingers accordingly: LL—left hand middle finger, ML—left index finger, MR—right index finger, RR—right middle finger.

The task was repeated in four blocks of 72 trials for a total of 288 trials. Before the session, participants were instructed to respond as quickly as possible and not correct errors. Between blocks, participants rested for a short period. The experiment, including the breaks, lasted approximately 11 min in total.

EEG Recording and Preprocessing

EEG data were recorded from 74 Ag/AgCl electrodes according to the International 10/20 System. The reference electrode was placed at Cz. Eye movements were monitored with two additional EOG channels placed below the left and the right eye. The impedance was kept below 15 kΩ for all electrodes.

During the recording, the EEG was digitized (250 Hz sampling rate, 0.3–70 Hz bandpass) and stored using a BrainScope EEG system (M&I, Prague). The EEG data was preprocessed in Vision Analyzer (Brain Products,

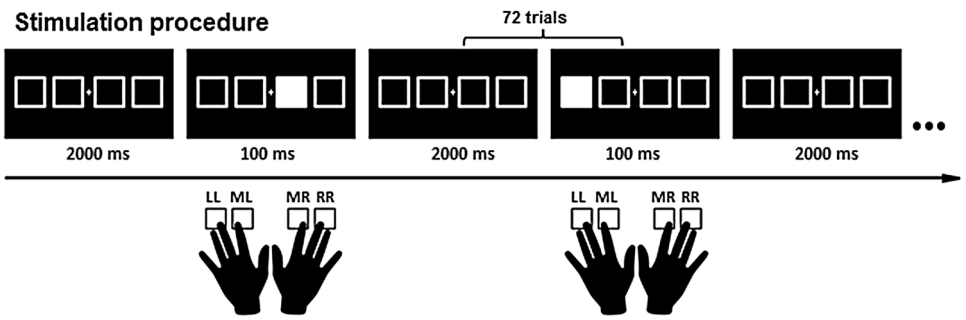


Fig. 1 Example of stimuli and stimulation procedure

Munich) software. A 50 Hz notch filter and 0.5–30 Hz bandpass filter were applied. Artifacts (eye movements) were removed by ICA (independent component analysis). Subsequently, the EEG recordings were visually inspected and epochs with further artifacts such as movement or muscle activity were rejected. The EEG recordings were then recalculated against the average reference, excluding the EOG channels. In order to assess the risk of potentially confounding effects of eye movements on RT and accuracy, we quantified the amount of horizontal eye movements and blinks that may have interfered with task execution. Since we had no eye-tracking data, we extracted these events based on spatial filters applied to the EEG. In the period that we considered crucial for the proper perception of the stimulus, i.e., in the 100 ms preceding the stimulus and the 150 ms following the stimulus onset, 0.4 % of all trials coincided with eye-blinks, and 1.3 % of all trials coincided with horizontal eye movements. The overall number of trials affected by either type of artifact amounted to 1.5 % of the total number of trials.

Analysis Methods

The mean RT of correctly answered trials and accuracy were calculated separately for each condition and subject. If participants pressed a response key earlier than 150 ms after stimulus onset or later than 1000 ms after stimulus onset, these answers were treated as outliers and excluded from the analysis. Error rates were calculated separately for errors made by pressing a wrong key on the stimulated side ("same-side errors"), on the other side ("other-side errors"), and pressing no key in time (omissions). Furthermore, omissions were calculated separately for left and right side stimulation. For behavioral data analysis, the Predictive Analysis SoftWare (PASW Statistics, Version 22.0.0, Polar Engineering and Consulting) was used. The variables of interest were RT of correctly answered trials and the accuracy of responses. A two-by-two factorial repeated-measures analysis of variance (ANOVA) was used to assess main and interaction effects regarding RT and accuracy. The two factors for the analysis were hemisphere (left vs. right) and laterality (middle or lateral).

ERP data was analyzed using Brain Vision Analyzer (Version 2.04, Brain Products, Munich) software and RAGU software (Koenig et al. 2011). The analysis of the ERP data had two purposes. First, we wanted to investigate the timing of the different brain processing steps as a function of target lateralization. The onset, offset, and amplitude of spatially defined ERP components were thus measured in each condition separately and compared using MS analysis techniques. The second aim was to find the scalp field topographies of processes accounting for variance in RT, both inter-individually between subjects, and intra-individually between trials.

For all analyses, the EEGs were segmented for each condition. Segments were set beginning at stimulus onset until 1000 ms after the stimulus. No baseline correction was applied. Only segments with correct responses were selected. The overall mean number of accepted segments was 56 ± 12, with no differences between conditions ($F_{(3,107)} = 0.1$). Mean ERPs within condition and subject were computed, followed by the grand means across subjects for each condition. In order to determine a useful analysis window, the topographic consistency test (TCT) (Koenig and Melie-García 2010) was applied. The TCT determines if an ERP topography at a given point in time contained components that were consistent across subjects. The TCT yielded significant ($p < 0.05$) evidence of consistency between 0 and 700 ms, corroborated by a significant overall test on the duration of the period found to be consistent (Koenig and Melie-García 2010). Therefore, further analyses were limited to this interval (0–700 ms).

For the MS analysis, MS cluster maps were computed based on the grand average ERPs of each condition. The number of clusters was defined by a recently developed cross-validation procedure. This procedure produces spatio-temporal MS models with a given number of clusters in subsets of the subjects (learning sets) and quantifies the amount of variance these models account for in the remaining subjects (test sets). The optimal number of clusters is reached when the amount of explained variance in the test sets does not increase further (Koenig et al. 2014). In the next step, MSs, defined as periods assigned to a single MS cluster, were identified in the grand mean ERP data. These MS assignments over time and conditions were the basis for the analysis of differences in MS quantifiers such as latencies and amplitude as functions of visual field and lateralization. In order to estimate the statistical significance of differences of MS quantifiers between conditions, a recently developed randomization test was applied (Koenig et al. 2014). This method does not fit MSs to individual data to obtain statistical significance but obtains estimates of p-values of an effect in the grand mean by comparing differences in MS features between conditions observed in the grand mean data to random distributions of these conditions as estimated using permutation procedures. The p value is then directly obtained from this comparison based on the rank of the observed effect compared to the effects obtained after the permutations. In this study, onset, offset, duration, and the area under the curve (AUC) of all MSs were compared between conditions using a 2 factorial design, with side (left–right), and lateralization (middle–lateral) as two experimentally independent factors accounting for the potential differences between conditions. Only results with $p < 0.05$ are reported here.

To find brain activation that correlated with RTs, we used covariance mapping analysis (Koenig et al. 2008). Covariance mapping is a novel ERP analysis method that accounts for the effects of a continuous external variable (in this case RT) upon ERPs. At a given time-point, it considers multichannel ERP to be superimposed on a constant topographic map whose contribution to the ERP is proportional to the external variable. Mathematically, covariance maps correspond to the forward solution of those sources that linearly co-vary, in their strength of activation, with this external variable. Thus, in contrast to correlation analyses of single channels, covariance mapping has the advantage of yielding results that directly correspond to intracerebral sources (Koenig et al. 2008) and avoiding problems of multiple testing across channels. Since the method is, in many ways, similar to the topographic analysis of variance (TANOVA) frequently used in ERP analyses, it has been labeled topographic analysis of covariance (TANCOVA).

On the within subject level, covariance maps were computed as function of condition using single trial ERPs and RTs. They were calculated in the time intervals of the N1 and the P3 defined across conditions, using the earliest onset and the latest offsets of these components. These were 112–248 ms for the N1 (MS 1/MS 2), and 248–460 ms for the P3 (MS 5). We employed an in-house plug-in for the Analyzer software for computation of these covariance maps. For the subsequent covariance analysis, single trial ERPs were averaged across time within these two intervals, yielding 4 covariance maps per subject and time window. The consistency of these covariance maps across subjects was again tested with the TCT. In order to visualize the consistency of the significant covariance maps, single sample t-maps against zero were calculated in each condition and analysis interval.

In order to account for the variance of the mean individual RTs, a covariance analysis was applied to the individual mean ERPs, using the individual mean RT as regressor. The significance of these covariance maps was tested by a randomization test that compared the overall strength of the observed covariance maps to the strength of covariance maps obtained when the assignment of the ERP data and the regressor had been randomly permuted (Koenig et al. 2008).

Results

Behavioral Results

Accuracy, mean RTs, and standard deviations (SD) for each stimulation condition are shown in Table 1. RT data with SDs are shown on box plots in Fig. 2.

Table 1 Accuracy, mean RTs, and standard deviations (SD) for each stimulation condition

	Accuracy		Reaction time (ms)	
	Mean	SD	Mean	SD
LL	0.980	0.024	450	46
ML	0.975	0.027	470	58
MR	0.970	0.028	457	56
RR	0.985	0.016	435	49

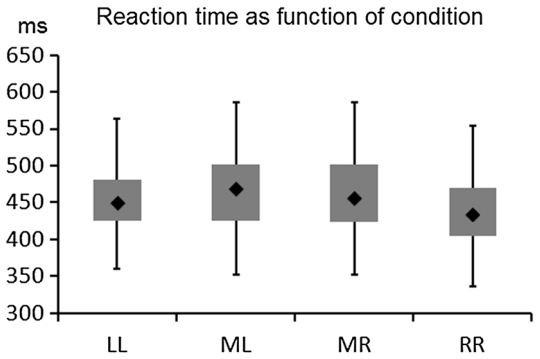


Fig. 2 Mean reaction times (*diamonds*), standard deviations (*boxes*), and group minimums and maximums (*whiskers*) of the four stimulation conditions

All response key presses were observed within time limits of correct responses and no outliers were found.

The two-by-two factorial repeated-measures ANOVA regarding accuracy of responses with factors hemisphere (left vs. right) and laterality (middle or lateral) resulted in a significant main effect of laterality [$F_{(1,\ 27)} = 6.132$, $p < 0.02$]. Accuracy was significantly higher in the lateral conditions (LL and RR) than the middle conditions (ML and MR). Neither a significant main effect of the factor hemisphere nor an interaction of both factors was obtained.

For incorrect answers, error rate on the same side was 0.015 ± 0.016, error rate on the contralateral side was 0.004 ± 0.006, omission rate was 0.003 ± 0.004, and omission rates between hemispheres did not vary (0.003 ± 0.006 for left side stimulation; 0.003 ± 0.005 for right side stimulation).

Regarding RT in correctly answered trials, the two-by-two factorial repeated-measures ANOVA revealed a significant main effect of the factor hemisphere [$F_{(1,\ 27)} = 7.575$, $p < 0.01$]. Mean RT was significantly increased in the left visual field (right hemisphere) conditions (LL and ML) as compared to the right visual field (left hemisphere) conditions (RR and MR). Also, a significant main effect of laterality [$F_{(1,\ 27)} = 12.871$, $p < 0.001$] was observed. The significantly longer RT

accounted for this main effect in middle conditions (ML and MR) as compared to lateral conditions (LL and RR). No significant interaction was observed.

ERP Results

Wave shapes showed little evidence for P1 but showed a large N1 with the expected strong lateralization. Medially presented stimuli (ML and MR) also evoked a smaller ipsilateral N1 component (see Fig. 3a). Wave shapes were not analyzed statistically. They were used in order to link the following MS analysis to the existing literature. Electrodes PO7 and PO8 were chosen because amplitudes of the N1 and the P3 components were largest (in μV) in electrodes where both the N1 and P3 were observed; O1, O2, PO3 and PO4 also displayed both N1 and P3.

The cross-validation of the optimal number of MSs reached a plateau after 6 clusters, such that the remaining analysis was based on 6 MS classes. The MS topographies obtained in the grand means and their times of presence are shown in Fig. 3b. MS 1 and 2 showed a complementary pattern; MS 1 was primarily evoked by left side stimulation (ML, LL), and MS 2 by right side stimulation (MR, RR). MS 1 and 2 corresponded to the lateralized N1 shown in Fig. 3a in latency and topography (occipital negativity contralateral to the stimulus). P3 potential corresponded to MS 5 in latency and topography. MS 4 was short and covered transition periods, and MS 6 was observed only after the response. MS 3 was not analyzed, because it was detected inconsistently during brief periods at the very beginning and the end of the analysis period (see Fig. 3b).

In the early time range, the statistical MS analysis confirmed the complementary pattern of MS 1 and 2. MS 1 and MS 2 were analyzed in a window from 112 to 248 ms that corresponded to the period of contralateralization. The results of the MS analysis are shown in Fig. 4 and Table 2.

The overall analysis showed a significant main effect for side. Stimulation of the right visual field induced more activity within the left hemisphere (AUC: MS 2, main effect of side: $p = 0.0001$), and stimulation of the left visual field evoked more activity in the right hemisphere (AUC: MS 1, main effect of side: $p = 0.0001$). Therefore, these two classes of MSs were associated with early ($\sim$110–240 ms) contralateral hemisphere activation. In addition, in MS 2, there was a significant interaction of side and lateralization (AUC: $p = 0.0001$). Inspection of Fig. 3 and post hoc tests showed that this interaction could be accounted for by larger middle than lateral AUC selectively for the right-side stimulation ($p = 0.023$).

Other MSs were analyzed in the full analysis window. Overall analysis of MS 4 showed that onset was significantly later in the middle compared to the lateral conditions ($p = 0.0001$). We also observed a significant interaction of side and lateralization ($p = 0.002$). A significantly later onset was observed for middle stimulation than for lateral stimulation in the left condition ($p = 0.009$, difference: 20 ms). The right condition analysis showed similar but smaller results ($p = 0.003$, difference: 12 ms).

MS 5 latency and topography corresponded to the P3. The overall analysis showed that the onset was later in middle compared to lateral conditions ($p = 0.002$), and a significant side by lateralization interaction for onset was also observed ($p = 0.025$). This interaction could be explained by a significantly earlier onset of MS 5 for lateral compared to middle stimulation after right side stimulation ($p = 0.02$, difference 12 ms), while no such difference could be found for the left side. The overall analysis of the AUC showed a significant main effect of side (AUC: $p = 0.009$), with higher amplitudes for right compared to left conditions. There was also a main effect of lateralization, with lateral conditions being larger than middle ones ($p = 0.026$).

The mean RT values in each condition were close to the offset of MS 5/onset of MS 6 (see Table 1; Fig. 4).

In MS 6, an overall analysis showed a significantly higher brain activation for right side stimulation than left side stimulation (AUC: $p = 0.003$), and a significant side by lateralization interaction was also observed ($p = 0.0001$). Further analyses accounted for this interaction with a larger AUC during the right lateral compared to the left lateral condition ($p = 0.02$), while no such difference was found in the middle conditions. MS 6 was the only MS where offsets were analyzed, because it ended the analysis. Offsets were significantly later in middle than in lateral conditions ($p = 0.0001$). A significant interaction of side and lateralization was also observed ($p = 0.0001$). A significantly later offset was observed for middle stimulation than for lateral stimulation in the left condition ($p = 0.002$, difference: 72 ms). The right condition analysis showed similar but smaller results ($p = 0.049$, difference: 20 ms). The lateral condition results showed a significantly later offset for right compared to left stimulation ($p = 0.015$, difference 52 ms).

Results of the Single Trial Covariance Analysis of RT

The TCT of the covariance maps of the single trial RTs was significant in three conditions, ML ($p < 0.006$), MR ($p < 0.001$), and RR ($p < 0.001$), in the early time interval. The corresponding t-maps are shown in Fig. 3c.

Interestingly, these covariance maps showed lateralized differences over the MC. In the first analysis interval, decreased RT was related to right negativity over the MC for left side stimulation, and left negativity over the MC for right side stimulation. The obtained covariance maps were strongest for the RR condition with the shortest RT.

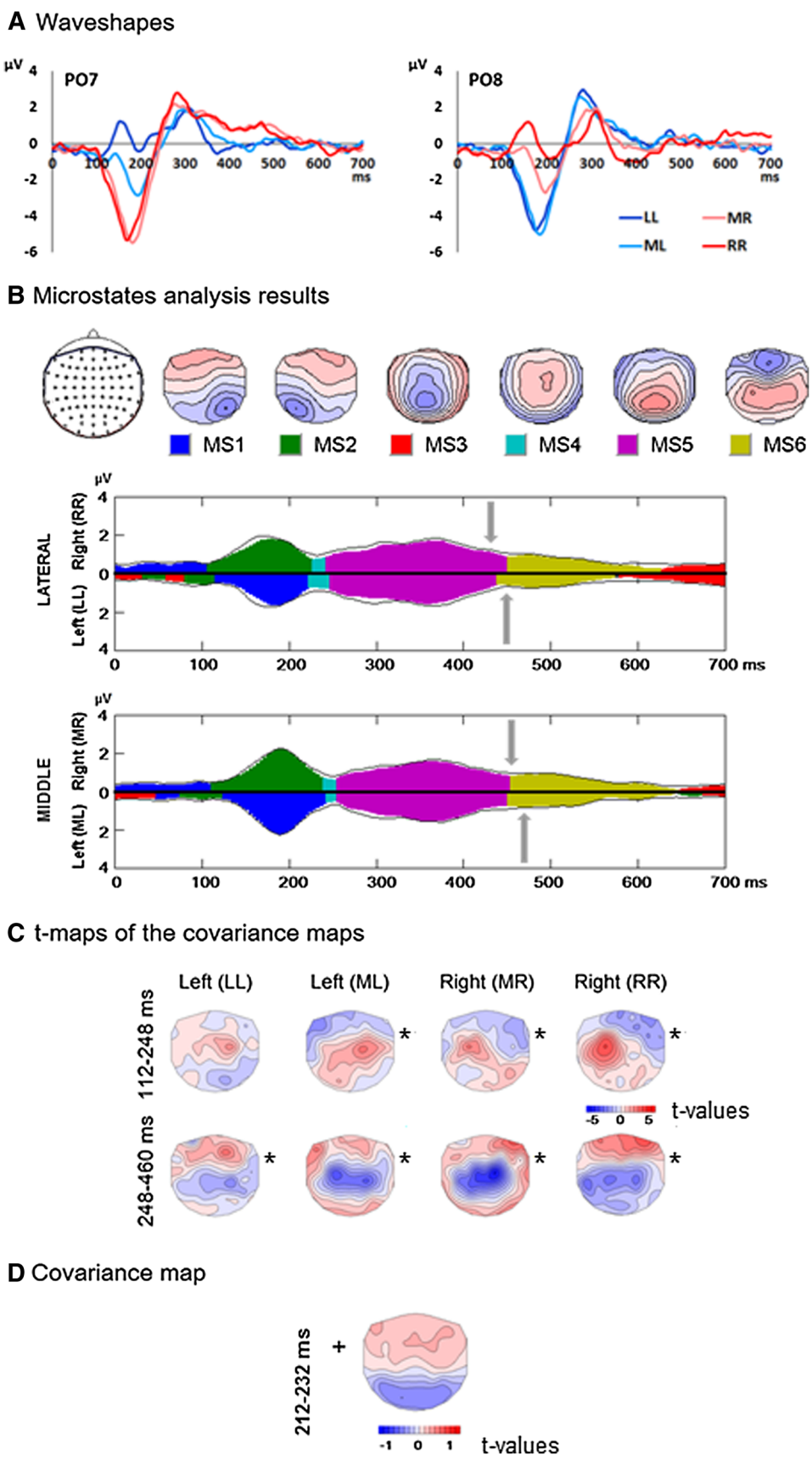
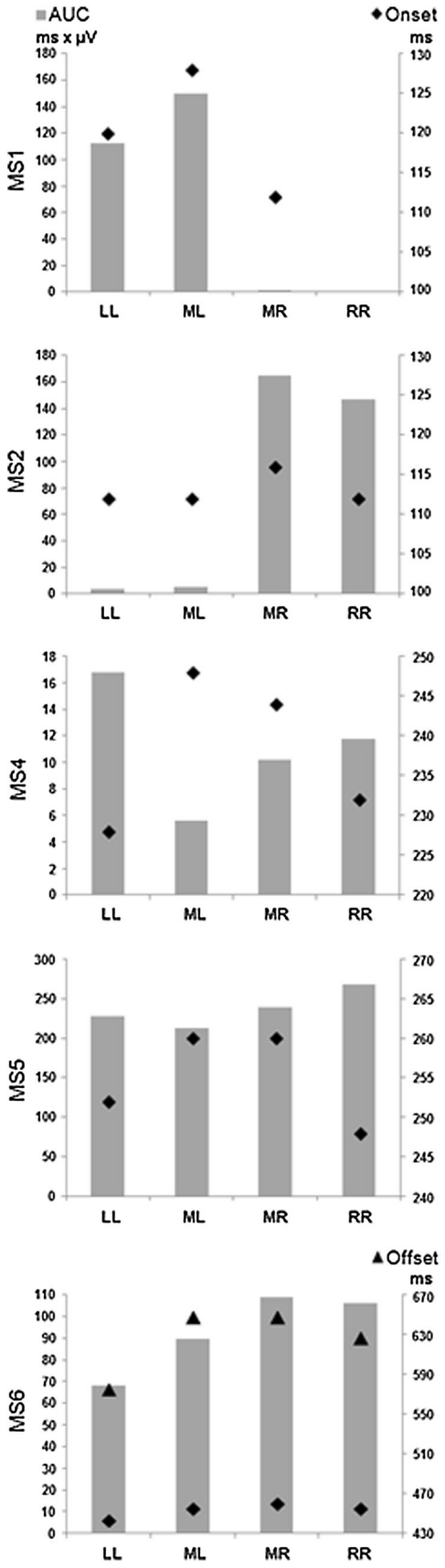


Fig. 3 **a** Wave shapes of the obtained grand average ERPs. Only wave shapes of electrodes PO7 and PO8 are presented. Wave shapes show ERPs in the left lateral (LL), left middle (ML), right middle (MR), and right lateral (RR) conditions. Y-axis scale is from −6 to 4 μV. **b** MSs analysis results. The displays of the ML and LL conditions have been flipped vertically and placed directly below the corresponding MR and RR displays to facilitate the comparison of the effects. *Colors* indicate the assignment of time to the different MS classes, while the height of the areas indicates the explained variance. The *thin black curved line* following the shape of the colored areas depicts the GFP; the *thick black line* indicates the zero baseline. *Arrows* indicate the mean RT in each condition. The y-axis scale is from 0 to 4 μV. **c** T-maps, computed across subjects, against zero, of the covariance maps obtained using single trial RT as regressor, in the two analysis windows. Significant t-maps are indicated with an asterisk. **d** Covariance map of the individual mean ERP with the mean individual RT showing how ERP potentials covaried with increasing RT. All topographies and maps are shown from above with the nose up



◀**Fig. 4** AUC and onset of MS 1, 2, 4, 5, and 6. MS 1 and MS 2 values are taken from analysis interval 112–248 ms, and MS 4–6 values are taken from the full analysis window 0–700 ms. Only the offset is shown for MS 6, because the onset of a new MS is the offset of the previous MS. For MS 1 and MS 2, on the ipsilateral side, onset of MS 1 is offset of MS 2, and vice versa. AUC and onset axis values differ for each MS

In the second analysis interval, the TCT was significant for all four conditions (LL, $p < 0.002$; ML, MR, and RR, $p < 0.001$). The t-maps across subjects showed that decreased RT was associated with a frontal negativity with a maximum lateralization to the side ipsilateral to stimulation and broad positivity over central electrode sites.

Results of the Covariance Analysis with RT Across Subjects

The standard TANCOVA with individual mean RT as predictor for the individual mean ERP yielded no significant results. However, when the data was normalized for Global Field Power (GFP), a significant ($p < 0.005$) main effect was observed in the 212–232 ms interval, where a frontal negativity and an occipital positivity correlated with decreased RT (Fig. 3d). This time interval is at the end of the N1 (i.e. MS 1 and 2) period, showing that brain activation during this particular time range is important for RT.

Discussion

We investigated hemispheric specialization and the speed of visual information processing in a simple CRT task using ERPs. In order to link our study to the existing DTI literature, we applied the same 4-CRT task stimulation procedure as Tuch et al. (2005).

Summing up the RT results, RTs were shorter for lateral compared to middle stimuli, and right hand responses were faster than left hand responses. However, the literature is contradictory regarding RT results. In an older SRT and 2-CRT study, the majority of participants showed faster left hand responses and faster responses to stimuli presented to the left visual field and these responses did not correlate with handedness (Annett and Annett 1979). Barthelemy and Boulinguez (2001) also reported faster left hand responses in CRT tasks. In contrast, other studies reported faster right hand responses in SRT (Kalyanshetti and Vastrad 2013) and CRT tasks (Steel et al. 2002). Though different non-cued tasks were used, in both studies, participants were instructed to respond to one stimulus with the left hand and to the other stimulus with the right hand, and the right hand responses of the right-handed subjects were faster. Moreover, SRT task results after visual, auditory, and cutaneous

Table 2 The p values of statistical analysis of microstate features (onsets and AUCs)

MS class	Features	Analyses including all conditions, grouped by two factors			Post-hoc analyses for subsets of all conditions			
		L–R	Mid–Lat	L–R*Mid–Lat	Left LL–ML	Right RR–MR	Middle ML–MR	Lateral LL–RR
MS 1	Onset	–	0.87	–	0.28	–	0.87	–
	AUC	*0.0001*	0.83	0.14	*0.0001* (ML > LL)	0.47	*0.0001* (ML > MR)	*0.0001* (LL > RR)
MS 2	Onset	1	1	0.46	1	0.73	0.33	–
	AUC	*0.0001*	0.57	*0.0001*	0.72	*0.023* (MR > RR)	*0.0001* (MR > ML)	*0.0001* (RR > LL)
MS 4	Onset	1	*0.0001*	*0.002*	*0.009*	*0.003*	0.83	0.68
	AUC	0.52	0.12	0.30	*0.02*	0.71	0.32	0.40
MS 5	Onset	1	*0.002*	*0.025*	0.15	*0.02*	1	0.89
	AUC	*0.009*	*0.026*	0.69	0.38	0.067	*0.026*	*0.03*
MS 6	Onset	0.16	0.87	0.065	0.19	0.92	0.97	0.15
	AUC	*0.003*	0.082	*0.0001*	0.065	0.75	0.12	*0.02*
	Offset	0.16	*0.0001*	*0.0001*	*0.002*	*0.049*	1	*0.015*

Only p values of the offset of MS 6 are shown because MS 6 ends the analysis window. MS 1 and MS 2 analysis interval was 112–248 ms, and MS 4–6 analysis window was 0–700 ms. The left half of the table shows the two main effects and interaction effects of 2 × 2 analyses including all conditions. The right half of the table provides post hoc results of subsets of conditions where this was justified by the result of the analysis including all conditions. A '–' indicates that the particular contrast could not be computed because a microstate was not observed in one of the conditions included in the contrast. Significant *p* values are indicated in italic. *Mid* middle, *Lat* lateral, *L* left, *R* right

stimulation revealed significantly faster right hand responses in right-handed groups for all modalities (Kalyanshetti and Vastrad 2013). These two tasks differed from the task used in our study, because we had four differently lateralized stimuli, and therefore the behavioral results are not directly comparable. However, all participants in our study were right-handed, so this right hand dominance (Kalyanshetti and Vastrad 2013; Steel et al. 2002) is in line with our findings. In addition, faster responses to stimuli presented in the right visual field compared to the left visual field were reported (Nobre et al. 2000), but no differences were found between response hands. Conversely, other papers reported faster left hand responses, but these authors used Posner-type paradigms with cues. Bestelmeyer and Carey (2004) used lateralized stimuli and auditory cues assigned to a particular side of stimulation and observed significantly faster left hand responses. Frecska et al. (2004) also reported faster left hand responses and maintained that these findings were due to right hemisphere dominance in visuospatial processing. The task in the latter study was different and more complex, because Frecska and colleagues applied two lateralized targets and two types of midline cues: a cue to the stimulus location and a cue to the response hand. Due to the complexity of their tasks and the use of cues, our result cannot be compared directly to these studies. The faster left hand responses in these two studies might be a result of cueing that enhanced visuospatial attentional networks predominantly in the right hemisphere as compared to our task.

Kolev et al. (2006) applied a 4-CRT task with 4 centrally presented letter stimuli, in which participants were to respond to each letter with a predefined finger. Participants also performed this task with corresponding auditory stimuli. Interestingly, RT was similar across both modalities for each finger. The slowest responses were produced by the left hand index finger, which corresponds to our findings in the ML condition. In contrast to our results, however, they observed the shortest RT for the right hand index finger, not the right hand middle finger as in our study. Thus, they found a zigzag pattern for RT, while we observed an inverse u-shaped pattern. However, their findings cannot be directly compared to our behavioral results due to a different configuration of stimuli—centrally presented verbal stimuli in their task versus horizontally aligned and lateralized geometric stimuli in our study. Our findings suggest that differentially lateralized presentation of stimuli (middle and lateral stimuli) affected RT; lateral stimuli evoked faster responses, because it was easier to discriminate positions of lateral stimuli compared to middle ones. The eccentricity was likely more important to RT than the response finger, since middle finger responses to lateral stimuli were faster, although index finger responses are typically expected to be faster than middle finger responses. In SRT and CRT tasks with lateralized stimuli, the right index finger was slower than the right middle, left index, and left middle fingers, and the left middle finger tended to be faster than the left index finger (Annett and Annett 1979). This is in line with the slower RTs for index fingers in our study, although the slowest

responses were observed for the left, not the right index finger.

When analyzing the mean ERPs, we found, as expected, that the early time range was dominated by strongly lateralized brain activity; this was apparent in MS 1, which represents the N1 component lateralized to the right hemisphere, and in MS 2, which represents the N1 potential lateralized to the left hemisphere. N1-related MSs were distributed over occipital and parietal electrode sites with negative peaks over the hemisphere contralateral to the stimulation. The visual N1 component is suggested to reflect discrimination and attention processes, including spatial attention. In a CRT and SRT study (Vogel and Luck 2000), the N1 was compared for different tasks, and the findings support the visual N1 component as an index of discrimination and attention processes. The N1 is also known to be more pronounced and have a higher amplitude contralaterally to the lateralized stimulation side (Störmer et al. 2009; Whitford et al. 2011), which corresponds with our findings.

The AUC of the N1 was larger over the left hemisphere (MS 2 > MS 1). This was confirmed by a post hoc analysis of the GFP that yielded a period of a consistent main effect of GFP for the factor side at 136–164 ms. This is in agreement with Nobre et al. (2000), who also showed stronger N1 activation over the left hemisphere. However, they found stronger N1 to be caused not only by lateralized stimulation but also by predictive cues toward the stimulation side, inducing a shift of spatial attention.

Fu et al. (2010) also showed an N1 component contralateral to the side of the visual stimulation, but they analyzed and described only C1 and P1 components. The P1 component is evoked by stimulus appearance, can be modulated by selective attention, and is usually observed 80–130 ms after stimulus onset (Fu et al. 2010; Hillyard and Anllo-Vento 1998; Mangun and Hillyard 1991). The P1 is observed for both cued or uncued (Mangun and Hillyard 1991; Störmer et al. 2009) and attended and unattended stimuli (Heinze et al. 1990; Hillyard and Anllo-Vento 1998; Johannes et al. 1995; Luck et al. 1990). Ramchurn et al. (2014) used no cues in their experiment and P1 was observed in their data. Similarly, we did not use any cueing. Michel et al. (1992) did not find a P1 component for Dynamic Random Dot stimuli but observed similar P1 amplitudes for both attended (rare) and unattended (frequent) high contrast stimuli. Although our stimuli contrast was high, we did not find a P1 component. The horizontal orientation of stimuli might explain the absence of P1, because in previous studies lateralized stimuli were presented above the horizontal meridian (Fu et al. 2010; Heinze et al. 1990) or around a fixation point (Luck et al. 1990). However, horizontally aligned stimuli presented to the left or to the right of the fixation cross also evoked P1 (Ramchurn et al. 2014) when stimuli appeared briefly. In contrast, we used four stimuli—two on each side instead of one—that were presented continuously as frames, and targets appeared only for 100 ms within one of these four continuously present frames. Thus, the absence of the P1 might be due to the particular setup of our stimuli, where only a relatively small part of the screen changed during stimulation.

We found a significantly stronger N1 activation for both conditions of middle stimulation (ML, MR) compared to lateral stimulation (LL, RR). Middle stimuli may stimulate a more binocular visual field. An N1 component observed ipsilateral to the stimulation side in the wave shapes of ML and MR conditions may be related to this interpretation.

The P3 component, corresponding by latency and topography to MS 5, had a widely distributed positivity over the bilateral occipital, parietal, and central electrode sites, with a maximum at Pz. This P3 was observed in all conditions. This is fully in line with the P3 literature, because the P3 is evoked in every task where the context has to be updated (Donchin 1981; Donchin and Coles 1988) or the "model of the environment must be revised" (Donchin and Coles 1988). In other words, the P3 is elicited when a fast decision has to be made about the stimulus (see Verleger 1997, for a review). Polich (2007) suggested that the P3 is observed "when stimulus detection engages memory operations." However, we would not argue that the design of our study engaged memory operations to elicit the P3, because participants responded to the location of each new stimulus irrespective of the location of a previous stimulus. This would not be a memory but a decision on an action related to the current stimulus, as discussed in the paper by Verleger (2008). As for the amplitude of the P3, we observed significantly higher brain activation for the right hemifield/left hemisphere compared to the left hemifield/right hemisphere stimulation, corresponding to faster right hand responses. These findings paralleled the results of both recent (Ramchurn et al. 2014) and older studies (Friedman 1984; Roth et al. 1978; Saville et al. 2011), where significantly greater P3 amplitudes were observed for faster relative behavioral responses. In our study, the strongest activation was in the RR condition, which also provoked the fastest responses. We expected the opposite P3 activation pattern in the ML condition, where RTs were slowest, and indeed, the AUC was lowest in the ML condition. We found a significant main effect of lateralization ($p = 0.026$) indicating that the AUC was higher in the lateral compared to the middle conditions. However, no significant interaction of side and lateralization was observed.

MS 6 occurred only after the response and had strong gradients near the MC. These gradients were formed by parietal positivity and frontal negativity with a peak over the frontocentral electrodes that may correspond to

evaluative processes. In literature, frontocentral negativity was reported to occur 0–150 ms after a response and reflect correct response evaluation in humans (Suchan et al. 2003, 2007). As in the previous MS, it showed a lateralization effect with a significantly higher brain activation for right side stimulation (AUC: $p = 0.003$), which may again reflect a right hand dominance. Offsets were significantly later in middle compared to lateral conditions ($p = 0.0001$), which, to some degree, mimics the differences in RTs.

The analysis of the single trial ERP correlates of RTs (covariance analysis) showed that, consistently across subjects, a negativity over the contralateral MC in the N1 component period correlated with trial-by-trial RT. In order to facilitate comparison of our results with well-known ERP components, we discussed correlations with a decreased RT. We found that the higher the observed negativity over the MC contralaterally to the stimulation side, the shorter the RT. This relation to variance in RT was most consistent across subjects in the RR condition, where mean RT was shortest. The location of the effect and its dependency on the side of stimulation suggested that the covariance maps related to the early MC preparation contralateral to the stimulation side, an effect that could be interpreted as LRP. LRP is a negative polarity ERP component observed over MC contralaterally to the responding hand that is considered to reflect motor response preparation (Leuthold 2011). LRP starts after the response-hand selection and at the beginning of motor programming (Masaki et al. 2004). On the other hand, this contralateral negativity probably might be interpreted as a N2-type component, more specifically, a N2cc-N2 central contralateral component. N2cc and LRP components can overlap, although N2cc was proposed to reflect the activity of the premotor cortex and ensure that the selection of a response is based on the location of the target and not biased by the direction of spatial attention (Praamstra and Oostenveld 2003; Praamstra 2006).

There were also consistent covariance maps in the P3 time period. These maps resembled the inverted P3 topography and showed less lateralization. This agrees with previous papers showing that the P3 amplitude showed a negative correlation with RT (e.g. Friedman 1984; Ramchurn et al. 2014; Roth et al. 1978; Saville et al. 2011). As a limitation of this study, the relatively small number of stimuli may have affected the statistical power of the covariance analysis. A larger number of repetitions may have revealed more findings.

The analysis of correlates of the individual mean ERPs and mean individual RTs yielded a somewhat different picture; the TANCOVA was only significant after data normalization ($p = 0.005$) and yielded a main effect in the 212–232 ms interval. The topography of this covariance map showed correlation between brain activation and RT; a stronger frontal negativity and an occipital positivity correlated with faster RTs. This pattern is very different from the pattern observed in the single trial results. Since the effect was in the last part of the N1 period, and since its topography resembles the average of the topographies of MS1 and MS2, one may speculate that the effects represent a prolongation of the N1, when RT is slower, and thus assumingly a prolongation of attentional processes. This may in consequence result in a prolongation of the later motor reaction. In agreement with the literature, this finding could be interpreted as the N2, but not the N1, because the N2 latency positively correlated with RT (Gajewski et al. 2008). The N2 latency also negatively correlated with the P3 amplitude (Gajewski et al. 2008), similar to the negative correlation of P3 amplitude and RT (Friedman 1984; Ramchurn et al. 2014; Roth et al. 1978; Saville et al. 2011) that was also observed in our study.

The ERP correlates of RT were very different when focusing on intraindividual trial-by-trial variability as compared to variability of mean RT between subjects. Boy and Sumner (2014) recently reported that intraindividual variance may arise from different sources than interindividual variance, and thus correlations in within-subject level cannot be simply transferred to the between-subject level and vice versa. That could explain the differences between the two types of covariance analysis results in our study. A limiting factor to be considered here is the random presentation of the stimuli in our study, because we did not exclude trials where stimuli appeared at the same position as in the previous trial. Although our task was not a Posner-type experiment with cues at the stimulus location (e.g. review Klein 2000), and although the interstimulus interval was 2000 ms, the previous stimulus could still have played the role of an exogenous cue for the subsequent stimulus. The stimulus reappearance at the same position in the subsequent trial could thus potentially delay RT through the inhibition of return (Klein 2000).

Numerous papers reported findings in hemispheric asymmetry and right hemisphere dominance in visuospatial information processing (Fink et al. 1997; Gitelman et al. 1999; Kim et al. 1999; Nielsen et al. 2013; Nobre et al. 1997; Sack et al. 2005; Sheremata et al. 2010; Stephan et al. 2003; Tuch et al. 2005; Weintraub and Mesulam 1987; Whitford et al. 2011). However, we observed a stronger activation in the left hemisphere, not the right. Our findings that RT was faster for stimuli presented to the right visual field may suggest that the right visual field has a priority due to the right hemisphere dominance. This priority may be explained by the fact that the right hemisphere directs attention not only to the left visual field, but also to the right one, and thus both hemispheres are involved in the processing of information in the right visual field (Nobre et al. 1997, 2000; Sheremata et al. 2010; Weintraub and Mesulam 1987).

We found that the right visual field/left hemisphere stimulation evoked stronger activation compared to the left hemifield/right hemisphere stimulation in N1 and P3 components periods. In addition, RTs were shortest for the right visual hemifield/left hemisphere stimulation (RR condition). Covariance analysis showed the importance of the MC preparation during an early information-preprocessing period to RT. This relation was most consistent across subjects in the RR condition.

Our data complements studies on white matter connectivity correlates of RT by providing detailed information about the timing of grey matter activation. These two perspectives on brain functionality are mutually informative. Our covariance analysis across subjects was similar to the analysis of DTI-RT correlates as conducted by Konrad et al. (2009) and Tuch et al. (2005). Both sets of findings indicate structures and processes related to attention are the source for individual differences in RT. However, while the DTI studies found RT and white matter properties predominantly correlated in fiber tracks important for visual and attentional processes in the right hemisphere (Konrad et al. 2009; Tuch et al. 2005), we had stronger activation and faster RTs for the left hemisphere. Additionally, we had a series of stable within-subject associates of RT which cannot be accounted for by structural differences. A reasonable neurobiological understanding of RT will thus require a model that considers structure–function interactions in various domains, such as response anticipation, attention, and response selection.

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