

The neurophysiological correlates of handedness: Insights from the lateralized readiness potential

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ABSTRACT

Handedness is the most investigated form of functional hemispheric asymmetries, but its neural correlates remain unclear. Functional imaging studies suggest differences between left- and right-handers in ipsilateral activation during unilateral hand movements, but do not allow for conclusions on the temporal dimension. In the Tapley and Bryden task, subjects have to draw as many dots as possible on a paper within 20 s using either the left or the right hand. We adapted the task for use during EEG in 36 left- and 36 right-handers. Subjects performed a visually guided response task with each trial consisting of eight motor responses. We investigated the lateralized readiness potential (LRP) at the first and last response of the sequence. Overall, increasing complexity of sequences was associated with earlier and less negative LRP peaks. For the last response, right-handers showed more negative LRP peak amplitudes than left-handers. The effect of handedness on LRP peak amplitude in the first response was modulated by task complexity with a more negative LRP peak amplitude in right-handers than left-handers in simple, but not in medium or complex trials. This effect might be due to more symmetrical processing in right-handers with increasing task complexity. These findings complement previous imaging studies and add a new perspective on the relationship between laterality and schizophrenia, associated with less pronounced LRPs and a higher prevalence of left-handedness.

1. Introduction

About 90% of humans are right-handed with slight geographical variation [1]. Handedness has been associated with intelligence [2], general cognitive abilities [3], spatial abilities [4], and executive functions [5], highlighting its societal relevance. It is typically found that left-handers are less lateralized than right-handers in hand preference [6,7] and hand performance tasks [8,9]. This pattern has also been found in monozygotic twins discordant for handedness [10].

While recent studies suggest genetic and early epigenetic regulation to affect the ontogenesis of lateralization [11,12], it remains unclear how these salient differences on the behavioral level manifest in brain structure and/or neural function. One possible scenario is that contrasting gray matter asymmetries in the region of hand representation are associated with left- and right-handedness. However, although gray matter asymmetries have been reported in the precentral gyrus [13–15], there is no reversal in left- compared to right-handers. In 45

male subjects, Amunts et al. [16] found that the central sulcus is deeper in the hemisphere contralateral to the dominant hand. This pattern was later confirmed for male, but not for female subjects [17]. However, in a large-scale study with more than 2000 subjects, none of 74 cortical regions showed a significant difference in cortical surface area between left- and right-handers after correction for multiple comparisons [18]. In voxel-based morphometry (VBM) studies, no effect on brain structure was found for handedness neither as a categorical measure [19] nor as a quantitative measure [20]. Thus, it has been suggested that not only gray matter asymmetries, but also inter- and intrahemispheric white matter have to be taken into account for a structural model of functional hemispheric asymmetries [21].

Several studies used simple finger tapping tasks during functional magnetic resonance imaging (fMRI) to assess differences in motor preparation between left- and right-handers. On the behavioral level, it has been reported that right-handers show better tapping performance with their dominant hand regardless of complexity level. In contrast,

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left-handers only show a left-hand advantage in simple tasks, while performance with the left and right hand is similar with increasing task complexity [22]. It was also shown that the difference between performance of the dominant and non-dominant hand is smaller for left-handers than for right-handers [23]. Several fMRI studies have focused on motor processing in right-handed subjects. It was shown that contralateral activation of the primary motor cortex is similar regardless of whether the left or the right hand is moved [24–27]. In contrast, ipsilateral activation differs between right- and left-hand movements with less ipsilateral deactivation during left-hand movements compared to right-hand movements [24,28,29]. As revealed by functional connectivity analysis and diffusion tensor imaging (DTI), ipsilateral activation is suppressed by the contralateral motor cortex, which is mediated by fractional anisotropy of the isthmus interconnecting the motor cortices [29]. In order to determine if ipsilateral deactivation is associated with handedness, Tzourio-Mazoyer et al. [23] tested 142 left-handers and 142 right-handers and confirmed that contralateral activation is similar during left- and right-hand movements in both left- and right-handers. In contrast, ipsilateral deactivation was stronger in right-handers when moving the right hand, but equal during left- and right-hand movements in left-handers [23]. Similar ipsilateral activation patterns in left- and right-hand movements in left-handers have also been reported by others [22,30].

However, the temporal resolution of fMRI makes it impossible to distinguish motor preparation from motor execution [31]. Thus, complementing studies using electroencephalography (EEG) with higher temporal resolution are essential to understand the neuronal processes underlying handedness. The readiness potential is an event related potential (ERP) component related to movements. About 750 ms prior to a voluntary movement, a distinct negativity starts over parietal and prefrontal areas. Starting about 400 ms before movement onset, this negativity increases faster and more pronounced on the contralateral hemisphere [32]. Source analysis of this component reveals that it is most likely generated in the primary motor cortex [33]. In right-handers, it has been shown that left-hand movements lead to an earlier contralateral readiness potential than right-hand movements [34] that is also less pronounced [33]. In order to control for noisy data and other lateralized components generated in different brain areas, a double subtraction technique was introduced to isolate motor-related lateralization. Potentials from electrodes close to the motor cortex (usually C3 and C4) are averaged for trials using the left hand and trials using the right hand separately. These potentials are then subtracted (right hand trials (C3 – C4) – left hand trials (C3 – C4)) to form the lateralized readiness potential (LRP) [35]. This process cancels out non-lateralized activation or lateralized activation that is not related to hand use. Importantly, the LRP has been found to increase with task complexity [33,36]. Task complexity is usually varied by the amount of movements in the same time interval [22], amount of involved fingers [33] or involved fingers for which the movement is perceived as tougher (e.g. the ring finger instead of the index finger) [37].

A recent study investigating the LRP in both left- and right-handers revealed that the LRP amplitude was larger for subjects with consistent hand preference than for subjects with inconsistent hand preference, irrespective of handedness direction. The LRP was assessed response-locked to a button press in reaction to the direction of an arrow, a task that produced only minor error rates and no behavioral differences between left- and right-handers [38].

Understanding the neurophysiology of handedness is a critical step in the comprehension of its ontogenesis, its association with cognitive functions [2–5] and neurodevelopmental traits [39,40]. Thus, we aimed to investigate the neurophysiological correlates of handedness by comparing the LRP between consistent left- and consistent right-handers in a task that clearly separates left- and right-handers on the behavioral level. We therefore implemented the Tapley and Bryden task [41] for use during EEG. In the classical Tapley and Bryden task, subjects are instructed to place as many dots as possible on a white sheet of

paper within a given time frame with the left and the right hand. This task has been found to produce consistent and reliable performance differences between the hands [41]. Moreover, task performance separates left-handed from right-handed subjects [42]. In the EEG version, eight squares were presented around a fixation cross on a computer screen and responses were made by clicking as fast as possible on these squares in a specified sequence, reflecting different levels of complexity. The completion of one trial required eight responses, which allowed us to analyze reaction times (RT, from stimulus onset until first response), completion times (CT, from stimulus onset until last response) and error rates (sum of errors). For the behavioral data, we hypothesized right-handers to perform better with the right than with the left hand, reflected in shorter RT, CT, and less errors. We also hypothesized left-handers to perform better with the left than with the right hand; however, with less pronounced differences between the hands. Moreover, we expected an effect of complexity with more errors and longer RT and CT with increasing complexity. If ipsilateral activation during unilateral movements differs between the left and right hand in right-handers, but not in left-handers, as suggested by fMRI research [22,23,30], this effect should also be reflected in the LRP. For the electrophysiological data, we thus hypothesized a less pronounced LRP (less negative peak amplitude, later peak latency) for left- compared to right-handers. Moreover, we expected an effect of complexity on the LRP with a more pronounced LRP with increasing complexity in the last response [33,36]. It has been shown that the amplitude of the motor-evoked potential (MEP) induced by a precue signaling a repetitive motor response (pressing a surface three times with the index finger) was significantly smaller compared to a precue signaling a sequential motor response (pressing a surface sequentially with the index, little, and middle finger) [43]. Based on these findings, we hypothesized an effect of complexity on the LRP in the first response as well. Moreover, based on behavioral data [22], the LRP was expected to be less affected by complexity in left-handers compared to right-handers.

2. Material and methods

2.1. Subjects

Overall, 80 subjects (40 female) participated in this study. Eight subjects had to be excluded from analysis due to low quality data. The final sample consisted of 72 subjects (37 female) between 18 and 35 years of age ($M = 23.86$, $SD = 3.99$). Handedness was determined using the Edinburgh handedness inventory (EHI) [44]. Half of the subjects were consistently left-handed (36 left-handers, 18 female), with an EHI lateralization quotient (LQ) below -60 ($M = -86.49$, $SD = 14.02$) and half of the subjects were consistently right-handed (36 right-handers, 19 female) with an EHI LQ above 60 ($M = 95.35$, $SD = 7.73$). Left- and right-handers did not differ significantly in age ($t(70) = 0.235$, $p = .815$) or years of education ($t(70) = 0.068$, $p = .946$). All subjects had normal or corrected-to-normal vision and had no history of neurological or psychiatric disease. Subjects received reimbursement or course credit for their participation. Written informed consent was obtained prior to participation. The study was in accordance with the declaration of Helsinki and received approval by the ethics committee of the Psychological Faculty at Ruhr University Bochum.

2.2. Tapley and Bryden task

Prior to the EEG version, subjects performed the Tapley and Bryden task in the classical paper-pencil version [41]. A trial consisted of 110 circles with a diameter of 5 mm placed on a white sheet of paper. Subjects were instructed to make dots in as many circles as possible within a time limit of 20 s. They had to follow the pattern of the circles and dots had to be in the circle and neither outside or on the edge. Subjects performed four trials and used their writing hand for the first

and fourth and their non-writing hand for the second and third trial. Mean numbers of properly filled circles were calculated for the left and right hand. A laterality quotient was calculated by the formula: Tapley LQ = (R - L) / (R + L) × 100. Moreover, Tapley LQs were generated for the first and the second trial per hand in order to calculate Guttman's split-half reliability coefficient.

2.3. Experimental paradigm

Stimuli were presented using the Presentation software (Neurobehavioral Systems, CA, USA). Stimuli were presented on a 17-inch screen at a viewing distance of 57 cm, which was ensured by a chin rest. At this distance, 1 cm on the screen is equivalent to 1° of visual angle. A fixation cross (0.4° × 0.4° degrees of visual angle) was presented centrally on the screen for the whole experiment. Subjects were instructed to fixate the cross to avoid distortions by eye movements.

A stimulus consisted of eight squares (each 0.5° × 0.5° degrees of visual angle) that were presented around the fixation cross. At any time, seven of the squares were presented in gray and one square was presented in red. The edge of the squares closest to the fixation cross was located 1° of visual angle from the fixation cross. Distance between squares was also 1° of visual angle. In order to complete a trial, subjects had to perform eight responses. They were instructed to click as fast and accurate as possible on the red square with a round cursor (0.3° × 0.3° degrees of visual angle) controlled with the computer mouse (see Fig. 1).

For a valid response, the cursor had to be entirely in the square without touching the edge. The complexity level (simple, medium, complex) was indicated by the respective German word appearing simultaneously above the stimulus (distance to stimulus 1° of visual angle) for the whole duration of the trial. In simple trials, subjects had to respond to the same stimulus eight times in a row as indicated by the same square appearing in red eight times in a row (see Fig. 1A). In medium trials, subjects had to respond to all eight squares in a counterclockwise manner (see Fig. 1B). In complex trials, subjects had to respond to all eight squares in a fixed order in which a square was never preceded or followed by an adjacent square (see Fig. 1C). There was no time constraint. The intertrial interval (starting after the last of the eight responses) was jittered randomly between 1200 ms and 1400 ms. The task consisted of four experimental blocks, two for each hand. Subjects performed the first and third block with the right hand and the second and fourth block with the left hand. Each block consisted of 72 consecutive trials. Complexity levels (simple, medium, complex) were randomly dispersed over the four blocks. Overall, subjects performed 144 trials with each hand (48 trials per complexity level). Within a complexity level, the starting point, i.e. the first square to respond to,

was equally distributed among the eight squares. Prior to the experiment, subjects performed 10 practice trials with each hand that were excluded from analysis.

2.4. EEG acquisition and analysis

EEG was recorded from 64 Ag-AgCL electrodes arranged according to the standard international 10–20 system using FCz as a primary reference. We used the standard BrainAmp amplifier and BrainVision recording software (Brain Products GmbH, Gilching, Germany) to record at a sampling rate of 1000 Hz. Impedances were kept below 10 kΩ.

EEG data were processed offline using the Brain Vision Analyzer software (Brain Products GmbH, Gilching, Germany). Raw data were filtered with 0.1 Hz low cutoff and 30 Hz high cutoff (24 dB/oct). Filtered data were visually inspected to exclude sections containing technical artefacts and remove channels with gross artefacts. An infomax independent component analysis (ICA) was applied to the remaining data to eliminate artefacts caused by horizontal or vertical eye movements or pulse. Previously removed channels as well as FCz were (re-) calculated via topographic interpolation with spherical splines. EEG data were epoched according to stimulus onset (-300 ms to 5000 ms). Data were corrected relative to baseline (-300 ms to stimulus onset). EEG data were further epoched response-locked, according to the first response (-800 ms to 400 ms) and according to the last response (-800 ms to 400 ms) within a trial (see Fig. 1). Automatic artefact rejection was applied to epoched data with maximum allowed voltage steps of 50 μV/ms, maximum allowed value differences of 200 μV within a 200 ms interval and lowest allowed activity of 0.5 μV within a 100 ms interval. We applied current source density (CSD) transformation to remove the reference potential from the data. For each complexity level (simple, medium, complex) and both time points (first and last response in a trial), epochs were averaged and the LRP was determined for electrodes C3 and C4 using the formula:

$$LRP = \text{right-hand trials (C3 - C4)} - \text{left-hand trials (C3 - C4)}$$

We performed a semiautomatic peak detection in the 160 ms prior to the response to determine LRP peak latency and LRP peak amplitude.

2.5. Statistical analysis

A *t*-test for independent samples was applied to Tapley LQ in order to test for differences between left- and right-handers.

For the EEG paradigm, we analyzed RT, CT, and sum of errors for each complexity level. A repeated-measures ANOVA was conducted for each RT, CT and sum of errors using hand (left & right) and complexity (simple, medium, complex) as inner-subject factors and handedness as a

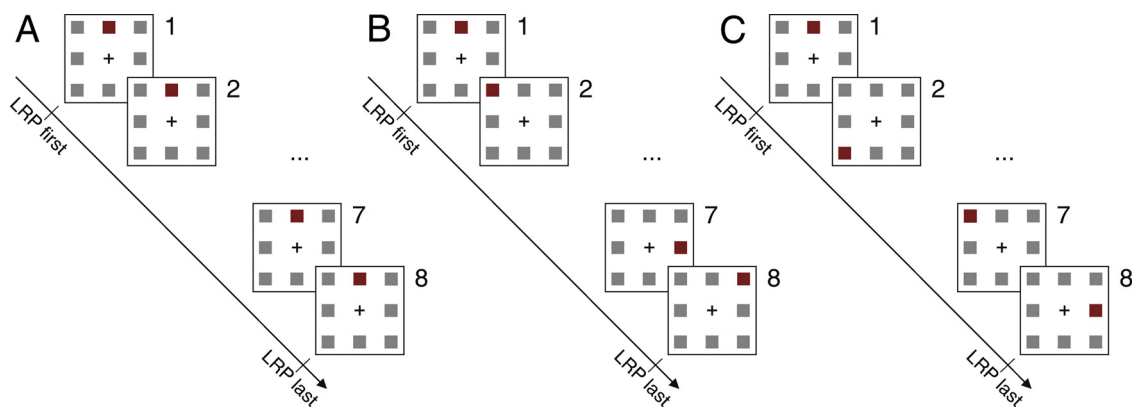


Fig. 1. Illustrations of complexity levels. A) Simple trials: Subjects responded to the same stimulus eight times in a row. B) Medium trials: Subjects responded to all eight squares in a counterclockwise direction. C) Complex trials: Subjects responded to all eight squares in a fixed order in which a square was never preceded or followed by an adjacent square. Each trial was followed by an intertrial interval that was jittered between 1200 and 1400 ms. The LRP was determined for both the first and the last response of each trial.

between-subject factor. Bonferroni-corrected post hoc tests were performed for all significant effects. Individual LQs were generated for RT, CT, and sum of errors for each complexity level determined by the formulas:

$$\text{RT LQ} = (\text{RT left} - \text{RT right}) / (\text{RT left} + \text{RT right}) \times 100$$

$$\text{CT LQ} = (\text{CT left} - \text{CT right}) / (\text{CT left} + \text{CT right}) \times 100$$

$$\text{Error LQ} = (\text{errors left} - \text{errors right}) / (\text{errors left} + \text{errors right}) \times 100$$

Thus, positive values of RT LQ, CT LQ, and Error LQ reflect right-hand dominance. Additionally, individual RT LQs and CT LQs were generated for the first 24 trials and the second 24 trials per hand separately in order to calculate Guttman's split-half reliability coefficient. Pearson correlation was used to analyze the associations between RT LQs, CT LQs and Error LQs for each condition with the Tapley LQ using Bonferroni correction for nine comparisons ($\alpha = 0.0056$).

For both the first and the last response, LRP peak latency and peak amplitude were analyzed with a repeated-measures ANOVA using complexity (simple, medium, complex) as inner-subject factor and handedness as between-subject factor. Bonferroni-corrected post hoc tests were performed for all significant effects.

Pearson correlation was used to determine the association between Tapley LQ and LRP peak amplitude for each condition (first and last response) using Bonferroni correction for six comparisons ($\alpha = 0.0083$). All statistical analyses were performed using SPSS (version 20, Chicago, IL, USA).

3. Results

3.1. Behavioral data

Tapley LQ differed significantly between left- and right-handers ($t(70) = -18.97, p < .001$) with left-handers showing a negative mean Tapley LQ ($M = -17.20, SD = 9.95$) and right-handers showing a positive mean Tapley LQ ($M = 20.85, SD = 6.77$). Only two left-handers showed positive Tapley LQs and none of the right-handers showed a negative Tapley LQ. Tapley LQs showed high split-half reliability (Guttman's split-half coefficient = .953). The same was true for RT LQs (Guttman's split-half coefficient = .849 (simple), .898 (medium), .774 (complex)) and CT LQs (Guttman's split-half coefficient = .915 (simple), .949 (medium), .953 (complex)).

For RT, the repeated-measures ANOVA revealed a significant main effect of hand ($F_{(1,70)} = 86.27, p < .001, \text{partial } \eta^2 = 0.55$) and a significant main effect of complexity ($F_{(2,140)} = 3.57, p < .05, \text{partial } \eta^2 = 0.05$), but no main effect of handedness ($F_{(1,70)} = 0.18, p = .675, \text{partial } \eta^2 = 0.003$). There was a significant hand by handedness interaction ($F_{(1,70)} = 24.33, p < .001, \text{partial } \eta^2 = 0.26$). As revealed by post hoc tests, the main effect of hand was based on faster overall reaction times with the right ($M = 1088.78 \text{ ms}, SE = 21.15 \text{ ms}$) compared to the left hand ($M = 1352.48 \text{ ms}, SE = 32.31 \text{ ms}, \text{corrected } p < .001$). The main effect of complexity was based on faster reaction times in simple ($M = 1208.21 \text{ ms}, SE = 25.22 \text{ ms}$) compared to medium trials ($M = 1240.41 \text{ ms}, SE = 26.87 \text{ ms}, \text{corrected } p < .01$, see Figure S1). Post hoc tests of the interaction effect of hand by handedness revealed that in right-hand trials, right-handers were faster than left-handers (right-handers: $M = 1028.57 \text{ ms}, SE = 29.91 \text{ ms}$; left-handers: $M = 1148.99 \text{ ms}, SE = 29.91 \text{ ms}, \text{corrected } p < .01$). This pattern was reversed in left-hand trials (right-handers: $M = 1432.32 \text{ ms}, SE = 45.70 \text{ ms}$; left-handers: $M = 1272.65 \text{ ms}, SE = 45.70 \text{ ms}, \text{corrected } p < .05$, see Fig. 2A).

For CT, there was a significant main effect of hand ($F_{(1,70)} = 134.04, p < .001, \text{partial } \eta^2 = 0.66$) and complexity ($F_{(2,140)} = 2492.55, p < .001, \text{partial } \eta^2 = 0.97$), but no main effect of handedness ($F_{(1,70)} = 0.68, p = .413, \text{partial } \eta^2 = 0.01$). Post hoc tests revealed that

right-hand trials were completed significantly faster ($M = 5244.35 \text{ ms}, SE = 97.06 \text{ ms}$) than left-hand trials ($M = 6645.77 \text{ ms}, SE = 134.89 \text{ ms}, \text{corrected } p < .001$). Moreover, simple trials ($M = 2700.32 \text{ ms}, SE = 44.43 \text{ ms}$) were completed faster than medium trials ($M = 6637.38 \text{ ms}, SE = 121.37 \text{ ms}$) and complex trials ($M = 8497.48 \text{ ms}, SE = 144.09 \text{ ms}, \text{corrected } p < .001$). Completion time also differed significantly between medium and complex trials ($p < .001$, see Figure S2). The interaction hand by handedness reached significance ($F_{(1,70)} = 35.39, p < .001, \text{partial } \eta^2 = 0.34$) with left-handers completing left-hand trials faster than right-handers (right-handers: $M = 7088.67 \text{ ms}, SE = 190.76 \text{ ms}$; left-handers: $M = 6202.87 \text{ ms}, SE = 190.76 \text{ ms}, \text{corrected } p < .01$). This effect was reversed for right-hand trials (right-handers: $M = 4967.19 \text{ ms}, SE = 137.27 \text{ ms}$; left-handers: $M = 5521.50 \text{ ms}, SE = 137.27 \text{ ms}, \text{corrected } p < .01$, see Fig. 2B). The interactions hand by complexity ($F_{(2,140)} = 113.45, p < .001, \text{partial } \eta^2 = 0.62$) and hand by complexity by handedness ($F_{(2,140)} = 24.65, p < .001, \text{partial } \eta^2 = 0.26$) also reached significance. Bonferroni-corrected post hoc tests revealed significant differences between left- and right-handers for each hand and each complexity level (all corrected $p < .05$).

For error rates, the ANOVA revealed a significant main effect of hand ($F_{(1,70)} = 8.00, p < .01, \text{partial } \eta^2 = 0.10$) and a significant main effect of complexity ($F_{(2,140)} = 272.84, p < .001, \text{partial } \eta^2 = 0.80$), but no main effect of handedness ($F_{(1,70)} = 0.09, p = .767, \text{partial } \eta^2 = 0.001$). As revealed by post hoc tests, significantly more errors were made with the left ($M = 67.53 \text{ errors}, SE = 3.54$) than with the right hand ($M = 60.40 \text{ errors}, SE = 3.28, \text{corrected } p < .01$, see Figure S3). Moreover, more errors were made in the complex condition ($M = 87.02 \text{ errors}, SE = 4.55$) than in the simple condition ($M = 20.57 \text{ errors}, SE = 1.26, \text{corrected } p < .001$). The sum of errors also differed significantly between simple trials and medium trials ($M = 84.02 \text{ errors}, SE = 4.27, \text{corrected } p < .001$). There was no significant difference between medium and complex trials (corrected $p = .443$, see Figure S4). The interaction hand by complexity also reached significance ($F_{(2,140)} = 4.23, p < .05, \text{partial } \eta^2 = 0.06$) with error rates differing significantly between the left and right hand in simple (right hand: $M = 15.67 \text{ errors}, SE = 1.13$; left hand: $M = 25.47 \text{ errors}, SE = 1.90, \text{corrected } p < .001$) and complex trials (right hand: $M = 82.38 \text{ medium}, SE = 4.67$; left hand: $M = 91.67 \text{ errors}, SE = 4.97, \text{corrected } p < .01$), but not in medium trials (corrected $p = .542$, see Figure S5).

In order to test whether the EEG Tapley version reflected results from the behavioral Tapley and Bryden task, RT LQs, CT LQs and Error LQs for each condition were correlated with the Tapley LQ. RT LQs (simple: $r = .530$, medium: $r = .539$, complex: $r = .521$, all $p < .0056$, see Figure S6) and CT LQs (simple: $r = .637$, medium: $r = .591$, complex: $r = .584$, all $p < .0056$, see Figure S7) were significantly correlated with Tapley LQ after correction for multiple comparisons. In contrast, Error LQs were not (simple: $r = .110, p = .357$, complex: $r = .079, p = .507$) or only nominally correlated (medium: $r = .244, p < .05$, see Figure S8) with Tapley LQ.

3.2. Electrophysiological data

LRP peak latencies were analyzed for the first and the last response of each trial. For the first response, the ANOVA revealed a significant main effect of complexity ($F_{(2,140)} = 8.97, p < .001, \text{partial } \eta^2 = 0.11$), but neither a significant main effect of handedness ($F_{(1,70)} = 0.41, p = .526, \text{partial } \eta^2 = 0.01$) nor a significant complexity by handedness interaction ($F_{(2,140)} = 0.49, p = .612, \text{partial } \eta^2 = 0.01$). Post hoc tests revealed that the LRP peaked significantly later in simple trials ($M = -48.57 \text{ ms}, SE = 3.07 \text{ ms}$) than in complex trials ($M = -65.01 \text{ ms}, SE = 3.43 \text{ ms}, \text{corrected } p < .001$). There was a trend towards significance for simple and medium trials ($M = -56.69 \text{ ms}, SE = 2.85 \text{ ms}, \text{corrected } p = .064$), but no significant difference between medium and complex trials (corrected $p = .117$, see Fig. 3A, black). For the last

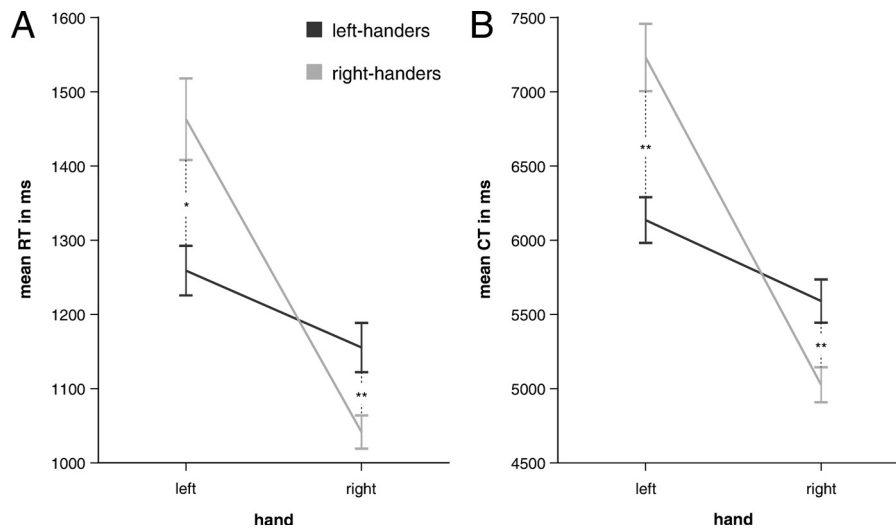


Fig. 2. Illustrations of hand by handedness interactions on A) reaction times (RT) and B) completion times (CT). Error bars indicate standard errors. * corrected $p < .05$; ** corrected $p < .01$.

response, the ANOVA also revealed a significant main effect of complexity on LRP peak latencies ($F_{(2,140)} = 12.45, p < .001$, partial $\eta^2 = 0.15$), but neither a significant main effect of handedness ($F_{(1,70)} = 0.99, p = .322$, partial $\eta^2 = 0.01$) nor a significant complexity by handedness interaction ($F_{(2,140)} = 0.71, p = .495$, partial $\eta^2 = 0.01$). Post hoc tests revealed significant differences between simple ($M = -45.53$ ms, $SE = 3.26$ ms) and medium ($M = -57.13$ ms, $SE = 3.29$ ms, corrected $p < .01$) and between simple and complex trials ($M = -63.63$ ms, $SE = 3.45$ ms, corrected $p < .001$). Peak latencies did not significantly differ between medium and complex trials ($p = .225$, see Fig. 3A, gray).

For LRP peak amplitudes of the first response, the ANOVA revealed a significant main effect of complexity ($F_{(2,140)} = 3.79, p < .05$, partial $\eta^2 = 0.05$) and a significant complexity by handedness interaction ($F_{(2,140)} = 3.18, p < .05$, partial $\eta^2 = 0.04$). There was no significant main effect of handedness ($F_{(1,70)} = 2.44, p = .123$, partial $\eta^2 = 0.03$). For the main effect of complexity, post hoc tests revealed significant differences between simple ($M = -10.91$ μ V, $SE = 1.00$ μ V) and complex trials ($M = -7.97$ μ V, $SE = 1.02$ μ V, corrected $p < .05$), but no significant differences between simple and medium ($M = -10.22$ μ V,

$SE = 1.09$ μ V, corrected $p = .999$) or medium and complex trials (corrected $p = .120$, see Fig. 3B, black). As revealed by post hoc tests, the interaction complexity by handedness was based on a significant difference in LRP peak amplitude between left- and right-handers in simple trials (left-handers: $M = -8.18$ μ V, $SE = 1.41$ μ V, right-handers: $M = -13.65$ μ V, $SE = 1.41$ μ V, corrected $p < .01$). There was no significant difference in medium (corrected $p = .303$) or complex trials (corrected $p = .943$, see Figs. 4, 5A). Moreover, first response LRP peak amplitude did not differ between simple, medium and complex trials in left-handers (all corrected $p > .05$). However, first response LRP peak amplitude did significantly differ between simple ($M = -12.49$ μ V, $SE = 1.92$ μ V) and complex trials ($M = -7.43$ μ V, $SE = 1.73$ μ V, corrected $p < .01$) in right-handers (see Fig. 4).

For LRP peak amplitudes of the last response, the ANOVA revealed significant main effects of complexity ($F_{(2,140)} = 10.59, p < .001$, partial $\eta^2 = 0.13$) and handedness ($F_{(1,70)} = 4.83, p < .05$, partial $\eta^2 = 0.07$), but no significant complexity by handedness interaction ($F_{(2,140)} = 1.06, p = .349$, partial $\eta^2 = 0.02$). For the main effect of complexity, post hoc tests revealed significant differences between simple ($M = -7.40$ μ V, $SE = 0.83$ μ V) and medium trials ($M = -3.24$

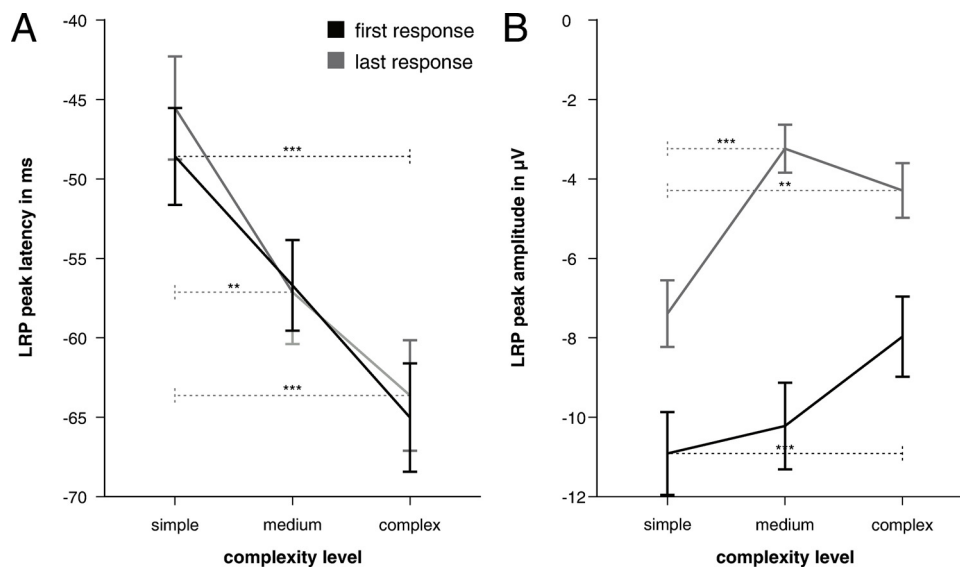


Fig. 3. Illustrations of main effects of complexity on A) LRP peak latencies and B) LRP peak amplitudes for both the first (black) and last response (gray). Error bars indicate standard errors. ** corrected $p < .01$; *** corrected $p < .001$.

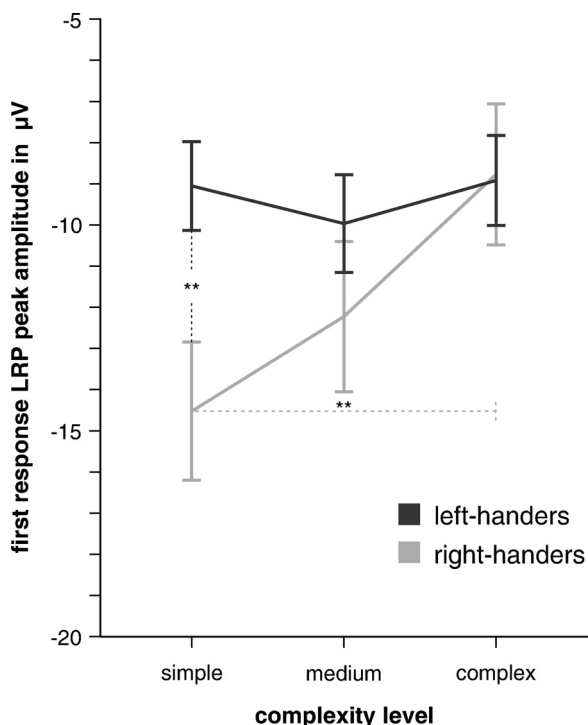


Fig. 4. Illustration of complexity by handedness interaction on LRP peak amplitude (first response). Error bars indicate standard errors. ** corrected $p < .01$.

μV , $SE = 0.58 \mu\text{V}$, corrected $p < .001$) and between simple and complex trials ($M = -4.29 \mu\text{V}$, $SE = 0.69 \mu\text{V}$, corrected $p < .01$). However, there was no significant difference between medium and complex trials (corrected $p = .572$, see Fig. 3B, gray). The main effect of handedness was based on more negative LRP peak amplitudes in right-handers ($M = -5.98 \mu\text{V}$, $SE = 0.65 \mu\text{V}$) as compared to left-handers ($M = -3.97 \mu\text{V}$, $SE = 0.65 \mu\text{V}$, corrected $p < .05$, see Fig. 5B).

3.3. Comparison of electrophysiological and behavioral data

As effects of handedness were found only for peak amplitudes, but not peak latencies of the LRP, peak amplitudes in the six conditions (simple, medium, complex, for both first and last responses) were correlated with Tapley LQ. Tapley LQ was significantly correlated with LRP peak amplitude for the last response in the medium condition ($r = -.347$, $p < .0083$) after correction for multiple comparisons. Tapley LQ correlated with LRP peak amplitude for the first response in the simple

condition but failed to survive correction for multiple comparisons ($r = -.263$, $p < .05$). The other correlations were non-significant (all $p > .05$).

4. Discussion

The aim of the current study was to examine the neurophysiological correlates of handedness. Thus, we aimed to use a task that clearly distinguished between left- and right-handers on the behavioral level.

4.1. The digital Tapley and Bryden task

The Tapley and Bryden task [41] has been reported to fulfill these criteria [42]. Indeed, there was hardly overlap in Tapley LQs between left- and right-handers in our sample with only two left-handers showing a positive Tapley LQ indicating better performance with the right hand. In contrast, none of the right-handers showed a negative Tapley LQ indicating better performance with the left hand. In the EEG version of the Tapley task, we confirmed that on the behavioral level, right-handed subjects reacted faster and completed trials faster using the right hand. In contrast to our hypotheses, left-handers also showed faster reaction and completion trials with the right hand than with the left hand. This effect might be due to most left-handers reporting to use the right hand for controlling the computer mouse. However, in line with our expectations, performance differences between the left and the right hand were much less pronounced in left-handers than in right-handers. Moreover, right-hand performance of left-handers was still significantly below right-hand performance of right-handers. The results are in line with numerous studies indicating less lateralized performance in left-handers compared to right-handers [8,9]. There was no effect of handedness on the sum of errors committed at either complexity level, indicating that this behavioral measure does not reflect the results from the classic paper pencil version of the Tapley and Bryden task. This is also reflected in strong positive correlations between Tapley LQ and RT LQs as well as CT LQs, but no association between Tapley LQ and Error LQs. Overall, these results suggest that the EEG version of the Tapley task is an appropriate measure to examine the neurophysiological mechanisms underlying handedness with reaction times and completion times reflecting the original task.

4.2. Effects of complexity

As the LRP varies with complexity [33,36], we integrated different complexity levels within the task. In our study, reaction times were significantly faster in simple compared to medium trials, although the only factor that distinguished the first response in simple and medium trials was the respective word written above the stimulus. This indicates

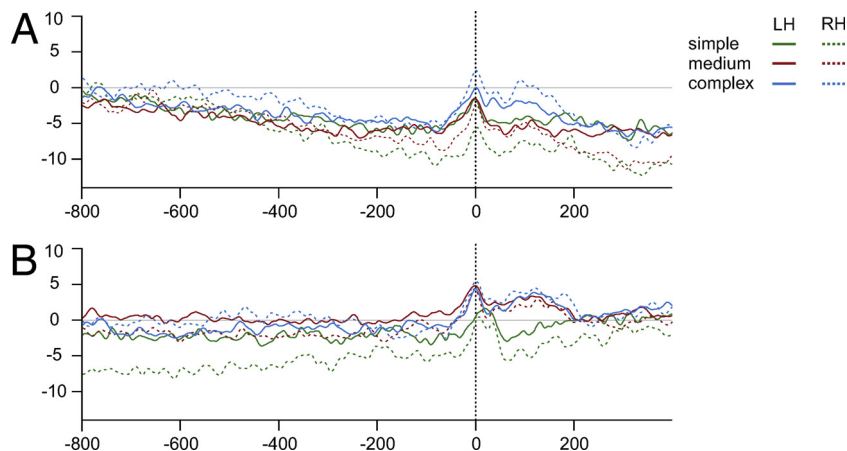


Fig. 5. Response-locked grand-average waveforms for simple, medium and complex trials in left- and right-handers for A) first responses and B) last responses.

that the announcement of higher complexity is sufficient to influence the initial reaction time. However, there was no difference in reaction times between simple and complex trials. For completion times, however, we found the expected increase with the level of complexity. Moreover, more errors were made in medium and complex trials as compared to simple trials, indicating that we successfully varied complexity levels in the EEG version of the Tapley task. However, there were no complexity by handedness interactions on either of the behavioral outcomes. In contrast, complexity levels did affect properties of the LRP.

We determined the LRP for both the first and last response of each trial. The first response in a trial differs between complexity levels only in the respective word indicating if the trial is simple, medium, or complex. However, the effect of this announcement on reaction times indicates differences in motor preparation depending on complexity. In the current study, we found a significant main effect of complexity on both LRP peak latency and LRP peak amplitude for both the first and the last response of each trial. In line with our hypothesis, the LRP for first responses peaked significantly earlier in complex compared to simple trials. The same was true for the LRP for last responses, which peaked significantly earlier in complex trials compared to both simple and medium trials. Since it is assumed that the period between movement-related ERPs and the actual reaction represents the time required for movement preparation [35], a more complex movement sequence requires more time for movement preparation, which is also reflected in longer reaction times, at least for medium compared to simple trials. For LRP peak amplitudes, however, the main effect was in contrast with our hypothesis, with more negative amplitudes in simple compared to complex trials (first response) and more negative amplitudes in simple compared to both medium and complex trials (last response). However, even though the main effect was significant, at least for the first response, the effect of complexity on peak amplitudes interacted with handedness, so the result pattern can hardly be interpreted without taking handedness into account.

4.3. Effects of handedness

For the past 20 years, fMRI studies have indicated that left- and right-handers differ in ipsilateral activation during unilateral hand movements. It has been shown that ipsilateral activation for left- and right-hand movements is similar in left-handers [22,23,30], while ipsilateral activation was more suppressed for right-hand (RH) movements compared to left-hand (LH) movements in right-handers [24,28]. The calculation of the LRP can thus also be described as:

$$\text{LRP} = \text{RH (contralateral (C) - ipsilateral(I))} - \text{LH (ipsilateral (I) - contralateral (C))} = \text{RH C} - \text{RH I} - \text{LH I} + \text{LH C}$$

The contralateral negative deflection should be similar in left- and right-handers during left- and right-hand movements, resulting in $\text{RH C} = \text{LH C}$ (both describing a strong negative deflection). In left-handers, RH I and LH I are equal (slightly negative), resulting in a negative deflection for the LRP. In right-handers, LH I is similar to left-handers, but RH I is suppressed (more positive) compared to LH I . Thus, the LRP should be more pronounced in right-handers compared to left-handers. This could be implemented by a more negative peak amplitude or an earlier peak latency.

There were no handedness effects on peak latencies for neither the first nor the last response, which is in contrast with a previous study finding earlier peaks for right-hand movements compared to left-hand movements in right-handers [34]. For the last response, we found the expected main effect of handedness on LRP peak amplitudes with more negative amplitudes for right-handers compared to left-handers. This is in line with our hypothesis and the idea that motor processing is more symmetrical in left-handers compared to right-handers, supported by findings of more symmetrical connectivity during fist closing [45] or

more symmetrical activation patterns during finger movements [46]. It has been proposed that the left hemisphere is dominant for response planning, while the motor dominant hemisphere (left for right-handers and right for left-handers) is responsible for response execution, leading to more symmetric motor processing in left-handers [47]. It can only be speculated, however, whether our result pattern is based on a less negative ipsilateral deflection in right-handers during right-hand trials compared to left-hand trials with equal ipsilateral deflection in left-handers during left- and right-hand trials. While it would be possible to look at ERPs for C3 and C4 individually, this approach is especially problematic for the last response. In contrast to the first response that is preceded by the intertrial interval, the EEG signal is more noisy prior to the last response due to preceding motor preparation and execution. The strength of the LRP is that it cancels out this noise [35], but it makes it impossible to infer the individual contributions of C3 and C4. Interestingly, a less pronounced LRP has also been reported for schizophrenia patients [48–50], for whom a higher prevalence of left-handedness has been confirmed by meta-analyses [51–53]. These findings support the idea of reduced laterality being associated with the pathophysiology of neuropsychiatric disorders such as schizophrenia [54,55].

Moreover, we found a significant hand by complexity interaction on LRP peak amplitudes for the first response. In line with our hypothesis, LRP peak amplitudes were constant over complexity levels in left-handers. In contrast, LRP peak amplitudes were significantly more negative in simple compared to complex trials in right-handers. It might be that in complex trials, bilateral motor processing is advantageous in right-handers. This idea is supported by studies showing that in less demanding tasks, subjects benefit from unilateral processing, while in more demanding tasks, dividing task processing between hemispheres leads to better performance [56,57].

The response-locked LRP represents neuronal processing of response execution [35]. Thus, going beyond what is feasible in fMRI studies, our study adds to the current literature by arguing for a neuronal basis of handedness that is not based on response selection or preparation but on a group difference in response execution. The fact that no such group difference was found in the study by Kourtis and Vingerhoets [38] suggests that a pronounced behavioral difference between left- and right-handers is necessary in order to reveal differences in neurophysiological processing. In the recent years, progress has been made in identifying molecular factors underlying functional hemispheric asymmetries such as handedness. However, genetic and epigenetic factors do not affect behavior directly, but via brain structure or function [58]. Future studies should thus focus on how molecular factors affect electrophysiological processing and in consequence affect behavior. For example, genetic variation in the leucine-rich repeat transmembrane neuronal 1 (*LRRTM1*) gene has been associated with handedness [59,60]. Research in rodents indicates that the encoded protein affects synapse morphology [61] and long-term potentiation [62,63], so it might be worthwhile to investigate potential effects of polymorphisms in *LRRTM1* on electrophysiological processes underlying handedness. The integration of molecular genetic analyses with electrophysiological techniques will help establishing a multifactorial model of handedness [58]. Moreover, these multi-method approaches will shed light on other laterality phenotypes, such as language lateralization, for which several candidate genes involved in dopaminergic and glutamatergic transmission have been identified [64,65], also possibly affecting electrophysiological processing of language [66,67].

4.4. Outlook and conclusion

A few aspects of this work have the potential to be optimized in future studies. First, the sample size of 36 subjects per group can only reveal large effects, while at least 100 subjects per group are necessary to reliably reveal smaller effects [68]. Large-scale studies are needed to provide consistency to findings in laterality research. As mentioned

above, a large-scale imaging study on cortical asymmetry [18] did not confirm findings obtained in smaller studies, illustrating the problem of underpowered studies. Second, participants could be phenotyped more extensively in future studies. For example, it has been shown that about 10% of left-handers show reversed laterality for praxis [69,70]. Thus, future research aimed at elucidating effects of handedness should include tests to determine whether potential handedness effects are introduced by subjects with reversed laterality.

In conclusion, we found a significant effect of handedness on LRP peak amplitudes in the last response of sequential movements, while the effect was modulated by task complexity for the first response. This study is the first to identify an effect of handedness instead of handedness consistence [38], which is most likely due to the digital Tapley task clearly distinguishing between left- and right-handers on the behavioral level. The finding that this behavioral difference is reflected in neurophysiological processing is an important step towards understanding the neuronal correlates of handedness.

Competing interests statement

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.bbr.2019.02.021>.

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