Running title: LATERALITY DURING WRITING

Cerebral laterality for writing in right- and left- handers: A functional transcranial Doppler ultrasound study

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Abstract

The cerebral lateralization of written language has received very limited research attention in comparison to the wealth of studies on the cerebral lateralization of oral language. The purpose of the present study was to further our understanding of written language lateralization, by elucidating on the relative contribution of language and motor functions. We compared written word generation with a task that has equivalent visuomotor demands, but does not include language (i.e., the repeated drawing of symbols). We assessed cerebral laterality using functional transcranial Doppler ultrasound (fTCD), a non-invasive, perfusion-sensitive neuroimaging technique in 23 left- and 31 right-handed participants (based on hand-writing preference, but results were similar for divisions based on the Edinburgh Handedness Inventory, Annett's Pegboard, and the Quantification of Hand Preference Test reaching task). Findings suggest that, in right-handers, the linguistic aspect of written word generation recruited left-hemispheric areas during writing, similarly to oral language production. In left-handers, we failed to observe the same effect. Moreover, we observed that right-hemispheric activation was higher for symbol copying (vs. written word generation) in right-handers only. The greater variability in cerebral laterality patterns within left-handers or the attentional demands of symbol copying could explain the different findings between right- and left-handers. Future work could investigate such demands using both simple and complex stimuli in the copying condition.

<u>Keywords:</u> cerebral language lateralization, functional transcranial Doppler ultrasound (fTCD), word generation, writing, handedness

1. Introduction

An overwhelming number of studies have investigated cerebral language lateralization using overt or covert oral language production or language comprehension tasks (e.g., Papadatou-Pastou et al., 2017; Groen et al., 2012; Petit, Badcock, & Woolgar, 2020). On the contrary, very few studies have investigated the cerebral lateralization of written language (e.g., Kondyli et al., 2017) or the neural underpinnings of writing in general (e.g., Bartoň, et al., 2020; Planton et al., 2013), although writing is currently starting to receive research attention (e.g., Karimpoor et al., 2018; Palmis et al., 2019; Planton, Jucla, Démonet, & Soum-Favaro, 2019; Yang et al., 2019). Importantly, only a handful of studies have investigated cerebral laterality for writing comparing left- and right-handers (Kondyli, et al., 2017; Siebner et al., 2002; Zaman et al., 2002).

Writing is a skill that demands the contribution of several cognitive and visuomotor functions and is widely used in education and everyday life for communication, as well as for archiving information, ideas, and stories across time and space. Handwriting is affected in a number of conditions, such as Alzheimer's disease (e.g., Hayashi et al., 2011), learning disabilities (Graham, Collins, & Rigby-Wills, 2017), schizophrenia (e.g., Tigges et al., 2000), cerebrovascular disease (e.g., Otsuki et al., 1999), and traumatic brain injury (Yorkston et al., 1997), possibly due to its complex nature. Therefore, it is important to reach a clearer understanding of its neural network, both when studying healthy individuals as well as pathological populations.

Left-handers constitute 10.6% of the population (Papadatou-Pastou et al., 2020), making it important to account for this phenotypical variation if we are to understand human brain function. Left-handers have in fact been recognized as a compelling and widely available, but largely untapped, resource for neuroscience studies (Willems, Van der Haegen, Fisher, & Francks, 2014). Right- and left-handers have been found to differ in the cerebral organization of oral language functions (e.g., Knecht, Dräger et al., 2000), although handedness is a weak indicator of cerebral lateralization for language, accounting for only 8-16% of the variance in cerebral lateralization (Groen et al., 2013). Strongly atypical individuals in terms of hemispheric lateralization are more likely to be left-handed, although individuals with typical and bilateral dominance can also be left-handed (Mazoyer et al., 2014). Moreover, it has been shown that stronger left-hand preference is linked to a higher chance of atypical language lateralization (Somers, Aukes et al., 2015). Thus, it can be argued that cerebral lateralization for writing could also differ between the two handedness groups. Indeed, continuous measures of both hand preference and hand skill correlate with cerebral laterality during written word generation (Kondyli et al., 2017). Moreover, more pronounced right-hemispheric lateralization is observed in left-handers compared to right-handers during written word generation compared to silent word generation (Kondyli et al., 2017).

The neural underpinnings of writing were initially studied in neurological patients. Lesion studies showed that impaired writing can result from localized brain damage in the superior parietal lobe, supramarginal gyrus, angular gyrus, Wernicke’s area, or Broca’s area (Roeltgen, 1993). For example, apraxic agraphia was found to be associated with damage in the left intraparietal sulcus (Beeson et al., 2003). Single-unit recordings in monkeys have indeed shown that neurons in the inferior anterior parietal cortex around the intraparietal sulcus are related to goal-directed hand and finger movements in extrapersonal space (Seitz et al., 1997).

A few recent fMRI studies have investigated the neural underpinnings of writing in the healthy human brain, pointing to a distributed network of regions that underlie writing. Central or linguistic aspects of writing were found to be located in the left posterior inferior temporal cortex, while motor aspects in other left-hemisphere regions, such as the intraparietal sulcus, the superior parietal lobule, the dorsolateral and medial premotor cortex, and the sensorimotor cortex (Beeson et al., 2003). The striatum was shown to have a role in integrating stored letter-shape information with motor planning and execution during handwriting (Bartoň et al., 2020). Furthermore, the left parietal lobule has been found to relate to the sequential execution of writing, along with the left premotor cortex, the sensorimotor cortex, and the supplementary motor area (Karimpoor et al., 2018; Menon & Desmond, 2001). The rostral part of the superior parietal lobe in the left hemisphere is critical for writing (Segal & Petrides, 2012), its position promoting interaction with other language and motor regions during writing tasks. Other left-hemisphere areas with increasing activation while writing are the middle frontal gyrus, the superior frontal gyrus, the inferior frontal gyrus, the superior temporal gyrus, and the middle temporal gyrus (Tam et al., 2011). Writing (versus drawing) was further found to increase left-sided activation in the dorsal and ventral premotor cortex, Broca’s area, pre-supplementary motor area and posterior middle and inferior temporal gyri, without parietal activation (Potgieser et al., 2015). Bilateral activity in the cerebellum has also been observed (Katanoda et al., 2011; Karimpoor et al., 2018; Segal & Petrides, 2012; Yang et al., 2019) and is considered indicative of the representation of finger movements (left cerebellar activation) and of the coordinated movement of the index finger, in contrast to simple movements (right cerebellar activation). The cerebellum along with the left dorsal premotor cortex further seems critical to the acquisition of handwriting (Palmis, Danna, Velay, & Longcamp, 2017)

A meta-analysis of 18 studies suggested that the core network of writing seems to consist of a wide network of both cortical and subcortical cerebral regions, comprising of primarily writing-specific areas (left superior frontal sulcus/middle frontal gyrus area, left intraparietal sulcus/superior parietal area, and right cerebellum), non-specific motor areas (primary motor and sensorimotor cortex, supplementary motor area, thalamus, and putamen) and areas related to linguistic processes (ventral premotor cortex and posterior/inferior temporal cortex) (Planton et al., 2013). Importantly, in a more recent study, Planton et al. (2017) found that the same ‘writing specific’ networks were recruited for both handwriting and drawing, with the only distinctive feature of handwriting as opposed to drawing being the left lateralization of the graphemic/motor frontal area (GMFA), a subpart of the superior premotor cortex.

However, the studies described above have investigated the neural underpinnings of writing only in right-handers. To date, merely three studies have included left-handers (Kondyli et al., 2017; Siebner et al., 2002; Zaman et al., 2002). Zaman et al. (2002) investigated normal and mirror writing with dominant and non-dominant hands. They showed that when writing with the dominant hand, the left sensory-motor cortex and right cerebellum were activated for right-handers for normal writing, but the right sensory-motor cortex and the left cerebellum for left-handers. In the case of mirror writing, the activation was bilateral in both groups regardless of whether they were using the dominant or non-dominant hand. Siebner et al. (2002) showed that, during writing, right-handers demonstrate left-hemispheric lateralization with activation of parietal and premotor association areas; converted left-handers demonstrate a more bilateral activation pattern, including the premotor, parietal and temporal cortex; while left-handers show a strong right-hemispheric lateralization. Siebner et al. (2002) also showed a graded increase in the activation of the right anterior supramarginal gyrus with the degree of left-handedness.

Neither Zaman et al. (2002) nor Siebner et al. (2002) compared writing with oral language or a non-linguistic motor activity. Zaman et al. (2002) studied writing with dominant versus non-dominant hands and Siebner et al. (2002) investigated the effects of switching writing hands at a young age. More recently, Kondyli et al. (2017) compared (silent) oral language production to writing in left- and right-handers. They found that during written word production, the degree of left-hemispheric lateralization was significantly increased for right-handers compared to silent word production, while left-handers presented left-hemispheric lateralization during silent word production, but right-hemispheric lateralization during writing. They concluded that a wider network of right-hemispheric areas is used during writing in left-handers. This wider network could support motor and/or linguistic aspects of writing. However, the two tasks employed in the Kondyli et al. (2017) study were not directly comparable, as only the writing task demanded visuomotor coordination and action, while the silent word production task merely demanded word generation without including a visuomotor component. Therefore, the language and motor components of writing were inadequately isolated.

When it comes to the measurement of cerebral laterality for written language, Zaman et al. (2002) and Siebner et al. (2002) employed positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), respectively. These techniques do not lend themselves to use in research studies with large sample sizes, mainly due to the high cost of the techniques involved, but also due to the complexity of data collection and analysis. As an illustration, Zaman et al. (2002), included only 12 left-handed participants (as well as 12 right-handed participants) and Siebner et al. (2002) only 6 left-handed participants (and also 11 right-handers and 11 ‘converted’ left-handers: the latter group comprising of adults who were innately left-handed for writing, but were forced to use their right hand as children and became proficient right-hand writers). In Kondyli et al. (2017), the sample was considerably larger (30 left-handers and 30 right-handers) as cerebral lateralization was assessed using a different technique, namely functional transcranial Doppler ultrasonography (fTCD). FTCD was also used in the present study.

FTCD is an efficient and reliable alternative to fMRI for the study of functional cerebral lateralization (Bishop, Watt, & Papadatou-Pastou, 2009). It is non-invasive and relatively inexpensive and can be easily applied to individuals of all ages (Badcock & Groen, 2017), in large cohorts (Knecht, Deppe et al., 2000), in longitudinal studies (Cuadrado et al., 1999), and in follow-up assessment (Lohmann et al., 2005). Results obtained with the use of fTCD are highly reproducible (Knecht, Deppe, Ringelstein, et al., 1998) and have very good agreement with those acquired using the intra-carotid amobarbital procedure (Wada test; Knake et al., 2003; Knecht, Deppe, Ebner et al., 1998). Deppe, Ringelstein, & Knecht, 2004). FTCD and fMRI assessments of language lateralization also correlate very well ($r = .95$; Deppe et al., 2000, $\rho = .75$; Sommers et al., 2011). FTCD lends itself to the study of writing, as its signal is not disrupted by movement artifacts (Kondyli et al., 2017).

Returning to the issue of handedness, writing hand is the most commonly used criterion to determine handedness (Papadatou-Pastou et al., 2019). However, writing hand gives a mismatch with hand preference inventories of 13.5% for left-handers (the mismatch is negligible for right-handers: 0.4%) (Papadatou-Pastou et al., 2013). Other measures of handedness comprise either hand preference inventories (asking which hand is preferred for a number of everyday activities) or hand skill tasks (measuring the relative skill of the two hands) and report direction (left-right) and/or degree of handedness. Direction of handedness is the measure typically reported, but it is suggested that the degree of handedness may be a better indicator of underlying brain pathology and/or psychological abnormalities than direction (Crow et al., 1998). When it comes to hand skill, Brandler et al. (2013) identified the first gene to be statistically associated with handedness using the pegboard task, which is a hand-skill task. This is opposed to the hand-preference measures that gave null results in previous large genetic screenings (Eriksson et al., 2010). Meta-analyses of handedness data suggest that research on handedness should include data on both hand preference and hand skill measures (Papadatou-Pastou et al., 2015; Papadatou-Pastou, 2016; Papadatou-Pastou et al., 2020). Using an inclusive set of handedness assessment criteria is indeed useful in order to explore their different properties, but also for comparison purposes with previous studies that may have used a single handedness criterion.

The primary aim of the present study was to extend our understanding of the cerebral laterality of written versus oral language in left-handers compared to right-handers by further elucidating the relative contribution of language and motor functions in cerebral laterality for writing. Comparing written to oral language generation, Kondyli et al. (2017) were unable to disentangle the motor and linguistic aspects of written word generation. The current study compares writing with a non-linguistic visuomotor task: written word generation versus written symbol copying – specifically the repeated writing of symbols (e.g., *, $, &). Symbol copying has equivalent visuomotor demands (fast and precise coordination of fingers, wrist and arm movements, planning of sequential action, management of visual landmarks, eye-hand coordination, and hand placement in space), but excludes language. Symbol copying more closely resembles the hand movements during writing in comparison to drawing, and symbol copying is not as intensively trained as the writing of letters. Cerebral lateralization will be assessed using fTCD and handedness will be assessed using writing hand, the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), Annett's Pegboard task (Annett et al., 1979), and the Quantification of Hand Preference Test (QHPT; Bishop, Ross, Daniels, & Bright, 1996). We hypothesize that:

(1) For right-handers, written word generation will result in more pronounced left-hemispheric activation compared to symbol copying. This is due to both tasks having similar motor demands (right-hand motor action) resulting in left-hemispheric activation, while the linguistic component of writing will add further left-hemispheric activation to the written word generation condition.

(2) For left-handers, symbol copying will result in a more pronounced right-hemispheric activation compared to written word generation. This is due to both conditions having similar motor demands (left-hand motor action) resulting in right-hemispheric activation, but the linguistic component of writing adding left-

hemispheric activation in the word generation condition (note, almost all right-handers are left-hemispheric dominant for language, but also the majority of left-handers).

(3) Comparing left- to right-handers, written word generation vs. symbol copying will result in more pronounced left-hemispheric activation in right-handers compared to left-handers. Symbol copying will act as an active baseline to written word generation, allowing for the linguistic-specific activation to be estimated. Therefore, right-handers should present with a more left-hemispheric activation pattern when isolating the linguistic aspect of writing, similarly to oral language tasks.

A secondary aim of this study was to use an inclusive set of handedness assessment criteria to group participants by handedness to test if different criteria affected the findings and differentially related to cerebral lateralization estimates. This deepens our understanding of handedness per se and further provide data that could be more readily comparable with studies that used a single handedness criterion. Based on previous work (Kondyli et al., 2017), we anticipate limited effect of the different measures.

2. Materials and methods

Participants

Fifty-four undergraduate and graduate students from [removed for blinding purposes] as well as members of the general public participated (mean age: 26.76 years, SD = 5.14, range: 19-40). Fourteen of the 20 male participants and 17 of the 34 female participants were right-handed, according to self-reported writing hand and the rest were left-handed (6 male and 7 female). Six of these participants had also taken part in the [removed for blinding purposes] study (2 left-handed females, two left-handed males, and two right-handed males). All participants were monolingual, native speakers of the [removed for blinding purposes] language and they had normal or corrected-to-normal vision. They had never been diagnosed with dyslexia or dysgraphia, were free of neurological problems or other problems affecting the mobility and normal function of their hands, had not taken medication that could affect the central nervous system for at least six months, and did not report current use of illicit drugs or other substance abuse. Thirteen potential participants were not included in the sample described above, because sonography failed due to inadequate ultrasonographic penetration of the skull by the ultrasound beam (19%, a rate similar to previous studies, e.g., Knake et al., 2003, who had an exclusion rate of 15% and Kondyli et al., 2017, who had an exclusion rate of 18.9%).

Assessment of handedness

Edinburgh Handedness Inventory (EHI): Hand preference was self-reported using the Greek translation of the Edinburgh Handedness Inventory (Oldfield, 1971). Participants indicated hand preference for ten activities, namely writing, drawing, throwing a ball, using scissors, using a toothbrush, holding a knife to carve meat, holding a spoon, holding a broom (upper hand), striking a match, and opening the lid of a box. Two additional activities referring to foot and eye preference were included (kicking a ball, looking with one eye). The participants were instructed to imagine or recall which hand, foot, or eye they use when they perform each activity before answering a question.

Possible responses included: "always left", "usually left", "no preference", "usually right", "always right".

A value of 0 was given to “always left” responses, 1 to “usually left” responses, 2 to “both equally” responses, 3 to “usually right” responses, and a value of 4 to “always right” responses. The total score of each participant was again divided by the maximum score (40), and multiplied by 100, with the LI ranging from 0 % (extreme left-handedness) to 100 % (extreme right-handedness). Individuals were classified as left-handers if their scores were below 50% and as right-handers if their scores were above 50%.

Pegboard: Annett’s pegboard task (Annett et al., 1979) was employed to measure relative hand skill. A 32 × 18 cm wooden equipment was used, which consisted of two attached wooden pieces with 10 holes drilled along their length. The distance between the two wooden pieces was 15 cm and the diameter of each hole was approximately 1.2 cm. Each peg was 7.0 cm in length and 1.0 cm in width. The task the participants were asked to carry out once seated in front of the pegboard, was to move all 10 pegs as quickly as possible from the full row to the empty row beginning on the side of the pegboard ipsilateral to the hand being used to perform the task. Trials for all participants started with the right hand and then the left and right hands alternated. The task was repeated three times for each hand. A stopwatch was used to time the participants. If a participant dropped a peg, the trial was repeated. Participants were instructed not to talk while carrying out the task, as talking might delay them.

The time that the first peg was touched by the participant until the time the last one was released was recorded for each trial (three trials for each hand). A Laterality Index (LI) was calculated using the formula: LI = [(RH-LH) / (RH+LH)]*100, where RH = mean time needed to move the pegs using the right hand and LH = mean time needed to move the pegs using the left hand. A negative score represented right-hand superiority, while a positive score represented left-hand superiority.

Quantification of Hand Preference Test (QHPT): Hand preference was observed using the QHPT (Bishop, Ross, Daniels, & Bright, 1996). Seven positions were marked on a table, each at a distance of 40 cm from the midpoint of a baseline, at successive 30° intervals. Three cards were placed at each position, totaling 21 cards. The participants were asked to stand in front of the table with their arms resting at their sides and to pick up a named card and place it in a box in front of them. The order of the cards was random, but it was kept the same for all the participants. The hand chosen to pick up each card was recorded.

A value of 0 in the case that the left hand was used to place the card into the box, 1 point in case of changing hands, and 2 points when the right hand was used. The total points assigned to each participant were then divided by the maximum score (40) and multiplied by 100, in order to calculate an LI. This LI varied from 0% (extreme left-handedness) to 100% (extreme right-handedness). Individuals were classified as left-handers if their scores were below 50% and as right-handers if their scores were above 50%.

Assessment of linguistic lateralization

Apparatus: A commercially available Doppler ultrasonography device (DWL Multidop

T2: manufacturer, DWL Elektronische Systeme, Singen, Germany) was used to measure bilateral blood flow. Two 2-MHz transducer probes were mounted on a flexible headset and placed at the left and right temporal windows of the participants who were seated in front of a computer screen.

Lateralization tasks: The tasks were a modification of the tasks by Kondyli et al. (2017), which were, in turn, based on word generation developed by Knecht, Deppe, Ebner et al. (1998). Each trial included: 35 seconds of rest, a cueing tone (accompanied by an event marker sent to the fTCD device) followed by a 5-second pause, a letter of the Greek alphabet or a symbol appearing on the center of the computer screen for 2.5 seconds, and a 12.5-second activity period. The cueing tone was used in order to (i) help focus the attention on the upcoming task and (ii) activate the attention of the dominant hemisphere. There were 40 trials in total, divided into two conditions: 20 letter trials corresponding to written word generation and 20 symbol trials corresponding to symbol copying. Ten consecutive trials of each condition were alternated with ten consecutive trials of the other condition (e.g., 10 letter trials followed by 10 symbol trials, 10 letter trials, and 10 symbol trials). The order of presentation of the trials was counterbalanced across participants.

For the written word generation condition, the participants were asked to write down as many words as possible starting with the letter appearing on the screen. For the symbol copying condition, the participants had to copy as many times as possible the symbol appearing on the screen. The 20 letters from the Greek alphabet were chosen out of the total 24 included in the alphabet after a pilot procedure described in Kondyli et al. (2017), which ensured that the letters chosen allowed participants to produce the most words possible. A pilot study with 6 participants (4 male, mean age: 26.6 years, SD = 4.13, range: 18-35) was run in order to ensure feasibility of the protocol. The results are not included in the present report.

FTCD data collection and analysis

Two transducer probes (2 MHz) attached to a flexible headband were placed at the temporal skull windows bilaterally. The right and left MCAs were insonated at the optimal depth for each participant (45-56 mm) and the angles of insonation were adjusted to obtain the maximal signal intensity. Visual stimuli (letters or symbols) were presented on a computer controlled by PsychoPy software (Neurobehavioural Systems; Peirce 2007, 2009; Peirce et al., 2019), which sent marker pulses to the Multi-Dop system to mark the start of each epoch. The spectral envelope curves of the Doppler signal were recorded with a rate of 100 Hz and stored for off-line processing.

Data were processed using DOPOSCCI 3.1.6 (Badcock, Holt, Holden, & Bishop, 2012; Badcock et al., 2018), a MATLAB-based toolbox (https://github.com/nicalbee). Left- and right-channel blood flow velocity was downsampled to 25 Hz, normalized to a mean of 100, and variability due to heartbeat was removed as described by Deppe et al. (Deppe et al., 1997), but using a linear correction (see Badcock et al., 2018). The data were epoched from 18 secs before to 36 secs after the cueing tone, with baseline correction between -18 to 0 secs relative to the cueing tone. Epochs containing CBFV values outside the range of 70% to 130% of the mean velocity or an absolute left-minus right channel difference of 20% were rejected. The remaining data were then averaged. The laterality index (LI) was calculated as the average left-minus-right channel difference within the period of interest (POI): 7-17 s after cueing. Note: the average of the POI, rather than an average around the peak, results in a more-normal distribution (Woodhead et al., 2018) that is also statistically unbiased in terms of finding a significant LI (Petit et al., 2020). Visual inspection of the overall evoked-flow plot suggested that a POI of 7-24 s after cuing included the maximum activation, activation lasting longer than anticipated, therefore the longer POI was also analysed. We calculated two LIs: LI_{words} for the written word generation condition and $LI_{symbols}$ for the symbol copying condition. Following Kondyli et al. (2017), if less than 10 epochs were accepted for either the word or the symbol conditions, the participant was excluded from the sample (*n* = 8 in this case, an exclusion rate similar to Kondyli et al., 2017).

Procedure

Upon arrival at the lab, the study was explained to the participants and they were encouraged to ask questions. They gave their written consent, but were explicitly told that they were free to leave at any time and without having to give any reason for doing so. The participants were tested individually in a quiet room. They were asked to sit in front of a computer and they were given the option to watch the first few minutes of a movie while the probes were being placed. The words/symbols task followed. Once the fTCD data collection was completed, the participants were asked to perform the pegboard task and the QHPT and to fill in the Greek version of the EHI. Participants were debriefed after the completion of the study.

Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences

(SPSS) v.25 (IBM Corp., 2017). In order to describe the data, basic descriptive statistics were calculated and LI categorizations were made. Group LI categorizations were based on one-sample *t*-tests against zero. Individual lateralization categorization was based on whether 95% confidence intervals for the LI overlapped with zero: left = lower-bound greater than zero, right = upper-bound less than zero, and bilateral (or symmetrical) = overlap with zero (Bishop et al., 2009).

Hypotheses 1 and 2 were tested via a two-by-two mixed-design analysis of variance (ANOVA) with writing hand (right or left) as the between-participants factor, condition (words and symbols) as the within-participants factor, and the LIs as the dependent variables. Partial eta squared (η_p^2) was used as the effect size measure, and post-hoc tests were pairwise comparisons with Bonferroni adjustment and Cohen's *d* as the effect size measure. The main analysis used handedness groupings based on writing-hand preference, and the analyses were replicated for handedness categorized by the other three measures. We did not test for sex differences, as the literature points to the direction of no differences (Kondyli et al., 2017) and the sampling was inadequate to test for effects of sex. Hypothesis 3 was tested via independent sample *t*-tests, performed on the written word generation minus symbol copying LIs by hand-preference groups.

In order to further explore whether different handedness measures related differently with cerebral lateralization, Spearman correlations were run for the two LIs (LI_{words} and $LI_{symbols}$) and the three behavioral measures of handedness (EHI score, Pegboard score, QHP score). Spearman (i.e., rank-based non-parametric) correlations were used to minimize the influence of extreme data points, common in fTCD lateralization data (note, no variable violated the assumption of normally distributed data).

3. Results

The event-related blood flow for each condition by handedness is presented in Figure 1 and the LIs are presented in Figure 2. Descriptive statistics for the LIs for both the 7-17 s and the 7-24 s POIs by handedness (according to writing hand) are presented in Table 1 and descriptive statistics for the handedness assessments are presented in

Table 2.

To examine the overall pattern of cerebral lateralization by condition and handedness, one-sample *t*-tests against zero were conducted. Both LIs were significantly left-lateralized for right-handers; words: $t(26) = 6.46$, $p < .001$, Cohen's $d = 1.24$; symbols: $t(26) = 3.02$, $p < .01$, Cohen's $d = 0.58$. The LIs indicated right-lateralization for left-handers but this was not significant for words: $t(18) = -1.85$, $p = .08$, Cohen's $d = -0.42$; only symbols: $t(18) = -2.34$, $p < .05$, Cohen's $d = -0.54$. Please note: the pattern of these results was the same for the 7 to 24 s period of interesting, however, all LIs were significantly different to zero.

Figure 1

Event-related blood flow for condition (written word generation = top row, symbol copying = second row, written word generation minus symbol copying = bottom row) by handedness (left-handers = left column, right-handers = right column). Left, right, and left minus right difference channels are depicted with their respective 95% confidence interval. Analysis baseline and period of interest timing are depicted by grey columns. Handedness groups according to the writing hand.

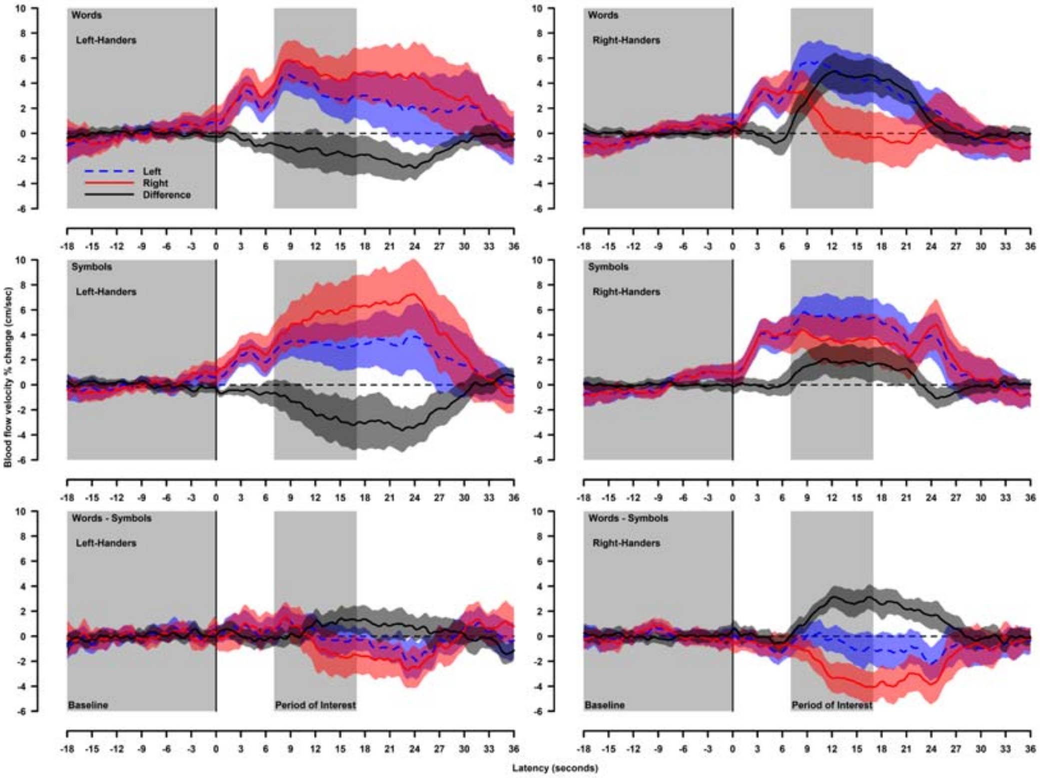

Figure 2

Group laterality indices (LIs) for condition (written word generation vs. symbol copying) by handedness (right-handers and left-handers denoted by circles with solid line and squares with broken line, respectively). Error bars represent the 95% confidence intervals. Handedness groups according to the writing hand. Grey symbols represent individual data points.

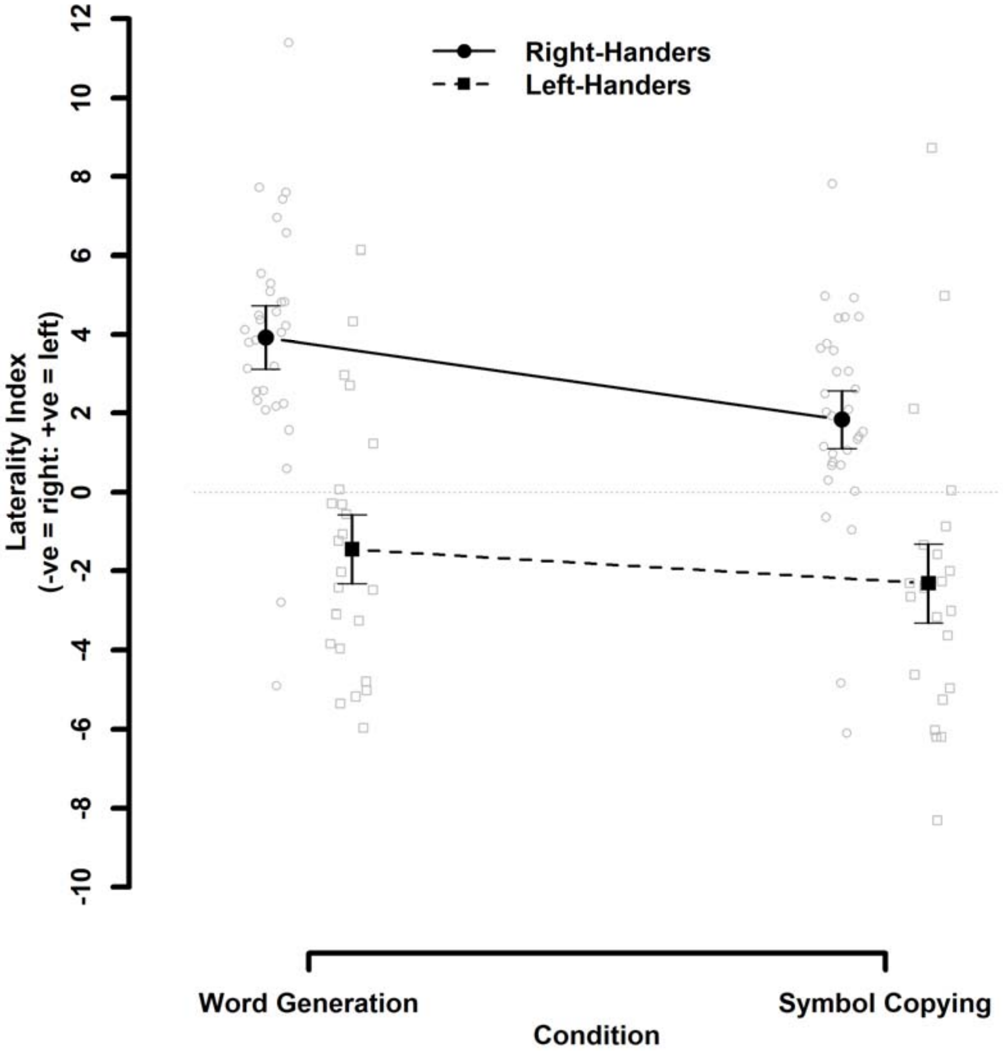

Table 1

Descriptive statistics for the functional transcranial Doppler sonography (fTCD) conditions. Handedness groups according to the writing hand.

Condition	Handedness	N	Mean number of epochs	Mean LI	SD	Range	Median
Period of interest: 7 to 17 seconds after cueing							
LI_{words}	R	27	18	3.86	3.1	(-4.91) - 11.4	4.12
	L	19	18	-1.39	3.29	(-5.97) - 6.14	-2.02
$LI_{symbols}$	R	27	17.85	1.64	2.82	(-6.1) - 7.82	1.53
	L	19	17.89	-2.06	3.84	(-6.2) - 8.73	-2.44
$LI_{difference}$	R			2.22	1.67	(-0.86) - 6.47	2.27
	L			0.67	1.79	(-2.59) - 3.91	0.78
Period of interest: 7 to 24 seconds after cueing							
LI_{words}	R	27	18	3.63	2.84	(-4.26) - 10.74	3.77
	L	19	18	-1.71	3.13	(-5.97) - 5.88	-2.1
$LI_{symbols}$	R	27	17.85	1.64	2.82	(-6.1) - 7.82	1.53
	L	19	17.89	-2.06	3.84	(-6.2) - 8.73	-2.44
$LI_{difference}$	R			2.27	1.66	(-0.67) - 6.05	2.16
	L			0.8	1.75	(-2.87) - 3.39	1.04

Table 2

Descriptive statistics for the handedness assessments by self-reported writing hand.
Note: EHI = Edinburgh Handedness Inventory 5-point, QHPT = Quantification of Hand Preference

Test	Handedness	N	Mean	SD	Median	Range
Edinburgh Handedness Inventory (EHI) 5-point	R	31	90.65	8.69	92	62 - 100
	L	23	34.26	16.65	30	20 - 84
Quantification of Hand Preference (QHPT)	R	31	-0.05	0.04	-0.06	(-0.2) - 0.04
	L	23	0.03	0.04	0.04	(-0.05) - 0.09
Annett Pegboard	R	31	58.53	30.04	57.14	0 - 100
	L	23	35.61	28.33	35.71	0 - 90.48

Figure 3 summarizes individuals' LIs in a scatter plot with the LI_{words} on the x axis and the $LI_{symbols}$ on the y axis. The numbers of cases per laterality categorization (left, bilateral, or right) are presented in Table 3. Of note, the only unpopulated quadrant of Figure 3 is the top-left, representing a negative LI for the written word generation (i.e., right lateralized), but a positive LI for the symbol copying (i.e., left lateralized). The quadrant representing a negative LI for symbol copying, but a positive LI for the written word generation (bottom-right) is sparsely populated but not empty. The bottom-left and the top-right quadrants house most left-handed and right-handed participants, respectively.

Figure 3

Scatter plot of laterality indices (LIs) for the written word generation and symbol copying conditions. All individual data points are presented with their 95% confidence intervals.

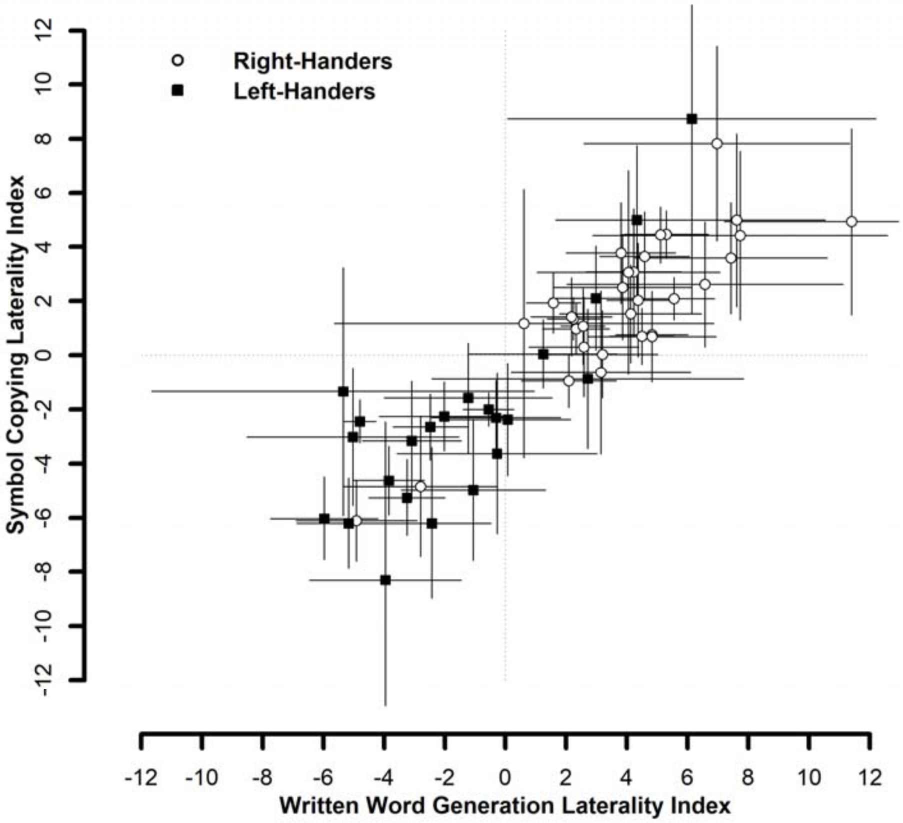

Table 3

Number of cases for each lateralization index (LI) classification for the written word generation and symbol copying conditions for the 7 to 17 and 7 to 24 second period of interest summaries, delineated by handedness for each handedness measure. Note: EHI = Edinburgh Handedness Inventory 5-point, QHPT = Quantification of Hand Preference Test

			Handedness by Handedness Measure					
			Left-Handers			Right-Handers		
LI Condition			Written Word Generation					
	Handedness Measure	LI Category	Left	Bilateral	Right	Left	Bilateral	Right
			Period of Interest: 7 to 17					
Symbol Copying	Writing Hand	Left	3	-	-	13	-	-
		Bilateral	-	2	-	12	-	-
		Right	-	5	9	-	-	2
	EHI	Left	13	-	-	3	-	-
		Bilateral	-	1	-	-	1	-
		Right	-	2	2	-	3	9
	Pegboard	Left	2	-	-	14	-	-
		Bilateral	-	2	-	10	-	-
		Right	-	5	8	-	-	3
	QHPT	Left	9	-	-	7	-	-
		Bilateral	-	2	-	3	-	-
		Right	-	-	1	-	5	10
			Period of Interest: 7 to 24					
	Writing Hand	Left	2	-	-	14	-	-
		Bilateral	-	1	1	9	1	-
		Right	-	4	10	-	2	1
	EHI	Left	14	-	-	2	-	-
		Bilateral	-	1	-	1	1	1
		Right	-	4	2	-	2	9
	Pegboard	Left	1	-	-	15	-	-
		Bilateral	-	1	1	8	1	-
		Right	-	5	9	-	1	2
	QTHP	Left	9	-	-	7	-	-
		Bilateral	-	2	-	3	-	1
		Right	-	2	1	-	4	10

Hypotheses 1 & 2

Hypotheses 1 and 2 were tested via a 2 (condition: words, symbols) by 2 (handedness:

left, right) mixed-design ANOVA. There was strong evidence of a main effect of condition, $F(1, 44) = 31.36$, $p < .001$, $\eta_p^2 = 0.416$, with the mean LI_{words} being higher (M = 1.69, SE = 0.60) compared with the mean $LI_{symbols}$ (M = 0.11, SE = 0.55); both show left-hemispheric (typical) cerebral laterality during written word generation and symbol copying – but see below interaction. In addition, there was strong evidence of a main effect of handedness according to writing hand, $F(1, 44) = 23.06$, $p < .001$, $\eta_p^2 = 0.344$, with right-handers producing a higher mean LI (M = 2.75, SE = 0.6) than the left–handers (M = -1.73, SE = 0.71), showing a left-hemispheric dominance for right-handers and a right-hemispheric dominance for left-handers. There was also strong evidence of a condition by handedness interaction, $F(1, 44) = 9.09$, $p < .01$, $\eta_p^2 = 0.171$ (see Figure 2). The effect of handedness held for both levels of condition: right-handers were left-lateralized for LI_{words} (M = 3.86, SE = 0.6) and $LI_{symbols}$ (M = 1.64, SE = 0.54) and left-handers were right-lateralized for LI_{words} (M= -1.88, SE= .96) and $LI_{symbols}$ (M= -3.24, SE= .98); and there was strong evidence for a difference for both conditions: words, $t(44) = 5.52$, $p < .001$, Cohen's $d = 2.94$; symbols, $t(44) = 3.77$, $p < .01$, Cohen's $d = 2.03$. However, the effect of condition did not hold for both levels of handedness. For right-handers, there was strong evidence for a higher LI_{words} compared to $LI_{symbols}$, $t(26) = 6.91$, $p < .001$, Cohen's $d = 1.33$; supporting Hypothesis 1 (*For right-handers, written word generation will result in more pronounced left-hemispheric activation compared to symbol copying*). This was not the case for left–handers, where there was no evidence for a difference between the means for LI_{words} and $LI_{symbols}$, $t(18) = 1.62$, $p = 0.49$, Cohen's $d = 0.37$; not supporting Hypothesis 2 (*For left-handers, symbol copying will result in a more pronounced right-hemispheric activation compared to written word generation*).

We conducted a further analysis to better understand the interaction. This was, also, based upon the visual appearance of a shift in the right-channel data between conditions in the right-handers: right activation appeared to be higher for symbol copying, relative to written word generation (see Figure 1 and Table 4 for the descriptive statistics). We were interested in the 3-way interaction of a 2 x 2 x 2 mixed-design ANOVA with writing hand (left vs. right) as the between-subjects factor and condition (words vs. symbols) and channel (left vs. right) as within-subjects factors. The interaction was statistically significant, $F(1, 44) = 9.11$, $p < .01$, $\eta_p^2 = 0.172$. Splitting the data by handedness, the interaction for follow-up 2 (condition: words, symbols) x 2 (channel: left, right) repeated-measures ANOVAs was significant for right-handers, $F(1, 26) = 47.83$, $p < .001$, $\eta_p^2 = 0.648$, but not for left-handers, $F(1, 18) = 2.6$, $p = 0.124$, $\eta_p^2 = 0.126$. This supports the observation that right-hemispheric activation was higher for symbol copying (vs. written word generation) in right-handers.

Table 4

Descriptive statistics (M and SEM) for average activation for left- and right-handers in the left and right channels for the written word generation and symbol copying condition. Note: the anomalous cell is bold.

Handedness	Left-Handers		Right-Handers	
Channel	Left	Right	Left	Right
Written Word Generation	3.54 (0.68)	4.96 (0.76)	4.94 (0.85)	**1.09 (0.8)**
Symbol Copying	3.24 (0.76)	5.39 (0.64)	5.3 (1.08)	3.75 (0.77)

Hypothesis 3

In order to test Hypothesis 3 (*Comparing left- to right-handers, written word generation vs. symbol copying will result in more pronounced left-hemispheric activation in right-handers compared to left-handers*) we conducted an independent sample *t*-test. Left-and right-handers showed positive difference scores, indicative of greater velocity in the left hemisphere, and the effect was stronger in right-handers compared with left-handers difference scores, with small to medium effect sizes irrespective of handedness measure (see Table 5). This supports Hypothesis 3.

Table 5

Descriptive and inferential statistics for the Written Word Generation minus Symbol Copying lateralization index difference for left- and right-handers based about Handedness Measure.

	Left-Handers		Right-Handers			
Handedness Measure	N	M (SEM)	N	M (SEM)	t	d
Writing Hand	19	0.67 (0.41)	27	2.22 (0.32)	3.01**	0.44
EHI	16	0.53 (0.47)	30	2.14 (0.3)	3.03**	0.45
Pegboard	19	1.03 (0.39)	27	1.97 (0.37)	1.71	0.25
QHPT	25	0.84 (0.35)	21	2.45 (0.35)	3.18**	0.47

Note: df = 44

Secondary analyses

The 2 x 2 mixed-design ANOVAs were repeated three times, each time using one of the other three handedness assessments (EHI, pegboard, QHPT) for identifying right- and left-handers. Results are presented in Table 6 and are in the same general direction as those obtained when handedness was assessed using the writing hand. However, the evidence for a main effect of handedness was weaker and did not pass the classical threshold of statistical significance for handedness grouping by pegboard ($p = 0.094$), compared to writing hand ($p < .001$), the EHI ($p = < .01$), and the QHPT ($p < .01$). Of note, when using the 7-24 POIs, the results showed the same patterns, but the effect sizes were slightly greater in magnitude.

Table 6

Results for 2 x 2 mixed-design ANOVA with condition (written word generation vs. symbol copying) as the within-subjects factor and handedness (according to writing hand: right vs. left) as the between-subjects factor and with laterality indices as the dependent variable. Note: EHI = Edinburgh Handedness Inventory 5-point, QHPT = Quantification of Hand Preference Task

Assessment	Test	df	F	η_p^2	p
EHI	Condition	1, 44	25.07	0.363	$p < .001$
	Handedness	1, 44	9.17	0.172	$p < .01$
	Condition * Handedness	1, 44	16.9	0.278	$p < .001$
Pegboard	Condition	1, 44	29.82	0.404	$p < .001$
	Handedness	1, 44	2.93	0.062	$p = .094$
	Condition * Handedness	1, 44	22.69	0.34	$p < .001$
QHPT	Condition	1, 44	42.69	0.492	$p < .001$
	Handedness	1, 44	10.14	0.187	$p < .01$
	Condition * Handedness	1, 44	8.27	0.158	$p < .01$

Table 7 shows the correlations between the two condition LIs, their difference, and the three behavioral measures of handedness. There was strong evidence that the LI_{words} correlates with all handedness measures, whereas for the $LI_{symbols}$, strong evidence of a correlation was only evident for the EHI and the pegboard scores, although there was some weak evidence for a correlation with the QHP score as well ($p = .075$). All correlations between the difference LI and the handedness measures were medium in magnitude. All correlations were in the direction of higher LI means (indicating typical cerebral lateralization; i.e., left) with a higher degree of right-handedness. Correlations were comparable, though fractionally smaller on average, for the 7 to 24 s period of interest.

Table 7

Non-parametric (Spearman) correlations between condition laterality indices, their difference, and handedness measures (*N* = 46).

Condition/Handedness Measure	2	3	4	5	6
1. Written Word Generation	.890**	.370*	.563**	-.633**	.405**
2. Symbol Copying	-	-.036	.440**	-.543**	.265
3 Words minus Symbols Difference	-	-	.403**	-.300*	.432**
4. Edinburgh Handedness Inventory (EHI)	-	-	-	-.688**	.574**
5. Annett Pegboard	-	-	-	-	-.409**
6. Quantification of Hand Preference Test (QHPT)	-	-	-	-	-

* p < .05, ** p < .01

4. Discussion

The present study used functional transcranial Doppler ultrasound (fTCD) to compare left- and right-handers in a written word generation task with a symbol copying task: similar with respect to visuomotor demands but excluding language. Our main objective was to elucidate on the relative contribution of language and motor functions in cerebral laterality for writing in left-handers compared to right-handers and specifically investigate whether the wider right-hemispheric network previously observed in left-handers compared to right-handers during written as opposed to oral language production (Kondyli et al., 2017) subserves linguistic or motor demands of writing.

Our first hypothesis, namely that a more left-lateralized pattern of cerebral activation during written word generation compared to symbol copying will be observed in right-handers, was supported. Both tasks have similar motor demands that result in left-hemispheric activation (i.e., right-hand action), but writing words further encompasses linguistic demands that are typically left-lateralized in right-handers. Therefore, our findings provide evidence that it is the linguistic aspect of the written word generation task that results in left-hemispheric activation in the case of writing, similarly to oral language production, in right-handers. However, our second hypothesis, namely that this pattern will also be observed in the left-handers, was rejected. When comparing left-handers to right-handers, the written word generation condition vs. the symbol copying condition resulted in more pronounced left-hemispheric activation in right-handers compared to the word generation condition vs. the symbol copying condition in left-handers, confirming Hypothesis 3. For this last analysis, the symbol copying condition was treated as an active baseline to written word generation.

The difference in findings between right- and left-handed participants could be due to the fact that cerebral laterality patterns are more varied in left-handers as opposed to right-handers. This was only the case in our data when handedness was assessed using the QHPT (Levene's test of equality of variances, Written Word Generation SD: right-handers = 3.31, left-handers = 3.92, $F(1, 44) = 3.01$, $p = 0.04$ (one-tailed); Written Word Generation SD: right-handers = 2.53, left-handers = 4.3, $F(1, 44) = 8.79$, $p < .001$). Another possibility is that the areas subserving language are wider in left- compared to right-handers, as suggested by Kondyli et al. (2017). Given that the right-channel activation was stronger in the symbol copying condition only for right-handers, an alternate explanation is a contribution of a right-hemispheric attentional network for the more-novel stimuli (i.e., the symbols), similar to what we see in visuospatial tasks (Rosch et al., 2012; Whitehouse & Bishop, 2009). This contribution was not apparent in left-handers; however, the written word generation task already demanded the activation of right-hemispheric areas in order to support the motor demands of writing, therefore the activation related to the symbol copying task, which had the same motor demands in addition to the attentional demands, potentially reached a ceiling (see Figure 1). Therefore fTCD may simple have been insensitive to this effect in left-handers. Future work could disentangle this by comparing copying of simple versus complex novel stimuli or over-learned nonverbal stimuli, such as shapes. This will be especially important to understand patterns in left-handers who did not show clear differentiation between written word generation and symbol copying. A fourth explanation could be that there is a graded increase in functional activation in areas of the right hemisphere, namely the right anterior supramarginal gyrus, with the degree of left handedness during handwriting (Siebner et al., 2002). These areas could respond to motor elements of writing, such as motor preparation before handwriting, with left-handers possibly having more difficulty with task initiation and hence showing greater effort related to movement preparation (Siebner et al., 2000). Of note, this suggestion was made on the basis of functional imaging studies on right-handers that pointed towards a role in movement preparation and selection for the left inferior parietal lobule (Deiber et al., 1996; Krams et al., 1998; Schluter et al., 2001).

Previous evidence from studies comparing handwriting to similar motor tasks, such as clock drawing or the drawing of simple geometric shapes or objects, has shown that frontoparietal networks are activated. These networks include the superior parietal cortex, the supplementary motor area, the dorsal premotor and ventral premotor cortices, and the cerebellum (Ferber, Mraz, Baker, & Graham, 2007; Gowen & Miall, 2006; Ino, Asada, Ito, Kimura, & Fukuyama, 2003; Makuuchi, Kaminaga, & Sugishita, 2003; Miall, Gowen, & Tchalenko, 2009). However, Planton et al. (2017) found that the distinctive feature between a non-linguistic motor task (drawing) and writing in a sample of right-handers is the left-lateralization pattern of the graphemic/motor frontal area. This left-lateralization pattern was replicated here in right-handers, but not for left-handers.

Of note, the main effect of handedness, with right-handers producing a higher mean LI than the left–handers, was weaker and did not hold up against the classical threshold of statistical significance when handedness was measured as hand skill, with the pegboard task, as opposed to when it was measured as hand preference, which is what the other three handedness measures assess (writing hand, EHI and QHPT). It could be argued that it is hand preference and not hand skill measures that is informative for cerebral laterality for writing. These results add to previous findings that point to the direction of treating hand skill and hand preference as two rather distinct concepts. For example, hand skill and hand preference have been suggested to be independently lateralized (Triggs et al., 2000). Another possibility is that the pegboard task as a measure of hand skill was not sensitive enough to capture the handedness effect. Indeed, different measures of hand skill have been found to have low correlation with each other (0.08-0.3), suggesting that they tap into different dimensions of laterality and that they cannot be used interchangeably (Buenaventura Castillo, Lynch, & Paracchini, 2019).

On a methodological level, these findings showcase why it is important to measure and report handedness using more than one measure, as recently suggested by Papadatou-Pastou et al. (2020). The fact that handedness studies may use different measures of handedness and different criteria to group participants, has been highlighted repeatedly in recent meta-analyses as introducing noise to the literature, creating an obstacle to cross-study comparisons (Markou, Ahtam, & Papadatou-Pastou, 2017; Ntolka & Papadatou-Pastou, 2018; Papadatou-Pastou, Martin, Munafo, & Jones, 2008; Papadatou-Pastou et al., 2019; Papadatou-Pastou & Tomprou, 2015). In the fTCD literature, recently Kondyli et al. (2017) reported findings using the same four measures that were reported here and we urge researchers to adopt this good practice.

We shall refrain from making recommendations as to which measure is preferred, because each one has its own merits. Writing hand is the easiest, most intuitive, and popular method to access hand preference (Papadatou-Pastou et al., 2020). EHI is the most popular hand preference inventory in the literature (Papadatou-Pastou et al., 2020) and thus lends itself to cross-study comparisons. Moreover, it is easily administered in group settings or even online. The pegboard task is a measure of hand skill, therefore representing an important dimension of handedness that could be –as mentioned above- independently lateralized from preference. The QHPT measures preference behaviorally using an activity (card-reaching in different locations) that is not typically practiced in everyday life and is thus not expected to be subject to cultural pressures. Moreover, using the QHPT, preference can be more readily quantified than when using an inventory that lists different, unrelated activities. The pegboard and QHPT are administered physically on a one-to-one basis, making data collection more demanding. Considering these different merits and properties of the four handedness measures, we urge researchers to use and report as many of these methods as practically possible so that a better understanding of the multifaceted phenomenon of handedness can be achieved.

A potential limitation of the study is that the fTCD detects the blood flow in the middle cerebral arteries (MCAs), which feed mainly frontal and temporal brain areas (van der Zwan & Hillen, 1991; van der Zwan et al., 1993). While temporal areas have been associated with the linguistic component of writing, motor areas are found in the frontal lobe. Therefore, it could be the case that activation of parietal areas previously found to be important for writing, such as the left intraparietal sulcus and the left superior parietal area (Planton et al., 2017), might be missed by fTCD. However, more recent findings show that the MCA territory is more extensive than previously described, occupying approximately 54% of the supratentorial parenchymal brain volume and including the intraparietal sulcus (Kim et al., 2019).

5. Conclusions

By comparing a visuomotor task that includes a linguistic component (written word generation) with a task that has similar visuomotor demands without a linguistic component (symbol copying) we were able to show that the linguistic aspect of writing results in left-hemispheric activation similarly to the case of oral language production tasks in right-handers. It is potentially right-hemispheric language areas that are more engaged in left-handers and not merely motor areas, although attentional demands of symbol copying and/or visuomotor control more generally could also be at play. These findings not only extend our knowledge on the cerebral laterality of written language, but also have implications for both healthy individuals as well as pathological populations that present with written language impairments (e.g., individuals with learning disorders, Alzheimer’s, or schizophrenia).

Disclosure of interest

The authors report no conflict of interest.

Data availability statement

All PsychoPy scripts, datasets, and analysis scripts have been uploaded to the Open Science Framework repository (https://osf.io/t79jh/)

Author contributions

MPP and NB conceived and designed the study, MPP wrote draft manuscript, MPP and NB analyzed and interpreted findings, NB created the tables and figures, PS, AT, DS, IK, and SS collected data and assisted in data handling and analysis, MPP supervised data collection. All authors reviewed and approved the final version of the manuscript.

Ethical statement

The study followed the declaration of Helsinki and has received ethical approval from the local ethics committee. All participants gave written informed consent.

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