Running title: LATERALITY DURING WRITING

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

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Draft version 1.0, 14.7.2020. This paper has not been peer reviewed. Please do not copy or cite without author's permission.

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 thus to further our understanding of written language lateralization, by elucidating on the relative contribution of language and motor areas. This was achieved by comparing written word generation with a writing task that has similar visuomotor demands, but does not include language (i.e., the repeated drawing of symbols). We assessed cerebral laterality in 54 left- and right-handed participants by means of functional transcranial Doppler ultrasound (fTCD), a non-invasive, perfusion-sensitive neuroimaging technique. Our findings suggest that, in right-handers, the linguistic aspect of the written word generation task recruited left-hemispheric areas during writing, similarly to oral language production. In left-handers, we failed to observe the same effect, possibly due to the great variability in cerebral laterality patterns within this group or alternatively due to the attentional demands of the symbol copying task. Future work could investigate such demands using both simple and complex stimuli in the copying condition.

Keywords: 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 limited work has been done on the cerebral lateralization of written language (e.g., Kondyli et al., 2017), but also on 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 that it is widely used in education and everyday life for communication, as well as for archiving information, ideas, and stories across time and space. Handwriting has been found to be 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 networks, both when studying healthy individuals as well as pathological populations.

In terms of possible differences between right- and left-handers when it comes to the neural underpinning of writing, this is again an important question to ask. 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). Moreover, as right- and left-handers have been consistently found to differ in the cerebral organization of oral language functions (e.g., Knecht, Dräger et al., 2000), 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 have been shown to correlate with cerebral laterality during written word generation (Kondyli et al., 2017). Moreover, more pronounced right-hemispheric lateralization was found 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 be related 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). A region that has been shown to be critical to writing is the rostral part of the superior parietal lobe in the left hemisphere (Segal & Petrides, 2012), as it is located in a position that promotes interaction with other language and motor regions during writing tasks. Other areas in the left hemisphere that show increased 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 thought to be 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 seem to be 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. Merely three studies to date have included left-handers in their sample (Kondyli et al., 2017; Siebner et al., 2002; Zaman et al., 2002). Zaman et al. (2002) investigated normal and mirror writing with the dominant and the non-dominant hand. 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.

However, 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 the dominant versus the non-dominant hand 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 not adequately isolated.

When it comes to the measurement of cerebral laterality for written language, the Zaman et al. (2002) and Siebner et al. (2002) studies 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 who 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 it can be 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 excellent agreement with those acquired using the intra-carotid amobarbital procedure (Wada test) and fMRI (Deppe et al., 2000; Deppe, Ringelstein, & Knecht, 2004). FTCD lends itself to the study of writing, as its signal is not disrupted by movement artifacts (Kondyli et al., 2017). Furthermore, fTCD data processing has progressed significantly in recent years, owing to the development of an open-access,

MATLAB-based toolbox (Badcock, Holt, Holden, & Bishop, 2012). This toolbox provides researchers with unprecedented control and therefore insights into their data, allowing them to establish gold-standard approaches to understanding lateralization assessed with fTCD.

Coming 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 has been 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, recently 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. 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 purpose 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 areas in cerebral laterality for writing. This will be achieved by comparing written-word generation with writing that 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 does not include language, specifically the repeated writing of symbols (e.g. *, $, &). Copying symbols resembles the hand movements during writing much more closely in comparison to drawing and moreover the copying of symbols 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), the Pegboard task, and the Quantification of Hand Preference test.

2. Material and methods

Participants

Fifty-four undergraduate and graduate students from [removed for blinding purposes] as well as members of the general public participated in the study (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. Six of these participants had also taken part in the Kondyli et al. (2017) study (2 left-handed females, two left-handed males, and two right-handed males). All participants were monolingual, native speakers of the Greek 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 was not possible due to inadequate ultrasonographic penetration of the skull by the ultrasound beam.

Assessment of linguistic lateralisation

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). The layout of each trial was the following: 35 seconds of rest, a cueing tone (this is the time point when the marker was 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 generation 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 for each participant, which were divided into two conditions: 20 letter trials corresponding to the

written word generation condition and 20 symbol trials corresponding to the symbol copying condition. 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 that feasibility of the protocol. The results are not included in the present report.

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 which hand they prefer to use 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%.

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 sample points per second 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 software (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. Epochs containing CBFV values outside the range of 70% to 130% of the mean velocity or an absolute left-right 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 plot suggested that a POI of 7-16

24 s after cuing might be also worth investigating. We calculated two LIs: LI_{words}, which represents the LI for the accepted epochs, where letters were the stimuli and $LI_{symbols}$, which represents the LI for the accepted epochs where symbols were used as stimuli. If less than 10 epochs were accepted for either the words or the symbols conditions, then the participant was excluded from the sample (n = 8 in this case).

Procedure

As soon as the participants arrived, the study was explained 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.

Statistical analysis

Further analyses were performed using the Statistical Package for the Social Sciences (SPSS) v.25 (IBM Corp., 2017). A mixed-design analysis of variance (ANOVA) was performed 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. The partial eta squared (η_p^2) statistic was used as the effect size measure. Post-hoc tests were run using pairwise comparisons with Bonferroni adjustment and

Cohen's *d* as an effect size measure. In order to test if the different handedness-assessment methods correlated differently with cerebral lateralization as measured with fTCD, 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). We did not test for sex differences, as the literature points to the direction of no differences (Kondyli et al., 2017) and the sample size was insufficient for this kind of analysis. To establish whether handedness group LIs were significantly different to zero, we used one-sample *t*-tests. Individual lateralization categorization was based on whether or not 95% confidence intervals for the LI overlapped with zero (effectively, one-sample *t*-tests): left = lower-bound greater than zero, right = upper-bound less than zero, and bilateral (or symmetrical) = overlap with zero (Bishop et al., 2009).

3. Results

Eight participants were excluded from the analysis because the data were too noisy and failed to give at least 10 good epochs per experimental condition (2 female right-handers, 2 female left-handers, 2 male right-handers, 2 male left-handers). The event-related blood flow for each condition by handedness is presented in Fig. 1 and the group averages are presented in Fig. 2. Descriptive statistics for the fTCD indices for both the 7-17 s and the 7-24 s POIs broken down by sex and handedness (according to writing hand) are presented in Table 1 and descriptive statistics for the handedness assessments are presented in Table 2. All analyses were run for both the 7-17 and 7-24 POIs, but only the results of the 7-17 POI are presented below, which did not differ in pattern from the 7-24 POI, though the effect sizes for the latter were larger in magnitude.

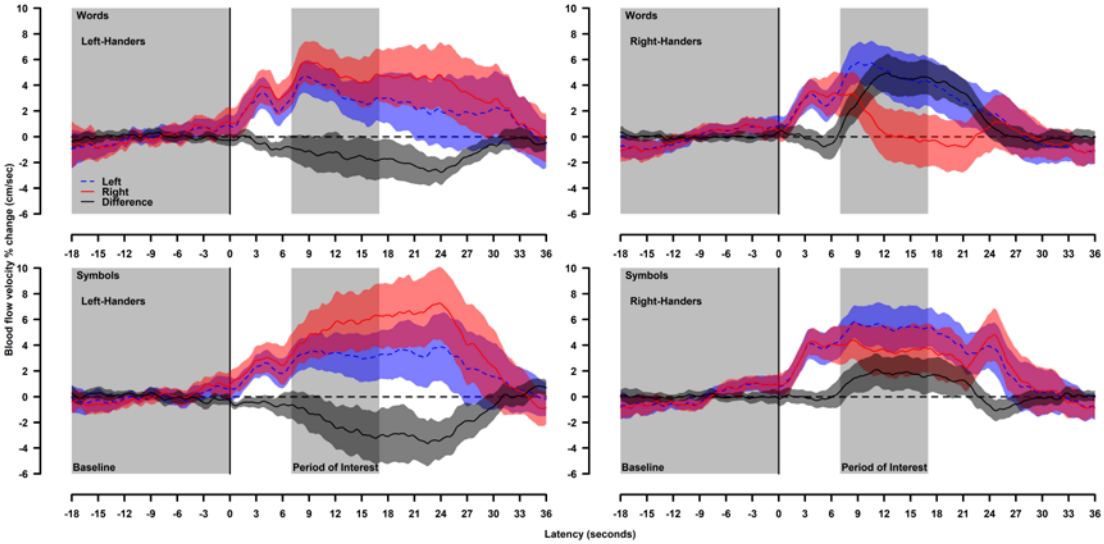

Fig. 1. Event-related blood flow for condition (Written Word Generation = top row, Symbols Copying = bottom row) by handedness (Left-Handers = left column, Right-Handers = right column). Left, right, and left minus right difference channels are depicted with their respective 95% confidence interval. Analysis baseline and period of interest timing are depicted by grey columns.

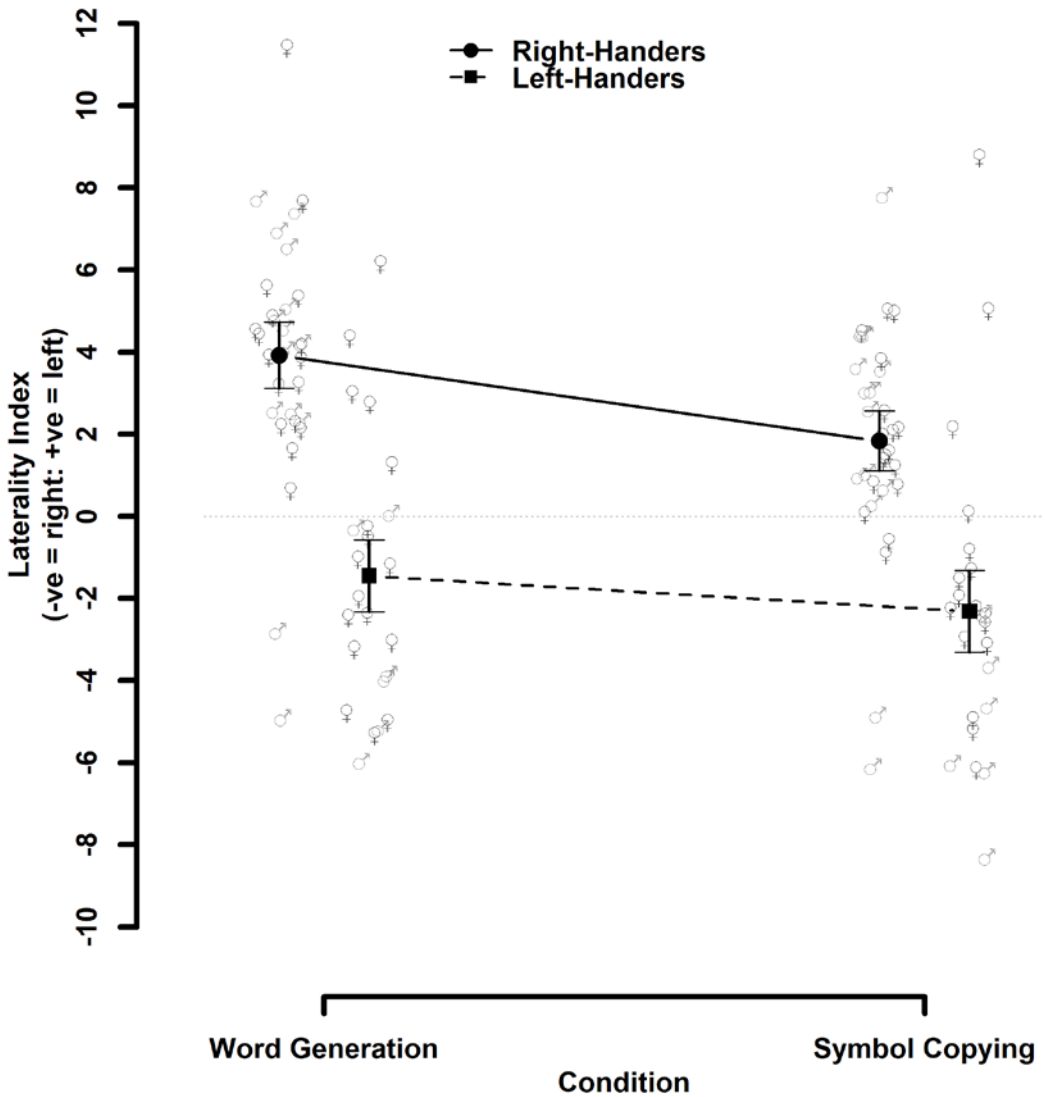

Fig. 2. Group laterality indices (LIs) for Condition (Written Word Generation vs. Symbol Copying) by handedness (Right-Handers and Left-Handers denoted by circles with solid line and squares with broken line, respectively). Error bars represent the 95% confidence intervals and individual data points depict participant sex using gender symbols.

Table 1. Descriptive statistics for the functional transcranial Doppler sonography (fTCD) conditions. Handedness groups according to the writing hand.

Task	Sex	Handedness	N	Mean number of epochs	Mean LI	SD	Range	Median
Period of interest: 7 to 17 seconds after cueing								
LI_{words}	M	R	12	17.75	3.2	3.73	(-4.91) - 7.43	4.14
		L	4	19	-3.73	2.68	(-5.97) - 0.07	-4.51
	F	R	15	18.2	4.39	2.51	(1.58) - 11.4	4.12
		L	15	17.73	-0.77	3.22	(-5.03) - 6.14	-1.23
$LI_{symbols}$	M	R	12	17.17	1.33	3.76	(-6.1) - 7.82	1.84
		L	4	18.25	-4.8	1.77	(-6.2) - -2.37	-5.32
	F	R	15	18.4	1.89	1.89	(-0.95) - 4.98	1.53
		L	15	17.8	-1.33	3.95	(-6.19) - 8.73	-2.31
Period of interest: 7 to 24 seconds after cueing								
LI_{words}	M	R	12	17.75	3.08	3.25	(-4.26) - 6.53	4.02
		L	4	19	-3.81	2.35	(-5.97) - -0.66	-4.31
	F	R	15	18.2	4.07	2.49	(0.78) - 10.74	3.71
		L	15	17.73	-1.15	3.13	(-4.85) - 5.88	-1.91
$LI_{symbols}$	M	R	12	17.17	1.33	3.76	(-6.1) - 7.82	1.84
		L	4	18.25	-4.8	1.77	(-6.2) - -2.37	-5.32
	F	R	15	18.4	1.89	1.89	(-0.95) - 4.98	1.53
		L	15	17.8	-1.33	3.95	(-6.19) - 8.73	-2.31

Table 2. Descriptive statistics for the handedness assessments. Note: EHI = Edinburgh Handedness Inventory 5-point, QHPT = Quantification of Hand Preference

Test	Sex	Handedness	N	Mean LI	SD	Median	Range
EHI	M	R	12	89.67	6.6	91	74-98
		L	4	44.5	21.99	38	26-76
	F	R	15	91.2	9.7	94	62-100
		L	15	32.53	16.47	30	20-84
QHPT	M	R	12	37.7	27.03	33.33	0-100
		L	4	20.83	18.99	22.62	0-38.1
	F	R	15	72.38	24.48	76.19	9.52-100
		L	15	33.81	25.41	33.33	0-73.81
Pegboard	M	R	12	-0.05	0.03	-0.04	-0.08-0.03
		L	4	0.04	0.04	0.04	-0.01-0.08
	F	R	15	-0.06	0.05	-0.07	-0.2-0.04
		L	15	0.04	0.03	0.04	-0.02-0.09

Fig. 3 summarizes the data in a scatter plot with the LI_{words} on the x axis and the $LI_{symbols}$ on the y axis. The equivalent numbers of cases per laterality categorization (left, bilateral, or right) are presented in Table 3. LIs are considered significantly right- or left-lateralized when their 95% CI does not overlap with zero. Otherwise, lateralization is considered bilateral. Of note, the only quadrant of Fig. 3 that is not populated is the top-left, representing a negative LI for the written word generation condition, but a positive one for the symbols copying condition. The quadrant representing a negative LI for the copying of symbols, but a positive LI for the written word generation (bottom-right) is similarly sparsely populated. The bottom-left and the top-right quadrants house most left-handed and right-handed participants, respectively.

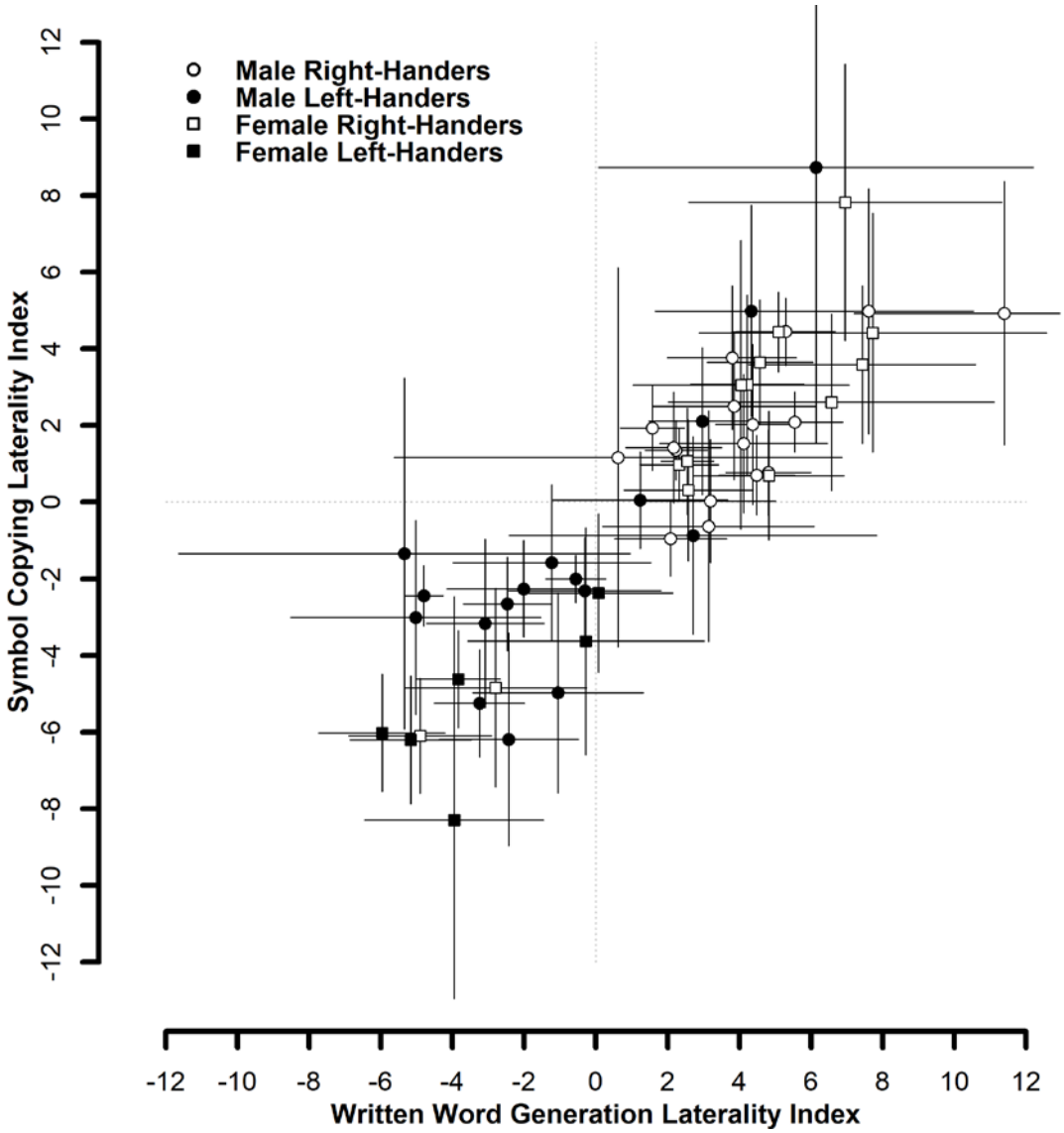

Fig. 3. Scatter plot of laterality indices (LIs) for the Written Word Generation and Symbol Copying Tasks. All individual data points are presented with the 95% confidence intervals.

Table 3. Number of cases for each lateralisation index (LI) classification for the Written Word Generation (Words) and Symbol Copying (Symbols) 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

	Task LI categorisation			Words			
	Symbols	Left		Bilateral		Right	
Handedness		Left-Handers	Right-Handers	Left-Handers	Right-Handers	Left-Handers	Right-Handers
Period of Interest: 7 to 17							
Writing Hand	Left	3	13	-	-	-	-
	Bilateral	-	12	2	-	-	-
	Right	-	-	5	-	9	2
EHI	Left	13	3	-	-	-	-
	Bilateral	-	-	1	1	-	-
	Right	-	-	2	3	2	9
Pegboard	Left	2	14	-	-	-	-
	Bilateral	-	10	2	-	-	-
	Right	-	-	5	-	8	3
QHPT	Left	9	7	-	-	-	-
	Bilateral	-	3	2	-	-	-
	Right	-	-	-	5	1	10
Period of Interest: 7 to 24							
Writing Hand	Left	2	14	-	-	-	-
	Bilateral	-	9	1	1	1	-
	Right	-	-	4	2	10	1
EHI	Left	14	2	-	-	-	-
	Bilateral	-	1	1	1	-	1
	Right	-	-	4	2	2	9
Pegboard	Left	1	15	-	-	-	-
	Bilateral	-	8	1	1	1	-
	Right	-	-	5	1	9	2
QTHP	Left	9	7	-	-	-	-
	Bilateral	-	3	2	-	-	1
	Right	-	-	2	4	1	10

In order to test for differences in the LIs of the two conditions as well as the effect of handedness, a 2 x 2 mixed-design ANOVA was run with condition (words or symbols) as the within-subjects factor and handedness according to writing hand (right or left) as the between-subjects factor. The two LIs (LI_{words} and $LI_{symbols}$) were the dependent

variables. 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), which shows left-hemispheric (typical) cerebral laterality during written word generation and copying symbols – 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 much 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. The results revealed evidence of an interaction between condition and handedness according to writing hand, $F(1, 44) = 9.09$, $p < .01$, $\eta_p^2 = 0.171$ (see Fig. 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 both were significantly different: LI_{words}, $t(44) = 5.52$, $p < .001$, Cohen's $d = 2.94$; $LI_{symbols}$, $t(44) = 3.77$, $p < .01$, Cohen's $d = 2.03$. However, the effect of condition did not hold for both levels of handedness. For right-handers, LI_{words} was significantly higher than $LI_{symbols}$, $t(26) = 6.91$, $p < .001$, Cohen's $d = 1.33$. This was not the case for left–handers, where the means for LI_{words} and $LI_{symbols}$ were not significantly different, $t(18) = 1.62$, $p = 0.49$, Cohen's $d = 0.37$.

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 in the symbol copying condition, relative to the written word generation condition (see Fig. 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 (right or left) as the between-subjects factor and condition (words or symbols) and channel (left or 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) x 2 (channel) 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 activation was higher for symbol copying (versus 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 conditions. Note: the anomalous cell is in 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)

The above analyses test for differences between the groups but not whether the LIs are significant per se. Based on one-sample *t*-tests against zero, 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.

The 2 x 2 mixed-design ANOVAs were repeated using the other three handedness assessments (EHI, pegboard, QHPT) for identifying right- and left-handers. Results are presented in Table 5 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 5. 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

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 = 0.094
	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 6 shows the correlations between the three behavioral measures of handedness and the two LIs. 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 were in the direction of higher LI means (indicating typical cerebral lateralization; i.e., left) with a higher degree of right-handedness.

Table 6. Non-parametric (Spearman) correlations between tasks.

Task	1	2	3	4	5
1. Written Word Generation^	-	.890**	.563**	-.633**	.405**
2. Symbol Copying^	-	-	.440**	-.543**	0.265
3. Edinburgh Handedness Inventory (EHI)	-	-	-	-.688**	.574**
4. Annett Pegboard	-				-.409**
5. Quantification of Hand Preference Test (QHPT)	-	-	-	-	-

^ 7 to 17 period of interest, ** p < .01

4. Discussion

The present study used functional transcranial Doppler ultrasound (fTCD) to investigate the specific contribution of language activation as opposed to motor activation during writing. This was achieved by comparing a written word generation task with a task with similar visuospatial demands that did not include language, namely copying symbols. Moreover, it aimed to compare left- and right-handers in the same tasks, in order to test two competing hypotheses, namely 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.

A more left-lateralized pattern of cerebral activation during written word generation compared to symbol copying was observed in right-handers, providing evidence that it is the linguistic aspect of the written word generation task that recruits left-hemispheric

areas in the case of writing, similarly to oral language production. However, this was not observed in the left-handers. 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. However, given that the right-channel activation was stronger in the symbol copying task for right-handers, an alternate explanation is a contribution of an attentional network for the more-novel stimuli, similar to what we see in visuospatial tasks (Rosch et al., 2012; Whitehouse & Bishop, 2009). 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 what's happening in left-handers who did not show clear differentiation between written word generation and symbol copying.

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 non-motor tasks and writing is the left-lateralization pattern. This pattern was replicated here, albeit only for right-handers.

Of note, the main effect of handedness 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 (writing hand, EHI and QHPT) assess. It could be argued that it is hand preference and not hand skill measures that are informative when it comes to reflecting 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).

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 ways to measure handedness and different criteria to group participants, has been highlighted repeatedly in recent meta-analyses of handedness as a factor that brings noise into the data and works as an obstacle to comparing the findings of different studies (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.

We shall refrain from making recommendations as to which measure should be preferably reported, because each one has its own merits. Writing hand is the easiest, most intuitive, and popular (Papadatou-Pastou et al., 2020) method to access hand preference. EHI is the most popular hand preference inventory in the literature (Papadatou-Pastou et al., 2020) and thus lends itself to comparing findings between studies. Moreover, it can be easily administered in group settings or even online. 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 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 and the pegboard need to be administered physically on a one-to-one basis, making data collection more demanding. Considering these different merits and properties of the four handedness assessment methods, 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 not have been captured using fTCD. Moreover, some of these areas are found to differentially activate in relation to the degree of left-handedness. Siebner et al. (2002), for example, found a graded increase in functional activation in the right anterior supramarginal gyrus with the degree of left handedness. Still, parietal areas have been suggested to 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).

5. Conclusions

By comparing a writing task that includes a linguistic component (written word generation) with a writing task that has similar visuomotor demands without a linguistic component (copying symbols) 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 could also be at play. These findings not only extend our knowledge on the cerebral laterality of written language, but could further 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).

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