RESEARCH ARTICLE

ACTA Vol. 15, No. 4, 2017, 407-432
NEUROPSYCHOLOGICA

Received: 01.05.2017
Accepted: 28.09.2017

A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

Cerebral laterality for the generation of silent and written language in male and female right- and left- handers: A functional transcranial Doppler ultrasound study

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SUMMARY

Background: The cerebral lateralization of language has attracted great research interest. Nevertheless, the bulk of the work focuses on language production and comprehension; research on cerebral lateralization during writing is limited.

Material/ Methods: The present study assessed cerebral lateralization in 60 participants (mean age = 26.65 years, SD = 6.05, range = 20-44), 30 right-handers (14 men) and 30 left-handers (16 men), during written language production by means of functional transcranial Doppler ultrasonography (fTCD) for the first time.

Results: Findings show that left-hemispheric lateralization is observed during silent word production, for both left- and right-handers. However, during written word production, the degree of typical (left) hemispheric lateralization was significantly increased for right-handers, while left-handers presented atypical (right) hemispheric lateralization. Importantly, the difference between silent and written word generation was significantly higher in left- compared to right-handers. No main effect of sex or interactions with sex were observed.

Conclusions: Findings suggest that a wider network of right-hemispheric areas is used during writing in left-handers. Thus, the known differences in cerebral lateralization between right- and left-handers are stronger during written language production. However, the relative contribution of language and motor areas needs to be further elucidated.

Key words: cerebral language lateralization, functional transcranial Doppler ultrasound (fTCD), word generation, writing, handedness

BACKGROUND

Asymmetry is one of the most studied phenomena in nature; it has been observed both in humans and a number of vertebrate and invertebrate animals (Corballis, 2014; Rogers, 2002; Schaafsma, Riedstra, Pfannkuche, Bouma & Groothuis, 2009; Schilthuizen & Gravendeel, 2012). Humans, in particular, have been shown to demonstrate asymmetries in terms of behavior, anatomy, and brain function (for a review see Rogers, Vallortigara, & Andrew, 2013). Language, which is a characteristic unique to our species, has been found to be the most lateralized cognitive function (for a review see Ocklendurg, Beste, Arning, Peterburs, & Güntürkün, 2014; Papadatou-Pastou, 2011). And while many studies have provided evidence on cerebral language lateralization using overt or covert oral language production or language comprehension tasks (e.g., Groen, Whitehouse, Badcock, & Bishop, 2012; Stroobant, Buijs, & Vingerhoets, 2009), cerebral lateralization during writing has only recently started to receive research attention (e.g., Dufor, & Rapp, 2013; Segal, & Petrides, 2012). The neural underpinnings of writing are of great interest, as writing is a rather recent cultural attainment with colossal implications. It is being utilized nearly every day, at least in western societies. It is one of the most important tools for communication across space and time and a skill that demands the contribution of several cognitive and motor functions (Planton, Jucla, Roux, & Démonet, 2013). Dissociated disorders of speaking and writing have been reported in aphasia (Basso, Taborelli & Vignolo, 1978), suggesting the neural underpinnings of writing might be different to that of oral language.

Cerebral laterality for language

From as early as 1865, when Paul Broca indicated that speech production is localized in the left inferior frontal lobe (Berker, Berker, & Smith, 1986), it has been widely accepted that the left hemisphere is dominant for language. This notion has been supported by a number of studies examining patients who became aphasic after suffering a stroke or lesion in the left hemisphere (Cao, Vikingstad, George, Johnson, & Welch, 1999; Gainotti, 1993; Ohyama et al., 1996; Weiller et al., 1995). The prevalence of the left hemisphere for language has been also shown by studies assessing the cerebral lateralization of language in epileptic patients, with no evidence of an early left-hemisphere injury, using the intracarotid amobarbital procedure (Wada test; Wada, 1949; Wada, & Rasmussen, 1960). Findings showed that the percentage of the right-handed patients demonstrating left-hemisphere lateralization for language ranged from 80% to 96% (Loring et al., 1990; Rasmunsen & Milner, 1977).

In addition, an extensive body of related evidence has been offered by studies on healthy participants, usually employing functional magnetic resonance imaging (fMRI). For example, Springer et al. (1999) reported that 95% of the healthy participants studied and 78% of the participants suffering from epilepsy were found to be left-hemisphere dominant, while a study by Pujol, Deus, Losila, and Capdevila (1999) showed that 96% of the participants demonstrated left-hemisphere language lateralization. Similarly, Vikingstad, George, Johnson, and Cao (2000) found that the lateralization of language in a sample of healthy right-handers was left-dominant, while Koeda et al. (2006) demonstrated that 81.5% of the participants in his study were also left-hemisphere dominant for language.

Other data concerning the left-hemisphere specialization for language processing has come from studies using the technique of functional transcranial Doppler ultrasonography (fTCD). Knecht et al. (2000) reported that 92.5% of the right-handed participants in his study were left-hemisphere dominant for language. Furthermore, in a study by Gutierrez-Sigut, Payne, and MacSweeney (2014), it was shown that language functions are lateralized to the left hemisphere for both overt and covert speech. Similarly, the findings of Stroobant et al. (2009), revealed that the majority of 30 healthy right-handed volunteers (90%), showed left-hemispheric dominance in four language tasks.

Language lateralization in left-handers has also attracted research attention. Pujol et al. (1999) found that 96% of the right-handed, but only 76% of the left-handed participants in their study were left-hemisphere dominant for language. Khedr, Hamed, Said, and Basahi (2002) reported similar figures: 87.5% of the strongly right-handed participants, but only 73.7% of the left-handed participants were left-hemisphere dominant for language. Moreover, Szaflarski et al. (2002), who examined language lateralization in ambidextrous and left-handed participants, found that 78% of the participants were left-hemisphere language dominant, 8% were right-hemisphere language dominant, and 14% demonstrated bilateral activation. Knecht et al. (2000) further found that not only the direction, but also the degree of handedness is a determinant factor for language lateralization. More specifically, while only 4% of the strong right-handers in his study were right-hemisphere language dominant, this percentage increased to 15% in ambidextrous individuals and 27% in strong left-handers.

Cerebral laterality for writing

In all of the above studies a variety of different components of language were assessed, such as overt and covert word production (Garn et al., 2009; Knecht, Drager et al., 2000) and language comprehension (Phillips et al., 2001; Plante et al., 2006); except for that of writing. Most of our current knowledge on brain areas involved in writing has come from lesion studies in patients with neurological problems (Menon & Desmond, 2001). For example, brain damage in the superior parietal lobe, supramarginal gyrus, angular gyrus, Wernicke's area, or Broca's area, has been found to be associated with difficulties in specific aspects of writing (Roeltgen, 1993). Additionally, apraxic agraphia has been found to be associated with the region surrounding the left intraparietal sulcus, including the superior parietal lobule and superior portions of the supramarginal and angular gyri (Beeson et al., 2003).

Recently, a limited number of fMRI studies have provided insights on the neural underpinnings of writing in the healthy brain. For example, Beeson et al. (2003) found that the central or linguistic aspects of writing are located in the left posterior inferior temporal cortex, while semantic retrieval of orthographic word forms is associated with the activation of the left inferior and dorsolateral prefrontal cortex. In addition, left-hemisphere regions, such as the intraparietal sulcus, the superior parietal lobule, the dorsolateral and medial premotor cortex, and the sensorimotor cortex for the hand, have been associated with the peripheral or motor components of writing. The critical role of the left parietal lobe for writing was confirmed by the results of another study conducted by Menon and Desmond (2001). More specifically, the activation of large clusters of neurons was observed both in the left inferior and superior parietal lobe, with the latter being related to the sequential execution components of writing. Activation of the left premotor cortex, the sensorimotor cortex and the supplementary motor area was also detected. Segal and Petrides (2012) further found that the cerebral region that is primarily associated with writing is the rostral part of the superior parietal lobe (area PE) in the left hemisphere. According to the authors of the study, area PE is located in a position that promotes interaction with various language and motor regions during writing. Increased activation in left-hemisphere areas, including the middle frontal gyrus, superior frontal gyrus, inferior frontal gyrus, superior temporal gyrus, middle temporal gyrus, and superior parietal lobule was also observed by Tam, Churchill, Strother, and Graham (2011).

A meta-analysis by Planton et al. (2013) showed that the cerebral network underlying writing consists of 12 cortical and subcortical regions including, primarily, left-hemisphere regions, such as the left superior frontal sulcus, the left middle frontal gyrus, the left intraparietal sulcus, the left superior parietal area and the right cerebellum. Duffor and Rapp (2013) identified brain regions that are uniquely activated for letter writing, namely the left fusiform gyrus, left superior frontal gyrus, left superior frontal sulcus, left middle frontal gyrus, left pre-central and post-central gyrus, left inferior parietal lobule, and right cerebellum. In addition, in a comparison between digit and letter writing, it was found that there is a preferential, but by no means exclusive, activation of the left superior parietal lobe and the dorsal aspects of inferior parietal cortex for writing letters (Longcamp et al., 2014). It was also demonstrated that the dorsal pre-motor cortex is an essential part of the cerebral network supporting writing. Brain activation for writing letters versus writing simple dots was also examined in a sample of ten healthy right-handers by Rektor, Rektorova, Mikl, Brazdil, and Krupa (2006). The results revealed a bilateral pattern of activation during letter writing. More specifically, both left hemisphere regions (premotor, sensorimotor, and supramarginal cortices and the thalamus) and right hemisphere regions (including the post central gyrus, inferior parietal, and premotor regions) were found to be significantly active during letter writing.

Some recent studies have examined right-handed individuals, while writing with their left, non-dominant hand. Horovitz, Gallea, Najee-Ullah, and Hallett (2013), for example, investigated the patterns of cerebral activation in 13 healthy right-handers during writing, zigzagging, and tapping. For each of these tasks the participants used their right hand, left hand, or right foot. Findings showed that writing with the dominant, right hand, caused significant activation in the left dorsal prefrontal cortex, the left intraparietal sulcus, the left anterior putamen, the left ventral premotor cortex, the left inferior, the superior parietal cortex, and the right cerebellum. A crucial finding was that skillful and well-established writing with the dominant hand is associated with the activation of a much wider neural network compared to writing with any other limb. In another study, Kushnir, Arzouan, Karni, and Manor (2013) assessed brain activation in nine right-handed healthy young adults during left-hand mirror writing. It was found that verbally dictated handwriting using the non-dominant hand caused a more symmetrical activity of the two hemispheres. This shows that grapho-motor aspects of writing can be mirrored in the non-dominant, right hemisphere. Consistent with this evidence are the findings by Sugihara, Kaminaga, and Sugishita (2006) who suggest that writing with the non-dominant (left) hand causes the activation of wider regions involving both the left and the right hemisphere in contrast to the strong left-lateralized activation patterns during writing using the dominant (right) hand.

Limitations of previous literature

Only two studies to date have investigated the neural underpinnings of writing in left-handers. Zaman, Wartolows, and Roberts (2002), studied the neural correlates of normal and mirror writing of the alphabet in changing from writing with the dominant to the non-dominant hand using fMRI. The results of this study indicated that in normal writing the left sensory-motor cortex and right cerebellum were activated for right-handed participants, but the right sensory-motor cortex and the left cerebellum were activated for left-handed participants, when they were writing with their dominant hand. In contrast, 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. Furthermore, a positron emission tomography (PET) study by Siebner et al. (2002), including right-handers, left-handers and converted left-handers (i.e., innately left-handed children who were forced to use their right hand for writing at school), showed that right-handers demonstrated typical (left) lateralization when writing with activation of parietal and premotor association areas. Converted left-handers demonstrated a more bilateral activation pattern, including the premotor, parietal and temporal cortex, while left-handers showed a strong right-hemispheric lateralization. Siebner et al. (2002) further found the graded increase in the activation of the right anterior supramarginal gyrus to be connected with the degree of left-handedness.

Investigating differences in the cerebral representation of writing between the two handedness groups is a worthwhile endeavor, as right- and left-handers have been consistently found to differ in the cerebral organization of other language functions, such as language production and comprehension, as described above. Moreover, left-handers constitute approximately 10% of the population (Perelle & Ehrman, 1994; Peters, Reimers, & Manning, 2006). Therefore, as argued by Willems et al. (2014), left-handedness is within the normal range of human diversity and it is important to account for this variation in all studied phenomena if we are to understand the functioning of the human brain.

While the relationship between handedness and the cerebral lateralization of language has been firmly established, the effect of gender on the lateralization of language processing is a source of controversy in the subject literature. Some studies have reported sex differences in the cerebral representation of language (e.g., Baxter et al., 2003; Clements et al., 2006; Grabowski, Damasio, Eichhorn, & Tranel, 2003; Jaeger et al., 1998; Kaiser, Kuenzli, Zappatore, & Nitsch, 2007; Kansaku, Yamaura, & Kitazawa, 2000; Rossell, Bullmore, Williams, & David, 2002; Shaywitz et al., 1995), typically showing that men demonstrate a stronger left-hemisphere lateralization for language, while women exhibit a more bilateral hemispheric activation when performing language tasks. However, a large body of studies provides evidence of no statistically significant difference between men and women with regards to the cerebral lateralization of language (Burman, Bitan, & Booth, 2008; Frost et al., 1999; Garn, Allen & Larsen, 2009; Gur et al., 2000; Haut & Barch, 2006; Plante, Schmithorst, Holland, & Byars, 2006; Springer et al., 1999). A meta-analysis by Sommer, Aleman, Bouma, and Kahn (2004), including 14 studies, yielded no significant difference in language lateralization between men and women. However, the studies included in the meta-analysis studied cerebral language lateralization using only oral language production or comprehension tasks. No study included a writing component. The question thus still remains as to whether sex differences in cerebral lateralization may be observed with other language tasks, such as writing. A robust sex difference exists in handedness, with left-handedness more common in males (Martin, Papadatou-Pastou, Jones, & Munafò, 2010; Papadatou-Pastou, Martin, Munafò, & Jones, 2008), thus, it could be the case that the sex difference in handedness also extends to writing and its neural correlates, as this is a highly complex manual skill, the most clear manifestation of handedness, and the most practised unimanual activity. Moreover, it could be that the effects of sex and handedness might be additive.

When it comes to the measurement of cerebral laterality for written language, the bulk of studies have employed fMRI. This technique provides excellent spatial resolution, but it is rather expensive for use in research studies with large sample sizes. An efficient and reliable alternative to fMRI for the study of functional cerebral lateralization is functional transcranial Doppler ultrasonography (fTCD; Bishop, Watt & Papadatou, 2009; Zvan, 2012). This is a non-invasive and inexpensive technique for the investigation of functional hemispheric differences that can be applied in individuals of all ages, in large cohorts and in longitudinal studies (Deppe, Ringelstein, & Knech, 2004), and it is also suitable for follow-up investigations of hemispheric involvement in language function (Knecht et al. 1998; Lohmann, Drager, Muller-Ehrenberg, Deppe, & Knecht, 2005). It has been shown that the results obtained with the use of fTCD are highly reproducible and have excellent correlations with those acquired using the intra-carotid amobarbital procedure and fMRI (Deppe et al., 2000; Deppe, Ringelstein & Knecht, 2004; Knecht et al., 1998; Schmidt et al., 1999; Somers et al., 2011; Rihs, Sturzenegger, Gutbrod, Schroth, & Mattle, 1999; Knake, et al., 2003). In addition, fTCD data are not affected by motor movements, which makes the method suitable for use in clinical and pediatric populations as well as for assessing language lateralization by employing tasks which require either oral speech production (Bishop et al., 2009) or writing, as in the case of the present study. To date, fTCD has been used successfully for the study of cerebral laterality for visuospatial memory (e.g., Whitehouse & Bishop, 2009); visuospatial attention (e.g., Rosch, Bishop, & Badcock, 2012); visual perception (e.g., Rey, Parkhutik, Temble, & AlcaAlc, 2011); and of course language, both in adult populations (e.g., Lust, Geuze, Groothuis, & Bouma, 2011. Stroobant, Buijs, & Vingerhoets, 2009) and amongst children (e.g., Bishop et al., 2009; Lohmann, Drager, Muller-Ehrenberg, Deppe, & Knecht, 2005; Stroobant, Van Boxstael, & Vingerhoets, 2011).

In most neuroimaging studies the writing hand is the criterion used to determine handedness. It has been shown, however, that the assessment of handedness by the writing hand gives a mismatch with hand preference measures of 0.4% for right-handers, but a 13.5% mismatch for left-handers (Papadatou-Pastou, Martin, & Munafò, 2013). Moreover, suggestions have been made by large meta-analyses of handedness data that original papers on handedness should include data on both hand preference and hand skill measures (Ntolka & Papadatou-Pastou, 2017; Markou, Ahtam, & Papadatou-Pastou, 2017; Papadatou-Pastou & Sáfár, 2016; Papadatou-Pastou & Tomprou, 2015); the former assess which hand is preferred over the other for a number of everyday activities, whereas the latter measure the relative proficiency of the two hands in performing skilled activities. These two types of assessment are correlated, however imperfectly (0.6 to 0.7; Todor & Doane, 1977), possibly due to the difference in distributions between preference and skill measures (negatively skewed and normal, respectively).

Scope of the present study

The scope of the present study is the investigation of the cerebral lateralization of written language by means of fTCD in right- and left-handers of the two sexes. Apart from data on the writing hand, data on hand preference and hand skill were also collected. In addition to the well-established differences between right- and left-handers in cerebral language lateralization during the silent word generation task (e.g., Knecht et al., 2000), we expect to find a more pronounced pattern of left lateralization during writing for right-handers and an attenuated pattern for left-handers (e.g., Siebner et al., 2002). We make no predictions for possible sex differences, as previous studies do not provide a clear picture to base our predictions on (e.g., Sommer, Aleman, Bouma, & Kahn 2004).

MATERIALS AND METHOD

Participants

Sixty volunteers (30 males), undergraduate and graduate students at the National and Kapodistrian University of Athens, as well as members of the general population, enrolled in the study (*mean age* = 26.65 years, *SD* = 6.05, *range* =

20-44). Of the male participants, 14 were right-handed and 16 left-handed, while half of the female participants (15) were right-handed, according to their self-reported writing hand. The writing hand was used as a criterion, as it is the most commonly used criterion within the neuroimaging literature.

Prior to being enrolled in the study, all of the participants had undergone screening to make sure that they were monolingual, native speakers of Greek, with normal or corrected-to-normal vision, and that they had never been diagnosed with dyslexia or dysgraphia. None of them had been under any medication that could have affected the central nervous system during the six months prior to the study, nor did they display any neurological problems. Furthermore, the participants had never experienced a serious head injury and they did not suffer from any medical condition that could affect the mobility and normal functioning of their hands. No participant reported any current use of illicit drugs or other substance abuse. Twenty more potential participants were seen, but were excluded from the sample, because sonography was not possible due to inadequate ultrasonographic penetration of the skull by the ultrasound beam (14 cases) or the data were too noisy (6 cases).

Assessment of linguistic lateralization

Apparatus: Bilateral blood flow was measured using a commercially available Doppler ultrasonography device (DWL Multidop T2: manufacturer, DWL Elektronische Systeme, Singen, Germany), using two 2-MHz transducer probes mounted on a flexible headset at the left and right temporal windows of the head.

Word Generation task: The Word Generation task was a modification of the task used by Knecht et al. (1998). Participants were seated in front of a computer screen and two probes were attached to their heads by means of an elastic headband. Each trial included 35 s of rest, a cueing tone, a 5 s gap, then a letter or letter pair was presented on a screen for 2.5 s, followed by a 12.5 s generation period, a cueing tone, and a 5 s report period. The cueing tone was used to help focus attention on the upcoming task and to activate the attention of the dominant hemisphere. There were a total of 40 trials, divided into two conditions; 22 letters and 18 letter pairs were presented in random order and no letter or combination of two letters was displayed more than once.

To ensure that all letters / letter pairs used in the study would allow participants to easily produce words beginning with these letters / letter pairs, all 24 letters comprising the Greek alphabet together with 26 common two-letter combinations (see Appendix, Table 4) initiating Greek words were tested in a pilot procedure. Sixty-one adult volunteers, graduate students at the Department of Education, National and Kapodistrian University of Athens (3 males, *mean age* = 31.08, *SD* = 7.86, *range* = 22-47) were asked to write down as many words as possible in response to a 2.5 s presentation of a letter (or combination of two letters) within 12.5 s. The 40 letters / letter pairs that resulted in more words produced by the participants were included in the present study (*mean* = 4.2 words produced).

The language task included two different conditions. In the first condition, participants had to silently think of as many words as possible starting with the letter / letter pair shown on the screen. In the second condition, participants had to simultaneously think of as many words as possible and write them down. The number of the letters / letter pairs shown in each condition was 20. Every ten epochs, the condition changed. Thus, when the task started with the silent generation condition for the first ten words, it continued with the written generation condition for the following ten and so on. Conditions were counterbalanced across sex and handedness groups.

After a second auditory signal following 15 s after the presentation of the letter, the participants had to report the generated words. In this way cooperation to the task was controlled for the silent work generation condition (i.e., that participants were indeed using the 15-s period to generate pertinent words). This task requirement was kept similar for the writing condition, to avoid any confounding effects. All words (or as many as possible) had to be reported within a 5-s time period. The next letter / letter pair was presented in the same way after a relaxation period of 35 s.

Assessment of handedness

Annett Pegboard (AP): Relative hand skill was measured using the Annett pegboard task (AP; Annett, Annett, Hudson, & Turner, 1979). The AP consists of a 32 × 18 cm wooden piece of equipment of two rows with 10 holes drilled along each length. The distance between the two rows was 15 cm and each hole is approximately 1.2 cm in diameter. The task of the participants, who were standing in front of the pegboard, was to move all 10 pegs (7 cm in length and 1 cm in width) as quickly as possible, from the filled row to the empty row, first by using the right hand and then by using the left hand, beginning on the side of the pegboard ipsilateral to the hand being used to perform the task. The task was repeated three times by both hands. Participants were timed using a stopwatch. If a participant dropped a peg, the trial was repeated.

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

Edinburgh Handedness Inventory (EHI): In order to assess self-reported hand preference, the Greek version of the Edinburgh Handedness Inventory (Oldfield, 1971) was also administered. Participants were instructed to indicate which hand they prefer to use while performing several simple, everyday activities, such as writing, drawing, and using scissors. Except for the ten questions referring to hand preference, there were two more activities referring to foot and eye preference. Participants were instructed to imagine or recall which hand they use when they perform each activity before answering a question. For each item of the questionnaire they were asked to choose between five different statements: „always left," „usually left," „no preference," „usually right," „always right."

Scoring

Annett Pegboard (AP): The time needed to move all the pegs using each hand was measured from the time that the first peg was touched by the participant until the time the last one was released. A Laterality Index (LI) was calculated using the formula: *LI = [(RH-LH) / (RH+LH)]*100,* where RH = the mean time needed to move the pegs using the right hand and LH = the mean time needed to move the pegs using the left hand. Based on the results of this calculation, a negative score represents right-hand superiority, while a positive score represents left-hand superiority.

Quantification of Hand Preference Test (QHPT): The score was calculated by giving a value of 0 when the left hand was used to place the card into the box, 1 point in the case of changing hands, and 2 points when using the right hand. The points were then added up, divided by the maximum score (40) and multiplied by 100. The LI obtained reveals the direction of lateralisation and varies from 0% (extreme left-handedness) to 100% (extreme right-handedness). Individuals with scores below 50% were considered to be left-handed and individuals with scores above 50% were considered to be right-handed.

Edinburgh Handedness Inventory (EHI): The score was calculated by giving a value of 0 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 LI was computed by adding up the scores for all items, dividing it by the maximum score (40), and multiplying by 100. Thus, the LI ranged from 0 % (extreme left-handedness) to 100 % (extreme right-handedness). Individuals with scores below 50% were considered to be left-handed and individuals with scores above 50% were considered to be right-handed.

FTCD data collection and analysis

The right and left MCAs were insonated at the optimal depth for each participant (45-56 mm) with two transducer probes (2 MHz) attached to a flexible headband and placed at the temporal skull windows bilaterally. The angles of insonation were adjusted to obtain the maximal signal intensity.[1] The visual stimuli (letters) were presented on a computer controlled by Presentation software (Neurobehavioural Systems), 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 analysed using DopOSCCI (Badcock, Holt, Holden, & Bishop, 2012), a MATLAB-based software (available under the GNU GPL license and accessible online at https://databank.ora.ox.ac.uk/general/datasets/dopOSCCI, the Oxford University DataBank). Left and right channel blood flow velocity was down sampled to 25 Hz, normalised to a mean of 100%, and any variability due to heart beat was removed as described by Deppe et al. (1997b). The data were epoched from 18 s before to 36 s after the cueing tone. Epochs containing cerebral blood flow velocity (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 over 2 s surrounding the peak difference with the period of interest being 10-18 s after cueing. We calculated two LIs: LI_{silent} which represents the LI for the accepted epochs when silent word generation was performed and $LI_{writing}$, which represent the LI for the accepted epochs when written word generation was performed. If less than 10 epochs were accepted for either the silent or the written word generation conditions, then the participant was excluded from the sample.

Procedure

Participants were tested individually in a quiet room. The study was explained as soon as they arrived and they were encouraged to ask questions. They gave written consent before taking part in the study, but were explicitly told they remained free to leave at any time and without having to give any reason for doing so. Participants were asked to sit in front of a computer screen and were given the choice to watch the first few minutes of a movie while the probes were being placed in position. The Word Generation task followed. Right after this procedure was over, participants were asked to perform 2 tasks, the AP task and the QHPT. Lastly, they were provided with the Greek version of the EHI. All participants were debriefed after the completion of the study.

Methods of statistical analysis

Further analyses were performed using the Statistical Package for the Social Sciences (SPSS) v.23. In order to investigate the working hypotheses, a repeated measures analysis of variance (ANOVA) was performed with sex (male of female) and writing hand (right or left) as the between-participants factors, condition (written or silent word generation) as the within-participants factor, and the LIs for the silent and the written word generation as the dependent variables. The partial eta squared (η^2) statistic was used as the effect size measure. Post-hoc tests were run using pairwise comparisons with Bonferroni adjustment. Correlation was assessed using Spearman coefficients. All *p*-values were two-tailed and the *a*-level was set at .05.

RESULTS

Table 1 presents the descriptive statistics for all the sex and handedness groups for the behavioral tests and Table 2 presents the descriptive statistics for all the sex and handedness groups (according to writing hand) for the fTCD indices[1]. The descriptive statistics for all the other handedness classification are to be found in the Appendix (See Appendix Tables 5-7). 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_{silent}, and $LI_{writing}$) and the three behavioural measures of handedness (EHI score, Pegboard score, QHP score) (see Table 3). The $LI_{writing}$ was significantly correlated with all handedness measures, whereas the LI_{silent} was not correlated significantly with any of the measures. All correlations were in the direction of higher LI means (indicating typical cerebral left lateralization) with a higher degree of right-handedness.

In order to test for possible sex and handedness differences in the cerebral lateralization for language in the two conditions, as well as their possible interactions, a 2 x 2 x 2 repeated measures ANOVA was run with handedness ac-

Table 1. Descriptive statistics for the behavioural tests

Test	Sex	Handedness	N	Mean LI	SD	Range	Median
Edinburgh Handedness Inventory (EHI) 5-point	M	R	14	86.71	10.60	64 - 100	87.00
		L	16	39.12	14.77	20 - 68	39.00
	F	R	15	92.93	5.59	78 - 100	94.00
		L	15	36.00	15.16	20 - 70	34.00
Quantification of Hand Preference (QHPT)	M	R	14	58.84	20.68	14.29 - 100	54.76
		L	16	41.67	15.98	0 - 61.90	47.62
	F	R	15	76.83	21.59	42.86 - 100.00	71.43
		L	15	50.32	14.81	4.76 - 66.67	57.14
Annett Pegboard (AP)	M	R	14	-0.050	0.025	(-0.079) - (-0.009)	-0.057
		L	16	0.022	0.072	(-0.077) - 0.213	0.002
	F	R	15	-0.042	0.043	(-0.127) - 0.026	-0.037
		L	15	0.027	0.034	(-0.050) - 0.076	0.031

Table 2. Descriptive statistics for the functional transcranial Doppler sonography (fTCD). Handedness groups according to the writing hand

Test	Sex	Handedness	N	Mean number of epochs	Mean LI	SD	Range	Median
Laterality Index for Silent Word Generation	M	R	14	16.64	3.079	2.15	(-1.49) – 6.70	2.755
		L	16	17.88	2.079	3.534	(-8.01) – 6.90	3.125
	F	R	15	17.33	3.115	2.544	(-3.87) – 7.49	3.33
		L	15	17.87	2.262	3.145	(-3.99) – 6.74	2.240
Laterality Index for Written Word Generation	M	R	14	15.21	4.644	2.843	(-1.00) – 9.43	3.885
		L	16	17.85	-2.614	3.771	(-9.77) – 4.00	-2.965
	F	R	15	16.87	4.833	3.539	(-3.45) – 11.43	5.120
		L	15	17.07	-2.405	3.941	(-7.09) – 3.95	-3.660

[1] The fTCD measurement of the CBFV is dependent on the angle of insonation (Bartels & Flugel, 1994). Changes in this angle from 0° to 30° can result in differences in the calculated, absolute CBFV to the magnitude of 15% between examinations or sides. Also, in a narrowed arterial segment incidentally insonated during the test, the absolute velocity increase in blood flow due to cerebral activation would be greater than in a regular segment. This is why the flow velocities used for statistical analyses were normalised. Flow velocities at rest were set as zero baseline and CBFV changes during the activated state were expressed as values in percentages relative to this baseline. The use of relative CBFV values eliminated the variability associated with changes in the insonation angle or vessel diameter.

Table 3. Non-parametric correlations

Test	1	2	3	4	5
1. Silent Word Production task	-	0.419**	0.095	-0.020	0.161
2. Writing Word Production task	-	-	0.643**	-0.403**	0.424**
3. Edinburgh Handedness Inventory (EHI)	-	-	-	0.620**	0.560**
4. Annett Pegboard (AP)	-	-	-	-	0.419**
5. Quantification of Hand Preference Test (QHPT)	-	-	-	-	-

**. Correlation is significant at the 0.01 level (2-tailed)

cording to writing hand (right or left) and sex (male or female) as the between- participants factors, and condition (written or silent word generation) as the within-participants factor. The LI_{silent}, and the $LI_{writing}$ were the dependent variables.

There was a significant main effect of condition, $F(1, 56) = 14.67$, $p < .001$, $\eta^2 = .21$. The mean LI_{silent} was significantly higher (M= 2.63, SE= .38) in comparison with the mean $LI_{writing}$ (M= 1.11, SE= .46), which shows a more pronounced left-hemisphere (typical) cerebral laterality during silent word generation when compared to written word generation. Moreover, there was a significant main effect of handedness according to writing hand $F(1, 56) = 30.31$, $p < .001$, $\eta^2 = .35$, with right-handers producing a much higher LI Mean (M= 3.92, SE= .53) than

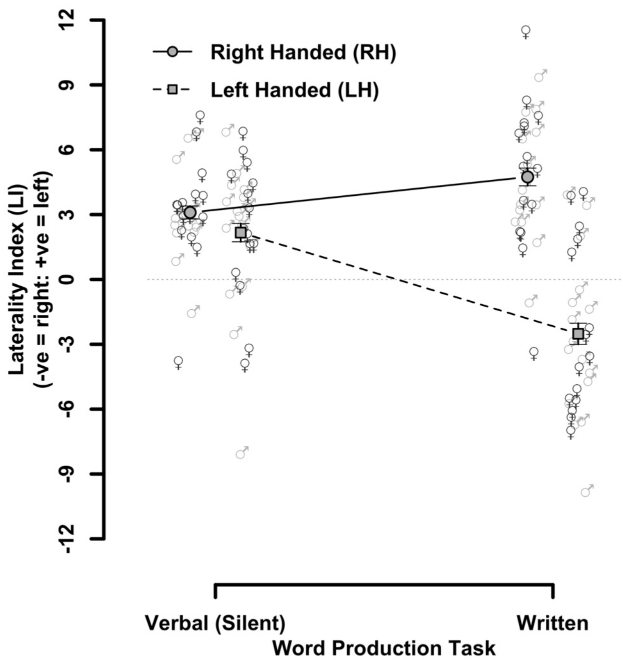

Fig. 1. Interaction between condition and handedness according to writing hand. Laterality indices (LIs) for the Word Production Task (Verbal vs. Written) for each handedness group (Right and Left denoted by circles with a solid line and squares with a broken line respectively). All individual data points (grey) and group means (black) are presented with the standard error of the mean

the left-handers (*M*= -0.17, *SE*= 0.52), showing a more pronounced left-hemispheric dominance for right-handers compared to left-handers. No significant main effect of sex was found, $F(1, 56) = .04$. $p = .84$. $\eta^2 < .01$.

The results revealed a significant interaction between condition and handedness according to writing hand, $F(1, 56) = 63.52$, $p < .001$, $\eta^2 = .53$ (see Fig. 1). For right-handers, an increase of the mean $LI_{writing}$ was observed (*M*= 4.74, *SE*= .66), in comparison with the mean LI_{silent} (*M*= 3.10, *SE*= .54). Whereas, for left–handers, there was a decrease of the mean $LI_{writing}$ (*M*= -2.51, *SE*= .64), as compared to the mean LI_{silent} (*M*= 2.17, *SE*= .52). No other interactions were found, $F(1, 56) = .01$, $p = .91$, $\eta^2 < .01$ for the interaction between condition and sex; $F(1, 56) = .01$, $p = .94$, $\eta^2 < .01$ for the interaction between condition, sex and handedness according to writing hand.

In order to investigate this finding further, we calculated the absolute difference between LI_{silent}, and $LI_{writing}$ for each participant ($LI_{difference} = | LI_{silent}, – LI_{writing} |$). We then performed an independent samples *t*-test with handedness as the group factor and found that the $LI_{difference}$ is significantly lower in right-handers compared to left-handers, $t(58) = -4.42$, $p < .001$ (mean $LI_{difference}$ = 2.51 for right-handers; mean $LI_{difference}$ = 5.10 for right-handers).

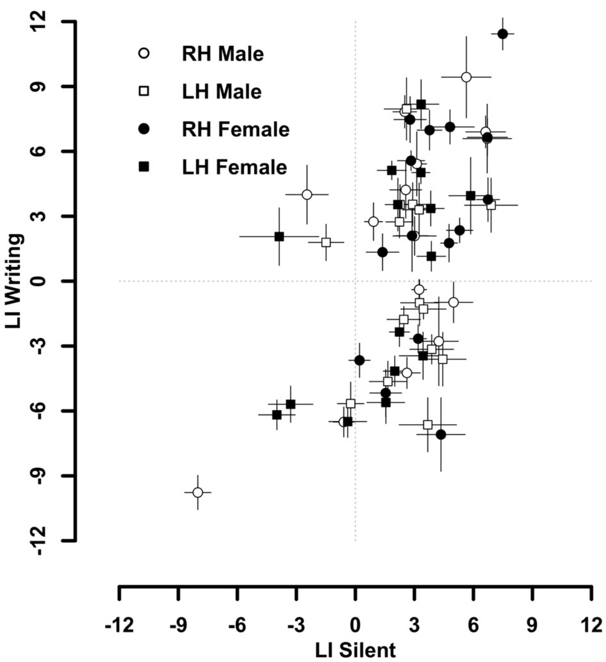

Fig. 2. Scatter plot of laterality indices (LIs) for the Word Production Task (Silent) and Word Production Task (Written). All individual data points are presented with the standard error of the mean

Fig. 2 summarizes the data by depicting the LI_{silent} on the x axis and the $LI_{writing}$ on the y axis. The majority of the participants (*n* = 32, 53.3%; 11 left-handers), showed a positive (i.e., left-lateralized) LI for both the written and silent word generation (top right quadrant). Six participants (8.3%; 4 left-handers) showed the reversed pattern with a negative (i.e., right-lateralized) LI for both the written and silent word generation (bottom left quadrant). Only 3 participants showed a positive LI for written word generation, but a negative one for the silent word generation (5%; 2 left-handers; top left quadrant), while 19 participants (31.6%; 11 left-handers; bottom right quadrant) showed a positive LI for silent word generation and a negative one for written word generation. Out of the 22 left-handers that showed left-lateralization for the silent word generation task, half of them showed right-lateralization for the written word generation task. For right-handers, out of the 29 that were left-lateralized for the silent word generation task, only 8 (27.5%) were right-lateralized for the written word generation task.

The analysis was repeated using all the handedness assessments (AP, QHPT, EHI). The results are presented in the Appendix (see Appendix, Table 8) and are in the same direction as the ones that were obtained when handedness was assessed using the writing hand.

DISCUSSION

In this study we investigated cerebral language lateralization during written word generation as compared to silent word generation, by means of fTCD in a sample of 60 healthy participants, balanced for sex and handedness. Our study provides the first evidence on the hemispheric dominance of left-handers during written word generation, with the use of fTCD. We observed a significantly more pronounced overall left-hemispheric (typical) dominance in right-handers compared to left-handers, as had been expected. Moreover, a more pronounced left-hemispheric dominance was observed during the silent word generation compared to the written word generation, over the whole sample. Importantly, a significant interaction between condition and handedness was found, with right-handers increasing the degree of left-hemispheric lateralization and left-handers presenting a more attenuated left-hemispheric lateralization during writing compared to the silent word generation. No main effect of sex or interaction with sex was found. The results were equivalent, regardless of whether the participants were grouped as right- or left-handers using writing hand, hand preference, or performance measures as the criterion.

Left-hemispheric dominance was demonstrated by right-handers during silent word generation in line with previous works (Pujol et al., 1999; Vikingstad, George, Johnson, & Cao, 2000; Khedr, Hamed, Said, & Basahi, 2002; Szaflarski et al., 2002; Koeda et al., 2006). Left-handers also exhibited left-hemispheric dominance, which, however, was much weaker than that observed in right-handers. This finding of the lower degree of left dominance during silent word generation for left-handers, further replicates the results of previous studies (Pujol et al., 1999; Knecht et al., 2000).

With regards to written word generation, it was observed that, for right-handers, the intensity of left-hemispheric dominance was stronger during written word generation compared to silent word generation. Left-handers presented a more pronounced atypical dominance when performing the written word generation task compared to the silent word generation task. This interaction between handedness and language generation (silent or written) can be explained by the fact that the motor areas of the left hemisphere control the movements of the right hand, while the corresponding regions of the right hemisphere control the movements of the left hand (Porac, Coren, & Duncan, 1980; Gilbert, & Wysocki, 1992). As a result, writing with the right hand would reinforce the intensity of blood flow in the left hemisphere, while, in contrast, writing with the left hand would reinforce the intensity of blood flow in the right hemisphere. Another possible explanation could be based on the fact that writing may provoke the activation of wider language regions of the brain in left- compared to right-handers, including the right-hemisphere.

The present design does not allow for the two competing hypotheses to be fully disentangled. However, it was shown that the difference in the LIs between silent and written word generation was statistically significantly higher in left-handers compared to right-handers. Therefore, this difference cannot be explained solely by a motor component. Had it been the case, then this difference would not have been statistically significant between the two handedness groups, as the motor component was added to both right- and left-handers. Moreover, previous findings support the suggestion of a wider right-hemispheric language network for left-handers. For example, Siebner et al. (2002) found that left-handers show a more bilateral activation compared to right-handers when performing the same writing task. Left-handers showed activation in the right lateral premotor, parietal, and temporal cortex, while right-handers in the left parietal and premotor areas (without the temporal component). Moreover, Siebner et al. (2002) showed a graded increase in functional activation in the right anterior supramarginal gyrus with the degree of left-handedness. They suggest that these findings might be attributed to a motor preparation before actual handwriting, with left-handers possibly having more difficulty with task initiation and hence showing greater effort related to movement preparation. They base this claim on studies in right-handers that suggest that the left inferior parietal lobule plays a central role in movement preparation and selection (Deiber et al., 1996; Krams et al., 1998; Schluter et al., 2001) as well as in studies showing that normal covert motor preparation can be impaired after lesions to the left supramarginal gyrus (Rushworth et al., 1997). Other research has shown that right-handers preferentially activate the left ventral LPC during cycling movements, while left-handers preferentially activate the right ventral LPC, irrespective of the hand used in both groups (Vivani et al., 1998). This is another one-sided activation that is differential in the two handedness groups and is irrespective of the actual motor movement (as it is irrespective of the hand used). In our study, continuous measures of handedness (namely the EHI, the AP task, and the QHPT) were correlated with cerebral laterality during written word generation, but not silent word generation. Specifically, it was shown that the more left-handed a participant was, the more they activated the right hemisphere during written word generation.

Future studies comparing written word generation with writing that does not include language (e.g., the repeated drawing of symbols) will be nevertheless valuable in moving us towards a more clear differentiation between these two possible explanations, the motor explanation and the wider language network explanation. However, an important first step in understanding cerebral laterality during written word generation was made by the present study, importantly showing that it is feasible to study cerebral lateralization during writing using the fTCD.

Another aim of our study was to investigate the presence of a possible sex difference in written language lateralization. No significant effect of sex was found for language lateralization overall, but also no interaction of sex with the two conditions (silent and written word generation), which adds to the previous evidence supporting that language functions are lateralized to the left hemisphere for both men and women (Burman, Bitan, & Booth, 2008; Frost et al., 1999; Garn, Allen, & Larsen, 2009; Gur et al., 2000; Haut & Barch, 2006; Plante, Schmithorst, Holland, & Byars, 2006; Springer et al., 1999). This finding suggests that possible detectable differences in language skills between the two sexes cannot be attributed, entirely, on differences in the laterality of cerebral function. Other factors, such as neuronal and anatomical differences at a microscopic level (Frost et al., 1999) or the existence of intrahemispheric differences in the cortical organization of language between males and females (Kimura, 1983) should be considered as well.

The main limitation of the present study is that functional transcranial Doppler ultrasonography (fTCD), in contrast to the fMRI, does not enable us to identify the specific areas of the brain that are activated during the tasks (see also Pachalska, MacQueen & Brown 2012). In addition, fTCD operates by acoustically penetrating the temporal bone. In our study this was not always attainable, as 14 participants lacked a "window." Possibly, a similar study using fMRI technology would clarify and enhance the results of our study.

CONCLUSIONS

This is the first study to investigate cerebral laterality for written language using fTCD. Furthermore, this was the first time that sex differences for the cerebral lateralization of writing were studied. Our findings suggest that there is a robust difference in the hemispheric lateralization for writing between right- and left-handers. Importantly, the difference between silent and written word generation was significantly higher in left- compared to right-handers, suggesting that this difference could be attributed, not merely to the added motor component, but also possibly to a wider network of right-hemispheric language areas used during writing in left-handers. Furthermore, our study provides evidence against the idea that language lateralization differs between men and women, not only for oral language, but also written language. Finally, the present study assessed the handedness of participants using three different measurements, in line with recent suggestions.

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APPENDIX:

Table 4. Letter and letter pairs used in the pilot study and the mean number of words generated. The 40 letters/letter pairs with a mean of 3.46 or higher were included as stimuli in the present study (n = 61 participants)

Letter / Letter Pair	Mean number of words generated	Standard deviation
ΣΕ	2.67	.995
Ω	2.80	1.123
ΓΚ	2.82	1.041
ΔΥ	2.95	1.132
ΤΖ	3.15	.963
ΤΟ	3.16	1.186
Ι	3.20	1.062
Υ	3.34	1.196
ΟΥ	3.38	1.067
ΤΣ	3.38	1.143
ΝΕ	3.46	1.042
ΝΤ	3.46	1.089
ΔΑ	3.48	.976
ΛΕ	3.49	1.233
ΣΥ	3.49	1.074
ΔΙ	3.57	1.335
ΛΑ	3.59	1.023
ΘΑ	3.61	.954
Η	3.69	1.057
ΤΑ	3.74	1.210
ΜΕ	3.77	1.007
ΜΠ	3.84	.860
Ο	3.90	1.121
ΜΑ	3.93	.981
ΚΟΥ	3.98	.866
ΠΕ	3.98	1.008
ΑΥ	4.07	.998
ΚΑ	4.13	.974
ΚΟ	4.26	1.063
Δ	4.28	1.067
Λ	4.31	1.218
ΠΑ	4.31	.992
ΓΕ	4.33	1.028
Σ	4.36	1.225
Ν	4.38	1.143
Ε	4.41	1.257
Τ	4.48	.942
Μ	4.52	1.246
Ξ	4.52	.849
Θ	4.61	1.021
Ζ	4.64	1.252
Φ	4.69	1.119
Α	4.70	1.174
Χ	4.70	1.070
Γ	4.70	1.022
Ψ	4.74	1.015
Ρ	4.74	1.237
Π	4.82	1.176
Β	4.82	1.148
Κ	5.61	1.215

Table 5. Descriptive statistics for the functional transcranial Doppler sonography (fTCD). Handedness groups according to the Edinburgh Handedness Inventory (individuals with scores 0-49 were classified as left-handed and individuals with scores 50-100 were classified as right-handed)

Test	Sex	Handedness	N	Mean number of epochs	Mean LI	SD	Range	Median
Laterality Index for Silent Word Generation	M	R	19	16.78	3.30	2.06	8.39	2.91
		L	11	18.18	1.24	3.86	13.00	3.01
	F	R	17	17.47	3.09	2.40	11.36	3.33
		L	13	17.77	2.16	3.36	10.73	2.24
Laterality Index for Written Word Generation	M	R	19	15.68	3.08	3.89	13.67	3.51
		L	11	17.64	-3.21	-3.21	13.77	-3.15
	F	R	17	16.82	4.09	4.03	15.59	5.02
		L	13	17.15	-2.54	4.09	11.04	-3.66

Table 6. Descriptive statistics for the functional transcranial Doppler sonography (fTCD). Handedness groups according to the Quantification of Hand Preference Test (individuals with scores 0%-49% were classified as left-handed and individuals with scores 50%-100% were classified as right-handed)

Test	Sex	Handedness	N	Mean number of epochs	Mean LI	SD	Range	Median
Laterality Index for Silent Word Generation	M	R	17	16.88	3.44	1.88	7.29	3.12
		L	13	17.85	1.38	3.73	14.91	2.46
	F	R	23	18.13	2.67	3.07	11.48	3.33
		L	7	15.86	2.74	2.13	6.25	2.83
Laterality Index for Written Word Generation	M	R	17	15.76	2.65	4.58	15.94	3.54
		L	13	17.23	-1.68	4.46	13.77	-1.77
	F	R	23	17.04	1.66	5.39	18.52	2.35
		L	7	16.71	-0.24	4.60	12.06	1.34

Table 7. Descriptive statistics for the functional transcranial Doppler sonography (fTCD). Handedness groups according to the Peg-Moving Task (individuals with positive scores were classified as left-handed while individuals with negative scores were classified as right-handed)

Test	Sex	Handedness	N	Mean number of epochs	Mean LI	SD	Range	Median
Laterality Index for Silent Word Generation	M	R	22	17.27	3.13	1.93	8.19	3.07
		L	8	17.38	0.93	4.59	14.91	2.14
	F	R	14	16.92	3.01	2.47	10.58	3.34
		L	16	18.19	2.41	3.19	11.48	2.53
Laterality Index for Written Word Generation	M	R	22	16.09	2.06	4.47	16.07	2.74
		L	8	17.25	-2.76	4.72	13.77	-3.70
	F	R	14	16.07	3.69	3.85	12.34	4.48
		L	16	17.75	-0.96	5.36	18.52	-2.50

Table 8. Results for 2x2x2 repeated measures ANOVAs with handedness (right or left) and sex (male or female) as the between subjects factors and condition (written or silent word generation) as the within subjects factor. Laterality indices (LIs) were the dependent variable

	Df	*F*	η^2	*p*
Handedness according to the Edinburgh Handedness Inventory				
Condition	1, 56	18.48	0.25	<0.01
Sex	1, 56	0.59	0.01	0.45
Handedness	1, 56	26.20	0.323	<0.01
condition*sex	1, 56	0.24	<0.01	0.62
condition*handedness	1, 56	25.90	0.32	<0.01
sex* handedness	1, 56	0.07	<0.01	0.80
condition * sex * handedness	1, 56	0.57	0.01	0.45
Handedness according to Annett's Pegboard task				
Condition	1, 56	10.60	0.16	0.02
sex	1, 56	1.80	0.03	0.19
handedness	1, 56	11.78	0.17	<0.01
condition*sex	1, 56	0.83	0.02	0.37
condition*handedness	1, 56	8.51	0.13	<0.01
sex* handedness	1, 56	0.24	<0.01	0.62
condition * sex * handedness	1, 56	0.40	0.01	0.53
Handedness according to the Quantification of Hand Preference test				
condition	1, 56	10.03	0.15	<0.01
sex	1, 56	0.07	<0.01	0.79
handedness	1, 56	4.64	0.08	0.04
condition*sex	1, 56	<0.01	<0.01	0.95
condition*handedness	1, 56	2.92	0.05	0.09
sex* handedness	1, 56	1.42	0.03	0.24
condition * sex * handedness	1	0.02	<0.01	0.90

Note: All *p*-values are two-tailed and the *a* = .05