Journal of Integrative Neuroscience

J. Integr. Neurosci. **2022**; 21(2): 064
https://doi.org/10.31083/j.jin2102064

Case Report

Reproducibility of hemispheric lateralization over several days using functional transcranial Doppler sonography (fTCD): a pilot single-case study of word fluency

Florian Heimann[1,*], Sabine Weiss[1,2,3], Horst M. Müller[1,3]

[1]Experimental Neurolinguistics Group, Department of Linguistics, Bielefeld University, 33615 Bielefeld, Germany
[2]Clinical Linguistics, Department of Linguistics, Bielefeld University, 33615 Bielefeld, Germany
[3]Center for Cognitive Interaction Technology (CITEC), Bielefeld University, 33615 Bielefeld, Germany
*Correspondence: florian.heimann@uni-bielefeld.de (Florian Heimann)
Academic Editor: Michael J. Spivey
Submitted: 13 February 2021 Revised: 4 March 2021 Accepted: 30 April 2021 Published: 23 March 2022

Abstract

Functional transcranial Doppler sonography (fTCD) is a time- and cost-effective, non-invasive approach to determining real time hemispheric lateralization and is well-suited for repetitive study designs comprising multiple days. To date, no study has examined the reproducibility of the direction and degree (strength) of lateralization during word fluency (WF) over multiple, consecutive sessions within a single person, although there are many studies of lateralization during language processing. Moreover, there is conflicting evidence as to whether there is a relationship between the degree of laterality and the word fluency performance. In this study, one right-handed male (aged 24 years) completed a total of seven examination sessions in the time span of 10 days. Each session comprised multiple phonological and semantic WF tasks. The maximum difference of relative cerebral blood flow velocity (CBFV) changes between the left and right middle cerebral artery (MCA) during WF was defined as the Lateralization Index (LI). The word-fluency performance and the LIs were used in a linear regression model to detect relative changes in the direction and degree of lateralization during repetitive WF tasks. The reproducibility of the direction of language-related lateralization is very stable over multiple sessions within this single person and the processed LIs were left-lateralized in every session for both WF tasks. In addition, performance during phonological WF could significantly predict the variability in the degree of lateralization. This result could not be confirmed for the semantic WF task. The results of this pilot study support the usage of fTCD as a reliable method for examining lateralization patterns, especially in longitudinal study designs. They also provide evidence for the notion that performance in WF tasks can be related to the degree of lateralization, at least intra-individually.

Keywords: Functional transcranial Doppler sonography; Language lateralization; Cerebral blood flow; Repetitive measures

1. Introduction

Most of the higher cognitive functions such as language processing and production are lateralized to one of the two hemispheres. To visualize these asymmetries, different neurophysiological methods and imaging techniques such as electroencephalography (EEG) or functional magnetic resonance imaging (fMRI) can be used [1–4]. Since many of these examination methods require high effort and expenses, more easy-to-apply, non-invasive and cost-effective real time methods as the functional transcranial Doppler sonography (fTCD) have emerged. fTCD shows high correlations with lateralization patterns measured by fMRI [5–8] or the Wada-Test [9] and is well suited for larger samples or study designs with multiple sessions [10]. It is currently applied in the examination of lateralization patterns in children [11–13] and adults [14–17]. Additionally, it is applied in examining other cognitive functions, i.e., arithmetic [18] or spatial skills [19,20]. Besides healthy subjects, it is used as a non-invasive diagnostic approach in clinical populations, i.e., children born deaf or with brain damage of different etiology [21,22] as well as patients with epilepsy [23] or Parkinson's Disease [24]. Furthermore, it is also an alternative for use in populations where fMRI examinations are impossible due to technical or medical reasons, such as metal implants, movement artifacts or, i.e., anxiety disorders. Since the mobile application of the fTCD allows for free head movement and speaking, it provides even more value in very young or uncooperative patients [25].

In fTCD, two ultrasound probes positioned on both temporal bones (Os temporale) simultaneously monitor the event-related changes in cerebral blood flow velocities (CBFV) in both middle cerebral arteries (MCA, Fig. 1). There is a high reproducibility of blood flow-velocity values in healthy individuals and patients with carotid artery stenosis for within-day as well as between-day measures [26], making it a reliable diagnostic tool. In general, fTCD can be used for detecting blood flow anomalies in cardiovascular diagnostics [27], but can also detect lateralization patterns during specific cognitive tasks [12]. According to Deppe *et al.* [5], velocities can be calculated via the for-

Copyright: © 2022 The Author(s). Published by IMR Press.
This is an open access article under the CC BY 4.0 license.

Publisher's Note: IMR Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Fig. 1. Application of the ultrasound probes during fTCD. Shown is the left ultrasound probe (A), which is connected to the TCD device.

mula:

$$dV(t) = 100\frac{V(t) - V_{pre.mean}}{V_{pre.mean}}$$

where V(t) is the CBFV over time and $V_{pre.mean}$ is the 5-second interval prior to the cueing tone and the following item presentation. A Lateralization Index (LI) can then be processed to indicate which of the two hemispheres works more dominantly, as its perfusion is closely coupled to metabolic mechanisms in the brain cells. The LI can be calculated via the formula:

$$LI_{fTCD} = \frac{1}{t_{int}} \int_{t_{\max}-0,5_{int}}^{t_{\max}+0,5_{int}} \Delta V(t)dt$$

where

$$V(t) = dV(t)left - dV(t)right$$

is the difference between the relative velocity changes of the left and right MCA. The time point t_{max} represents the latency of the absolute maximum of $\Delta V(t)$ within the word generation interval, t_{int} is the integration interval (2 seconds) which is also described as activation window. A positive LI indicates left and a negative right hemisphere dominance for language processing and the degree of lateralization is described by the magnitude of LI values. Comparing the direction and degree (often referred to as strength) of lateralization of language functions, this method shows high correlations with results from the Wada Test [28] and fMRI examinations [5,21]. Although fMRI is far superior in terms of spatial resolution, both temporal resolution and event-related changes in blood flow velocities are well pictured in the fTCD.

When determining which language tasks are suitable for reliable fTCD results, research suggests that expressive language functions, i.e., word and sentence production, are generally stronger lateralized than their receptive counterparts, i.e., auditive discrimination/identification [29–31]. In language production, fTCD and fMRI studies reveal that lexical-semantic tasks show a stronger degree of lateralization than syntactic ones [2,32,33]. An often-used paradigm delivering reproducible patterns in Lateralization Indices comprises phonological and semantic word fluency tasks [14,34]. In a phonological WF task, the participant is asked to find as many words beginning with a presented letter within a specific time span. In the semantic WF task, a semantic category is presented and the participants have to find as many words as possible matching the respective category. Both can be performed in a covert setting, which is currently the gold standard, in which a silent word-finding phase is followed by an overt reporting phase [35], and in an overt setting with immediate, open word production. The direction and degree of lateralization do not differ between these two conditions [36]. Unsworth *et al.* [37] attempted to model the cognitive processes underlying both WF tasks and described working memory capacity and vocabulary size as predictors of subsequent WF performance. Concerning the cerebral blood flow pattern as a neurophysiological correlate for these different underlying processes, recent findings by Gourovitch *et al.* [38] which used WF tasks during PET indicated that phonological WF led to increased levels of CBFV in the inferior frontal and temporoparietal cortices. Semantic WF was associated with increased CBFV in the left temporal cortex when the two WF tasks were compared directly. The anterior cingulate cortex, the left prefrontal regions, the thalamus, and the cerebellum showed comparatively increased CBFV values in both tasks.

Still, study designs with both WF tasks and repetitive follow-up measurements are rare. Knecht *et al.* [10] found a high test-retest reliability in healthy individuals for hour up to 14 months after the initial examination (r = 0.95; p = 0.0001) for the direction and degree of the LI during a phonological WF task. Additionally, Stroobant *et al.* [39] described a significant test-retest reliability (r = 0.61 to 0.83) for lateralization patterns of multiple tasks. This allows for reliably detecting shifts in task-related hemispheric perfusion exceeding 1% of the mean CBFV making them a valid source for longitudinal study designs. However, both studies only provided one follow-up measurement at different intervals relative to the first examination for each participant, lacking comparability and leaving open how changes in WF performance would alter the degree of the LI in a more continuous study design. Similarly, Woodhead *et al.* [17] also found a high stability of mean LI values over different language tasks, but again only used two measuring points. In addition, there was a lack of information on whether performance during these tasks affected the degree of language lateralization. In an approach to studying this effect, other authors found no correlation between the performance in covert WF tasks and the degree of lateralization measured by the LI in healthy adults [32,40,41], but found a positive correlation between the number of words produced during phonological WF in an overt condition [36]. However, they did not use follow-up measurements to evaluate the stability of their findings. Other authors tried to examine the correlation between task difficulty and the degree of language lateralization for several different language tasks, but found contradicting results ranging from the correlation of the LI values across several language functions [22,29,42] to significant differences across different language tasks [30,43]. Lohmann *et al.* [44] performed a study with ten sessions of parallel fMRI and fTCD and found no trend in the lateralization pattern with a consistent LI during fTCD, but a decreasing degree of language lateralization over the sessions during fMRI.

Complementing the aforementioned findings, the current pilot study investigates (1) the reproducibility of the direction and degree of LI measurements over seven consecutive examinations in a single person using fTCD. (2) WF performance is assessed in both a phonological and a semantic WF task with multiple items per session to assess the impact of changes in WF performance on the direction and degree of language lateralization. Therefore, we need to test the following hypotheses: (1) at each of the seven sessions (over a short period of time) a consistent direction of lateralization of the measured LI should be found. (2) WF performance is positively correlated with the degree of the LI.

2. Materials and methods

2.1 Participant

A male student of Bielefeld University, a native German speaker, 24 years of age and right-handed with a lateralization quotient of 80 according to the Edinburgh Handedness Inventory [45] took part in the experiment. The participant had corrected-to-normal vision and did not chronically take any medication in the last seven days before the experiment. He was paid for his participation. This study was approved by the ethics committee of Bielefeld University (ethics approval No. 2021-028). Written consent regarding data collection and publication was obtained from the participant.

2.2 Stimuli

Five items for phonological and five items for the semantic word fluency task were selected as experimental stimuli. For the phonological WF task, the five items were the letters A, K, H, B and S. These are the five most frequent German initial letters (defined by total amount of words beginning with the aforementioned letters) according to the Wahrig-Brockhaus Lexikon of German Language [46]. For the semantic word fluency task, we used the five categories *furniture*, *drinks*, *animals*, *electronic gadgets* and *diseases*. They were chosen from a collection of semantic categories frequently used in German aphasia therapy or in children with semantic impairment (Memogym: Prolog). All semantic categories had to fit the criterion that a possible member of one category could not be assigned to any of the other categories. The stimuli were arranged and presented in Cogent2000, a MATLAB-based toolbox, which was installed on a PC (Windows XP). Before the presentation of each item, electric trigger signals were sent from the PC (Windows XP) to the fTCD-Computer (MultiDop T2, DWL, Singen, Germany) via a customized cable connecting the PC's DB-25 parallel port to the fTCD-Computer's Av-in-port to mark the beginning of each trial. The latter then recorded lateralization patterns extracted from the participants blood flow patterns in the left and right MCA.

2.3 Procedure

The study consisted of seven examination sessions each lasting 30 minutes (15 minutes of probe positioning and 15 minutes of WF) over a ten-day period with never more than one day of rest between sessions. A schematic representation of the procedure is shown in Fig. 2, upper part. The participant was seated in front of a computer monitor at a distance of 50 cm between the participant's eyes and the screen with no other applications on the table in front of him or on the plain wall behind the screen. The letters and semantic categories for both WF tasks were visually presented in a light grey serif-free font (Helvetica size 40) on a black background on a 15" LCD Monitor. The visual angle between the participants' eyes and the center of the monitor, on which the WF items were presented was 1.15°. Before the trial was started, we conducted one exemplary phonological and semantic trial to ensure the participant understood the task. The items used in these exemplary trials were other letters/semantic categories than in the main trial. Additionally, all items were presented in randomized order and the WF task (phonological vs. semantic) was counterbalanced in every session. There was a total of 5 trials per task per session, each lasting one minute. The WF paradigm was performed in an overt setting, since recent evidence suggests that the overt WF leads to LI values comparable to the covert WF, which has long been considered the gold standard [36]. Moreover, the overt setting is much more widespread as a criterion for WF performance (in the German-speaking countries) in healthy populations as well as patients with speech and language disorders of different etiology. Each trial started with a 30 s resting period. The item presentation (t0) was then followed by a WF period of 30 s. Before each item presentation there was a 10 s baseline interval ranging from –15 to –5 s relative to the item presentation for subsequent analysis (Fig. 2, baseline (BL)).

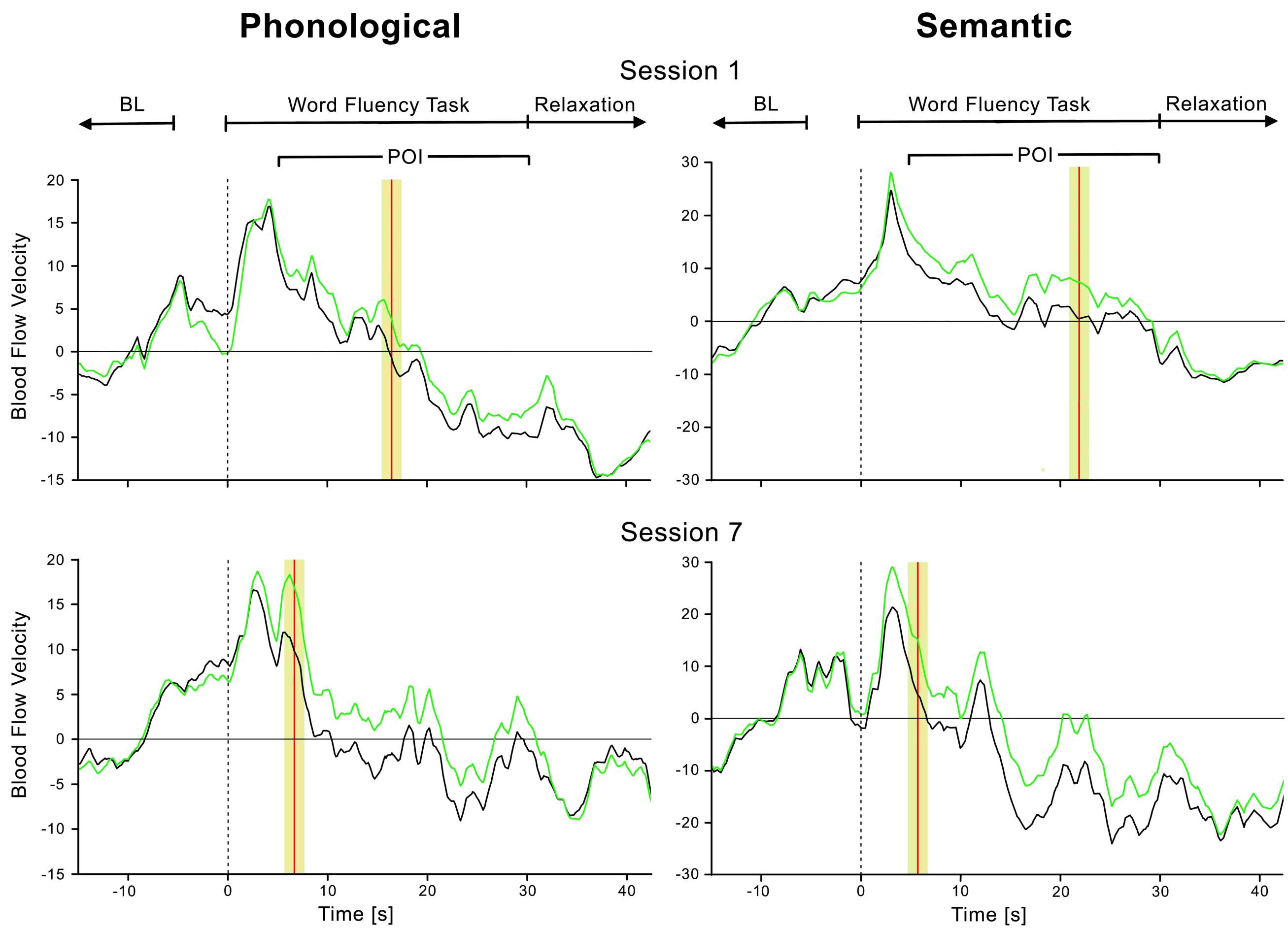

Fig. 2. Mean blood flow velocities of the left (green) and right (black) middle cerebral arteries (MCA) during the phonological and semantic WF task of the first and seventh (last) session. The velocity values were normalized and averaged over all five consecutive WF trials. The item presentation and overt word production start at 0 s and last up to 30 s (x-axes). To account for the process of neuro-metabolic coupling, the period of interest (POI) begins 5 s after the item presentation. After a subsequent relaxation phase of 30 s, the next item is presented. The vertical red line indicates the largest difference between the CBFV values of both MCAs and the highlighted 2 s interval around this time point is the activation window, where the LI is calculated. A 10 s (from –15 to –5 s) interval before each item presentation is used as the baseline (BL) for rCBFV values.

For the fTCD measurement, the 2 MHz ultrasound probes on the mobile device were adjusted at an insonation depth of 52 mm in order to measure the CBFV in the M1 segments of both MCAs. Moreover, the detection sensitivity was set to 38%, standard Volume = 12, Output = 420 and Filter = 150 in the DWL Multidop QL Software Routine Version 2.5 (Singen, Germany).

Recorded fTCD data was analyzed using dopStep Master, which evolved from dopOSCCI, a Matlab (Mathworks, Natick, MA, USA) based software package [47]. Its programming is based on the software package AVERAGE [48] and can be used with various TCD devices and allows for subtle quantitative off-line analysis of Doppler flow signals. First, the channels for the left and right MCA as well as the trigger channel were set. The latter contains markers required to be stored in the data file in order to time-lock the task-related activity and are commonly sent via the parallel port. To prevent interference from involuntary cardiac events with the examination of the task-related signals, the activity within a single heart cycle was averaged, which resulted in a step-like summary of the activity as opposed to the natural variations in blood flow velocity during a heartbeat. Additionally, the time span between two event markers was set to 60 s and the range of blood flow was limited to 150 cm/s to exclude any measurement or movement artifacts. As probe angles might differ between the two sides [22], data from the left and right MCA are normalized to a mean of 100 using the following equation:

$$\frac{(100 \times \text{ data })}{\text{mean } (\text{ data })}$$

where data refers to a collection of blood flow velocity values. The epochs themselves were specified from –5 to 30 s

IMR Press

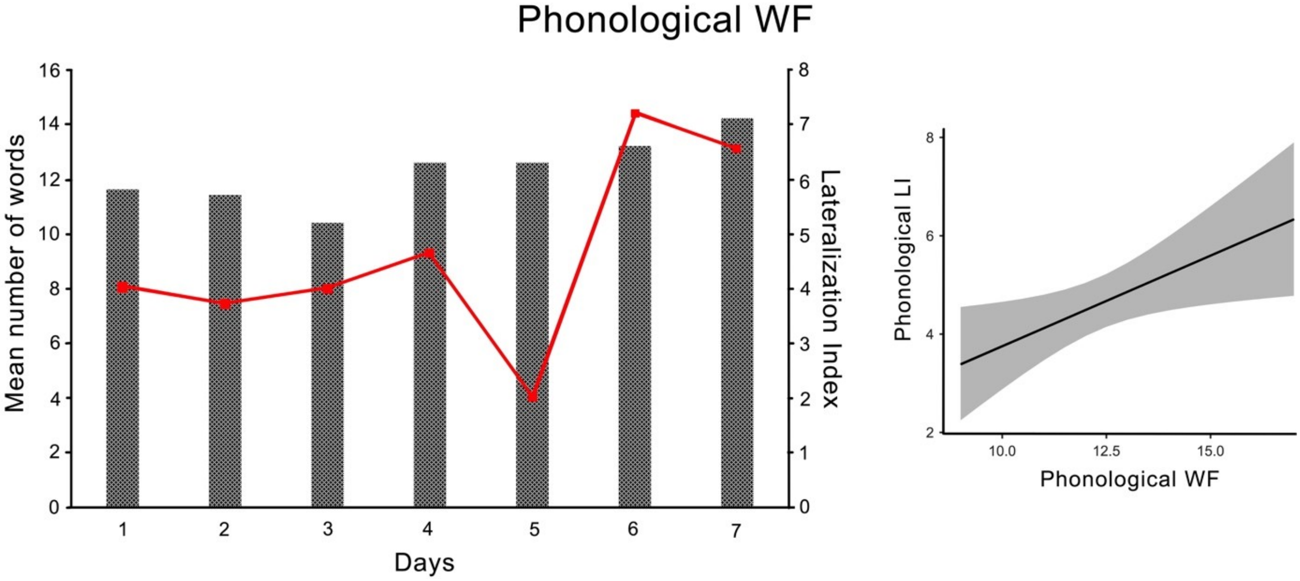

Fig. 3. Phonological Word Fluency Task. Left panel: average number of produced words (columns) and Lateralization Index (line graph) in the phonological WF task for each session. Right panel: Estimated marginal means of the regression between WF performance (x-axis) and the degree of language lateralization as indicated by the LI (y-axis) for the phonological task.

relative to the event marker at 0 s (t0), with the time span from –15 to –5 s before t0 serving as the baseline CBFV. The period of interest was specified to begin 5 seconds after t0 and to last until 30 seconds relative to the event marker to consider the process of neuro-metabolic coupling. The activation window itself, which describes the time interval with the largest event-related changes in CBFV in both MCAs, indicates the time across which the LI will be calculated and was set to 2 seconds. The presented rCBFV values were averaged over all five phonological/semantic WF trials for each of the seven respective sessions. Since the participant completed five phonological and semantic WF trials in each of the seven sessions, we were able to compute the LI values on the basis of a total of 70 valid WF trials with the aforementioned time frame.

In a first step, we performed univariate one-way ANOVAs with session as factor and mean WF performance as the dependent variable to compare changes in WF performance across all sessions. In a second step, we tested our hypothesis that a consistent direction of lateralization would be found, and our second hypothesis that WF performance correlates positively with the degree of the LI. For this, we performed a linear regression with WF performance as a predictor and the LI values as the dependent variable.

3. Results

The mean number of produced words by the participant during both WF tasks were normally distributed for the phonological (Kolmogorov-Smirnov, d = 0.12, $p < 0.66$) and for the semantic task (Kolmogorov-Smirnov, d = 0.09, $p < 0.93$). The results for the mean number of words produced during the phonological or semantic WF task in each session are summarized in Table 1. In the first session, the participant produced a mean number of 11.6 words per item in the phonological and 12.6 words in the semantic word fluency task. In the seventh and final session, he produced an average of 14.2 words in the phonological and 17.2 words in the semantic WF task.

Table 1. Mean number of words produced during the phonological and semantic WF task at each session.

Session	Phonological WF task		Semantic WF task	
	M	SD	M	SD
1	11.6	0.55	12.6	2.30
2	11.4	1.14	13.8	2.17
3	10.4	0.89	14.4	1.95
4	12.6	1.14	15.6	4.22
5	12.6	2.19	17.0	4.00
6	13.2	1.30	20.0	2.35
7	14.2	1.92	17.2	4.82

We performed univariate one-way ANOVAs comparing the WF performance across all sessions for each WF task. There was a main effect of the factor session ($F(6,28) = 3.99$, $p < 0.005$) for the phonological and a main effect for the semantic WF task ($F(6,28) = 2.85$, $p < 0.03$). The results of the Tukey post-hoc tests for phonological WF across all sessions is shown in Table 2, and for the semantic WF task in Table 3.

The participants' WF performance during the phonological WF task tended to increase from session to session and indicated a general learning effect during this task. In particular, the sixth and seventh sessions had a tendency to

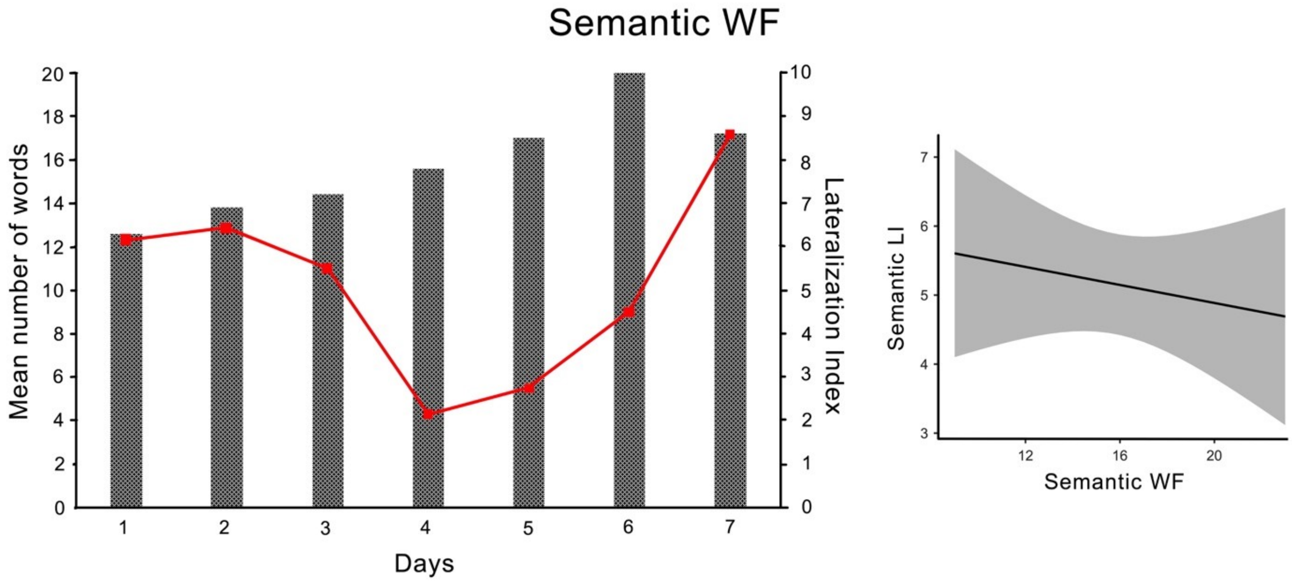

Fig. 4. Semantic Word Fluency Task. Left panel: average number of produced words (columns) and Lateralization Index (line graph) in the semantic WF task for each session. Right panel: Estimated marginal means of the regression between WF performance (x-axis) and the degree of language lateralization as indicated by the LI (y-axis) for the semantic task. Although semantic WF could not predict the corresponding LI, there may be a negative trend in the correlation of the data.

differ from the first three sessions. Exceptions were the first sessions, where the learning effect did not yet occur, and the fourth and fifth sessions, during which the same number of words were produced. In the semantic WF task, the performance in the sixth session was slightly better than the first four. The participant also showed a general learning effect on this task with an improvement in mean word production, although he produced fewer words in the last session than in the sixth session. Presumably, since only five values per session were included in the analysis, most of the individual comparisons did not reach the level of significance after the Tukey correction.

In addition, the participant demonstrated a robust, left-lateralized pattern for both WF tasks in all seven sessions, although the degree of language lateralization varies. The left-lateralized pattern is indicated by the positive LI values in Table 4 and results from higher mean blood flow velocity in the left compared to the right MCA. A somewhat unclear finding is that sessions 3 and 5 showed strongly lateralized LI values which, according to LI calculations with dopStep Master [47], were not significantly lateralized. Since no artifacts were found in the analysis this result is likely due to normal variation in the Doppler signal within one individual.

Fig. 2 shows the difference in the mean blood flow velocities of the left and right MCA during the phonological and semantic WF task for the first and the last session. In both presented sessions, the participant shows a higher mean blood flow velocity in the left hemisphere 2 to 3 seconds after the start of the WF-Task (item presentation), which exceeded that of the right hemisphere until about 5 s after the WF task ended. In the last session, we observed an earlier differentiation of the CBFV values compared to the first, which already took place in the first few seconds and thus within the period of the task-related neuro-metabolic coupling. This may be due to an anticipation effect which could reduce the reliability of LI values in the last session compared to the first session somewhat.

To determine whether these changes in WF performance might affect language lateralization in this individual, we conducted a linear regression with the mean WF performance as predictor and the LI values as the dependent variable. Data were normally distributed for the phonological WF task (Kolmogorov-Smirnov, d = 0.148, $p \leq 0.42$) and for the semantic WF task (Kolmogorov-Smirnov, d = 0.18, $p \leq 0.18$) for all seven sessions. For the phonological WF task (Fig. 3), we showed that WF performance could significantly predict the degree of language lateralization although only 15% of the variance in LI values can be explained ($R^2 = 0.15$; F(1,33) = 5.78, $p \leq 0.022$, b = 0.37, $\beta = 0.39$). This could be because the subject's performance varies over the session. For the semantic WF task (Fig. 4), WF performance could not predict the degree of language lateralization ($R^2 = 0.01$; F (1,33) = 0.47, $p \leq 0.48$, b = –0.07, $\beta = -0.12$).

4. Discussion

Our main research question was whether fTCD can provide reproducible results in an individual regarding the direction and degree of language-related lateralization over multiple follow-up examinations within a ten-day period. This reproducibility was investigated using phonological

Table 2. Results of the Tukey post-hoc tests for phonological WF performance for each session including uncorrected and corrected *p*-values.

Session	Session	Mean difference	t	*p*	p_{tukey}
1	2	0.200	0.224	0.824	1.000
	3	1.200	1.346	0.189	0.824
	4	–1.000	–1.122	0.271	0.916
	5	–1.000	–1.122	0.271	0.916
	6	–1.600	–1.795	0.083	0.562
	7	–2.600	–2.917	0.007	0.087
2	3	1.000	1.122	0.271	0.916
	4	–1.200	–1.346	0.189	0.824
	5	–1.200	–1.346	0.189	0.824
	6	–1.800	–2.020	0.053	0.425
	7	–2.800	–3.142	0.004	0.054
3	4	–2.200	–2.469	0.020	0.209
	5	–2.200	–2.469	0.020	0.209
	6	–2.800	–3.142	0.004	0.054
	7	–3.800	–4.264	<0.001	0.003
4	5	0.000	0.000	1.000	1.000
	6	–0.600	–0.673	0.506	0.993
	7	–1.600	–1.795	0.083	0.562
5	6	–0.600	–0.673	0.506	0.993
	7	–1.600	–1.795	0.083	0.562
6	7	–100.000	–1.122	0.271	0.916

Table 3. Results of the Tukey post-hoc tests for the semantic WF performance for each session including uncorrected and corrected *p*-value.

Session	Session	Mean difference	t	*p*	p_{tukey}
1	2	–1.200	–0.5747	0.570	0.997
	3	–1.800	–0.8620	0.396	0.975
	4	–3.000	–1.4367	0.162	0.778
	5	–4.400	–2.1072	0.044	0.376
	6	–7.400	–3.5440	0.001	0.021
	7	–4.600	–2.2030	0.036	0.326
2	3	–0.600	–0.2873	0.776	1.000
	4	–1.800	–0.8620	0.396	0.975
	5	–3.200	–1.5325	0.137	0.724
	6	–6.200	–2.9693	0.006	0.078
	7	–3.400	–1.6283	0.115	0.666
3	4	–1.200	–0.5747	0.570	0.997
	5	–2.600	–1.2452	0.223	0.870
	6	–5.600	–2.6819	0.012	0.140
	7	–2.800	–1.3410	0.191	0.827
4	5	–1.400	–0.6705	0.508	0.993
	6	–4.400	–2.1072	0.044	0.376
	7	–1.600	–0.7663	0.450	0.986
5	6	–3.000	–1.4367	0.162	0.778
	7	–0.200	–0.0958	0.924	1.000
6	7	2.800	1.3410	0.191	0.827

and semantic WF tasks. It was hypothesized that a left lateralized LI should be found at each of the seven sessions and that WF performance correlates with the degree of the LIs.

In concordance with Knecht *et al*. [10], we found a highly reproducible direction of hemispheric lateralization towards the left hemisphere in each of the seven examination sessions for both WF tasks in this individual. However, the degree of the lateralization varied considerably in both tasks. The calculation of a linear regression showed that variations in the individual's WF performance predict the variable degrees of LI values, at least in the phonological task. This could indicate that although the direction of language lateralization shows high stability, positive as well as negative shifts in phonological WF performance can lead to a corresponding variability in LI values. This would lead to the assumption that the degree of lateralization is not a static construct for a person, but instead fluctuates depending on the task performance. In contrast, the LI scores could not be predicted by the semantic WF performance in our study because the linear regression showed no statistical significance. Possibly, the semantic fluency task is more complex than the phonological fluency task [34], allowing for a greater cognitive load which could explain the greater variability in the data of this single subject.

A further possible explanation for these findings could be the difference in underlying cerebral blood flow patterns during word generation between the two tasks. Although there is an increase in CBFV patterns in certain cortical, subcortical and cerebellar areas, phonological WF is associated with increased CBFV values in the inferior frontal cortex and temporoparietal cortex. In contrast, during semantic WF, the patterns of increased CBFV shift more towards the left temporal cortex [38]. This could be a result of other, partly non-linguistic cognitive processes (i.e., using mental images, semantic features). Although Unsworth *et al*. [37] found no significant differences in the influence of the underlying cognitive processes on WF performance, the distinct regional cerebral blood flow patterns may explain the measured differences in the strength of the correlation between WF performance and the degree of lateralization. Further research is needed to better understand the cognitive mechanisms underlying these WF tasks and their interconnection between regional cerebral blood flow patterns. Nevertheless, our results may indicate that changes in word production, at least when mainly phonological tasks are solved, are associated with the degree of language lateralization.

Concerning the quantitative performance in word production, during the phonological WF tasks, the participant produced more words in the last session compared to the first three, and there is an outlier in WF performance during the third session which is significantly lower compared to the remaining four sessions. A similar improvement was

Table 4. LI values for each session for both the phonological (phon) and semantic (sem) WF task. LI values >0 indicate a left lateralized pattern, LI values <0 indicate a right-lateralized pattern. The LIs that differed significantly from zero are indicated by an asterisk (p < 0.05). The LI values and the standard deviation (SD) were calculated across all 5 phonological/semantic WF items.

Session	LI phon	SD	LI sem	SD
1	4.05	2.36	6.17*	0.52
2	3.74*	1.34	6.45*	0.46
3	4.01	0.24	5.50*	0.94
4	4.65*	1.45	2.14	1.35
5	2.03	0.89	2.76	1.45
6	7.23*	0.68	4.52*	0.79
7	6.54*	0.78	8.60*	1.62

also measured in the semantic WF task, in which the participant's WF performance was significantly better in the sixth session compared to the first four and decreased again in the last session. This indicates that repetitive training of both WF tasks in healthy adults results in a practice effect.

In our study, the courses of mean word production and LI values are clearly related in this individual during the phonological WF tasks. While these results may not hold true for the entire population, especially left-handed and ambidextrous persons, they point out that the lack of correlation between these two parameters described by Lust *et al*. [41] could be a result of their just one-day study design. The results may be different in elderly populations or in patients with underlying neurological diseases and disorders. Comparing these results from a young, male participant with persons showing a different handedness and with different age groups will be a subject further research will have to address. In addition, future studies will need to be conducted in a larger sample with comparable multi-session measurements to further substantiate our results.

To sum up, the results of our study support the suitability of fTCD as a tool to reliably identify patterns of lateralization and to illustrate correlations between cerebral lateralization patterns over multiple, consecutive sessions and performance in WF tasks in a single person. In terms of the reproducibility of the language-related lateralization patterns of this young male participant, this study confirms that fTCD is a viable alternative to fMRI examinations when temporal resolution of perfusion patterns is more of concern than spatial resolution, or when a cost-effective alternative is required.

5. Conclusions

In this pilot study, we measured the reliability of the reproducibility of lateralization patterns in a young, healthy adult during phonological and semantic WF tasks. We found a stable, left-lateralized pattern of LI values and a significant effect showing that LI values fluctuate depending on task performance during phonological WF in this individual. Further studies with larger samples are needed to compute a reliable model that provides better insight into the relationship between word production and lateralization patterns and clarifies differences in the phonological and semantic WF. The high stability of the direction of the measured language lateralization across multiple different sessions supports the assumption that fTCD is well suited for study designs over longer periods of time or for studies with less cooperative participants such as children or patients with dementia.

Author contributions

All authors, FH, SW, HM contributed to the study conception and design. FH conducted the fTCD measurements and drafted the manuscript. All authors, FH, SW, HM analyzed the data and revised the manuscript. All authors, FH, SW, HM read and approved the final manuscript.

Ethics approval and consent to participate

The underlying study was approved by the ethics committee at Bielefeld University (ethics approval No. 2021-028). Written consent regarding data collection and publication was obtained from the participant. A copy of the consent form for review is available from the author FH upon request.

Acknowledgment

We would like to acknowledge the consistent support by Nicholas A. Badcock (Macquarie University, Sydney, Australia) in the adaptation and usage of the dopStep Master toolbox. We thank the anonymous reviewers for the very helpful comments on the first draft of the manuscript.

Funding

This study was supported by the "German Research Foundation" (Cluster of Excellence "Cognitive Interaction Technology", EC 277).

Conflict of interest

The authors declare no conflict of interest.

References

[1] Szaflarski JP, Holland SK, Schmithorst VJ, Byars AW. FMRI study of language lateralization in children and adults. Human Brain Mapping. 2006; 27: 202–212.

[2] Holland SK, Vannest J, Mecoli M, Jacola LM, Tillema J, Karunanayaka PR, *et al*. Functional MRI of language lateralization during development in children. International Journal of Audiology. 2007; 46: 533–551.

[3] Szaflarski JP, Rajagopal A, Altaye M, Byars AW, Jacola L, Schmithorst VJ, *et al*. Left-handedness and language lateralization in children. Brain Research. 2012; 1433: 85–97.

[4] Steinmann S, Amselberg R, Cheng B, Thomalla G, Engel AK, Leicht G, *et al*. The role of functional and structural interhemispheric auditory connectivity for language lateralization—

a combined EEG and DTI study. Scientific Reports. 2018; 8: 15428.
[5] Deppe M, Knecht S, Papke K, Lohmann H, Fleischer H, Heindel W, *et al*. Assessment of hemispheric language lateralization: a comparison between fMRI and fTCD. Journal of Cerebral Blood Flow and Metabolism. 2000; 20: 263–268.
[6] Jansen A, Flöel A, Deppe M, van Randenborgh J, Dräger B, Kanowski M, *et al*. Determining the hemispheric dominance of spatial attention: a comparison between fTCD and fMRI. Human Brain Mapping. 2004; 23: 168–180.
[7] Hattemer K, Plate A, Heverhagen JT, Haag A, Keil B, Klein KM, *et al*. Determination of Hemispheric Dominance with Mental Rotation Using Functional Transcranial Doppler Sonography and fMRI. Journal of Neuroimaging. 2011; 21: 16–23.
[8] Somers M, Neggers SF, Diederen KM, Boks MP, Kahn RS, Sommer IE. The Measurement of Language Lateralization with Functional Transcranial Doppler and Functional MRI: a Critical Evaluation. Frontiers in Human Neuroscience. 2011; 5: 31.
[9] Knecht S, Deppe M, Ebner A, Henningsen H, Huber T, Jokeit H, *et al*. Noninvasive determination of language lateralization by functional transcranial Doppler sonography: a comparison with the Wada test. Stroke. 1998; 29: 82–86.
[10] Knecht S, Deppe M, Ringelstein EB, Wirtz M, Lohmann H, Dräger B, *et al*. Reproducibility of functional transcranial Doppler sonography in determining hemispheric language lateralization. Stroke. 1998; 29: 1155–1159.
[11] Bishop DV, Badcock NA, Holt G. Assessment of cerebral lateralization in children using functional transcranial Doppler ultrasound (fTCD). Journal of Visualized Experiments, 2010; 43: e2161.
[12] Haag A, Moeller N, Knake S, Hermsen A, Oertel WH, Rosenow F, *et al*. Language lateralization in children using functional transcranial Doppler sonography. Developmental Medicine & Child Neurology. 2010; 52: 331–336.
[13] Petit S, Badcock NA, Woolgar A. Finding hidden treasures: a child-friendly neural test of task-following in individuals using functional Transcranial Doppler ultrasound. Neuropsychologia. 2020; 146: 107515.
[14] Knecht S, Dräger B, Deppe M, Bobe L, Lohmann H, Flöel A, *et al*. Handedness and hemispheric language dominance in healthy humans. Brain. 2000; 12: 2512–2518.
[15] Duschek S, Schandry R. Functional transcranial Doppler sonography as a tool in psychophysiological research. Psychophysiology. 2003; 40: 436–454.
[16] Plante E, Almryde K, Patterson DK, Vance CJ, Asbjørnsen AE. Language lateralization shifts with learning by adults. Laterality. 2015; 20: 306–325.
[17] Woodhead ZVJ, Bradshaw AR, Wilson AC, Thompson PA, Bishop DVM. Testing the unitary theory of language lateralization using functional transcranial Doppler sonography in adults. Royal Society Open Science. 2019; 6: 181801.
[18] Connaughton VM, Amiruddin A, Clunies-Ross KL, French N, Fox AM. Assessing hemispheric specialization for processing arithmetic skills in adults: a functional transcranial doppler ultrasonography (fTCD) study. Journal of Neuroscience Methods. 2017; 283: 33–41.
[19] Groen MA, Whitehouse AJO, Badcock NA, Bishop DVM. Does cerebral lateralization develop? a study using functional transcranial Doppler ultrasound assessing lateralization for language production and visuospatial memory. Brain and Behavior. 2012; 2: 256–269.
[20] Rosch RE, Bishop DVM, Badcock NA. Lateralised visual attention is unrelated to language lateralisation, and not influenced by task difficulty - a functional transcranial Doppler study. Neuropsychologia. 2012; 50: 810–815.
[21] Chilosi AM, Bulgheroni S, Turi M, Cristofani P, Biagi L, Erbetta A, *et al*. Hemispheric language organization after congenital left brain lesions: a comparison between functional transcranial Doppler and functional MRI. Journal of Neuropsychology. 2019; 13: 46–66.
[22] Payne H, Gutierrez-Sigut E, Woll B, MacSweeney M. Cerebral lateralisation during signed and spoken language production in children born deaf. Developmental Cognitive Neuroscience. 2019; 36: 100619.
[23] Conradi N, Hermsen A, Krause K, Gorny I, Strzelczyk A, Knake S, *et al*. Hemispheric language lateralization in presurgical patients with temporal lobe epilepsy: Improving the retest reliability of functional transcranial Doppler sonography. Epilepsy & Behavior. 2019; 91: 48–52.
[24] Gutteridge DS, Saredakis D, Badcock NA, Collins-Praino LE, Keage HAD. Cerebrovascular function during cognition in Parkinson's disease: a functional transcranial Doppler sonography study. Journal of the Neurological Sciences. 2020; 408: 116578.
[25] Deppe M, Ringelstein EB, Knecht S. The investigation of functional brain lateralization by transcranial Doppler sonography. NeuroImage. 2004; 21: 1124–1146.
[26] Kaczynski J, Home R, Shields K, Walters M, Whiteley W, Wardlaw J, *et al*. Reproducibility of Transcranial Doppler ultrasound in the middle cerebral artery. Cardiovascular Ultrasound. 2018; 16: 15.
[27] Ringelstein EB, Kahlscheuer B, Niggemeyer E, Otis SM. Transcranial Doppler sonography: anatomical landmarks and normal velocity values. Ultrasound in Medicine & Biology. 1990; 16: 745–761.
[28] Wada J, Rasmussen T. Intracarotid Injection of Sodium Amytal for the Lateralization of Cerebral Speech Dominance. Journal of Neurosurgery. 1960; 17: 266–282.
[29] Badcock NA, Nye A, Bishop DVM. Using functional transcranial Doppler ultrasonography to assess language lateralisation: Influence of task and difficulty level. Laterality. 2012; 17: 694–710.
[30] Bradshaw AR, Thompson PA, Wilson AC, Bishop DVM, Woodhead ZVJ. Measuring language lateralisation with different language tasks: a systematic review. PeerJ. 2017; 5: e3929.
[31] Bradshaw AR, Woodhead ZVJ, Thompson PA, Bishop DVM. Investigation into inconsistent lateralisation of language functions as a potential risk factor for language impairment. European Journal of Neuroscience. 2020; 51: 1106–1121.
[32] Payne H, Gutierrez-Sigut E, Subik J, Woll B, MacSweeney M. Stimulus rate increases lateralisation in linguistic and nonlinguistic tasks measured by functional transcranial Doppler sonography. Neuropsychologia. 2015; 72: 59–69.
[33] Payne MH. Assessing language lateralisation using functional transcranial Doppler sonography [Doctor's thesis] University College London. 2018.
[34] Cerhan JH, Ivnik RJ, Smith GE, Tangalos EC, Petersen RC, Boeve BF. Diagnostic utility of letter fluency, category fluency, and fluency difference scores in Alzheimer's disease. The Clinical Neuropsychologist. 2002; 16: 35–42.
[35] Bishop DVM, Watt H, Papadatou-Pastou M. An efficient and reliable method for measuring cerebral lateralization during speech with functional transcranial Doppler ultrasound. Neuropsychologia. 2009; 47: 587–590.
[36] Gutierrez-Sigut E, Payne H, MacSweeney M. Investigating language lateralization during phonological and semantic fluency tasks using functional transcranial Doppler sonography. Laterality. 2015; 20: 49–68.
[37] Unsworth N, Spillers GJ, Brewer GA. Variation in verbal fluency: a latent variable analysis of clustering, switching, and overall performance. Quarterly Journal of Experimental Psychology. 2011; 64: 447–466.

[38] Gourovitch ML, Kirkby BS, Goldberg TE, Weinberger DR, Gold JM, Esposito G, *et al*. A comparison of rCBF patterns during letter and semantic fluency. Neuropsychology. 2000; 14: 353–360.
[39] Stroobant N, Vingerhoets G. Test-retest reliability of functional transcranial Doppler ultrasonography. Ultrasound in Medicine & Biology. 2001; 27: 509–514.
[40] Illingworth S, Bishop DVM. Atypical cerebral lateralisation in adults with compensated developmental dyslexia demonstrated using functional transcranial Doppler ultrasound. Brain and Language. 2009; 111: 61–65.
[41] Lust JM, Geuze RH, Groothuis AGG, Bouma A. Functional cerebral lateralization and dual-task efficiency—Testing the function of human brain lateralization using fTCD. Behavioural Brain Research. 2011; 217: 293–301.
[42] Bruckert L. Is language laterality related to language abilities? [doctor's thesis]. University of Oxford. 2016.
[43] Woodhead ZVJ, Thompson PA, Karlsson EM, Bishop DVM. An updated investigation of the multidimensional structure of language lateralization in left- and right-handed adults: a test–retest functional transcranial Doppler sonography study with six language tasks. Royal Society Open Science. 2021; 8:200696.
[44] Lohmann H, Deppe M, Jansen A, Schwindt W, Knech S. Task Repetition can Affect Functional Magnetic Resonance Imaging-Based Measures of Language Lateralization and Lead to Pseudoincreases in Bilaterality. Journal of Cerebral Blood Flow & Metabolism. 2004; 24: 179–187.
[45] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971; 9: 97–113.
[46] Wahrig-Burfeind R, Wahrig G. Brockhaus WAHRIG Deutsches Wörterbuch (9th edn). Wissenmedia: Gütersloh. 2012.
[47] Badcock NA, Holt G, Holden A, Bishop DVM. DopOSCCI: a functional transcranial Doppler ultrasonography summary suite for the assessment of cerebral lateralization of cognitive function. Journal of Neuroscience Methods. 2012; 204: 383–388.
[48] Deppe M, Knecht S, Henningsen H, Ringelstein EB. AVERAGE: a Windows® program for automated analysis of event related cerebral blood flow. Journal of Neuroscience Methods. 1997; 75: 147–154.