Finding Hidden Treasures: A Child-Friendly Neural Test Of Task-Following In Individuals Using Functional Transcranial Doppler Ultrasound

Authors, Affiliations

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Abstract

Despite growing interest in the mental life of individuals who cannot communicate verbally, objective and non-invasive tests of covert cognition are still sparse. In this study, we assessed the ability of neurotypical children to understand and follow task instructions by measuring neural responses through functional transcranial Doppler ultrasound (fTCD). We used fTCD to record the blood flow velocity to the two brain hemispheres of twenty children (aged 9 to 12) while they performed either a language task or a visuospatial memory task, on identical visual stimuli. We extracted measures of neural lateralisation for the two tasks separately to investigate lateralisation, and we compared the left-right pattern of activation across tasks to assess task-following. At the group level, we found that neural responses were left-lateralised when children performed the language task, but not when they performed the visuospatial task. Furthermore, with unbiased analyses and controlled paradigms, lateralisation was lower than expected from the literature in individual children. Nonetheless, the pattern of hemispheric activation for the two tasks allowed us to confirm task-following in the group of participants, as well as in over half of the individuals. This provides a promising avenue for a covert and inexpensive test of children's ability to covertly follow task instructions and perform different mental tasks on identical stimuli.

Introduction

Modern neuroscience is taking a growing interest in the mental life of individuals who may not be able to overtly display the extent of their cognitive abilities. In the case of vegetative patients, or minimally verbal autistic individuals, for example, recent evidence has shown intact consciousness and language comprehension, despite an absence of communicative behaviour. It appears that for these populations, cognitive abilities may be under-estimated by standard assessments. For this reason, it is crucial to develop a reliable test of covert cognitive abilities that does not rely on behavioural responses. In this study, we developed a paradigm to examine typically-developing children's task-following abilities directly from their brain activity, using a portable and easy-to-setup neuroimaging technology.

Previous research has used functional Magnetic Resonance Imaging (fMRI) to study cognitive abilities in non-communicative patients. In a seminal study, Owen et al. (2006) instructed a patient in vegetative state to modulate her brain activity by alternatively performing one of two mental imagery tasks (imagining playing tennis or imagining walking around her house). The patient's brain responses were similar to a group of neurotypical adults, suggesting that the patient was able to understand the instructions and wilfully modulate her brain response. These results have been replicated and expanded in several studies requiring patients to follow different instructions, such as imagining moving their right versus left hand, counting versus listening to words, or naming pictures (Bekinschtein et al., 2009; Monti, Coleman, & Owen, 2009; Rodriguez Moreno, Schiff, Giacino, Kalmar, & Hirsch, 2010). These studies all found preserved task-following abilities in a number of patients who were previously thought to lack consciousness. However, these promising initial results are mitigated by the inherent limitations of fMRI. Firstly, the high cost and low availability of MRI make large sample studies complex and expensive, and may be a barrier for routine clinical use. Furthermore, the requirements to lie still in the scanner, and the noise associated with the scanning procedure make this method inaccessible to some populations such as young children and some autistic individuals.

Recently, research teams have begun to use functional transcranial Doppler ultrasonography (fTCD) as a non-invasive and relatively inexpensive alternative to fMRI. Being relatively insensitive to movements, fTCD allows for testing a wider range of populations, including those with difficulties staying still such as children (Lohmann, Ringelstein, & Knecht, 2006) and even infants (Kohler et al., 2015). It is also portable and relatively inexpensive, allowing it to be used outside of the laboratory, and in larger populations. FTCD uses two probes placed on participants' left and right temples to measure the blood flow velocity through the right and left middle cerebral arteries. It is inferred that faster blood flow to one hemisphere results from higher neural activity in that region. Thus, fTCD

allows for an indirect measure of brain activation in the two hemispheres, and can be used to examine the lateralisation of neural responses associated with different cognitive processes.

Our interest was in deriving an implicit measure of language comprehension in non-speaking populations such as minimally-verbal autistic children. We combined the logic of task-following paradigms, in which evidence for wilful modulation of neural activity must reflect comprehension of verbal instructions, with the accessible technology of fTCD. In particular, we sought to use fTCD to provide a measure of differential brain activation in response to different tasks. We designed two tasks to invoke activity that was lateralised to the left or the right hemispheres: a word generation task and a visuospatial memory task, respectively. During both tasks, participants were presented with a spatial array in which a single letter was presented in several locations. In the word generation task, participants were asked to silently generate as many words as possible starting with this letter. During the visuospatial memory task, participants were asked to study the location of letters and remember their location after the letters disappear. These two types of tasks typically dominantly activate the left and the right hemisphere, respectively (Bishop, Watt, & Papadatou-Pastou, 2009; Groen, Whitehouse, Badcock, & Bishop, 2012; Rosch, Bishop, & Badcock, 2012). Here, we examined task-related fTCD responses in a group of 20 participants aged 9-12 years.

In developing our approach, we sought to redress three limitations that would otherwise prevent the clinical application of this method as a test of task-following. First, an issue in extant fTCD research is the heterogeneity in paradigms used to measure different cognitive processes. For instance, most researchers estimate language lateralisation using word generation paradigms that involve generating language after viewing a letter on a screen or a short animations (Badcock, Nye, & Bishop, 2012; Rosch et al., 2012; Woodhead, Rutherford, & Bishop, 2018). On the other hand, to estimate visuospatial lateralisation, researchers have used tasks with complex visual displays, such as finding rabbits hiding in different holes, or lines masked by complex visual dynamic masks (Groen, Whitehouse, Badcock, & Bishop, 2011; Rosch et al., 2012). As such, the difference in lateralisation between tasks may correspond to changes in the visual and auditory stimuli instead of differences in language and visuospatial processes. Our paradigm overcomes this limitation by presenting the same stimuli in both language and visuospatial tasks.

Second, we highlight a statistical flaw in that the way that lateralisation indices (LIs) are analysed, which systematically over-estimates laterality. Typically, LIs are calculated by finding the peak in the left-right blood flow velocity difference, then averaging the velocity values over a time-window (usually 2 s) centred on that peak (e.g., Badcock, Nye, et al., 2012; Deppe, Knecht, Lohmann, & Ringelstein, 2004; Groen et al., 2011; Kohler et al., 2015; Woodhead et al., 2018). This quantifies the *maximum* difference of the waveform, which can then be compared between tasks groups. However, because of the way it is derived (taking a maximum from a continuous waveform), it is statistically

flawed to compare this difference to zero, for example, to infer that the group or individuals have "significant" lateralisation. We show through simulation that this method, which is unfortunately common practice in fTCD research, will inflate type I (false positive) error. This flaw, also known as 'double dipping', is well known in fMRI and electroencephalography research (Kilner, 2013; Kriegeskorte, Simmons, Bellgowan, & Baker, 2009) and applies equally to fTCD data. To avoid this issue, we compute the mean velocity difference over a pre-defined period of interest that is independent of the collected data, and can therefore legitimately be compared to zero to infer significance of lateralisation. Simulations confirm that this method does not produce a bias towards false positives.

A final consideration is that the typical pattern of left-sided language dominance and right-sided visuospatial dominance is only seen in the majority of children, not all of them. Current estimates are that around 7.5% to 25% of the population have right hemisphere language and around 10% to 15% have bilateral representation of language functions, with the remaining 60% to 80% having the typical left representation of language (Knecht et al., 2000; Lust, Geuze, Groothuis, & Bouma, 2011; Whitehouse & Bishop, 2009). Similarly, visuospatial functions are not supported by the right hemisphere in every individual (Badcock, Nye, et al., 2012; Rosch et al., 2012). In their respective studies, Whitehouse and Bishop (2009) found that 25% of adults had either a bilateral or a left-hemisphere dominance for visuospatial memory, while Groen et al. (2012) found this pattern in 29% of children. Thus, for our purpose of measuring task-following on an individual-subject basis, it is not sufficient to rely exclusively on the lateralisation of a single cognitive task. Instead, it may be much more powerful to compare lateralisation between tasks. Moreover, this will allow us to be sensitive both to differences in the lateralisation of response to each task and to differences in the timecourse with which the lateralisation occurs. For example, the difference may manifest as subtle changes of left and right hemisphere activation across time, even if both tasks are lateralized to the same hemisphere.

Using our controlled stimuli and unbiased analyses, we found that the lateralisation of both language and visuospatial functions was weaker than typically reported. Nonetheless, we found robust evidence that the two tasks relied on different brain processes, as indicated by a difference in the pattern of hemispheric activation in the group. At the individual level, we could detect task-following abilities in 55% of children using this approach. This provides a possible avenue for a covert and inexpensive assessment of task-following in children.

Methods

All presentation scripts, analysis scripts, and raw data are available at https://osf.io/xygjv/.

Participants

Twenty-two children were recruited using the Neuronauts database of the Australian Research Council Centre of Excellence in Cognition and its Disorders. All participants were native English speakers, and they received $20 for their participation. The data from two participants were excluded due to failing to record data (one participant) and computer crashing (one participant). The final set of data thus came from 20 participants (age range: 9 to 12 years old, *M=10:7, SD=1:1,* 10 male and 10 female). Seventeen of the participants were right-handed, and three were left-handed, based upon parent reports. This study was approved by the Macquarie University Human Research Ethics Committee (Reference number: 5201500074). Participants' parents or guardians provided written consent and the children provided verbal consent.

Apparatus

We acquired blood flow velocity data using a Doppler ultrasonography device (Delica EMS-9UA, SMT medical technology GmbH&Co Wuerzburg, Germany), with probes held in place bilaterally over the left and right temporal windows via a headset. We adjusted the probes until we obtained a good signal of the blood flow through the left and right middle cerebral arteries. The experimental paradigm was presented using Psychtoolbox version 3 (Brainard, 1997; Kleiner et al., 2007) on Matlab, on a 27-inch monitor screen located at 80cm from the participants. Responses to the trials were given via a button box (Cedrus RB-830).

Paradigm

In order to engage children with the task, we presented the paradigm as a game in which the children collected treasure. A male and a female "pirate" gave auditory instructions and feedback on each trial. The pirates' voices were recorded by actors who were native Australian English speakers. Male and female voices were included for diversity and were not related to the two tasks (both voices instructed both tasks with equal probability). Each participant completed 40, one-minute trials, switching tasks every 10 trials. In total, they completed 20 trials of the word generation task (task 1), and 20 trials of the visuospatial memory task (task 2). The order of the task was counterbalanced across participants.

Each trial started with a baseline period of 10 s, during which the participants fixated on a black cross in the centre of a white screen. Then either the male (first half of the experiment), or the female (second half of the experiment) pirate was presented on screen, and greeted the participant. The pirate asked the participant to get ready, and gave the instructions for the task. The instructions were "Think of words that begin with this letter" for task 1, and "remember my treasure map" for task 2. Then a treasure map appeared, with 8 repetitions of a letter randomly distributed on the screen (see Figure 1). The characters were displayed in black, presented at a visual angle of approximately 1°. The treasure

map remained visible for 5 s during which children silently generated words (task 1) or studied the position of the letters (task 2). A white screen was then displayed for 10 s, during which the children continues to generate words (task 1) or remembers the position of the letters (task 2). Finaly the map reappeared with the letters either exactly at the same location as the first map (in half of the trials), or with one letter displaced from its original location. The pirate would then ask “Did you think of lots of words?” (task 1) or “Is this the same treasure map?” (task 2), and the children would answer “yes” or “no” by pressing either a right or left button on a button box in front of them. The buttons’ position was counterbalanced across participants. A 5 s animation was then presented, showing the treasure that the pirate collected during the trial, with the pirate giving encouraging auditory feedback (e.g., “you’re winning!”, “blow me down, that was brilliant!”, “Pieces of eight, you’re doing great!”). Then the pirate’s voice would indicate that the child should take a break by saying e.g., “time for a rest” and a short animation showed a relaxing situation in which the pirate was yawning or sailing away for the night. This was included to encourage participants to stop performing the tasks, with the intention of encouraging task-related activation to return to baseline. Finally, a blank white screen was presented for 10 s of normalization, then the next trial began. Each trial featured a different letter, with all the letters of the Roman alphabet being presented once in each task, except for the letters K, Q, W, X, Y, and Z, which were not used as words starting with these letters are rare. The order of the letters was randomized for each participant. Each letter was seen once in a single task before being repeated in the other task. The order of the letters was reversed in the second task, for each participant. Thus, the paradigm was designed so that the two tasks consisted of identical visual stimuli and identical structure, and differed only in auditory instructions. Any difference in the hemispheric activation must therefore be attributed either to the subtly different auditory stimulation, or to the difference in the mental task.

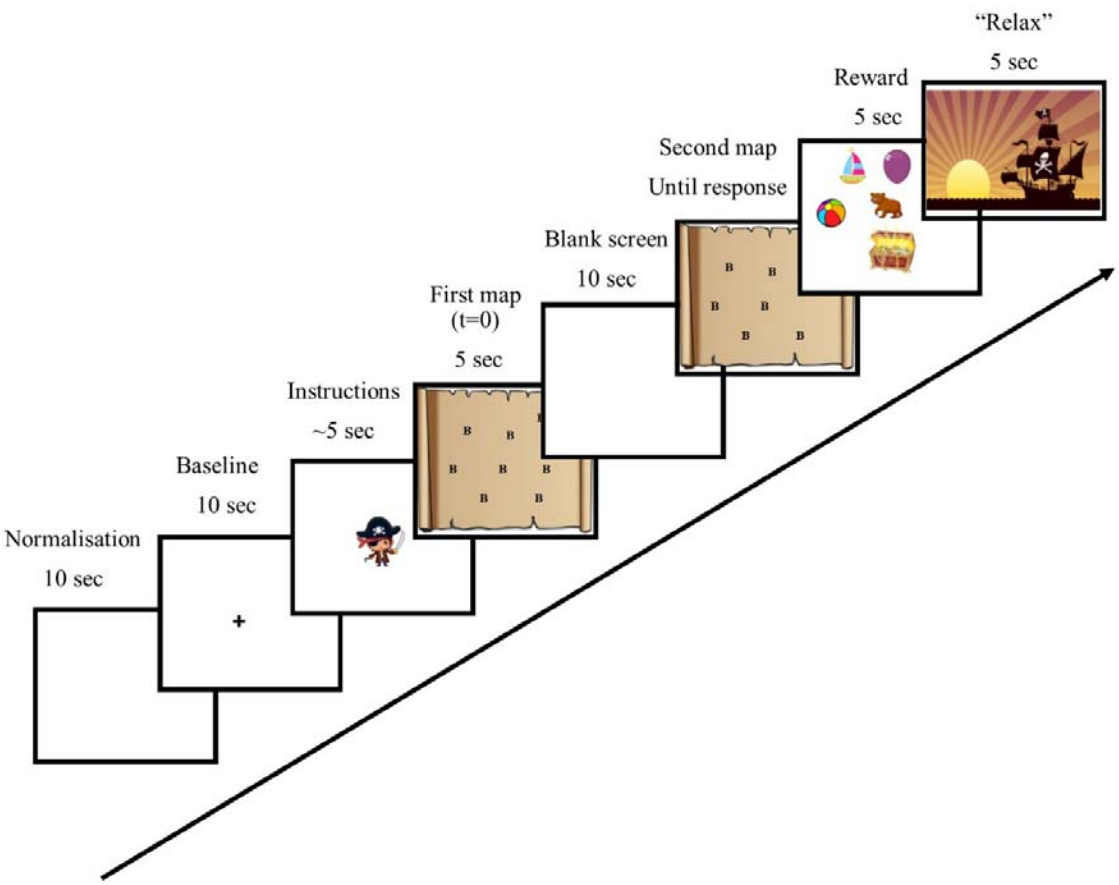

Figure 1: Trial structure. After normalisation and baseline, a pirate was presented and introduced the task. Then a treasure map with letters appeared and children started generating words (language task) or remembering the location of the letters (visuospatial memory task). The map then disappeared, and reappeared with all letters at the same location, or with one letter that changed location. A reward screen then appeared, followed by an animation instructing children to relax.

Data preprocessing

We preprocessed the fTCD data using DOPOSCCI (Badcock, Holt, Holden, & Bishop, 2012; Badcock et al., 2018) with MATLAB version R2017B (Mathworks Inc., Sherborn, MA, USA). We first downsampled the raw data to 25Hz, then we removed the heart cycle by determining local peaks and using linear heart cycle correction based on previous work (Badcock, Nye, et al., 2012). To correct for overall differences in the strength of the signal from the right and left probe (e.g., due to a difference in the alignment of the probes), we normalised the signals to a mean of 100% on a trial-by-trial basis. We then created epochs, -15 to 40 s, relative to the onset of the first visual map display (see Figure 1). At this stage, we rejected epochs with extreme values (beyond ± 50% of the mean signal), corresponding to poor insonation or excessive head movement. Finally, we performed a baseline correction for each epoch by removing the averaged value of the signal from -15 to -10 s before stimulus onset.

Lateralisation Index

First, for comparison with previous literature, and to test for differences in lateralisation between two tasks using similar stimuli, we calculates LIs. Typical fTCD lateralisation research calculates LIs by finding the peak in the mean velocity difference between the two hemispheres within a period of interest (POI), then comparing the signal averaged in a time-window around this peak against zero. This approach provides a metric that can be compared between groups or conditions, but, because of the way it is derived, it cannot be compared to chance at the individual or group level. To demonstrate that deriving the LI in this was increases the risk of reporting false positives, we ran two simulations, one computing a hypothetical LI using the traditional peak method, and one calculating LIs by averaging over the entire signal in a pre-defined POI. As an approximation of fTCD data, we generated twenty noisy time-series of 1200 timepoints (approximately the size of our current epoch) by selecting a random number between -20 and 20 at each timepoint. Next, we chose an *a priori* POI spanning 200 timepoints (approximately 10 seconds of data, which corresponds to what is typically used in fTCD litterature). We then either (a) found the peak in the data within the POI, then averaged the signal over time within a 2 second (50 timepoints) time window centred on the peak, or averaged the signal over the entire POI. For both simulations, we computed a t-test of this value against zero (no information in the signal), equivalent to testing the LI to zero in an individual. We ran these steps 10,000 times and obtained the percentage of simulations for which the LI was significantly different from zero, at alpha = 5%, *i.e.*, the false positive error rate. The peak method yielded a false positive error rate of 6.53%, which represents an inflation of false positives relative to the desired error rate of 5% (as there was no signal in the data). Note that this underestimates the problem in real fTCD data, which will increase with smoothness in the timeseries data. The averaging method yielded a slightly conservative false positive error rate of 4.75%. If we further entered the LI for each individual into a group level test against chance, our simulation returned 5.93% error rate for the peak method and only 5% (chance) for the mean method. Therefore, we used the mean method for LI calculation in individuals and at the group level.

For each task separately, we first averaged the signal from all the accepted epochs, for the right and the left probes. We then calculated the difference between the left and right signals over time. We defined a language POI as 4 to 14 s after the first map onset, in accordance with previous research that found the highest left-hemisphere activation during this POI for the word generation task (Bishop et al., 2009; Groen et al., 2011, 2012). We defined a visuospatial POI as 20 to 35 s after the first map onset based on previous findings of highest right-lateralisation during this time-window (Groen et al., 2011, 2012; Rosch et al., 2012). For each task, we assessed the left-minus-right signal difference within the corresponding POI using a grand average within the POI and performing a one-sampled t-test between this difference and zero. This was done at the group level (across participants) and at the individual level (across trials within participants). We additionally calculated Cohen's d (effect size).

Split-half reliability

Next, we estimated the reliability of the LI by calculating the split-half reliability for each task. This was done using Pearson's correlation between the LI of each participant for the odd and the even trials. We found good reliability for the word generation task ($r = .58$, $p = .0068$), and for the visuospatial memory task ($r = .75$, $p < .001$).

Hemispheric differences analyses

Finally, to address our main question of whether the two tasks yielded different patterns of hemispheric activation, we compared the left-minus-right difference between tasks. We performed a two-tailed paired-sample t-test for the average blood flow velocity within the language task POI. This POI was chosen as it has showed the strongest lateralisation for language, and no lateralisation for visuospatial processing, in previous research (Badcock, Nye, et al., 2012; Groen et al., 2012; Whitehouse & Bishop, 2009), so we expected the lateralisation for the two tasks to be maximally different during this period. By only analysing the left-right difference once (in just the language POI), we avoid the need to correct for multiple comparisons thus maximising our statistical power. We performed this analysis at the group level, with a paired t-test across participants, and at the individual level, with a paired t-test across trials (pairing the letters in each condition) within participants. At the group level, with 20 participants, we had .56 power to detect a medium effect size (Cohen's $d = .50$), and .92 power to detect a large effect size ($d = .80$) for alpha = 5%. Similarly, at the individual level with 20 trials, we had .56 power to detect a medium effect size ($d = .50$), and .92 power to detect a large effect size ($d = .80$).

Results

We examined children's hemispheric activation upon performing two mental tasks, word generation or visuospatial memory. For each task after every trial, participants had to press a button to indicate whether they could generate many words, and whether the visual display was modified, respectively.

Behavioural responses

We considered the participants to have behaviourally performed the tasks based upon the high accuracy for the visuospatial memory task (mean accuracy = 88%, range = [70%, 100%]) and the high percentage of trials for which they reported to have thought of many words (M = 77%, range = [45%, 100%]).

Group LI

Group level results are shown in Figure 2. We first illustrate the timecourse of the left and right hemispheres blood flow velocity for each task (Figure 2A and 2B). We then subtracted the right from the left activation, for each task, within their respective POI (Figure 2C and 2D). We calculated the significance of the LI for both tasks by comparing the left-right activation to 0. The LI for the word

generation task was positive (M = 1.78 cm/s, SD = 3.33, 95% confidence interval (CI) = [.66, 2.90], Figure 2A and 2C) and significantly different from 0 ($t_{(19)}$ = 3.33, p = 0.0035, Cohen's d = .744) indicating left lateralisation at the group level. The LI for the visuospatial memory task was negative (M = -0.62 cm/s, SD = 1.57, 95% CI = [-1.36, 0.11]], Figure 2B and 2D) but was not significantly different from zero in the time window of interest ($t_{(19)}$ = -1.78, p = 0.0908, Cohen's d = -.3983).

Group hemispheric differences

At the group level, blood flow velocity during word generation was significantly different from during the visuospatial memory task. The word generation task was significantly more left-lateralized than the visuospatial memory task (word generation minus visuospatial memory = 2.21 cm/s, $t_{(19)}$ =4.11, p<.001, Fig 2E).

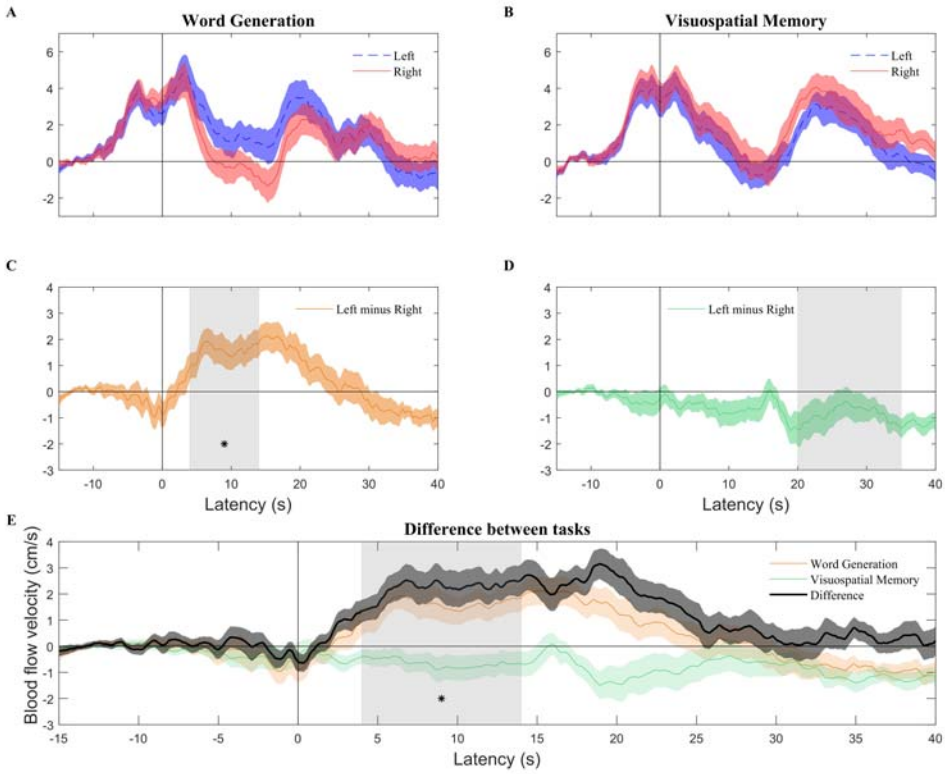

Figure 2: Grand average blood flow velocity for the left (dotted blue line) and right (solid red line) channels (**A**, **B**), and the left-minus-right difference (**C**, **D**) over time for the word generation (**A**, **C**) and visuospatial memory (**B**, **D**) task. **E** shows the left-minus-right difference (i.e., same as middle panels) for the word generation task (orange line) and the visuospatial memory task (green line), and the difference of these differences (black line). Grey areas indicate the periods of interest. Black asterisks indicate significant effects.

Individual LIs

We then examined the significance of LIs in individuals by comparing left-right differences to 0 in the language POI (4 to 14 s) for the language task and the visuospatial POI (20 to 35 s) for the visuospatial memory task. At the individual level (Figure 3), language was significantly lateralised to the left hemisphere for 50% of children (10/20), and to the right hemisphere for 5% of children (1/20). Visuospatial memory was significantly lateralised to the right hemisphere for 20% of children (4/20), and to the left hemisphere for 10% of children (2/20). The remaining participants did not show evidence of significant lateralisation. In addition, we examined the association between lateralisation for language and visuospatial memory. Although 9 of the 20 participants fell into the quadrant where they were numerically left lateralised for language and right lateralised for visuospatial memory, we found a significant correlation between the two functions (ρ = .48, p = 0.034). This indicated that participants with stronger left lateralisation for language also tend to have more leftwards lateralisation for visuospatial memory, and vice versa.

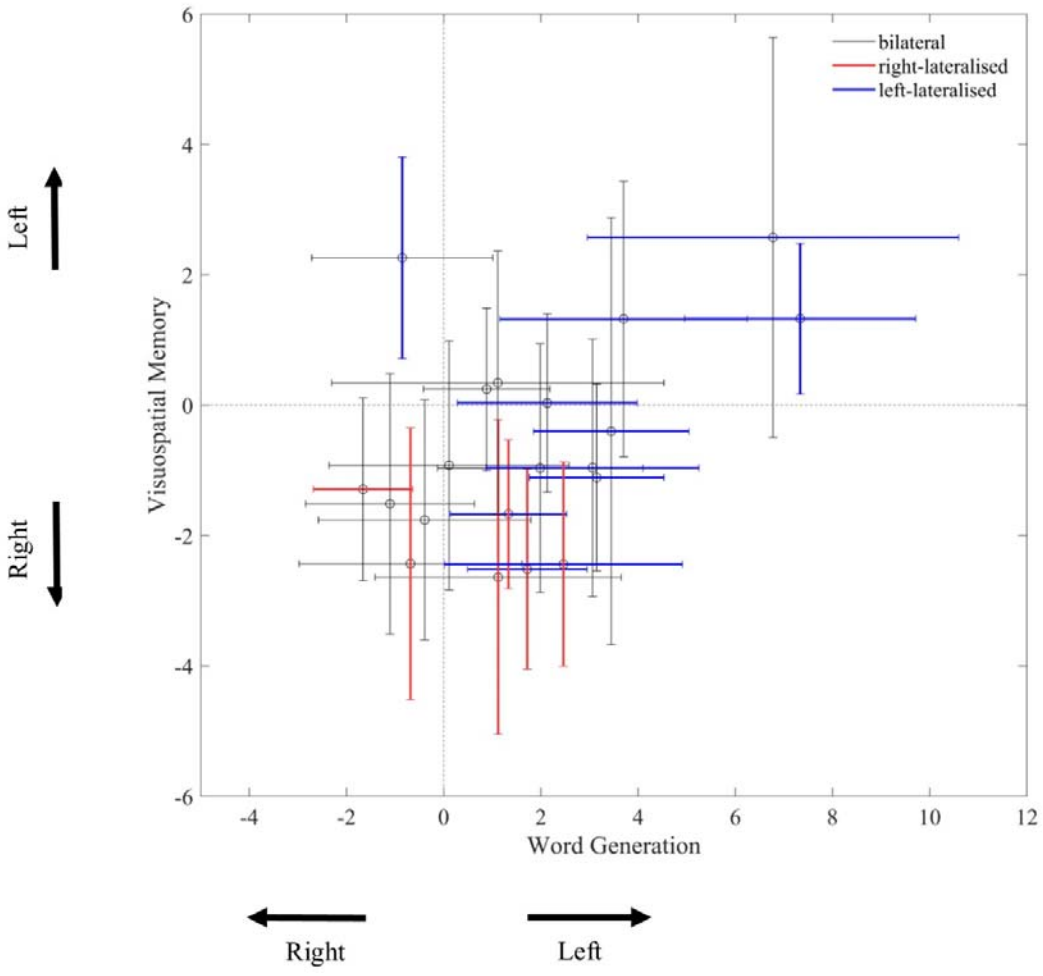

Figure 3. Scatterplot of laterality indices (LIs) of each participant for the word generation (POI = 4 to 14 s) and the visuospatial memory tasks (POI = 20 to 35 s), with 95% confidence interval for each participant (across trials). Participants with confidence intervals (CIs) overlapping zero are not considered to be lateralised (grey errors bars). Participants with CIs strictly < 0 are right-lateralised (red error bars), and participants with CIs strictly > 0 are left-lateralised (blue error bars).

Individual hemispheric differences

Finally, our main question was whether we could use our fTCD paradigm as an implicit measure of task-following in individual children. We assessed the sensitivity of detecting task-related hemispheric activation in individuals by comparing the left-minus-right differences between tasks. A significant effect of task was found in 55% (11/20) of our participants (see Figure 4), indicating clear evidence for task-following in just over half of individuals. In all the individuals with a significant difference between tasks, blood flow was more left-lateralised in the language task than in the visuospatial task. We did not find any significant correlation between the size of the left-right difference and children's performance on the behavioural tasks (word generation task: $\rho = -.28$, $p = .24$, spatial memory task: $\rho = .10$, $p = .66$).

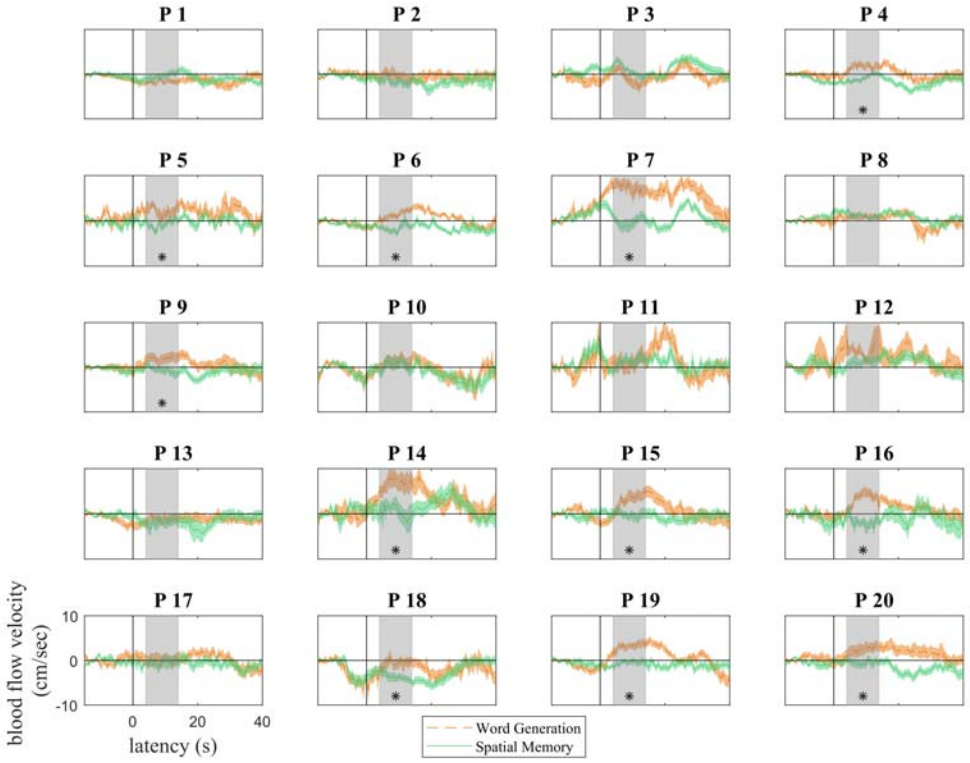

Figure 4. Individual participants pattern of activation (left-minus-right) for the word generation (dotted-orange line) and visuospatial memory (solid-green line) task, plotted ± standard error of the mean. Grey area indicates the

period of interest for our analyses. Black asterisks indicate a significant difference in the POI. Eleven participants showed a statistically significant difference between the two tasks.

Discussion

In this study we proposed a rigorous method for evaluating task-following in children based on the lateralisation of brain functions using functional transcranial Doppler ultrasound (fTCD). We designed a controlled, child-friendly paradigm in which children either silently generated words beginning with a particular letter (language task) or remembered the spatial location of letters on a screen (visuospatial task). We computed the left and right hemispheric blood flow velocity while performing the tasks, and we inferred task-following from the difference in velocity between the two tasks. At the group level, we replicated previous literature in finding a significant left-lateralisation for the language task in children (Bishop et al., 2009; Groen et al., 2011, 2012). However, we did not observe the expected right-lateralisation for the visuospatial memory task. We also found less marked lateralisation of language and visuospatial memory in individuals, compared to what was expected from the literature. Upon comparing lateralisation between the two tasks, we could infer task-following at the group level, as well as in 55% of our individual participants.

As expected from the literature, we found significant left-lateralisation of language at the group level. However, at the individual level, the lateralisation was not as pronounced as expected. Only 50% (10/20) of children had significant left-lateralisation of language, and 25% (5/20) had significant right-lateralisation of visuospatial memory. This rate is lower than previously reported, i.e., around 70% of people being left-lateralised for language (e.g., Knecht et al., 2000; Lust, Geuze, Groothuis, & Bouma, 2011; Whitehouse & Bishop, 2009), and 70% of people being right-lateralised for visuospatial memory (e.g., Groen et al., 2012; Whitehouse & Bishop, 2009). The numerically lower lateralisation found in our study may reflect two crucial differences from previous fTCD research. First, previous fTCD studies that observed differential lateralisation in response to language and visuospatial tasks have used paradigms involving different stimuli in the two tasks (Badcock, Nye, et al., 2012; Groen et al., 2011, 2012; Woodhead et al., 2018). This makes it difficult compare the results directly and conclude that differences are due to task, rather than stimuli. In contrast, our paradigm used identical displays of letters in both conditions, with only one minor variation in the auditory task instructions, making it more likely that differences in blood flow velocity are due to participants performing the task itself, rather than responses to different stimuli.

The second explanation for our lower lateralisation in individuals is that many previous analyses of lateralisation have been biased towards an increased detection of lateralisation. Previous fTCD research typically finds the peak in the left-minus-right blood flow velocity and concludes that if this difference is significantly different from zero, there is evidence for lateralisation. This method introduces statistical bias, because it finds a maximum in the data and compares this maximum to

zero, thus increasing the type I error (probability of incorrectly rejecting the null hypothesis when it is true). In this study, we overcame this problem by computing the difference in the left-right blood flow velocity difference over an entire pre-defined POI (as introduced by Woodhead et al., 2018), which brings the type I error back to the scientific standard of 5%. We believe that researchers interested in using fTCD to examine lateralisation of brain function must take care when making inferences based on peak LI analyses. This method is suitable to compare lateralisation between tasks or between groups, but should not be used to test whether individual or group lateralisation is different from chance, because the multiple comparisons inherent in selecting the peak from continuous data have not been accounted for. To check whether the LI analyses do make a difference in the lateralisation that we estimate, we ran a follow-up analysis of our data using the peak method that we believe to be flawed. Using this method, "significant" left lateralisation of language was still found in 50% of participants, but right lateralisation of visuospatial memory increased from 20% to 50% of participants. This shows that indeed the peak method increases bias towards lateralisation. However, this increase does not account for the entire difference that we observe compared to previous literature. This suggests that at least some of the difference between our results and previous literature may be due to differences in the stimuli used or population examined. Our findings suggest that the lateralisation of children age 9-12 may not be as strong as previously suggested. However, our sample size was small (n=20) and a larger study, with appropriate statistics, would be needed to get a reliable estimate of the population's lateralisation.

Upon analysing the association between the lateralisation for the two tasks in individuals, we found a significant positive correlation between language and visuospatial memory lateralisation. In other words, despite the group-level typical left lateralisation for language and right lateralisation for visuospatial memory, individuals who were more left lateralised for language were also more leftwards lateralised for visuospatial memory. This correlation is consistent with previous reports (e.g., Flöel, Buyx, Breitenstein, Lohmann, & Knecht, 2005; Whitehouse & Bishop, 2009). It can be taken as evidence against a causal view of hemispheric specialisation in which localisation of one function to one hemisphere causes localisation of the other function to the other hemisphere (e.g., language is left lateralised *because* visuospatial memory is right lateralised; Whitehouse & Bishop, 2009). However, the data are also not well explained by the dominant alternate view, in which hemispheric lateralisation of each function is independent (Bryden, Hécaen, & DeAgostini, 1983), as this predicts no association in LI between tasks. Instead, our data suggest an *association* in which individuals who tend to rely more on their left hemisphere in one task, will also tend to rely more on this hemisphere in other task.

The second aim of this study was to design a paradigm that could be used to assess task-following abilities in non-verbal individuals. To this end, we computed the patterns of left-minus-right hemispheric activation in response to the two tasks. A consistent difference in the LI between tasks,

irrespective of the direction of this difference, would indicate the involvement of different brain activity in response to the two instructions, and thus indicate preserved understanding of instructions. However, even though we found a robust statistical difference in the activation for the tasks at the group level, we could only observe a statistical difference in 55% of individual participants. The current study used 20 trials per condition, in line with previous fTCD research (Badcock, Nye, et al., 2012; Groen et al., 2011; Whitehouse & Bishop, 2009). However, with 20 trials, we had only .56 power to detect a medium effect size (d=.50), in the individual subject analysis, so we may have failed to detect differences in the remaining individual children due to insufficient numbers of trials. Another possibility is that some children were not sufficiently engaged in the task or did not perform the task. However, we did not observe any correlation between children's behavioural accuracy and the size of their differential neural responses. Additionally, even though children reported the task to be engaging, it involved a long baseline period during which they were asked to clear their mind and "think of nothing". This might not be trivial, particularly for children, and it is possible that some participants engaged in language-related processes during the baseline period. This would have impacted the lateralisation of the language task, potentially reducing the difference in the activation between the tasks. Because our ultimate goal would be to use this paradigm in populations who have unreliable behavioural responses, we chose not to ask participants to generate words out loud at the end of each trial. Instead, we only checked for compliance by asking participants whether they could generate many words or not. It is thus hard to assess whether participants were following the instructions properly for the language tasks. In the future, researchers may consider asking neurotypical children to report the words they generated, to being to explore the contribution of task compliance to individual differences in lateralisation.

Conclusion

We measured brain activation in children using a portable and inexpensive neuroimaging device, fTCD. We analysed lateralisation of neural blood flow in response to a language task and a visuospatial memory task performed on identical visual stimuli. Two main findings emerge. First, we were able to observe task-following from the brain data of half the participants, making our results a promising basis for future clinical tests. By analysing the hemispheric activation pattern across the two tasks, clear differences were observed in 55% of individual children. Second, our results indicate that the lateralisation of neurotypical children may not be as pronounced as previous research suggests. While previous fTCD research found left-lateralisation of language in about 70% of children, we were only able to see this pattern in 50% of our participants. Similarly, typical fTCD research found right-lateralisation of visuo-spatial memory in 70%, while we found this pattern in 20% of our participants. This was potentially due to controlled stimulus presentation, and/or less

biased statistical assessment of lateralisation. Overall, our methods constitute a promising step towards the neural measurement of task-following abilities in children. These methods, however, need refining before they can be used as an assessment tool in special populations, possibly with more trials, an independent index of subject compliance, and refined paradigms to maximally differentiate between the two hemispheres.

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