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Research Report

Cortical collateralization induced by language and arithmetic in non-right-handers

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ABSTRACT

The functional overlap of language and arithmetic is debatable. Although some studies have reported independent representations of arithmetic and language in the brain, other studies have reported shared activity of the two cognitive domains in the inferior frontal gyrus. Although most previous studies have evaluated right-handed individuals, variability of hemispheric dominance in non-right-handed individuals should provide important information on the functional collateralization of these two cognitive domains. The present study evaluated the cortical lateralization patterns of the two cognitive domains using functional magnetic resonance imaging in 30 non-right-handed participants who performed language and arithmetic tasks. We found that language and arithmetic tasks demonstrated shared activity in the bilateral inferior frontal gyrus (IFG). Furthermore, the lateralization patterns of language and arithmetic tasks were correlated with each other. Most participants with language dominance in the left hemisphere also exhibited dominance of arithmetic tasks in the left hemisphere; similarly, most participants with language dominance in the right hemisphere exhibited dominance of arithmetic tasks in the right hemisphere. Among all the brain regions, the precentral gyrus, which is located slightly posterior to the IFG, exhibited the highest correlation coefficient between laterality indices of language and arithmetic tasks. These results suggest a shared functional property between language and arithmetic in the brain.

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1. Introduction

The functional overlap of language and arithmetic is controversial. Lesions in the left hemisphere typically result in aphasia (Crosson et al., 2007; Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004), and patients with aphasia tend to have acalculia (Baldo & Dronkers, 2007; De Luccia & Ortiz, 2016). Neuroimaging studies on language tasks often demonstrate left-lateralized activation patterns in the inferior frontal gyrus (IFG) (Jansen et al., 2006; Josse, Seghier, Kherif, & Price, 2008), similar to the activation observed in arithmetic tasks (Delazer et al., 2003; Ischebeck, Zamarian, Egger, Schocke, & Delazer, 2007; Menon, Rivera, White, Glover, & Reiss, 2000; Qin et al., 2014). A previous meta-analysis has revealed that the IFG exhibited left dominance for addition and subtraction tasks (Arsalidou & Taylor, 2011). Indeed, arithmetic is a cognitive domain that has been repeatedly examined to identify its relationship with language function. A study on theoretical linguistics has proposed that the syntactic component in natural language plays an essential role in the natural number system (Hiraiwa, 2017). Previous lesion (Klessinger, Szczerbinski, & Varley, 2007; Varley, Klessinger, Romanowski, & Siegal, 2005) as well as neuroimaging (Amalric & Dehaene, 2016; Fedorenko, Behr, & Kanwisher, 2011; Maruyama, Pallier, Jobert, Sigman, & Dehaene, 2012; Monti, Parsons, & Osherson, 2012) studies have reported that language and arithmetic functions are independent of each other. However, other studies asserted that the left IFG controls the linguistic component shared with the arithmetic component (Hung et al., 2015; Makuuchi, Bahlmann, & Friederici, 2012; Nakai & Okanoya, 2018; Nakai & Sakai, 2014; Pollack & Ashby, 2018). Some studies have also suggested that the memory load during arithmetic tasks induced activations in the IFG (Delazer et al., 2003; Ischebeck et al., 2007; Menon et al., 2000; Qin et al., 2014). Nieder (2016) suggested that the memory load during mental calculation depends on how many digits are stored before reaching the result, while IFG activation was observed even after controlling for the number of stored digits in the memory (Nakai & Sakai, 2014).

The commonality/independence of language and arithmetic has been previously discussed on the basis of the activation overlap of related tasks (Makuuchi et al., 2012; Maruyama et al., 2012). However, the overlapping activation of two cognitive domains does not indicate that it also reflects variability of individual activation patterns. Collateralization of two cognitive domains may indicate that such individual variability is also shared; moreover, it provides additional evidence supporting the commonality of these domains (Cai & Van der Haegen, 2015). To provide clarity on the contradictory literature regarding the neural basis of language and arithmetic, it is important to ascertain how the lateralization patterns of the two cognitive domains are related.

Hemispheric lateralization is considered to be a ubiquitous property of the neural architecture in humans (Toga & Thompson, 2003) and has been evaluated using the Wada test (Wada & Rasmussen, 1960), electrical stimulation mapping (Ojemann, Ojemann, Lettich, & Berger, 1989), the dichotic listening task (Kimura, 1961), visual half-field task (Hunter & Brysbaert, 2008), and neuroimaging techniques such as functional magnetic resonance imaging (fMRI) (Jansen et al., 2006; Josse et al., 2008) and magnetoencephalography (Pirmoradi, Béland, Nguyen, Bacon, & Lassonde, 2010). Laterality patterns have also been studied in patients with aphasia (Rasmussen & Milner, 1977) and those with split-brain (Gazzaniga, 2005) by assessing cortical stimulation using transcranial magnetic stimulation (Knecht et al., 2002). Studies using different methods have reported converging evidence for a left hemisphere dominance in approximately 95% of right-handers (Carey & Johnstone, 2014; Knecht et al., 2000; Knecht et al., 2000, Knecht, 2000; Pujol, Deus, Losilla, & Capdevila, 1999). In contrast, the percentage of left hemisphere dominance in non-right-handers was approximately 70% (Carey & Johnstone, 2014; Knecht et al., 2000; Pujol et al., 1999; Szaflarski et al., 2002a, 2002b), whereas other non-right-handers exhibited right dominance or bilateral patterns. It has been argued that most fMRI studies on language processing have evaluated right-handed participants and ignored the variability of hemispheric dominance patterns (Willems, Der Haegen, Fisher, & Francks, 2014). To identify a group-level brain activation result, excluding non-right-handers may reduce the variability of activated regions and increase the effect size. Conversely, this variability provides important information that may shed light on the laterality patterns of different cognitive domains.

Collateralization of different cognitive domains suggests a functional interaction among them (Cai & Van der Haegen, 2015). Several cognitive domains exhibit collateralization with respect to language processing, whereas other cognitive domains exhibit lateralization in the opposite hemisphere. Studies have reported that the complex motor movement was collateralized with language processing (Vingerhoets et al., 2013), whereas some studies have reported that attention and language tasks relatively activate the contralateral hemispheres (Cai, Van der Haegen, & Brysbaert, 2013; Powell, Kemp, & García-Finaña, 2012). However, it is still largely undetermined how the laterality patterns of language and arithmetic are associated in non-right-handers and which brain regions show such collateralization. If arithmetic processing was, indeed, based on the linguistic component shared in the IFG, arithmetic tasks would induce language-like lateralization in the IFG.

In the present study, we recruited 30 non-right-handed participants (including both left-handers and ambidextrous individuals) and evaluated lateralization using fMRI. Language lateralization, assessed by the Wada test and MRI, has shown that fMRI is a reliable noninvasive measurement of laterality (Binder et al., 1996; Woermann et al., 2003). The participants in the present study performed language, arithmetic, and working memory (WM) tasks in the MRI scanner (Fig. 1). The language and arithmetic (hereafter referred as Lang and Arith, respectively) tasks were based on those described by Makuuchi et al. (2012) to ensure that they had similar structures. Because Makuuchi et al. (2012) did not use control tasks for general cognitive load, we used a control WM task as described by Fedorenko et al. (2011). We hypothesized that brain activation induced by Lang and Arith tasks would exhibit similar lateralization patterns in the IFG. Specifically, we predicted that, if the Lang task induced left-lateralized activation, the Arith task also induced left-lateralized

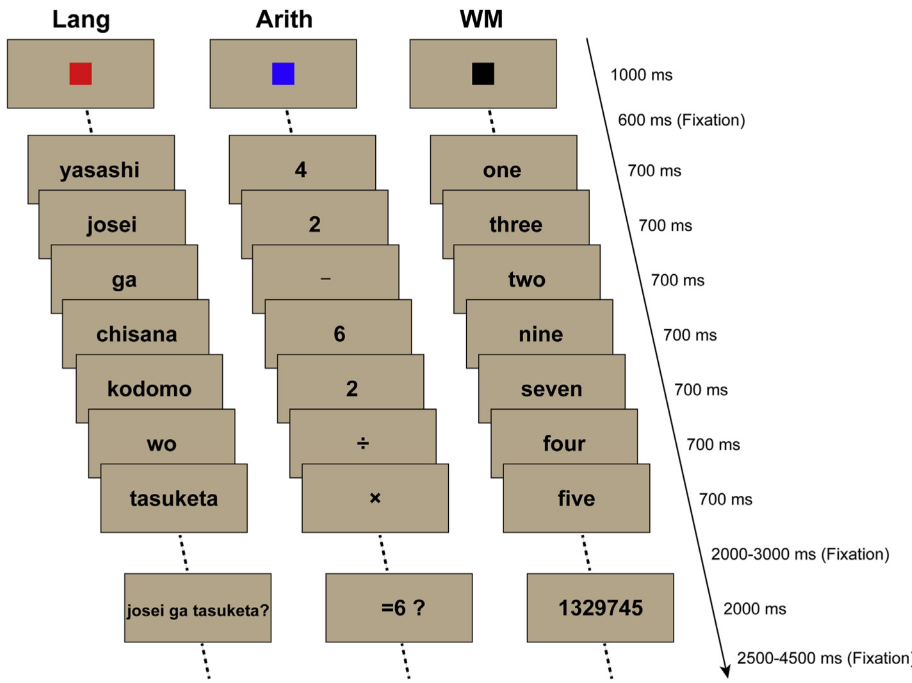

Fig. 1 – Task design. Language (Lang, left-most panel), arithmetic (Arith, center panel), and working memory (WM, right-most panel) tasks are described. Although the stimuli in the Lang task were presented using Japanese letters, they are described here using the Roman alphabet for general understanding. Each task comprised seven target stimuli and one probe stimulus.

activation (and vise-versa). We also predicted that the degree of lateralization in the Lang task and that in the Arith task is correlated. To the best of our knowledge, the present study addresses for the first time how lateralization patterns in language and arithmetic are related in non-right-handers.

2. Materials and methods

We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. *Participants*

Thirty healthy Japanese undergraduate students participated in this study (age, 19–25 years; mean age, 20.6 years; three females). Sample size was determined based on the previous fMRI study on the functional collateralization of non-right handers (Cai et al., 2013). All the participants were classified as non-right-handers (including both left-handed and ambidextrous) based on self-reported handedness, which was confirmed using Edinburgh Handedness Inventory (Oldfield, 1971), the FLANDERS questionnaire (Nicholls, Thomas, Loetscher, & Grimshaw, 2013; Okubo, Suzuki, & Nicholls, 2014), and the dot-filling test (Tapley & Bryden, 1985). We only recruited non-right-handers because they tend to show larger variability in the hemispheric lateralization than right-handers (Carey & Johnstone, 2014; Knecht et al., 2000; Pujol et al., 1999; Szaflarski et al., 2002a, 2002b) and they are appropriate for analyzing collateralization in language and arithmetic. No participant had a history of neurological disorders. Prior to their participation in the study, written informed consent was obtained from all the participants. The study was approved by the Ethics Committee of the University of Tokyo.

2.2. *Handedness assessment*

We used three types of handedness assessment. The first assessment included Edinburgh Handedness Inventory (Oldfield, 1971), which comprises 10 items, wherein the participants indicated their tendency of hand usage in their everyday activity by filling a single tick in the left or right column if they tended to use the indicated hand, two ticks if their preference was so strong that they would never try to use the other hand unless absolutely forced to, and a single tick in both the columns if they were indifferent to the hand usage. The laterality quotient (LQ) was calculated using the following formula:

$$LQ = 100 \cdot \frac{S_R - S_L}{|S_R| + |S_L|}$$

where S_R and S_L indicate the total number of ticks assigned to the right and left columns, respectively.

The second assessment included the FLANDERS questionnaire, which also comprised 10 items (Nicholls et al., 2013; Okubo et al., 2014), wherein the participants indicated their tendency of hand usage in their everyday activity by filling a single tick in the left or right column if they tended to use the indicated hand. The LQ was evaluated on the basis of the total number of ticks assigned to the right and left columns using the abovementioned formula.

Finally, the dot-filling test (Tapley & Bryden, 1985) is a performance-based assessment of handedness, wherein the participants were provided a piece of paper having four blocks on the top-left, top-right, bottom-left, and bottom-right sides. Each block comprised dot patterns with 110 dots. The participants were instructed to fill in as many dots as possible in 20 sec using either their right or left hand. Dot patterns in the top-left and bottom-right blocks were filled by their dominant hand, whereas those in the top-right and bottom-left blocks were filled by the other hand. The LQ was evaluated on the basis of the total number of dots filled by the left and right hands using the abovementioned formula.

2.3. *Stimuli and tasks*

Three fMRI tasks were used in this study. The Lang and Arith tasks were adopted from a study by Makuuchi et al. (2012), whereas the WM task was adopted from a study by Fedorenko et al. (2011). The fMRI experiment comprised four scanning sessions, each consisting of 24 trials (eight trials under each of the three conditions [Lang, Arith, WM]). These three conditions were randomly arranged in an event-related design, and a total of 96 trials were performed.

To gain familiarity with the task, the participants underwent short practice sessions before the fMRI sessions began. The trial order was randomized throughout the fMRI sessions, and counter-balanced across different participants to reduce the practice effect among the stimuli. Half of the participants responded using their right thumb, whereas the remaining half responded using their left thumb. The same number of button presses was required for all tasks. Each participant used the same hand for all the three tasks. The participants used earplugs in the scanner. Stimuli were presented on a liquid crystal display monitor (resolution: 1920 × 1080 pixels), which participants viewed through a mirror. A fixation point was displayed at the center of the screen during the presentation of the fixation screen, and participants were asked to fix their eyes on it. Presentation software (version 19.0; Neurobehavioral Systems, Albany, CA, USA) was used to control the stimulus presentation and collection of behavioral data.

Each trial began with the presentation of a red, blue, or black square cued at the center of the screen for 1000 msec, indicating the Lang, Arith, or WM task, respectively (Fig. 1). After 600 msec, the target stimuli were sequentially presented. The duration of the single frame was 700 msec (600 msec stimulus and 100 msec fixation except for the last frame). The stimuli comprised seven frames (total duration, 4800 msec). After 2000–3000 msec of fixation, the probe stimulus was presented for 2000 msec. The duration of a single trial was 10500–12500 msec. The intertrial interval was jittered in 2500–4500 msec.

In the Lang task, a single sentence that comprised seven words was presented in the format Adj1-N1-*wa/ga*-Adj2-N2-*wo/ni*-V (e.g., “yasashi-josei-ga-chisana-kodomo-wo-tasuketa,” *a kind woman saved a small kid*), wherein each element was presented in a separate frame (Adj, adjective; N, noun; V, verb; “ga,” “wa,” “wo,” and “ni” are Japanese case participles) (see Appendix A for the list of all sentences used in the current study). In 50% of the sentences, the verb was active (with the second case particle “wo”), and in the remaining 50%, the verb was passive (with the second case particle “ni”). The probe stimulus was a shortened sentence that comprised [N1/N2-*ga*-V (subject–verb phrase, e.g., “josei-ga-tasuketa?,” *did a woman save?*)], [N1/N2-*wo*-V (object–verb phrase)], or (N-wa-Adj1), [N2-wa-Adj2 (subject–predicate)]. In half of the probe stimuli, the combination of noun–adjective and noun–verb was broken by replacing the noun (i.e., N2 to N1 or N1 to N2), which, accordingly, did not match the content of the target stimulus. To prevent the participants from predicting the upcoming sentence form, we included both subject–verb and object–verb sentences. The nouns always referred to humans, and the verbs were always in the transitive past tense. All sentences comprised a different set of nouns, adjectives, and verbs. The participants were asked to judge if the content of the probe sentence was consistent with the content of the target sentence by pressing one of two buttons.

In the Arith task, we used the reverse Polish notation used in a previous study (Makuuchi et al., 2012), in which the operator is always presented after two digits rather than positioned between two digits as in normal notation (e.g., “2 4 +” and not “2 + 4”). It has been reported that the reverse Polish notation reduces the performance load compared with a normal notation (Kasprzyk, Drury, & Bialas, 1979). Additionally, reverse Polish notation does not require parentheses and, thus, reduces ambiguity in sequentially presented paradigms. We presented arithmetic expressions comprising digit–digit–operator–digit–digit–operator–operator sequence [e.g., “4,” “2,” “−,” “6,” “2,” “÷,” and “×,” that corresponded to “(4−2) × (6 ÷ 2)” in a normal notation]. The probe stimulus was a single digit with an equal sign on the left and a question mark on the right (“ = 6?”). In half of the probe stimuli, the presented digit was replaced with an incorrect digit (e.g., “ = 5?”). The participants were asked to judge if the result of the calculation was equal to the probe digit.

In the WM task, we sequentially presented seven digits in a Japanese word format (e.g., “ichi san ni kyu nana yon go,” *one three two nine seven four five*). The probe stimulus was seven digits in an Arabic digit format (e.g., “1 3 2 9 7 4 5”). In half of the probe stimuli, an adjacent digit pair was reversed (e.g., “1 3 2 9 7 4 5” became “1 3 2 9 7 5 4”). Participants were asked to judge if the target digits were the same as probe digits. In all the Lang, Arith, and WM tasks, participants were asked to respond during the presentation of the probe stimuli.

2.4. *MRI data acquisition*

The fMRI experiment was conducted using a 3.0-T scanner (MAGNETOM Prisma; Siemens, Erlangen, Germany) with a 64-channel head coil. We scanned 35 interleaved axial slices of 3.2 mm thickness with a .8-mm gap, parallel to the anterior and posterior commissure lines, using a T2-weighted gradient-echo echo-planar imaging (EPI) sequence [repetition time (TR) = 2000 msec, echo time (TE) = 30 msec, flip angle (FA) = 90°, field of view (FOV) = 192 × 192 mm^2, and resolution = 3 × 3 mm^2]. We obtained 178 volumes during each session, each following four dummy images, which allowed for an increase in the MR signals. For the anatomical reference, high-resolution T1-weighted images of the whole brain (176 sagittal slices, $1 \times 1 \times 1$ mm^3) were acquired from all the participants using a magnetization prepared rapid acquisition gradient-echo sequence (MPRAGE, TR = 2000 msec, TE = 2.9 msec, FA = 9°, and FOV = 256×256 mm^2).

2.5. fMRI data analysis

The fMRI data was analyzed using the SPM12 statistical parametric mapping software (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm/). The acquisition timing of each slice was corrected using the first slice as a reference for the EPI data. We realigned the EPI data from multiple sessions to the mean image across all sessions. The T1-weighted structural image of each participant was coregistered to the mean functional image generated during realignment and was then spatially normalized to the Montreal Neurological Institute (MNI) space with the new unified normalization-segmentation tool in SPM12. Following spatial normalization, the resultant deformation field was applied to the realigned functional imaging data and resampled into 2-mm isotropic voxels. Subsequently, an isotropic Gaussian kernel of 8 mm full-width at half maximum was used to smooth all normalized functional images. Low-frequency noise was removed using high-pass filtering at 1/128 Hz.

We adopted an event-related design using regressors comprising 4.8 sec box-car functions starting from the onset of the first frame of the target stimulus, convolved with the hemodynamic response function. We constructed three regressors of the Lang, Arith, and WM conditions. Six motion parameters generated during realignment were also included as regressors of no interest. The statistical threshold was set at $p < .001$ for the voxel level and $p < .05$ for the cluster level [family-wise error (FWE) correction for multiple comparisons] across the whole brain. To test the hypothesis that both Lang and Arith tasks coactivated the IFG, we performed a conjunction analysis using the Lang–WM and Arith–WM contrasts. The conjunction analysis was performed using the minimal sufficient statistic (Nichols, Brett, Andersson, Wager, & Poline, 2005), which used the smallest t-value among all the included contrasts in each voxel.

For the region of interest (ROI)-based beta estimate analysis, we defined 46 left and right pairs of anatomical ROIs according to the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002).

2.6. Laterality index

We calculated Laterality index (LI) values using the bootstrapping approach (Wilke & Lidzba, 2007; Wilke & Schmithorst, 2006). In this approach, 100 bootstrapped resamples were generated from the original voxels in the target ROI, and LI values were calculated on the basis of activation of all combinations (10,000) using the following equation:

$$\mathrm{LI} = 100 \cdot \frac{P_L - P_R}{|P_L| + |P_R|}$$

where P_L and P_R indicate the activation amplitude in the target ROI in the left and right hemispheres, respectively.

After trimming the upper and lower 25% of the resulting LI values, a mean LI value of the trimmed distribution was selected. This procedure was repeated 20 times using different thresholds ranging from 0 to the maximum value in the target ROI (with equally sized steps), and a weighted mean of multiple thresholds was calculated.

2.7. Analysis procedure based on LI

To test our hypothesis of collateralization of Lang and Arith tasks, we performed the following analyses. First, we calculated the Spearman's correlation coefficients between LIs in Lang–WM and Arith–WM contrasts in the triangular part of the IFG (IFGtri). To determine the relationship between behavioral performance and brain lateralization, we calculated correlation coefficients between LI values obtained in Lang–WM and Arith–WM contrasts and LQ values obtained using the Edinburgh Handedness Inventory, FLANDERS questionnaire, and dot-filling test. For exploratory purposes, we also calculated the LI values of Lang–WM and Arith–WM contrasts across all ROI pairs in the AAL atlas and calculated their correlation coefficients in all contralateral anatomical ROI pairs. To demonstrate the consistency of the correlation between language and arithmetic LIs using different laterality measures, we calculated LI values on the basis of the bootstrapping approach and determined LI values in the IFGtri and across the whole brain (Wilke & Lidzba, 2007).

LI values were calculated using the LI toolbox (Wilke & Lidzba, 2007). Pirateplot visualization was performed using a freely available code implemented in MATLAB (Phillips, 2017). MRIcron software (https://people.cas.sc.edu/rorden/mricron/index.html) was used for visualizing individual activation contrasts and anatomical IFG ROI (Fig. S1). Task presentation code, stimuli, and analysis code is available in Open Science Framework (OSF, https://osf.io/4r35q/). No part of the study procedure or study analyses was pre-registered prior to the research being conducted.

3. Results

3.1. Behavioral results

To confirm that the participants recruited in this study were non-right-handers, we evaluated their handedness using three different measures. The LQs were -61.1 ± 5.9 (min, −100; max, 0), -74 ± 6.2 (min, −100; max, 10), and -27.4 ± 1.9 (min, −56.8; max, −4.2) according to the Edinburgh Handedness Inventory (Oldfield, 1971), FLANDERS questionnaire (Nicholls et al., 2013; Okubo et al., 2014), and dot-filling test (Tapley & Bryden, 1985), respectively.

To show that task difficulty was controlled, we examined response accuracies from three tasks during the fMRI experiment. Response accuracies for the three tasks were 92.4 ± 1.4 (Lang), 93.7 ± 1.3 (Arith), and 88.1 ± 1.8 (WM). The Wilcoxon signed-rank test revealed that both Lang and Arith tasks demonstrated greater accuracy compared with the control WM task ($p < .0092$). Reaction times (RTs) for the three tasks were 1685 ± 37 msec (Lang), 1225 ± 27 msec (Arith), and 1766 ± 37 msec (WM). The Wilcoxon signed-rank test revealed that RTs for the WM task were significantly longer than for those for the Lang and Arith tasks ($p < .010$). The RTs for the Lang task were also significantly longer than those for the Arith task ($p < .0001$). These results indicate that the control WM task was the most difficult of the three tasks.

3.2. *Whole brain fMRI results*

We predicted that the bilateral IFG is a shared region for Lang and Arith tasks. To verify the plausibility of this prediction, we first examined whether Lang and Arith tasks showed overlapping activation in the bilateral IFG. Direct comparison between the Lang and WM tasks showed significant activation in the left medial orbitofrontal cortex (MOFC), bilateral superior frontal gyrus (SFG), left supplementary motor area (SMA), bilateral IFG, bilateral middle temporal gyrus (MTG), left superior temporal gyrus (STG), right anterior temporal lobe (ATL), left precuneus, and bilateral cerebellum (peak $p < .001$, cluster $p < .05$, with FWE correction) (Fig. 2A, Table 1). Direct comparison between the Arith and WM tasks showed significant activation in the bilateral IFG, bilateral middle frontal gyrus (MFG), bilateral inferior temporal gyrus (ITG), bilateral supramarginal gyrus (SMG), bilateral angular gyrus (AG), superior parietal lobule (SPL), and bilateral cerebellum (Fig. 2B, Table 1). Conjunction analysis of Lang–WM and Arith–WM contrasts showed activation only in the bilateral IFG (Fig. 2C, Table 1), indicating that the bilateral IFG is a shared substrate for the Lang and Arith tasks used in the present study.

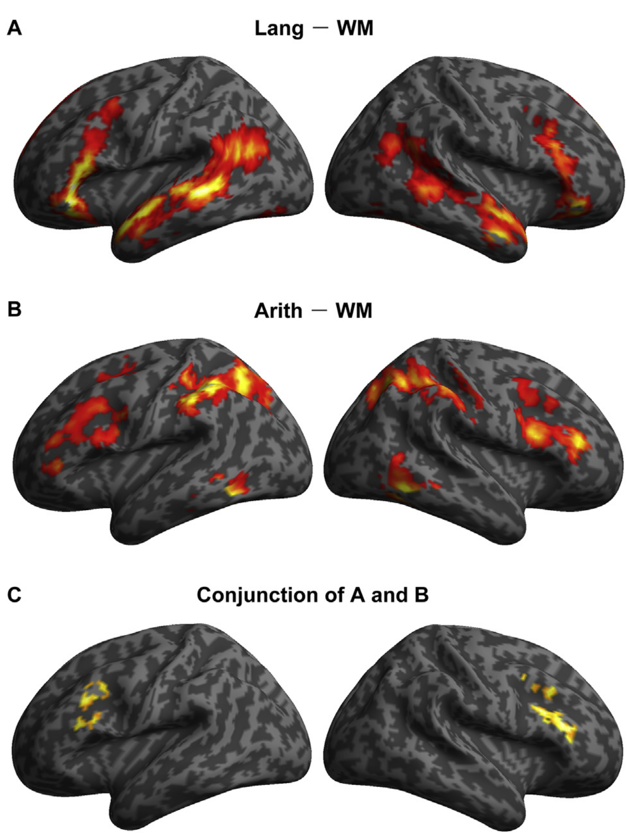

Fig. 2 – Shared activity of language and arithmetic tasks in the IFG. Group-level contrast of Lang–WM (A), Arith–WM (B), and the conjunction result of the two contrasts (C) are rendered on the standard brain. Peak level, $p < .001$; cluster level, $p < .05$ (with FWE correction).

3.3. *Laterality indices*

To evaluate individual variability in hemispheric lateralization, we calculated LI values in the IFGtri by using the bootstrapping approach (Wilke & Schmithorst, 2006). This approach is threshold independent and has been frequently used in recent studies on laterality (Bradshaw, Bishop, & Woodhead, 2017). Participants exhibited LI values ranging from −100 to 100 (Fig. 3). We fixed the p value at $p = .001$, and assigned participants with LI > 20 as left dominant, LI < −20 as right dominant, and $|LI| \le 20$ as bilateral. This laterality threshold was adopted from previous studies (Seghier, 2008; Springer et al., 1999). On the basis of the LI in the Lang–WM contrast, 19 participants (63.3%) were classified as left dominant, 8 (26.7%) as right dominant, and 3 (10.0%) as bilateral. On the basis of the LI in the Arith–WM contrast, 16 participants (53.3%) were classified as left dominant, 5 (16.7%) as right dominant, and 9 (30.0%) as bilateral. In Fig. 4, we present brain images of three participants who showed right dominance, left dominance, or bilateral activations with respect to both Lang and Arith tasks. Some participants showed opposite lateralization patterns (Fig. S1). Two participants were classified as left dominant in the Lang–WM contrast, while they were classified as right dominant in the Arith–WM contrast. Another three participants were classified as right dominant in the Lang–WM contrasts and left dominant in the Arith–WM contrasts.

3.4. *Correlations between LIs and hand preference*

Correlation coefficients between the LQs obtained in the behavioral batteries and LIs obtained on the basis of brain

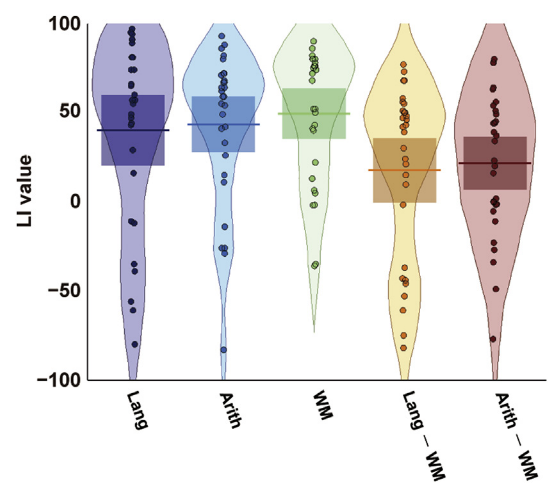

Fig. 3 – Distribution of laterality indices in all tasks. Pirateplots showing distribution of laterality index (LI) values in the Lang, Arith, WM tasks (without baseline contrast), as well as Lang–WM and Arith–WM contrasts. For each task or contrasts, a smoothed density curve of the LI distribution is shown, with the mean bar (horizontal bar) and the 95% confidence interval (shaded area around the mean).

Table 1 – Direct comparison of the Arith, Lang, and WM tasks.

Brain region	BA	Side	x	y	z	T-value	Voxels
Lang–WM							
MOFC	11	L	−2	50	−16	11.06	342
SFG	10	L	−6	56	28	9.50	2738
	9		−8	50	46	8.24	
SMA	6	L	−8	18	62	6.65	
SFG	10	R	8	54	22	7.46	
	9	R	6	50	38	5.92	
			12	40	54	5.72	
IFG	47	L	−48	26	−4	15.00	9280
	45		−54	24	14	11.18	
MTG	21	L	−56	−36	0	13.58	
STG	22	L	−54	−4	−12	11.82	
			−50	10	−18	11.71	
			−56	−20	−4	11.02	
IFG	47	R	44	34	−14	10.78	6754
	44	R	42	20	24	9.19	
	45	R	56	30	8	8.34	
ATL	38	R	46	16	−22	9.53	
MTG	21	R	56	2	−20	11.84	
			68	−44	4	8.46	
Precuneus	7	L	−2	−56	26	8.98	1162
Cerebellum		L	−14	−82	−38	6.17	249
Cerebellum		R	20	−80	−36	9.20	553
Arith–WM							
IFG	45	L	−42	42	4	6.67	1930
			−48	26	24	5.55	
	44	L	−50	8	28	6.55	
			−46	26	40	5.187	
MFG	9	L	−46	16	48	3.58	
	8	L	−28	14	56	6.52	606
IFG	45	R	42	32	18	7.93	2380
	44	R	52	12	26	7.77	
MFG	6	R	36	6	42	4.58	
	8	R	36	8	58	3.68	
ITG	37	L	−52	−52	−12	8.21	346
ITG	37	R	52	−52	−10	8.70	722
SMG	40	L	−50	−40	44	11.50	4241
			−56	−30	40	9.02	
AG	7/39	L	−34	−60	48	9.74	
			−28	−68	36	7.82	
SPL	7	L	−18	−70	60	6.61	
AG	7/39	R	30	−66	46	8.27	3662
SMG	40	R	46	−36	48	8.10	
			58	−20	34	5.66	
SPL	7	R	46	−40	60	5.72	
Cerebellum		L	−28	−76	−50	5.49	273
			−10	−78	−26	4.10	
Cerebellum		R	26	−64	−32	6.73	302
			32	−72	−46	6.09	
Conjunction of (Lang–WM) and (Arith–WM)							
IFG	45	R	48	30	18	5.92	724
	44		48	18	28	5.55	
	44		36	8	40	4.05	
IFG	45	L	−48	26	24	5.55	418
	44		−40	10	38	4.59	
	44		−54	16	18	3.84	

Stereotactic coordinates (*x, y, z*) in the Montreal Neurological Institute (MNI) space (mm) are shown for each activation peak with Z-values, for the Lang–WM, Arith–WM, and conjunction of Lang–WM and Arith–WM contrasts. AG, angular gyrus; ATL, anterior temporal lobe; DPMC, dorsal premotor cortex; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; LPMC, lateral premotor cortex; MFG, middle frontal gyrus; MOFC, medial orbitofrontal cortex; MTG, middle temporal gyrus; SFG, superior frontal gyrus; SMA; supplementary motor area; SMG, supramarginal gyrus; SPL, superior parietal lobule. L, left hemisphere; R, right hemisphere.

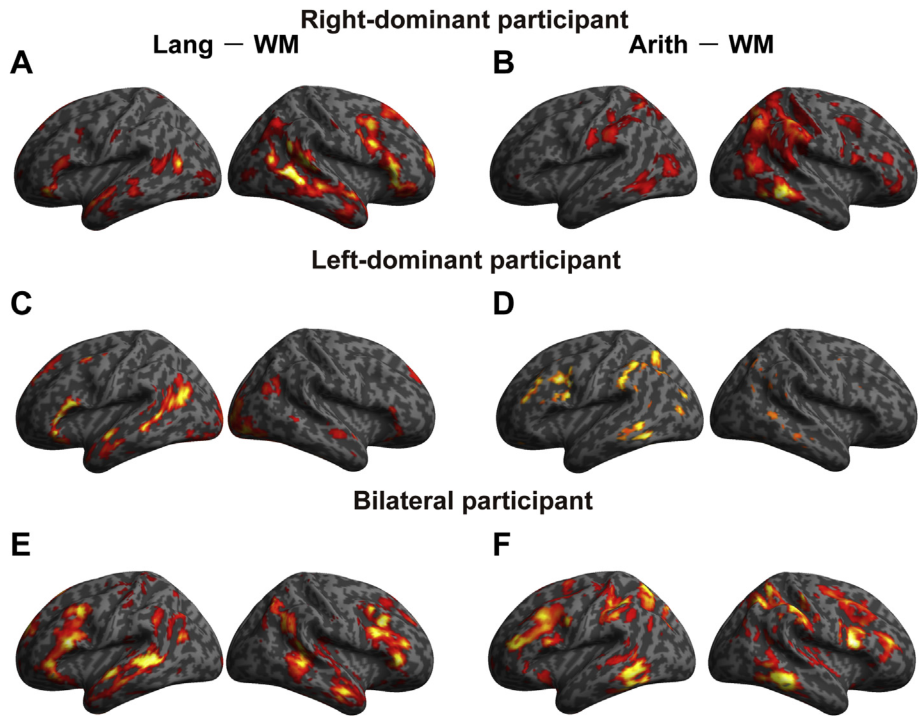

Fig. 4 – Examples of right-dominant, left-dominant, and bilateral participants. (A–B) Examples of Lang–WM and Arith–WM contrasts in a representative right-dominant participant (participant ID05), (C–D) left-dominant participant (ID10), and (D–E) bilateral participant (ID03). Images were rendered on the standard brain. Uncorrected $p < .001$ (peak level).

activation from the Lang–WM contrast were calculated; no significant Spearman's correlation coefficient was found (Edinburgh Handedness Inventory, $\rho = .10$, $p = .30$; FLANDERS questionnaire, $\rho = .19$, $p = .16$; dot-filling test, $\rho = .13$, $p = .24$). For the Arith–WM contrast, a significant negative correlation was observed between the LIs and LQs obtained with the Edinburgh Handedness Inventory ($\rho = -.39$, $p = .031$) and FLANDERS questionnaire ($\rho = -.39$, $p = .033$); however, this was not below the significance level with Bonferroni correction for multiple comparisons. Furthermore, no significant correlation was observed with the dot-filling test ($\rho = .09$, $p = .31$), indicating that individual variability in cortical lateralization does not directly correspond to individual variability in handedness assessments.

Half of the participants used their left hand for button responses, while the remaining half used their right hand. We then tested whether the hand selection affected LI values. The Wilcoxon signed-rank test revealed no significant difference in LI values between left-hand and right-hand assigned participants in the Lang–WM contrasts ($p = .67$), as well as in the Arith–WM contrast ($p = .32$). These results indicate that the selection of response hands did not affect the LI values.

3.5. *Correlations between LIs for Lang and Arith in the IFG*

The comparison of results obtained from the Lang and Arith tasks revealed that some participants were categorized as left dominant in the Lang–WM contrast but as bilateral in the Arith–WM contrast. The categorization of left/right dominance was also dependent on the lateralization threshold of $|LI| = 20$. To examine the interdomain relationship of laterality between language and arithmetic, we calculated the Spearman's correlation coefficient between LI in Lang and Arith tasks in the IFGtri (Fig. 5A) and found that the correlation between language and arithmetic LIs was not significant ($\rho = .30$, $p = .055$). We also examined whether the baseline contrast affected LI values. We calculated LI values in the Lang, Arith, and WM tasks without baseline and found no significant correlations between the Lang and Arith tasks ($\rho = -.02$, $p = .29$), Lang and WM tasks ($\rho = .062$, $p = .38$), or Arith and WM tasks ($\rho = .22$, $p = .12$).

3.6. *Correlations between LIs for Lang and Arith across all ROIs*

To examine collateralization patterns across the whole brain, we calculated the LI values of Lang–WM and Arith–WM contrasts and their Spearman's correlation coefficients in all contra-lateral anatomical ROI pairs across the whole brain. This analysis was performed for an exploratory purpose. To examine ROIs related to language and arithmetic processing, we selected regions where we obtained suprathreshold activation in more than two-thirds of participants with a liberal threshold of uncorrected $p < .01$ (Fig. 5B). This inclusion criterion was determined prior to the data analysis. We found that most perisylvian language-related regions [precentral

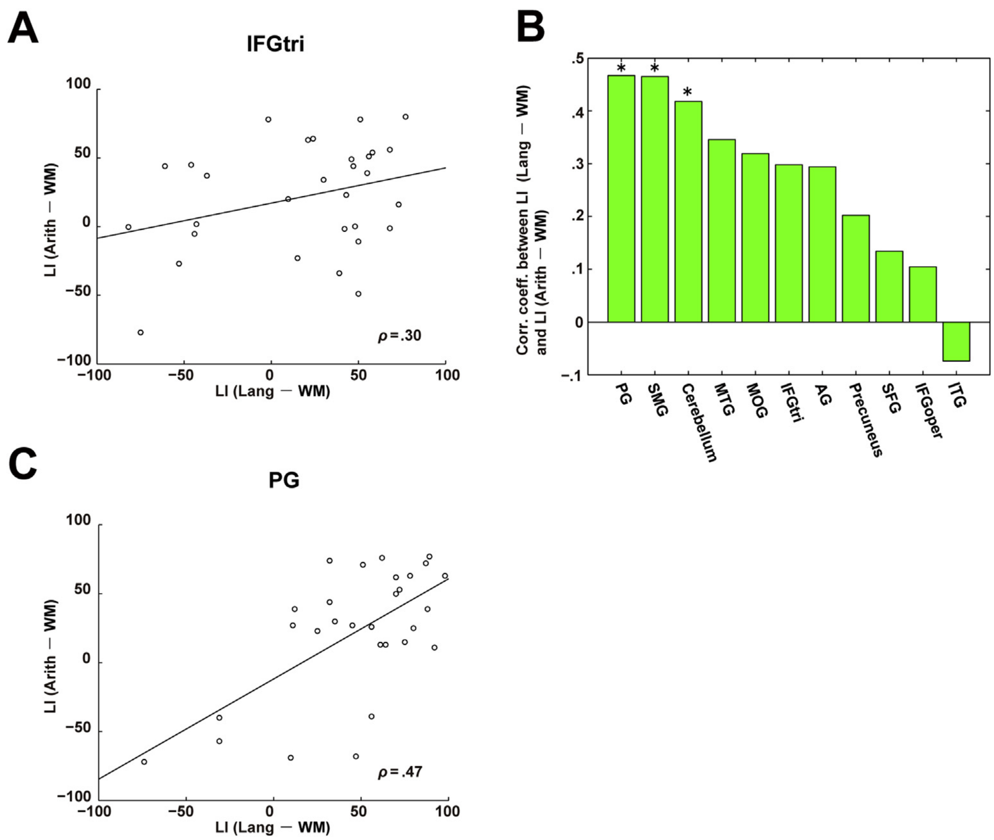

Fig. 5 – Correlation of laterality in language and arithmetic. (A) Scatter plot shows correlation between LI value of Lang–WM contrast and that of Arith–WM contrast in the IFGtri. (B) A list of LI value correlation coefficients in candidate brain regions using a bootstrapping approach. AG, angular gyrus; IFGoper, opercular part of inferior frontal gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; PG, precentral gyrus; SFG, superior frontal gyrus; SMG, supramarginal gyrus. *, uncorrected $p < .05$. (C) Scatter plot shows correlation between LI value of Lang–WM contrast and that of Arith–WM contrast in the PG.

gyrus (PG), IFG, MTG, AG, and SMG] showed positive correlation coefficients between language and arithmetic. Among all regions, PG, SMG, and cerebellum were significantly correlated ($p < .016$). The PG, which is located slightly posterior to the IFG, showed the highest correlation coefficient (Fig. 5C).

4. Discussion

In the present study, 30 non-right-handers performed Lang and Arith tasks, during which brain activation was monitored using fMRI. The results showed shared activity of language and arithmetic in the bilateral IFG. We found variable laterality patterns, including right dominance, left dominance, and bilaterality in both Lang and Arith tasks. Furthermore, we demonstrated that the LI values in language and arithmetic were positively correlated in the regions around the IFG.

The IFG is considered as one of the central regions for language processing (Price, 2010). Additionally, activation in the left IFG has been identified in studies on arithmetic processing (Delazer et al., 2003; Evans, Flowers, Luetje, Napoliello, & Eden, 2016; Ischebeck et al., 2007; Menon et al., 2000; Qin et al., 2014). Other studies have also found IFG activation in terms of the syntactic component in arithmetic tasks (Hung et al., 2015; Nakai & Sakai, 2014). Makuuchi et al. (2012) have reported shared activity in the bilateral IFG for Lang and Arith tasks. Syntactic interaction between language and arithmetic has also been demonstrated in the bilateral IFG (Nakai & Okanoya, 2018). The findings of the present study are in line with those reported previously and suggest that a shared component in the Lang and Arith tasks induces overlapping activation in the bilateral IFG.

The involvement of the IFG in the syntactic component of language processing has been previously demonstrated (Musso et al., 2003; Pallier, Devauchelle, & Dehaene, 2011), and its association with phonological and semantic components has also been reported (Costafreda et al., 2006; Katzev, Tuscher, Hennig, Weiller, & Kaller, 2013; Sahin, Pinker, Cash, Schomer, & Halgren, 2009). Because the aim of the present study was to investigate the hemispheric collateralization of language and arithmetic in general, we did not examine how detailed components of linguistic (phonology, semantics, and syntax) and arithmetic (numerical cognition, linguistic components, and memory components) information contributed to collateralization, which is a limitation of the study. It is also worth considering whether the activation overlap and shared lateralization of language and arithmetic were caused by covert articulation because the IFG is well known to be related to speech production (Price, 2010). Using the verbal WM task as a basic control, we excluded the possible effects of covert articulation and memory load from both Lang and Arith tasks. Future studies must aim to elucidate what types of subcomponents in language and arithmetic provide the collateralization.

The positive correlation coefficient between the LI values of language and arithmetic supports the view that the IFG is a shared brain region for both Lang and Arith tasks. Although we demonstrated activation overlap between language and arithmetic, overlapping (average) activation for the two cognitive domains did not indicate that the two domains were also common in activation patterns of individual variability. Collateralization of the two cognitive domains provided supporting evidence for the commonality of these domains (Cai & Van der Haegen, 2015). We showed that language and arithmetic are also common in terms of collateralization, thereby supporting the view that language and arithmetic share their neural basis.

Pinel & Dehaene (2010) examined collateralization of language and arithmetic in right-handers and reported collateralization between different brain regions, such as the posterior superior temporal sulcus during sentence processing and the intraparietal sulcus during calculation. The results of the present study differ from this previous study in two aspects. First, we recruited non-right-handers, who exhibit larger variability in their lateralization patterns (Knecht et al., 2000; Pujol et al., 1999; Szaflarski et al., 2002a, 2002b) and would be suitable for examining cortical collateralization patterns of different cognitive domains (Cai & Van der Haegen, 2015). Second, Pinel & Dehaene (2010) examined collateralization between different brain regions but did not examine a lateralization pattern in a single cortical region for language and arithmetic.

In whole-brain LI analysis, the PG, which is located slightly posterior to the IFG, exhibited the highest LI correlation coefficient. The slight spatial difference from the group contrast result (Fig. 2) might be caused by the difference in the calculation method used. The group contrast result was related to the amplitude in a single ROI, whereas the LI correlation result was calculated using the bilateral ROI data. High amplitude in a ROI of a single hemisphere does not necessarily reflect large interhemisphere differences.

Although we found overall positive correlation between the LI values in language and arithmetic, five participants (16.7%) deviated from the hypothesized collateralization between language and arithmetic in the IFGtri (Fig. S1). Previous studies on the collateralization of different cognitive domains also reported individual variability regarding inconsistent lateralization of non-right-handers. For the language and spatial attention, Cai et al (2013) reported that one out of 29 participants (3.5%) showed inconsistent lateralization if a control spatial processing task is used as the baseline; however, four other participants also showed inconsistent lateralization (17.0%) if resting condition is used as the baseline. In the study of Powell et al (2012), 15 out of 40 participants (37.5%) showed inconsistent lateralization. For the language and tool use, Vingerhoets et al (2013) reported that one out of 19 participants (5.3%) showed inconsistent lateralization. Regarding the collateralization between different ROIs, Van der Haegen et al (2012) reported that 10 out of 57 participants (17.5%) showed inconsistent lateralization between IFG and ITG (based on the criterion of $|LI| < 20$). In the current study, the individual variability of inconsistent lateralization is within the range of previous studies.

This discrepancy might be caused by the individual variability of activated regions. Individual activation cluster does not always match the anatomical reference ROIs. Individual activation maps indicate that the Arith−WM contrast tended to be located in the anterior and dorsal parts of the IFGtri ROI, whereas the Lang−WM contrast tended to be located in the posterior part (Fig. S1). Another possibility is that individual differences in language experience affected arithmetic-induced activations. A previous study has reported that language-specific experience modulates the activation patterns in the IFG during arithmetic task (Lin, Imada, & Kuhl, 2012). Further research on a large scale is warranted to clarify how lateralization is affected by the individual variability.

5. Conclusion

We conclude that language and arithmetic processing in non-right-handers exhibits collateralization primarily around the IFG and that such collateralization patterns are based on the shared linguistic component across language and arithmetic.

Declaration of Competing Interest

The authors declare no competing interests.

Data availability

The conditions of our ethics approval do not permit public archiving of anonymised study data. Readers seeking access to the data should contact the corresponding author K. O. or the local ethics committee at the Graduate School of Arts and Sciences, the University of Tokyo. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. There is no conditions for requestors to obtain the data.

Open practices

The study in this article earned an Open Materials badge for transparent practices. Materials for the study are available at OSF, https://osf.io/4r35q/.

CRediT authorship contribution statement

Tomoya Nakai: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Funding acquisition. **Kazuo Okanoya:** Conceptualization, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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Appendix A. Sentence stimuli used in the Lang task.

1. A doting father celebrated his beloved son. Did the father celebrate?
2. A mean mother pinched her clumsy friend. Did the mother pinch?
3. A scheming manager hired an excellent lawyer. Was the lawyer hired?
4. An arrogant senior citizen kicked a busy station attendant. Was the station attendant kicked?
5. A new company president was hit by an old employee. Did the employee hit?
6. A reckless middle school student was caught and admonished by a small policewoman. Did the policewoman catch and admonish?
7. A weak entertainer was criticized by his short-tempered manager. Was the entertainer criticized?
8. A beautiful actress was scolded by her harsh director. Was the actress scolded?
9. A plump fish dealer introduced an interesting chef. Was the fish dealer plump?
10. An insistent detective investigated a flirtatious musician. Was the detective insistent?
11. A cheerful nurse encouraged a sad-looking patient. Was the patient sad-looking?
12. A famous doctor called a high-handed clerk. Was the clerk high-handed?
13. A loud tourist was shouted at by a large shopkeeper. Was the tourist loud?
14. A sophisticated actor was supported by spectators easily moved to tears. Was the actor sophisticated?
15. A serious researcher was disparaged by a stubborn professor. Was the professor stubborn?
16. A thinnish cameraman was hit by a moody singer. Was the singer moody?
17. A famous fortuneteller threatened an unfortunate woman. Did the woman threaten?
18. An energetic grandmother appreciated her hard-working grandchild. Did the grandchild appreciate?
19. A kind high school student saved a small kitten. Was the high school student saved?
20. A talented newcomer sued a violent section manager. Was the newcomer sued?
21. A young elementary school student was bullied by a big middle school student. Did the elementary school student bully?
22. A noisy entertainer was warned by a strict train conductor. Did the entertainer warn the conductor?
23. A brutal felon was defeated by a big-hearted martial artist. Was the martial artist defeated?
24. A stingy rich person was glared at by his petite wife. Was the wife glared at?
25. A cold manager fired an incompetent employee. Was the manager incompetent?
26. A patient teacher taught a nervous student. Was the teacher nervous?
27. A laudable staff member guided a young visitor. Was the visitor laudable?
28. A clever technician persuaded an obstinate superior. Was the superior clever?
29. A timid class teacher was reprimanded by an unreasonable principal. Was the class teacher unreasonable?
30. A wise interpreter was praised by a handsome foreigner. Was the interpreter handsome?
31. An obedient announcer was beaten up by a sly bureau director. Was the bureau director obedient?
32. A kind author was lectured by a self-important editor. Was the editor kind?

Appendix. BSupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2019.11.009.

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