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Manual praxis and language-production networks, and their links to handedness



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ABSTRACT

While Liepmann was one of the first researchers to consider a relationship between skilled manual actions (praxis) and language for tasks performed “freely from memory”, his primary focus was on the relations between the organization of praxis and left-hemisphere dominance. Subsequent attempts to apply his apraxia model to all cases he studied – including his first patient, a “non-pure right-hander” treated as an exception – left the praxis-handedness issue unresolved. Modern neuropsychological and recent neuroimaging evidence either showed closer associations of praxis and language, than between handedness and any of these two functions, or focused on their dissociations. Yet, present-day developments in neuroimaging and statistics allow us to overcome the limitations of the earlier work on praxis-language-handedness links, and to better quantify their interrelationships. Using functional magnetic resonance imaging (fMRI), we studied tool use pantomimes and subvocal word generation in 125 participants, including righthanders ($N_{RH} = 52$), ambidextrous individuals (mixedhanders; $N_{MH} = 31$), and lefthanders ($N_{LH} = 42$). Laterality indices were calculated both in two critical cytoarchitectonic maps, and 180 multi-modal parcellations of the human cerebral cortex, using voxel count and signal intensity, and the most relevant regions of interest and their networks were further analyzed. We found that atypical organization of praxis was present in all handedness groups (RH = 25.0%, MH = 22.6%, LH = 45.2%), and was about two and a half times as common as atypical organization of language (RH = 3.8%; MH = 6.5%; LH = 26.2%), contingent on ROI selection/LI-calculation method. Despite strong associations of praxis

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and language, regardless of handedness and typicality, dissociations of atypically represented praxis from typical left-lateralized language were common (~20% of cases), whereas the inverse dissociations of atypically represented language from typical left-lateralized praxis were very rare (in ~2.5% of all cases). The consequences of the existence of such different phenotypes for theoretical accounts of manual praxis, and its links to language and handedness are modeled and discussed.

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1. Introduction

Skillful use of hands for complex movements and handling of tools, as well as the ability to communicate using language are some of the most fundamental human traits. Likewise, the lateralization of the neural processes and mechanisms underlying these faculties are critical hallmarks of the human brain functioning. Interestingly, in the vast majority of people the left cerebral hemispheres play a dominant role in the control of these functions (e.g., Goodglass & Kaplan, 1963). Whether or not this phenomenon also reflects some common neural underpinnings and shared cognitive processing has been of research interest, and a question of debate for well over a century.

Some evidence suggesting that the control of skilled or purposeful manual actions (praxis) and language production might be linked was already stemming from seminal descriptive observations made by an early student of Carl Wernicke, the German neurologist Hugo Liepmann (Liepmann, 1908). While Liepmann was definitely not the first to report such associations, as the German linguist Heymann Steinthal (Steinthal, 1881) already described a musician with impaired grasping of tools, including his violin (and called this disorder *apraxia*), together with speech impairments (aphasia), it was Liepmann who related the concept of apraxia to left-hemisphere dominance, and strengthened the notion that, similarly to aphasia, apraxia is a cognitive deficit of motor control (Liepmann, 1908, 1920, 1925). In Liepmann's view (1900; Liepmann, 1905), apraxia is a disorder on its own, and can occur independently from fundamental motor, perceptive or communicative disorders, albeit frequently co-occurring with them (for review, see Goldenberg, 2003). In fact, although Liepmann was among the first researchers to consider links between praxis and language for tasks performed “freely from memory” (Liepmann, 1912), as the control of movements performed without objects could be similar to the control of spoken language, he eventually abandoned this notion. Instead, he postulated that apraxia is a result of disrupted connections between intact (tool/action) concepts and motor centers (i.e., the concepts could not be reliably retrieved or transmitted, especially from one hemisphere to the other). Thus, not being impressed by the observations that both praxis and language typically depend on the left hemisphere resources (Liepmann, 1908), and being able to demonstrate that apraxia is not a result of lost comprehension, his primary focus diverted from any putative praxis-language links. Indeed, he focused on the more apparent and, potentially,

more important relations between the general organization of manual praxis and hemisphere dominance. Later on, while developing his disparate apraxia concepts (e.g., Liepmann, 1908; 1920; 1925), he did not explore the issue of praxis-language relationships any further.

As convincingly argued by Goldenberg (2013b), most of the theories of apraxia either emphasized its association with language functions (e.g., Duffy & Duffy, 1981; Finkelnburg, 1870; Goldenberg, Hartmann, & Schlott, 2003; Goldenberg & Randerath, 2015; Head, 1920; Jackson, 1893; Pickett, 1974; Steinthal, 1881; Wang & Goodglass, 1992) or with handedness, or rather hand dominance mechanisms (Goodglass & Kaplan, 1963; Liepmann, 1908). The latter approach (as of Geschwind, 1965, p. 609: “the apraxia frequently accompanies the aphasia but is independent of it”) gradually evolved into accounts emphasizing higher-order motor control issues, and the critical involvement of the left-hemisphere inferior parietal lobule (IPL) and/or associated left-lateralized networks, regardless of handedness and language functions (e.g., Frey, Funnell, Gerry, & Gazzaniga, 2005; Goldenberg, 2009; Buxbaum, Shapiro, & Coslett, 2014; for recent reviews, see; Goldenberg, 2013a; Baumard, Osiurak, Lesourd, & Le Gall, 2014; Buxbaum & Randerath, 2018). Yet, numerous dissociations between praxis, and/or language, and handedness (e.g., Alexander & Annett, 1996; Raymer et al., 1999) or praxis and language in both their typical and atypical forms (e.g., Margolin, 1980; Rapcsak, Gonzalez Rothi, & Heilman, 1987), seem to indicate that, at an individual-subject level, neither of the postulated associations are mandatory, and the general model itself does not account for all known exceptions. Namely, apraxia can, in fact, dissociate both from aphasia and handedness in disparate combinations (Goldenberg, 2013b, see also; Borod, Carper, Naeser, & Goodglass, 1985). On the other hand, many people with atypically represented language functions show similar lateralization of praxis skills, regardless of their handedness (Meador et al., 1999). While the latter results may be influenced by epilepsy-related functional reorganization, there are also reports of congruent atypical organization of praxis and language, despite no documented history of early brain injuries or seizures. For example, a right-handed individual studied by Fischer and collaborators (Fischer, Alexander, Gabriel, Gould, & Milione, 1991) showed reversed praxis asymmetries congruent with the right-sided lateralization of language, and Lesourd with colleagues (Lesourd, Naegele, Jaillard, Detante, & Osiurak, 2020) recently reported a case of a left-handed individual with a partial association of bilaterally organized praxis and left-lateralized language.

Nonetheless, most of the modern neuropsychological investigations on the laterality of praxis and language have been usually single case, or small group studies, and the seminal paper by [Goldenberg \(2013b\)](#) was a large project but limited to one handedness group, namely lefthanders. Such reports, even if meta-analyzed ([Carey & Johnstone, 2014](#)), cannot provide a full picture of various relationships between the organization of the neural substrates of skilled actions, language production, and handedness. Furthermore, making inferences about functional lateralization based on the workings of a lesion-damaged brain can be tricky (see [Johnstone, Karlsson, & Carey, 2020](#) for a few more arguments), and was already compared to the process of figuring out how a radio works by the removal of its pieces ([Gregory, 1961](#)). Therefore, a large-scale investigation in healthy individuals is greatly needed.

Capitalizing on the attainments of earlier studies on putative language-praxis links in healthy, though often atypical, individuals ([Kroliczak, Piper, & Frey, 2011](#); [Vingerhoets et al., 2013](#); [Kroliczak, Piper, et al., 2020](#)), and previous investigations of praxis skills in righthanders and/or lefthanders ([Buchwald, Przybylski, & Kroliczak, 2018](#); [Kroliczak & Frey, 2009](#); [Kroliczak, Piper, & Frey, 2016](#); [Przybylski & Kroliczak, 2017](#); [Styrkowiec, Nowik, & Kroliczak, 2019](#); [Vingerhoets, Acke, Vandemaële, & Achten, 2009](#); [Vingerhoets et al., 2012](#)), in this project on praxis-language-handedness relationships we studied a sizable sample of non-right handers (including ambidextrous individuals), in addition to consistent righthanders. Using functional magnetic resonance imaging (fMRI), we exploited its tremendous potential for quantifying hemispheric organization of functions ([Johnstone et al., 2020](#)) in tool use pantomimes and subvocal word generation, across all handedness groups. Our goal was threefold: (1) to corroborate the existence of strong associations (i.e., significant positive correlations of laterality indices, LIs) between praxis and language across numerous regions of interest (ROIs), regardless of handedness; (2) to establish the incidence rate of atypical organization of praxis and atypical organization of language (known to be present in all handedness groups, but most frequent in lefthanders); and (3) to analyze the patterns of dissociations identified in our sample.

Based on our earlier work ([Bidula & Kroliczak, 2015](#)), we hypothesized that the praxis-language links would be weaker in righthanders and mixedhanders than in lefthanders. Furthermore, we suspected that it will be the case only for participants with typical organization of functions, even regardless of handedness. (Therefore, not all lefthanders would show such stronger links; the ones with the typical lateralization of functions would not.) We expected that atypical organization of praxis or language would be more common among lefthanders, and that the most common dissociation would be the one for right-lateralized praxis, and left-lateralized language (with the inverse dissociations being very rare; [Kroliczak, Piper, et al., 2020](#)).

We found that dissociations of atypically organized (i.e., bilateral or right-hemispheric) praxis from typically represented (left-lateralized) language were between six to eight times more frequent (depending on the criterion) than the inverse dissociations of atypically organized language from typically represented (i.e., left-lateralized) praxis. Critically,

never in mixedhanders and only rarely in righthanders has atypical representation of language dissociated from typically left-lateralized praxis. Consistent with an earlier patient study ([Finkel, Hogrefe, Frey, Goldenberg, & Randerath, 2018](#)), we also uncovered that even in the case of dissociations, praxis and language were linked across many ROIs. As hypothesized, participants with atypically organized/lateralized functions showed stronger praxis-language links. Our discussion of the existence of different praxis-language-handedness phenotypes ([Vingerhoets, 2019](#)), their frequencies and their interrelationships clearly illustrates their significance for the understanding of general functional organization of the nervous system one century after Liepmann's seminal work ([Osiurak & Bartolo, 2020](#)).

2. Experiments

2.1. Methods

2.1.1. Participants

One hundred and twenty five healthy volunteers, native speakers of Polish, 52 righthanders [mean age (M_A) = 22.1, standard deviation (SD) = 1.9], 31 mixedhanders (M_A = 22.9, SD = 4.2), and 42 lefthanders (M_A = 23.1, SD = 3.2), typically students of, or graduates from, Poznań universities, were tested in two consecutive, larger fMRI projects. Volunteers were required to be healthy adults, between the age of 18 and 40. Exclusion criteria involved no medically documented history of neurological or psychiatric disorders, no contraindications to undergoing MRI, and no obvious brain malformations (visible in the obtained scans). These criteria were established prior to data acquisition, their analyses, all manipulations, and all measures used in our projects. Only praxis and language neuroimaging data from the obtained three samples were used in this report. There were 63 participants whose unique neural characteristics of productive language and resting state connectivity were described elsewhere ([Bidula, Przybylski, Pawlak, & Kroliczak, 2017](#)), further 21 participants included in a short communication devoted exclusively to lefthanders ([Kroliczak, Piper, et al., 2020](#)), as well as an additional cohort of 41 participants, whose neuroimaging results in relevant praxis and language production tests have never been described before. Except for initial tests within two ROIs carried out for consistency with our earlier studies, all key analyses performed in this project are completely different from any of our previous reports. The tested sample included 64 females and 61 males, M_A = 22.6 years, and SD of ± 3.1 years (range = 20, min. 19 and max. 39) at the time of fMRI testing. Because our main goal was to find out as many disparate combinations of multiple asymmetries as possible, a large group of non-right handers was included to increase the likelihood of identifying rare individuals who either show right-hemisphere dominance for praxis and/or language, or their combinations with other (e.g., bilateral) types of organization (e.g., [Johnstone et al., 2020](#); [Kimura, 1983](#); [Knecht et al., 2000](#)). As indicated by the revised Edinburgh Handedness Inventory (EHI, [Oldfield, 1971](#)), our participants varied from strongly right handed, through ambidextrous (mixed handed), to strongly left handed: the

mean laterality index, $LI = 10.0$, $SD = 75.8$; range = 200, min. = -100 , max. $+100$. To be quite conservative while identifying ambidexterity (e.g., Whitehouse, Badcock, Groen, & Bishop, 2009, where scores $\geq +40$ denote right-handed, ≤ -40 denote left-handed, and ambidextrous or mixed-handed individuals are placed in between), we adopted the $\geq +33.3$ and ≤ -33.3 LI cutoffs for assigning volunteers to the right-handed and left-handed groups, with mixed-handed individuals located in between. With these criteria, the mean LIs for the three sampled groups were the following: righthanders₍₅₂₎ $LI = 89.1$, $SD = 16.3$, mixedhanders₍₃₁₎ $LI = .2$, and $SD = 21.4$, and lefthanders₍₄₂₎ $LI = -80.6$, $SD = 16.5$. The required sample size was determined by percentages of atypical organization/lateralization of praxis and language functions from our earlier and/or source studies (Kroliczak et al., 2011; Kroliczak et al., 2016; Kroliczak, Piper, et al., 2020), as well as its incidence in a large sample of healthy participants balanced for handedness (Mazoyer et al., 2014; Mellet et al., 2014; see also; Woodhead, Thompson, Karlsson, & Bishop, 2021). All volunteers signed written informed consents for participation in these studies (embedded pseudorandomly among other localizer tasks), approved by the Bioethics Committee at Poznań University of Medical Sciences (Ethical Approval No. 63/12), and complying with the principles of the 2013 WMA Declaration of Helsinki. (No part of this study was pre-registered prior to the research being conducted.)

2.1.2. Tasks

2.1.2.1. PRAXIS TESTS. In the main, “grasp and tool use gesture” task employed here (as in Przybylski & Kroliczak, 2017), the participants planned and immediately executed tool use pantomimes, in response to tool images, displayed via a coil-mounted mirror on the monitor behind the scanner. Such visual tool use pantomimes (similarly to our haptic tool use task, with a different method of stimulus delivery; Nowik, Styrkowiec, & Kroliczak, 2019; Styrkowiec et al., 2019), were therefore substantially different from typical tool use pantomimes. Namely, in addition to simulated grips (coarticulated with the ‘use component’ of the movement), gesture retrieval was not based on linguistic cues (e.g., action words) but pictures of tools. In the control task, participants were requested to manually count parts of non-tool objects. Specifically, raising the palm only with the extended thumb meant that the control object consisted of just one part, extending the thumb and index finger meant two parts, whereas the extension of the thumb, index, and middle finger meant three parts or more. There were five 24-sec (or 20-sec) blocks involving visual tool use pantomimes in response to 12 (or less) tool stimuli displayed serially for 2 or 3.3 sec, respectively, and five 24-sec (or 20-sec) blocks of the control manual part counting in response to non-tool stimuli, also shown serially. Finally, additional five 24-sec (or 20-sec) blocks of resting intervals were introduced pseudorandomly between the two task blocks. [For more details see Przybylski & Kroliczak, 2017; all digital materials, including presentation codes, experimental stimuli, and protocol adjustments (see also 2.1.2.2) are publicly available at <https://osf.io/63hjt/>; Kroliczak et al., 2021.] Two different, pseudorandom orders of task and rest blocks were assigned to each participant, further

pseudorandomly balanced across hands tested in a given-day session. Participants were tested twice, typically on two consecutive days, with the order of the left and right hand used for pantomiming also counterbalanced.

2.1.2.2. LANGUAGE PRODUCTION TESTS. We used a cued verbal fluency test, with six 30-sec task blocks, typically interchanged with six 30-sec rest blocks (e.g., Kroliczak et al., 2011). Participants’ task was to silently (covertly or subvocally) generate as many words as possible, starting with letters A, G, K, L, M, or T, shown pseudorandomly above the fixation cross (again, displayed on the monitor behind the scanner, and watched via a coil-mounted mirror). These six letters were selected based on earlier studies, which indicated that most of the words native speakers of Polish spontaneously generate begin with such letters. In nearly half of the participants, we introduced additional 30-sec blocks of a control task, in which in response to a scrambled letter (i.e., a meaningless arrangement of letter parts), participants were asked to covertly generate the (Polish) non-word “Zaza”, in a pace that they subvocally generated words in a previous main task block. In this modified experiment (with some of the letters exchanged in each run), the task, control, and rest blocks were reduced to four instances, each. Even then, we still obtained excellent task-related signals in individual runs. As in the previous task, participants were tested twice, typically on two consecutive days, with the order of the test appearance also counterbalanced. All digital materials are publicly available at <https://osf.io/63hjt/> (Kroliczak et al., 2021).

2.1.3. fMRI data acquisition, pre/processing, and functional analyses

All neuroimaging data were acquired with the use of a 3-T Trio MRI scanner (Siemens Medical Solutions), enabling echo planar imaging (EPI), with a 32-channel PA head coil, for Radio Frequency transmission/signal reception, courtesy of the Laboratory of Brain Imaging at the Nencki Institute of Experimental Biology in Warsaw. The echoplanar BOLD images were acquired using T2*-weighted segmented gradient-echo imaging sequence with the following parameters: field of view (FOV) = 196 mm; 64×64 matrix; in-plane resolution = 3.06×3.06 mm; flip angle (FA) = 90° ; time to echo (TE) = 30 msec; time to repetition (TR) = 2,000 msec. Each volume contained 35 contiguous axial slices of 3.1 mm thickness. The first four volumes in each scan series were always discarded. Standard, anatomical scans were acquired in both sessions, with the use of a 3D T1-weighted magnetization prepared rapid gradient echo (MP-RAGE) pulse sequence, with the following parameters: TE/TR = 3.32/2,530 msec; inversion time (TI) = 1,200 msec; FA = 7° ; 176 contiguous axial slices; in-plane resolution = 1.0×1.0 mm; slice thickness = 1.0 mm; voxel matrix size = 256×176 ; FOV = 256 mm. Finally, fast spin echo T2-weighted anatomical images were also collected, with the following parameters: TR = 3,200 msec; TE = 402 msec; FA = 120° ; 512×512 voxel matrix size; FOV = 256 mm; 176 contiguous sagittal slices; in-plane resolution = $.5 \times .5$; slice thickness = 1 mm. The obtained DICOM images were converted to NIfTI (FSL) format using MRI-Convert software (<http://lcn.uoregon.edu/~jolinda/MRIConvert/>). All anonymized raw data acquired in

this project are publicly available at <https://osf.io/63hjt/> (Kroliczak et al., 2021). Both the pre-processing, and subsequent image processing steps were the same as in a pipeline described earlier by Bidula and Kroliczak (2015). Namely, structural T1-, T2-, and functional T2*-weighted images were processed, co-registered, and analyzed using FSL (FMRIB's Software Library v6.0.1; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>), including FSL's FMRI Expert Analysis Tool (FEAT) v.6.00 (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). The non-brain tissues were removed with the Brain Extraction Tool (BET), and the FSL motion correction algorithm (MCFLIRT) was applied to attenuate signal changes due to small head displacements (despite the heads being largely immobilized with padding). The images were then spatially smoothed, using a Gaussian kernel with a full width at half-maximum (FWHM) of 6.2 mm (i.e., twice the isotropic voxel size of 3.1 mm), and temporally smoothed using high pass filter cutoff of 90.0 sec (estimated from the model).

Individual runs were analyzed separately at the first level. Prior to statistical analyses of the data, signal autocorrelations were corrected using a default pre-whitening procedure implemented in FSL, and hemodynamic responses were modeled using a double-gamma function. In each experiment, activity from the whole task intervals, and the whole rest blocks, was modeled, and critical contrasts (i.e., praxis, language versus control tasks) from individual runs were first averaged, separately in each subject, using the fixed effects model. In the group analyses, random-effects components of mixed effects variance were modeled and estimated with the default FSL method and settings: the FLAME Stage 1 procedure, with the resulting (Gaussianized t/F) Z-statistic images typically thresholded at least at $Z > 3.1$, $p = .001$, and corrected for multiple comparisons using additional clusterwise significance threshold of $p = .05$, i.e., the family-wise error rate (FWER) was always controlled at $\alpha = .05$. All processed data acquired in this project are publicly available at <https://osf.io/63hjt/> (Kroliczak et al., 2021).

Neural activity from the following critical groups, and their direct contrasts, is displayed. First we show praxis-related activity (versus a control task) in its typical form, regardless of the organization of language, and language-related activity in its typical form, regardless of the organization of praxis. Then, atypical representation of praxis is shown, regardless of language organization, and atypical representation of language is displayed, regardless of praxis organization. (When the typical and atypical groups are limited to individuals with both functions – praxis, language – similarly organized, largely the same networks of neural activity would be revealed.) Finally, direct contrasts of praxis in its typical versus atypical form, as well as language in its typical versus atypical form are shown in both directions.

Localization of clusters with significant brain activity was verified by projecting and visualizing the obtained volumetric outcomes with the use of the Connectome Workbench v1.2.3. (cf. Marcus et al., 2011; Glasser, Smith, et al., 2016). In this software, the group statistical imaging maps can be overlaid, e.g., by means of trilinear interpolation, onto different brain – midthickness or pial, inflated or flat – surfaces, which can be additionally demarcated with borders of 180 functional areas, based on multi-modal parcellation (with some further details

described below). Most of the neuroanatomical labels (including the less known ones) applied throughout this report are also taken from the “connectome workbench” atlas (Glasser, Coalson, et al., 2016); i.e., the nomenclature from the connectome workbench (by Glasser, Coalson, et al., 2016) will be often used here. A reader unfamiliar with this terminology, or its roots, is suggested to read the following publication by Triarhou (2007), with a proposed number system for disparate cortical areas discovered and described by the fathers of the cytoarchitectonic systems.

2.1.4. ROIs (regions of interest)

Based on the earlier work, comparing the impact of ROI selection, and LI calculation methods (e.g., Chlebus et al., 2007) to the outcomes of the Wada test (McElligott, 2011) used for the identification of the language dominant hemisphere, and its relation to the organization of praxis skills in individuals with different handedness status (Kimura, 1983; Kroliczak et al., 2011), two sets of cytoarchitectonic maps for preliminary ROI analyses were utilized first. Namely, the left and right Brodmann areas [BAs]44/45 were chosen as critical for language production (healthy adults show fMRI signal increases in this vicinity during language and movement tasks, e.g., Binkofski et al., 2000; Amunts, Schleicher, & Zilles, 2004). The left and right [BAs]40, defined as divisions PF and PFm of IPL, were chosen as critical for praxis production (healthy adults show hand-independent signal increases in this vicinity during gesture planning and/or execution; e.g., Kroliczak et al., 2016; Moll et al., 2000; Rumiaty et al., 2004). Both of these sets were taken from Juelich Histological Atlas implemented in FSL. Prior to their application in custom-made scripts, and for consistency with our earlier projects (e.g., Kroliczak et al., 2011), these maps were first thresholded at the 50th% of their maximum probability values (Eickhoff et al., 2007), with the use of an “fslmaths” operation.

The main set of ROIs was derived from the multi-modal parcellations of the human cerebral cortex (Glasser, Coalson, et al., 2016), developed within the Human Connectome Project (HCP) initiative (Glasser, Smith, et al., 2016). There are 180 areas per hemisphere, delineated in a semi-automated fashion, and there is no overlap between them as they are constrained by changes in cortical architecture, as well as function, connectivity, and/or topography. These parcellations are very handy in identifying – e.g., quantifying or visualizing, and interpreting differences in functional organization of the cerebral cortex, including its variation across individuals. Their limitation is such that the 180 areas were not obtained on a volumetric basis, and a volumetric version (of the HCP-MMP1.0 parcellation by Glasser, Coalson, et al., 2016) had to be independently created. Based on its FreeSurfer form, the atlas was first converted to volumetric space – its projection to the ICBM 152 2009a NLIN version (in MNI space) by Andreas Horn (Horn, 2016). Subsequently, using FSleyes (<https://zenodo.org/record/3937147>), these ROIs were resampled – with the use of the nearest neighbor interpolation – to the MNI152_T1_2 mm_brain space.

Initially, we calculated LIs across the whole set of the 180 bilateral parcellations. Subsequently, the most relevant 48 ROIs—based on theoretically informed selection of cortical areas critical for praxis and language tasks (e.g., Garcea,

Greene, Grafton, & Buxbaum, 2020; Goldenberg & Randerath, 2015; Krolczak et al., 2016; Labache et al., 2019; Mazoyer et al., 2016; Vigliocco, Krason, Stoll, Monti, & Buxbaum, 2020), as well as their networks were further analyzed. All these ROIs, with the reduced set of 48 color coded, are shown in Fig. 1. Centroids of these parcellations, used for further visualizations of LIs, are also marked within the ROIs, and their labels and coordinates are shown in Supplemental Table 1.

2.1.5. LI (lateralization index) calculations

Custom-made scripts for LI calculations utilized “fslmaths” and “fslstats” functions implemented in FSL. As in the case of the ROI selection, our LI-calculation methodology was based on the results of a comparison of various methods of their computations (Chlebus et al., 2007) to the outcomes of the Wada test (McElligott, 2011) in patients suffering from medically intractable epilepsy. Most importantly, our method of choice is conceptually identical with (but simpler than) an approach implemented in an LI toolbox (Wilke & Lidzba, 2007), running within other neuroimaging software environments. It capitalizes on threshold-independent estimates of cerebral asymmetries in individual participants as the most reliable method, and is therefore preferable (e.g., Johnstone et al., 2020; Krolczak, Piper, et al., 2020). For the purpose of this work, we used the approach already exploited by members of our group elsewhere (Krolczak et al., 2011), with an extension of threshold-independent estimates from comparisons of the spatial extent of neural activity to the strength of the observed

neural signals (signal amplitude/intensity changes, expressed in percent signal change, %SC) in the two hemisphere ROIs.

Only voxels with positive Z values in unthresholded activity maps were used in LI calculations (an approach similar to Jansen et al., 2006). Yet, consistent with other threshold-independent methods, we sampled the neural activity within ROIs at several different levels. Specifically, both when using the spatial extent of task-related activity – i.e., when simply counting the number of voxels in the left- and right-hemisphere ROIs, and while using the amplitudes/intensity of task-related activity – i.e., when comparing %SC in the left- and right-hemisphere ROI voxels, we first calculated single LIs at six percentage of maximum, individual activity thresholds. Namely, for each participant, we did it separately at 90, 80, 70, 60, 50, and 40% thresholds, relative to a maximum Z value observed in an individual Z-stat image within a given ROI pair. The final LI is the average of the individual six LIs, an approach guarding against biasing our interpretation by the use of just one threshold. Indeed, our conclusions are further strengthened by the use of two complementary methods, and ultimately their compilation. That is, the final individual LI was in fact the mean LI based on both voxel count (VC) and signal intensity (SI). Namely, they were combined (i.e., averaged, hence VCSI), as they are very consistent and highly correlated (e.g., when their distributions are compared, “Very similar lateralization curves result with almost perfect correlations”, p. 132, Wilke & Lidzba, 2007). In each participant, hemispheric dominance was assessed with the use of the following formula: $LI = [(L-R)/(L+R)] \times 100$, wherein L and R stands for specific VC and SI values, first obtained separately when testing the left-, and right-hemisphere ROI. The same LI cut-offs of $\geq +33.3$ and ≤ -33.3 , as for handedness, were used for identifying neural activity within an ROI pair as typical (left lateralized) versus atypical, with the latter including either bilateral organization, involving the two hemispheres in a balanced manner (i.e., LIs between $+33.3$ and -33.3), and right lateralized neural activity (≤ -33.3).

2.1.6. LI network analyses and visualization

All the main correlational analyses of praxis - language LI networks, performed separately in groups having either typically or atypically represented both functions, or their dissociations, utilized Spearman's rho non-parametric statistical tests. Two approaches were used. Seed-based connectivity analyses were performed first, with the following ROIs: PFm, PF, PFT, AIP, PH and FST for praxis (while looking for correlations with the 48 nodes during performance of the language task), and 6r, 44, 45, IFSa, MI, and AVI for language (while looking for correlations with the 48 nodes during the praxis task). Subsequently, LI network analyses were performed in nodes whose laterality was significantly different between the two – i.e., typical, and atypical – groups (Bonferroni-corrected $p < .001$). Additional seed-based connectivity analyses (with the same seeds) were also performed in individuals showing a dissociation of atypically represented – bilateral or right-lateralized – praxis, and typically represented (left-lateralized) language. The very rare cases of inverse dissociations of atypical language and typical praxis were not included. For more detailed information on the group sizes in LI network analyses, see Table 1. The final,

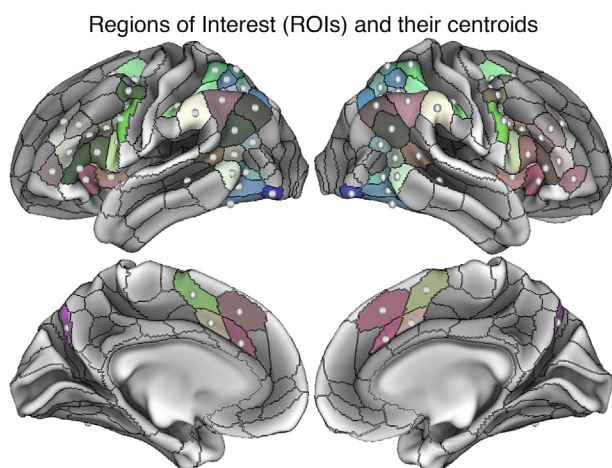


Fig. 1 – The multi-modal parcellations of the human cerebral cortex serving as regions of interest (ROIs). The borders of all 180 areas per hemisphere that were delineated within the Human Connectome Project (HCP) initiative (Glasser, Smith, et al., 2016) are shown, with a subset of 48 ROIs selected for further analyses color coded (as in the original atlas). The surface-based “centroids” of these ROIs are also shown, as they were used for further visualizations in correlational analyses of laterality indices (LIs). Notably, because these areas were created using surface-based analyses, their volumetric versions obtained by their projections to the MNI space by Horn (2016), were used in this project.

Table 1 – Frequency of individuals with different combinations of lateralization of handedness (Edinburgh Handedness Inventory, EHI), as well as praxis and language, based on a combined Laterality Index (LI) from voxel count (VC) and signal intensity (SI) – hence VCSI – in the left and right hemisphere regions of interest (ROIs; Brodmann area [BA]40 for praxis, and BA44/45 for language).

Handedness: EHI ($-33.3 < \text{Mixed} < +33.3$)	Lateralization of neural activity for praxis and language skills VCSI based LIs; $-33.3 < \text{Mixed} < +33.3$								Total	
	Both functions atypical		Atypical language only		Atypical praxis only		Both functions in typical forms			
Righthanders ($\geq +33.3$)	1	1.9%	1	1.9%	12	23.1%	38	73.1%	52	41.6%
Mixedhanders	2	6.5%	0	.0%	5	16.1%	24	77.4%	31	24.8%
Lefthanders (≤ -33.3)	9	21.4%	2	4.8%	10	23.8%	21	50.0%	42	33.6%
Total	12	9.6%	3	2.4%	27	21.6%	83	66.4%	125	100.0%

control, exploration was performed for nodes whose laterality did not differ between the typical and atypical groups. All these analyses were performed with IBM SPSS Statistics for Macintosh v.26 (release 26.0.0.1), Armonk, NY: IBM Corp. They were preceded by data preprocessing and extraction with the use of an interactive computational environment of the IPython Notebook (Jupyter Notebook), wherein custom-made scripts utilized Python functions from the following modules: scikit-learn & nilearn (Abraham et al., 2014), SciPy (Virtanen et al., 2020), and pandas (McKinney, 2010). Moreover, we utilized free and open source tools from the RStudio. The revealed significant between-task correlations were visualized with the use of BrainNet Viewer (v1.7 of the 2019-10-31 release), a “Network Visualization Tool” (Xia, Wang, & He, 2013). All the scripts and processing steps involved in LI calculation, including analysis codes, as well as the methods, and the layouts of component matrices, for network visualizations are provided at <https://gitlab.com/mikbuch/lincalc> and described by Buchwald & Kroliczak, (Submitted); see also Kroliczak and collaborators (2021).

2.1.7. Assessment of the incidence of functional atypicality, the strength and links between variables, and mediation analyses

The likelihood of an atypical organization of praxis to occur was based on Bayes Factor (BF) computed with default prior for hypergeometric sampling (Jamil et al., 2017). Additional tetrachoric correlation coefficients (used instead of Pearson's coefficients, because the assumptions of constant variance and linearity were violated) were computed to assess the strength of the links between the three variables of interest: praxis, language, and handedness. In mediation analyses, a Bayesian method of parameter estimations is also typically adopted (e.g., Nuijten, Wetzels, Matzke, Dolan, & Wagenmakers, 2015). Yet, due to the curvilinear relationship between the variables, the Natural Effect Framework by Loey's and collaborators (Loey's et al., 2013) was used to assess the indirect effect of the relationship between handedness and language and/or praxis LIs, with standard errors based on the non-parametric bootstrap. The utilized flexible mediation analysis approach is based on Causal Mediation Analysis (CMA; Imai, Keele, & Tingley, 2010) which, counter to the popular approach by Baron and Kenny (Baron & Kenny, 1986), also allows to estimate path coefficients in the mediation

model for non-linear relationships. Odds Ratio and 95% Confidence Intervals were also calculated.

2.2. Results

2.2.1. Distributions, associations and dissociations of LIs for praxis and language in two primary cytoarchitectonic ROIs

Consistent with our earlier studies (Bidula & Kroliczak, 2015; Bidula et al., 2017), in Fig. 2 we first present a preliminary distribution of praxis (Fig. 2A) and language (Fig. 2B) LIs from the two cytoarchitectonic pairs of ROIs of our choice, i.e., BA40 for praxis, and BA44/45 for language (For clarity, Supplemental Fig. 1 shows the extent and overlap of these ROIs with the ones from the connectome workbench.) Because the final LIs were collapsed across VC (voxel count) and SI (signal intensity), resulting in VCSI LIs, the contributing distributions are shown separately in Supplemental Figure 2. (These two kinds of LIs were highly correlated.) As the layout of the participants in panel A and B is the same – i.e., they are sorted by handedness, right to left, and then by praxis LIs, in the descending order – the cases of associations and dissociations of praxis and language can be easily spotted, as well. Their frequencies, including different combinations of handedness, praxis and language lateralization (i.e., their disparate phenotypes) are summarized in Table 1 (and Supplemental Tables 2 and 3). Of course, these LIs would slightly differ, depending on the location and extent of the selected ROI, as well as the method used for LI calculation (cf. Bidula et al., 2017).

Our sample is not representative of a general population, as the research initially aimed to include a similar number of participants in each handedness group. The tasks turned out to be challenging for some mixedhanders, who upon closer testing ended up assigned to righthanders or lefthanders. As the table corroborates, atypical bilateral organization, and/or atypical right-sided lateralization of functions was clearly more common among non-righthanded individuals. Yet, never in mixedhanders, and rarely in righthanders, atypical representation of language dissociated from typically lateralized praxis. It was not the case the other way, i.e., atypical praxis can easily dissociate from typically lateralized language in all handedness groups. Frequencies of atypical representations would increase/change if more specific ROIs – here: the ones from

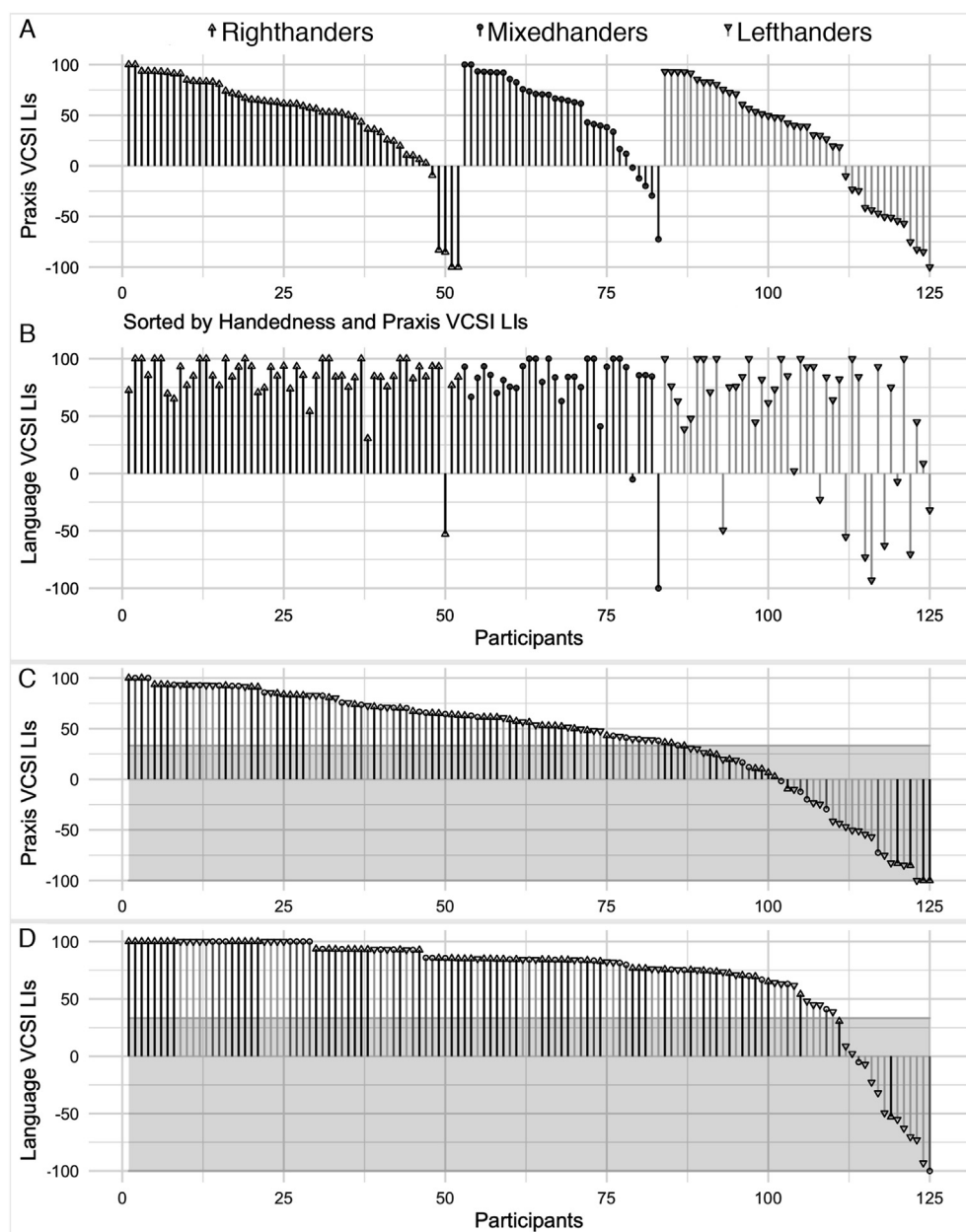


Fig. 2 – Distributions, associations, and dissociations of laterality indices (LIs) collapsed across voxel count (VC) and signal intensity (SI) - VCSI. (A) Distribution of LIs for praxis representation assessed in Brodmann area [BA]40 – our primary region of interest (ROI) for the assessment of neural activity associated with visual tool use pantomimes. Within handedness groups, these LIs are shown in the descending order of the praxis LIs, from typical to atypical. (B) Distribution of LIs for language representation assessed in the Broca's area (BA44/45) – our primary ROI for the assessment of neural activity associated with silent word generation. Each symbol/bar represents one individual. The order of the participants in panel A and B is the same. (C) Praxis LIs in the descending order, regardless of handedness. (D) Language LIs in the descending order, regardless of handedness. The latter two panels illustrate participants assigned to the typical and atypical groups used in subsequent functional magnetic resonance (fMRI) analyses. +100 - complete left, -100 - complete right laterality.

the 180 multimodal parcellations – or their combinations were selected for calculation of LIs. E.g., an exclusion of the PFm parcel (by Horn, 2016), and instead an inclusion of PFt for praxis, and exclusion of either area 45 or 6r for language, could sometimes lead to a somewhat different – perhaps a more reliable – group assignment (cf. Supplemental Figure 1).

2.2.2. fMRI activity maps

2.2.2.1. PRAXIS AND LANGUAGE ORGANIZATION REGARDLESS OF HANDEDNESS.

The outcomes from the whole group analyses of praxis and language at the lowest acceptable threshold of $Z > 3.1$, $p = .001$, with FWER $\alpha = .05$, are shown in supplemental materials (Supplemental Figure 3AB). With 125 contributing participants, the extent of the obtained activity at this

significance threshold is rather large in both cases. To make sure that only the most critical areas are displayed, the subsequent maps, namely in Fig. 3A–D (as well as Supplemental Figure 3CD) were thresholded at the 50% of their maximum Z values, which – for the rather high maximal Zs almost always obtained – is well above or near the lowest acceptable threshold. Notably, with this approach, a comparable number of significantly active voxels is observed in each task (Jansen et al., 2006).

As can be seen in Fig. 3A, the neural activity associated with praxis in its typical form is widespread and often bilateral, but still greater and/or wider in the left hemisphere praxis representation network (PRN; Frey, 2008; Kroliczak et al., 2016; see also Kroliczak, Piper, et al., 2020). For example, contributions from the anterior supramarginal gyrus (aSMG or area PFt), anterior intraparietal sulcus (AIP), and a small cluster within a subdivision of the middle frontal gyrus (MFG; namely area 46) were observed exclusively on the left. In the vicinity of the temporo-parieto-occipital junction (TPOJ), with the exception of TPOJ2, the left hemisphere activity, which extended both dorsally and posteriorly (to subdivision PGi), and more ventral areas (MT, MST, FST, and PHT) was clearly more widespread, too. All fMRI group data are publicly available at <https://osf.io/63hjt/> (Kroliczak et al., 2021).

Similarly to our earlier reports (Kroliczak, Piper, et al., 2020; Potok, Maskiewicz, Kroliczak, & Marangon, 2019; Kroliczak, Potok, & Nowik, 2020), contributions from mid SMG (area PF), the bordering parietal opercular, as well as the frontal opercular, and insular cortices also showed greater engagement on the left. Finally, the involvement of the parieto-occipital medio-dorsal regions was primarily left hemispheric, although further projections from this vicinity to the superior, dorso-dorsal and medio-dorsal streams were more balanced.

The neural activity associated with typically organized language production (subvocal word generation) is shown in Fig. 3B. There is mainly left-lateralized engagement of frontal and prefrontal regions typically associated with word production, starting from ventral to more dorsal premotor sites (i.e., 6r, 6v, 55b, 6a), through the middle and inferior frontal (IFG) gyri (e.g., areas p9-46v, 46, IFSa-IFSp, and 44, 45, respectively), as well as frontal opercular (e.g., FOP4) and insular cortices (AVI, MVI). Of note is the exclusive engagement of a small cluster within the superior temporal subdivision labelled STSdp. The contributions from the supplementary and presupplementary motor cortices were greater on the left, too. So were the inputs from the lateral, and ventral visual cortices (FST, PH). Interestingly, several functional subdivisions of the intraparietal sulcus (IPS) also showed only the left-lateralized involvement. The activity of early visual cortex (EVC) was more balanced.

The panels in Fig. 3C,D show the praxis- and language-related neural activity in their atypical forms. As can be seen in Fig. 3C, the neural activity in atypically represented praxis was largely balanced, or leaning towards right-hemisphere advantage, with the exception of the exclusive involvement of the IFSa. As shown in Fig. 3D there was nearly mirror-reversed neural activity observed in the atypically represented language. A direct contrast of praxis in its typical and atypical form, shown in Fig. 3E, revealed only the advantage of

critical left parietal (PFt, PF, an anterior part of PFm; AIP, 7PC) and temporal areas (FST, and partly PH). The inverse contrasts disclosed a significantly greater engagement of just one cluster, involving areas PGs, PGp, IPO and IP1 in atypical individuals. Fig. 3F depicts the advantage of left-hemisphere areas in typical, and right-hemisphere pre/frontal areas in atypically represented language.

For completeness, it should be stated that righthanders in this study did not show any significant difference in the control of praxis (tool use pantomimes) when compared directly to lefthanders, and the more so to mixedhanders. Mixedhanders did not differ from lefthanders, either, at least when the whole-brain patterns of neural activity were compared.

2.2.2.2. THE PRAXIS–LANGUAGE LI CORRELATION NETWORKS. Analyses of the praxis–language LI correlations were performed on inputs from the following contrasts: praxis versus the control task, and language versus baseline (with the latter chosen for consistency with earlier comparisons to the Wada test; e.g., Chlebus et al., 2007). It should be added, though, that LIs from the language versus the control task contrast were nearly identical to the ones with baseline as a reference. Indeed, they were highly correlated: Pearson correlations of .886** (two tailed), and Spearman's rho of .737** (two tailed) were observed for VC, as well as .886** (two tailed) and .706** (two tailed), respectively, for SI.

Figure 4 AB displays two sets of LI networks showing significant correlations in two groups of participants, i.e., wherein praxis and language were either typically lateralized or atypically represented. Both the seed-based analyses (Fig. 4A) and testing of correlations in nodes with significantly different laterality between the two groups (Fig. 4B) revealed that in typically lateralized praxis and language the significant links are substantially weaker and more diffuse. Indeed, both analysis types indicated that a greater number of nodes showed consistent changes in neural activity for their typical forms, even though the disclosed distributions were not necessarily the same.

In individuals where the two functions got reorganized (being either bilateral or right-lateralized), the observed links between praxis and language were much stronger but, simultaneously, the number of nodes working in concert decreased. Interestingly, counter to the typically organized functions, none of the atypical temporal nodes showed changes in neural activity consistent with the ones observed in frontal and prefrontal cortices. Moreover, the lateralization of the temporo-parietal responses was always more tightly linked in atypically represented praxis and language. So were the parieto-prefrontal nodes.

The seed analysis performed in the cases of dissociated – bilateral or right-lateralized – praxis from typically organized language, revealed yet another pattern of responses. As shown in Fig. 4C, the strengths of the correlations were in the intermediate range, with little overlap with the typical and atypical groups. There were less consistent responses between parietal and frontal nodes, counter to the lateralization of neural activity observed mainly within and between temporal and parietal nodes. Nevertheless, the strongest affinities were observed for praxis in the anterior supramarginal gyrus (area

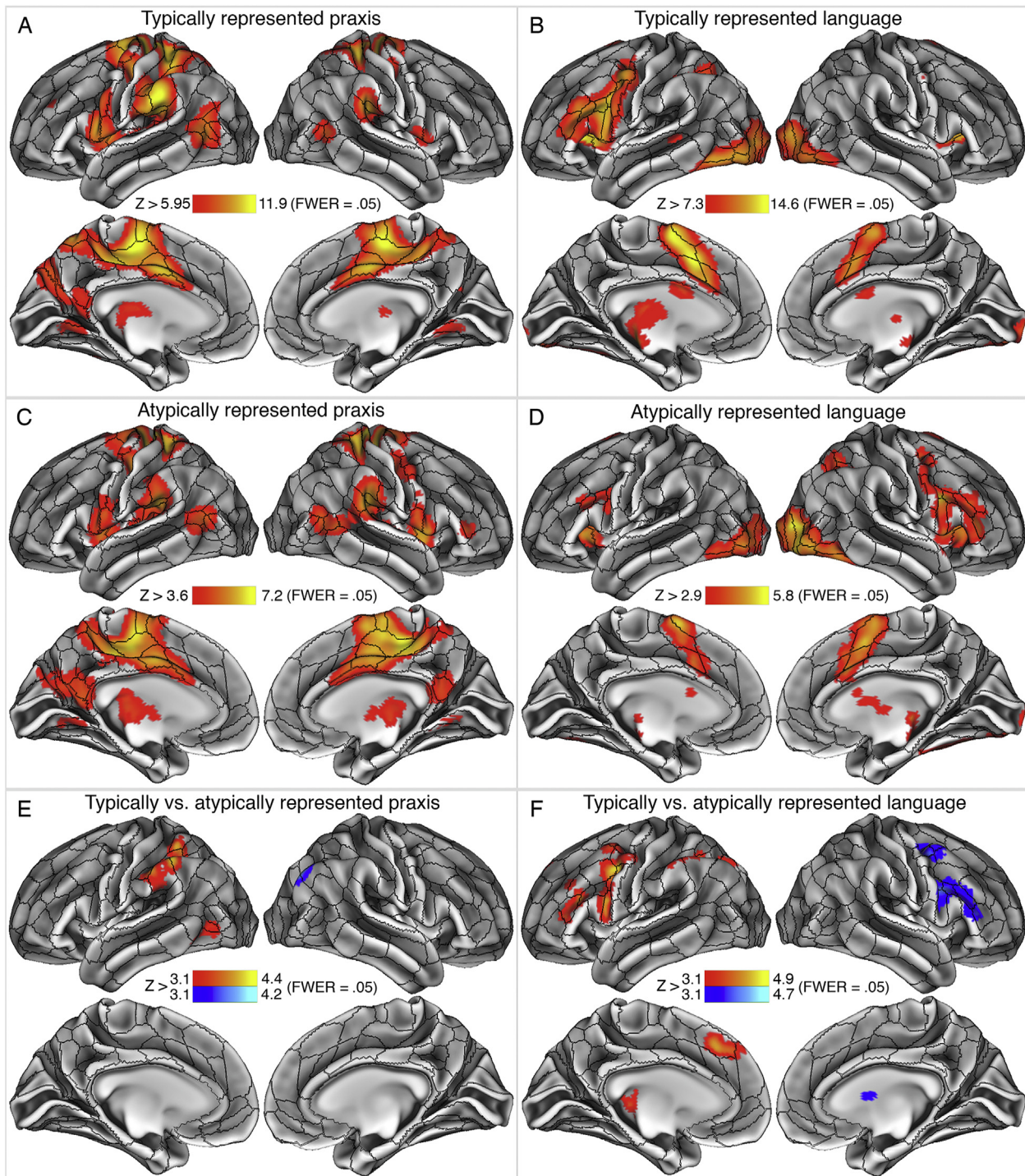


Fig. 3 – Neural representations of praxis and language in their typical and atypical forms, and their direct contrasts. The groups are differentiated based on VCSIs shown in Fig. 2C,D. (A) The advantage of the left-hemisphere praxis representation network (PRN) in the typically organized praxis (tool use pantomimes). (B) The nearly exclusive engagement of left-hemisphere lateral pre/frontal and parietal areas in the typically organized language (subvocal word generation). (C) Largely balanced neural activity in atypically represented praxis. There is some advantage of few right-hemisphere areas, and the exclusive involvement of the IFSa parcel. (D) Nearly mirror-reversed neural activity in atypically organized language. (E) A direct contrast of praxis-related neural activity in its typical and atypical form. There was a significantly greater engagement of critical left parietal and temporal areas. (F) An advantage of left-hemisphere areas in typical, and some right-hemisphere pre/frontal areas in atypical representation of language. Only volumetric surface renderings are shown, either thresholded at half of the maximum Z value, or using $Z > 3.1$, and always with a corrected cluster significance threshold of $p = .05$. In panels (E) and (F), warm colors (yellow-red) depict significantly greater neural activity for typically represented functions, and cold colors (dark to light blue) depict significantly greater neural activity for atypically represented functions.

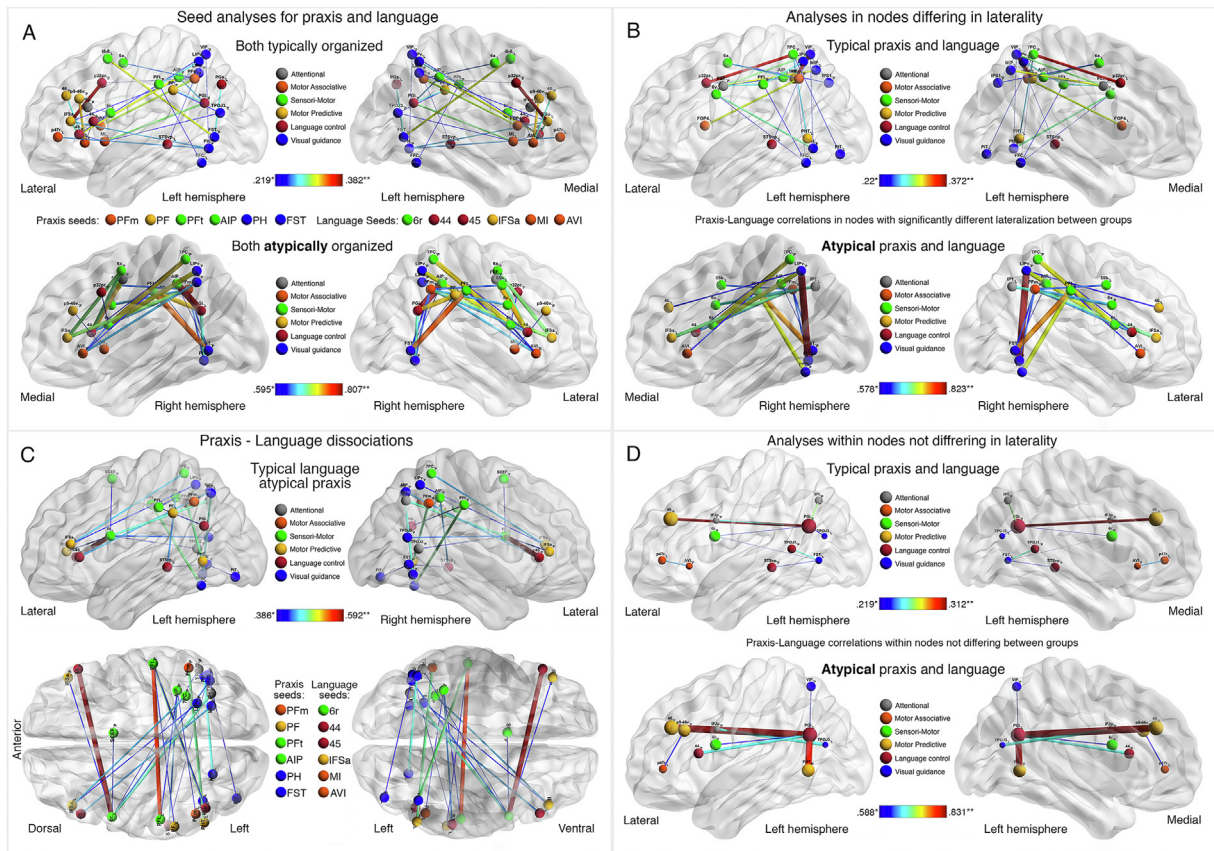


Fig. 4 – The networks of significantly correlated LIs in individuals with typically, and atypically represented praxis and language, as well as in the cases when they dissociated. (A) Seed analyses. The selected seeds are shown in the figure. The links between praxis and language are weaker and more diffuse in the typical group. When both functions are atypically represented, the tighter links were observed between several temporal, parietal and frontal nodes. (B) Praxis-language LI correlation analyses in nodes differing significantly in their laterality between the typical and atypical group. These outcomes are consistent with the ones obtained for seeds, especially for the atypical group. (C) The between-task correlations when praxis dissociates from typically lateralized language, as revealed by seed analyses. In addition to notable differences in contributions of the two hemispheres, the pattern of nodes showing correlated activity is different both from the typical and atypical group, with intermediate correlation strengths. (D) Correlations in nodes which do not differ significantly in their laterality for the two tasks in the two groups. As before, all these groups were distinguished based on LIs obtained in independent ROI sets. Subscripts P and L at the end of the ROI name/symbol or acronym indicate a praxis or language related node, respectively. Notably, a node can serve both functions and show significant correlations in both domains. It is then marked with a subscript “P superimposed on L”, or vice versa. The color-coded links, always indicating significant correlations were scaled in accordance with correlation strengths. The node colors specify the predominant basic functions of these areas, e.g., blue for visual, green for motor processing, etc., as defined in the “connectome workbench” parcels.

PFt) and language in its left-hemisphere counterpart, and for language in area 6r and praxis in area 45. In fact, not only showed the 6r language node the strongest, but also the most frequent correlations, with temporal (TPOJ2,3), parietal (IP1) and frontal praxis nodes. Interestingly, in the group with both functions atypically represented, area 6r for language showed more consistent responses with LIP, and 7PC for praxis.

Finally, the common processes or mechanisms for praxis and language were infrequent in nodes which do not differ significantly in their laterality for the two tasks. As disclosed in Fig. 4D, there were only two exceptions: area 46 and 6r for praxis and PGI for language, which showed consistently strong and weaker responses, respectively, in both typical

and atypical group. All data for network analyses and visualizations of their outcomes are publicly available at <https://osf.io/63hjt/> (Kroliczak et al., 2021).

2.2.3. The probabilities of atypical praxis–language associations and the outcomes of mediation analyses

We found that atypical praxis is 2,773 times more likely to occur with atypical language than the null effect (of no chance for them to occur together). The chance factor for this case is $OR = 28.9$ [$CI_{.95} = (5.6, 241.8)$]. This means that if we find that in a given individual the language organization is atypical, there is a 28.9 times higher chance for the praxis organization to be atypical too (rather than typical).

The incidence of atypicality (scores below 33 points on LIs) was related to handedness, as determined by the EHI. Namely, left-handed participants more often had an atypical lateralization of praxis and/or language than right-handed persons [OR = 3.0, CI.95 = (1.25, 7.17), BF10 = 3.70]. Ambidextrous (mixedhanded) participants were different from left-handed [OR = 3.43, CI.95 = (1.22, 9.67), BF10 = 2.99] but not from right-handed participants [OR = 1.14, CI.95 = (.40, 3.27), BF10 = .34].

The analysis of relations between the examined variables revealed a complex, non-linear character. Specifically, while in the majority of cases with right-lateralized language there is also right-lateralized praxis, people who have atypical lateralization of praxis do not necessarily have atypical organization of language. This particular relation seems to be affected by handedness, as defined by EHI. The correlation between the lateralization of praxis and language is $r_{\text{tet}} = .70$ (with the splitting of both indicators at LI of 33). The 95% highest density interval is from $r_{\text{tet}} = -.10$ to $r_{\text{tet}} = .80$, because the distribution of possible (assuming a different point for dichotomization) correlation coefficients is very skewed.

The outcomes of the subsequent analyses were obtained with the assumption that handedness can affect language laterality only indirectly, e.g., by influencing the praxis network, which is, in turn, more closely related to the language network. The alternative model of indirect relationships between the variables was also considered. Consistent with the layouts seen in Fig. 5, we took it into account that the relationships are curvilinear.

The following Fig. 6 presents both models with path coefficients and proportions of the mediated effect. The outcomes verify the hypothesis of the influence of handedness on the language laterality as mediated by the praxis laterality. Of particular interest, though, are the results of testing a competing hypothesis that handedness affects the

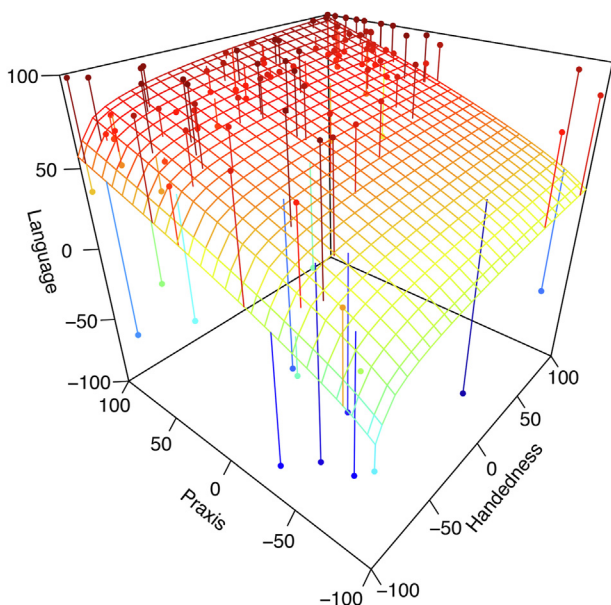


Fig. 5 – Associations of praxis and language laterality indices with handedness, as measured with EHI.

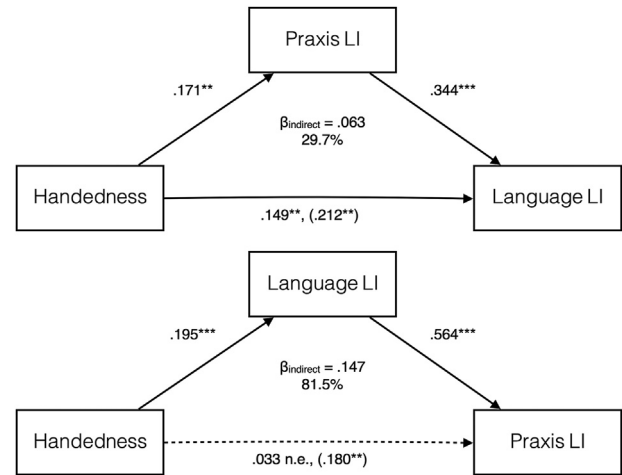


Fig. 6 – Path coefficients and proportions of the mediated effect obtained within the Natural Effect Framework, using the flexible mediation analysis approach based on causal mediation analysis (CMA). TOP – handedness and language laterality as mediated by the praxis laterality. BOTTOM – the alternative model of indirect relationships between variables. The mean regression coefficient between predictor and dependent variables without controlling for mediator variable is in parentheses. n.e. - no evidence, * - BF10 [3–10], * - BF10 [30–100].**

lateralization of the praxis as mediated by lateralization of the language.

The obtained results for the first model indicate that the postulated mediation could be complementary – about 29.7% variance of lateralization of language has its source in the handedness factor mediated by the lateralization of praxis [indirect path $a \times b = .06$, CI.95 = (.025, .187), BF10 = 3.29]. The remaining 70.3% of variance is directly explained by handedness [direct path $c = .149$, CI.95 = (.069, .384)]. Nevertheless, we obtained results indicating the full mediation model in the case when lateralization of language mediates the influence from handedness to lateralization of praxis. The mean indirect effect from handedness to the lateralization of praxis [path $a \times b = .147$, CI.95 = (.073, .418), BF10 = 91.4] explains 81.5% of the relation between variables and a direct path between handedness and praxis laterality is probably null [$p(\tau' \neq 0 | D) = .86$]. Comparing these models using the Bayes approach, we conclude that second model is almost 28 times more likely (BF_{med1} = 91.4 vs BF_{med2} = 3.3), given the data we have so far.

3. Discussion

In his attempts to defend the idea, or rather to convincingly demonstrate, that apraxia is an impairment of its own, not merely an augmentation or side effect of aphasia, agnosia, or even ataxia, Liepmann (1900; 1908; 1920; 1925) proposed and developed an idealized theoretical model, wherein essential nodes for praxis were located in the left hemisphere of the brain. It became apparent to him that this cerebral hemisphere not only controls skilled actions of the right hand but,

being indirectly vital for the higher-order control of the left hand, can be considered a hemisphere dominant for praxis in all right-handed people. Such an idealization was one of the first critical steps in understanding the studied phenomenon (cf. Nowak, 1982), because the abstracted, though empirically grounded, model could then be applied to the majority of human population. After all, most people are right handed (McManus, 1985).

Extensive testing of such a model would entail its concretization to other handedness categories. Yet, Liepmann initially (Liepmann, 1900) misperceived his patients' handedness, and then, upon admitting that the "imperial counsellor" was a non-right hander, treated him as an exception to the rule (Liepmann, 1908, 1925). Last but not least, because Liepmann was able to convincingly demonstrate that apraxia is not a result of lost comprehension, and was unimpressed by the fact that praxis and language representations co-exist in the same cerebral hemisphere, further concretization of his model to any putative praxis-language links, the more so a falsification of this idea (cf. Popper, 1963), was well outside of his interests.

The main goals of this work were the following: to further investigate the previously mentioned and rather underappreciated links between praxis and language, and to test if and how this model applies to handedness. In other words, our aim was to shed a new light on this tricky triad (cf. Vingerhoets, 2014), by looking for their disparate phenotypes, assessing their probabilities, and closely inspecting their ranges of associations and dissociations – in mixedhanders, lefthanders, and righthanders – in order to understand both their neural underpinnings, as well as the underlying processes and cognitive mechanisms.

In addition to corroborating the existence of a very strong link between praxis and language organization in the brain (Kroliczak et al., 2011; Vingerhoets et al., 2013; Kroliczak, Piper, et al., 2020), our present research indicates that this relationship is rather complex (non-linear) and non-symmetrical. While a possession of atypical organization/lateralization of language made it way more likely for praxis to be atypical, too, the inverse association was markedly weaker. Namely, people with atypical neural representation of praxis did not necessarily have atypical representation of language, with the incidence rate being more than twice as high for atypical praxis. Moreover, but as expected, this relationship was clearly influenced by handedness, with left-handed individuals having atypically represented lateralization of praxis and/or language substantially more often than righthanders. Interestingly, mixedhanders were in between, i.e., they did not differ from righthanders, but there was some difference when they were compared with lefthanders. Counterintuitively, however, our model suggested that handedness (as measured by self-report) affected the lateralization of praxis more when this impact was mediated by the lateralization of language, rather than directly. An alternative model in which handedness affects language organization directly, as well as indirectly via praxis, gained less support from our work. Yet, these are not all the crucial findings that emerged out of this project.

Arguably the most intriguing, but definitely quite telling, results are as follows. Never in mixedhanders, and very rarely

in righthanders, atypical representation of language dissociated from praxis, i.e., praxis was then always atypical, too. On the other hand, individuals with atypical praxis which dissociated from typically lateralized language were found in all handedness types. Such dissociations were in fact quite common, whereas the inverse dissociations of atypically represented language from typical left-lateralized praxis were very rare even among lefthanders. Most importantly, but still consistent with an idea that praxis and language are linked, is their interrelationship when they "dissociate" from each other. Namely, our study clearly showed that some of their underlying mechanisms are then still positively (but, in the case of some nodes, also negatively) correlated, e.g., right-hemisphere increases of neural activity for praxis were in such individuals' brains associated with increases of language-related activity in some of their left-hemisphere counterparts or their vicinities. Last but not least, both the associations of praxis and language in their typical (left-hemisphere) and atypical (bilateral or right-hemisphere) forms, as well as their dissociations, were observed in the workings of numerous brain regions or extensive networks of brain areas. In fact, the LI correlation networks disclosed in this study point to intricate interrelationships in numerous praxis-language related nodes of the three phenotypes – typical or atypical for both praxis and language, and with praxis dissociated from typically lateralized language. (The fourth group, with language dissociated from typically lateralized praxis was too small to be studied in isolation.) What these outcomes mean to developing a more comprehensive model of praxis representation in the brain, and its links to language representation and handedness will be discussed next.

These findings, once again, favor the interpretation that the observed relationships between praxis and language are contingent on a common cerebral specialization. Possibilities that we consider include the ability to construct symbolic representations, and/or to represent motor sequences, or sequential hierarchies (Kimura & Archibald, 1974; Greenfield, 1991; Bradshaw & Nettleton, 1982; but see also Arbib, 2008; Corballis, 2003; 2017; Rizzolatti & Arbib, 1998). Therefore, they even tend to be reorganized together following a pressure for their atypical forms. Namely, as we have convincingly demonstrated (Kroliczak et al., 2011; Kroliczak, Piper, et al., 2020), but now with a very large cohort, spanning all handedness types, and with even greater natural variation in their organization or laterality, we see little evidence for accidental reshuffling of praxis and language to one hemisphere or the other (Goldenberg, 2013b). Indeed, the more atypical they are, the more correlated they tend to be (see Fig. 4A,B). Furthermore, even if these two functions are dissociated, they still seem to depend on neural resources, and cognitive processes or mechanisms, that are linked (Fig. 4C). The outcomes of the LI network analyses revealed the exemplary sets of disparate cortical areas – in addition to a few selected a priori for testing in the past (Kroliczak et al., 2011; Vingerhoets et al., 2013), which show such praxis-language links, sometimes in the least expected contexts. In fact, our investigation reveals that the studied effect is contingent on rather large networks, but can still be quite specific – one can easily distinguish their different phenotypes, depending on distinct patterns of node

combinations, as well as notable differences in the strengths of their links (cf. Vingerhoets, Li, et al., 2018). The latter differences, in particular, can have substantial impact on neurocognitive efficiency and performance of related, and complementary tasks (see also Chernoff et al., 2020; Vingerhoets, Gerrits, & Bogaert, 2018). Therefore, we are convinced that more in-depth analyses of LI correlation networks of the kind we showed can be critical for more profound understanding of cognitive neural architecture in participants with both typical and atypical organization of praxis and language, and the patterns of their segregations from each other, and from other brain functions (Badzakova-Trajkov, Haberling, Roberts, & Corballis, 2010; Cai, Van der Haegen, & Brysbaert, 2013; Haberling, Corballis, & Corballis, 2016; Vingerhoets, Gerrits, & Bogaert, 2018; Johnstone et al., 2020; for reviews see; Badzakova-Trajkov, Corballis, & Haberling, 2016; Vingerhoets, 2019).

Constituting over one fifth of our current sample, individuals revealing dissociations of the studied two functions deserve more detailed consideration. The predominant phenotype involved atypical, bilateral organization or right lateralization of praxis and quite standard, left-lateralized language production. Yet, very rare cases with right-hemisphere dominant language, and left-hemisphere lateralization of praxis were observed, too. In the first group of individuals, consistent with the notion that the brain maximizes its efficiency by elimination of redundant mechanisms, in association with enhancement of parallel processing, as well as segregation of unrelated functions (e.g., Vallortigara, Rogers, & Bisazza, 1999; Vingerhoets, 2019), an atypically early acquisition of unimanual manipulation preferences, i.e., the one preceding a development of hand preference – see Michel (2018), postulating that a different order of development is a norm! – could be a foundation for later developing/maturing praxis skills. It could be also argued that the latter – i.e., late developing praxis – would be then more dependent on lower-level mechanisms for hand manipulation. While we put forward this argument before, though exclusively referring to lefthanders (Kroliczak, Piper, et al., 2020), the current research indicates that this principle can be putatively generalized to atypical development of praxis in ambidextrous or mixed-handed, as well as right-handed individuals. In less extreme cases, given that left-lateralization of praxis is a norm, the putative pressure could lead to bilateral organization of praxis.

More importantly, if hand-preference mechanisms get implemented in the brain considerably earlier than speech production mechanisms (a situation quite likely in lefthanders; Johnston, Nicholls, Shah, & Shields, 2009; but now worth testing in mixedhanders and righthanders, too), then the factors underlying unimanual manipulation and hand-preference mechanisms could jointly exert a pressure sufficient for the segregation of praxis (its right-lateralization) from the left-lateralized language (Kroliczak, Piper, et al., 2020). In such a case, even the control of manual skills in righthanders would depend on bilateral or right-lateralized mechanisms (a hypothesis easily testable in a longitudinal study; cf. Michel, Babik, Nelson, Campbell, & Marcinowski, 2013; Michel, Nelson, Babik, Campbell, & Marcinowski, 2013). However, if speech development precedes, or is at least

simultaneous with the acquisition of hand preference, then praxis and language could/should be tightly linked, by sharing common mechanisms or more general processing resources (Kroliczak, Piper, et al., 2020; cf.; Klichowski, Nowik, Kroliczak, & Lewis, 2020). In sum, it is our contention that developmental orders of skill acquisition could determine whether the predominantly observed language-praxis organization and/or their dissociations from hand dominance mechanisms are present or not.

Nevertheless, while praxis and language rarely or never dissociate in righthanders or mixedhanders, occasional displacements of language alone to the right hemisphere were observed in lefthanders. Because the kind of redundancy elimination or processing enhancement that could be a factor here is uncertain, these extremely rare phenotypes could in fact constitute a canonical case of accidental reshuffling postulated by Goldenberg (Goldenberg, 2013b, 2013c). Yet, this rare pattern of language being segregated from praxis to the right hemisphere could also mean a co-localization of all major language functions (e.g., production, intonation, prosody, or stress) into one “non-dominant” hemisphere (a possible pseudo crowding effect, cf. Badzakova-Trajkov et al., 2016; Vingerhoets, 2019; after all these functions are related). Therefore, we see little evidence supporting the idea of random reshuffling even here.

In sum, this study is one of the first to disclose the complex interrelations among nearly fifty nodes in neural networks. Based on the correlational network analyses, supported by the traditional group-level results, we corroborated our earlier proposal that there are various common neural mechanisms by which praxis and language skills are linked in their typical and atypical forms (Kroliczak, Piper, et al., 2020). This work also demonstrates that dividing study participants into typical and non-typical (or atypical, rather than into righthanders, lefthanders, and mixedhanders) turns out to be more fruitful, at least in this particular line of research.

4. Conclusions

Despite numerous cases of dissociations between atypical, bilaterally organized or right-lateralized praxis and left-lateralized language, and a much less common inverse dissociation of these functions, the neural underpinnings of tool use pantomimes and language production were again shown to be closely linked. These relationships are observed both when studied across the whole spectrum of individuals with disparate hand dominance mechanisms (handedness) and, separately (i.e., regardless of handedness), in participants with largely typical, as well as atypical organization of these functions. Notably, the links were much tighter in the latter group. The only advantage of looking at handedness we saw in this context was to find out that right-lateralized language rarely segregated from praxis in righthanders and mixedhanders. Such a phenotype might therefore be maladaptive, and putatively unrelated developmental pressures are responsible for its occurrence in lefthanders. Further research is no doubt needed to resolve this issue, as well as a few more questions inspired by the outcomes of this work.

Authors' contributions

GK conceived the project, obtained funding, supervised the project's development at all stages, initiated data acquisition and participated in data analyses, adopted new data-visualization protocols, wrote the first draft and revised the manuscript. MB participated in data analyses and created the data analysis pipeline, as well as various methods of data reporting and visualization. PK analyzed a subset of the data, interpreted its outcomes, and described them. MK contributed to an early draft of the manuscript, and interpreted some of the results. WP was responsible for data conversion, preprocessing, and early analyses. AMN contributed to participant recruitment, and screening, ran behavioral tests on study participants and compiled all the data. JR contributed to drafting and revising the manuscript (being an invaluable source of knowledge on Liepmann's work). BJP contributed to developing, validating, and implementing our method of LI calculations, as well as drafting and revising the manuscript.

Open practices

The study in this article earned Open Data and Open Materials badges for transparent practices. Materials from this study are available at <https://osf.io/63hjt/>.

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Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cortex.2021.03.022>.

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