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# The role of left fronto-parietal tracts in hand selection: evidence from neurosurgery

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## Abstract

Strong right-hand preference on the population level is a uniquely human feature, although the neural basis for this is still not clearly defined. Recent behavioural and neuroimaging literature suggests that hand preference may be related to the orchestrated function and size of fronto-parietal white matter tracts bilaterally. Lesions to these tracts induced during tumour resection may provide an opportunity to test this hypothesis. In the present study, a cohort of seventeen neurosurgical patients with left hemisphere brain tumours were recruited to investigate whether resection of certain white matter tracts affects the choice of hand selected for the execution of a goal-directed task (assembly of jigsaw puzzles). Patients performed the puzzles, but also tests for basic motor ability, selective attention and visuo-constructional ability, preoperatively and one month after surgery. An atlas-based disconnectome analysis was conducted to evaluate whether resection of tracts was significantly associated with changes in hand selection. Diffusion tractography was also used to dissect fronto-parietal tracts (the superior longitudinal fasciculus) and the corticospinal tract. Results showed a shift in hand selection despite the absence of any motor or cognitive deficits which was significantly associated with patients with frontal and parietal resections. This was not evident in those with resections in other lobes. In particular, the shift in hand selection was significantly associated with the resection of dorsal fronto-parietal white matter connections, but not with the ventral fronto-parietal tract. Dorsal white matter pathways contribute bilaterally to control of goal-directed hand movements. We show that unilateral lesions, that may unbalance the cooperation of the two hemispheres, can alter the choice of hand selected to accomplish movements.

## 1. Introduction

Handedness commonly refers to the tendency to use one hand over the other. Although the right and left hands are nearly identical in their basic anatomy and motility, approximately 90% of the human population show a strong preference for using the right hand to perform skilled movements (McManus, 2009; Corballis 2003). Curiously, the subjective choice to select one hand to accomplish a specific task (hand preference) and the actual competency of this hand (manual specialisation) are related, but not always corresponding, dimensions of handedness (Bryden, Pryde & Roy, 2000; Herve et al. 2005; Angstmann et al. 2016; Jäncke et al. 1998). Previous studies have examined whether hand preference correlates with anatomical asymmetries (McManus et al. 2019), and how altering hand preference can affect neural structures (for review see Marcori et al. 2019). However, less is known as to whether hand preference can also be altered by changing anatomical structure. This can be tested directly in the clinical setting by evaluating hand preference before and after neurosurgical interventions, which provides a unique opportunity to evaluate the neural basis of hand preference.

Manual dexterity primarily relies on the ability to perform independent finger movements, which requires monosynaptic corticospinal fibres from primary motor cortex to spinal motoneurons (Porter & Lemon, 1993). The corticospinal tract is broadly left-lateralised, with greater left to right decussation of the pyramids (Flechsig, 1876). Further, the left corticospinal tract has a more dorsal decussation at the midline in almost 90% of cases (Yakovlev & Rakic, 1966). Despite similarity in the prevalence of leftward corticospinal asymmetry and right-handedness, both post-mortem and neuroimaging studies have demonstrated the two to be unrelated (Lawrence & Kuypers, 1968; Kertesz & Geschwind, 1971; Westerhausen, 2007). It has been reported that handedness is associated with morphology of the central sulcus, in proximity to the primary motor and somatosensory hand region (Steinmetz et al. 1991; Amunts et al. 2000; Germann et al. 2019), although other studies have not replicated this result (Guadalupe et al. 2014; Jang et al. 2017; Ocklenberg et al. 2016). An intriguing observation is that central sulcus morphology is flexible, in that this region remodels in corrected left-handers to follow a more 'right-handed' shape (Sun et al. 2012). It is well established that the precentral gyrus is highly plastic, thus handedness-related structural differences may reflect repeated lifelong use of one hand over the other (Steele & Zatorre, 2018; Simone et al. 2019). Given the lack of association between handedness and the asymmetry of cortical areas hosting corticospinal fibres for motor

output, it is thus plausible that this difference may reflect structural asymmetry of pathways involved in earlier stages of action preparation.

Skilled manual action requires sensorimotor transformations to coordinate adequate muscle synergies to perform finger movements. Sensorimotor integration requiring visual and somatic information is mediated by a widespread fronto-parietal circuit (Turella & Lingnau, 2014), which has been well studied in macaques (Borra et al. 2017) but only partially in humans (Binkofski et al. 1999). In particular, neurons tuned to eye and hand movements in monkey fronto-parietal regions code primarily for the contralateral limb, but also for the ipsilateral limb (Cisek et al. 2003). This observation has also been demonstrated in humans, using transcortical magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI) (Schluter et al. 2001; Begliomini et al. 2008, Gallivan et al. 2013), indicating there is bilateral but left-lateralised fronto-parietal specialisation for visuomotor control of movement that is handedness-independent (Sainburg et al. 2002; Begliomini et al. 2018). This is intriguing given the well-established right hemisphere dominance for visuospatial attention (Corbetta & Shulman, 2002). The superior longitudinal fasciculus (SLF) consists of three bilateral branches (SLF I,II,III) that connect widespread premotor regions (superior, middle and inferior frontal gyri) and the superior and inferior parietal lobule (Thiebaut de Schotten et al. 2011). There is growing evidence that these tracts may support different aspects of motor control in humans (Buch et al. 2012; Rodriguez-Herreros et al. 2015; Budisavljevic et al. 2017). In a previous study, we demonstrated that the structural asymmetry of the dorsal and ventral branches of the SLF (SLF I and SLF III), rather than corticospinal tract asymmetry, differs between self-reported right- and left-handers, which is also linked with differences in manual specialisation measured using a visuomotor task (Howells et al. 2018). Both groups had similar left fronto-parietal tract volume and performance with the right hand: results were driven by differences in tract volume in the right hemisphere and left hand performance. This indicates that lateralised motor behaviour may not be the result of a dominant sensorimotor circuit in only one hemisphere, but rather depends on the relationship between two homologous circuits in both hemispheres.

A lesion disrupting one hemisphere may therefore unbalance this bilateral system, modifying lateralised motor behaviour of the hands however this has not yet been studied in humans. We therefore set out to test whether surgical resection of tracts in one hemisphere can alter lateralised hand use in seventeen patients undergoing neurosurgery for a brain tumour. We aimed to assess whether resection of certain fronto-parietal tracts (the SLF) or corticospinal tract are associated with changes in lateralised motor behaviour. Tractography is currently the only technique available for studying structural connections in the living human brain and

is commonly used to evaluate the relationship between structural asymmetry based on unique tractograms and individual differences in behaviour (Catani et al. 2007; Forkel et al. 2014; Forkel & Catani 2018). However in clinical circumstances there are often limited opportunities to access this type of data, thus atlases of white matter tracts in healthy adults have been created to estimate the extent of tract disconnection based on lesion location (the “disconnectome” approach, Catani et al. 2012; Fox et al. 2018, Thiebaut de Schotten & Foulon, 2017). We used both High Angular Resolution Diffusion Imaging (HARDI) spherical deconvolution deterministic tractography (9 patients) and the disconnectome approach (17 patients) to assess which tracts were resected in our cohort. All patients performed a range of neuropsychological tests before and at 1 month after surgery, including handedness inventories and a reach-to-construct task requiring completion of a jigsaw puzzle (Gonzalez et al. 2006, 2007). We tested whether changes in test performance and lateralised manual behaviour following surgery was linked to resection of specific tracts.

## 2. Methods

### 2.1 Participants

Seventeen neuro-oncological patients who were candidates for awake surgery to remove a brain tumour were enrolled in this study (Table 1). Patients were recruited using the following inclusion criteria: (i) a unilateral lesion in the left hemisphere, (ii) no previous surgery or radiotherapy (iii) no language or visual field deficits, (iv) no previous neurological or psychiatric conditions (v) no history of fractures involving the bones of the hand or fingers that might require restricted healing for longer than six months. All patients gave written informed consent to the surgical and direct electrical stimulation mapping procedure (IRB1299), and to the analysis of data for research purposes which followed the principles laid out in the Declaration of Helsinki. Study procedures and analysis were not preregistered prior to research being conducted. Patients were assessed for self-rated handedness using the Edinburgh Handedness Inventory (EHI, Oldfield, 1971). On this scale of hand preference patients could score between -100 and 100, where under -60 indicated non-right-handed (referred to from now on as left-handed), over 60 indicated right-handed and a score between -60 and 60 indicated mixed-handedness. 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. The data used for analysis are publicly available through the Open Science Framework (<https://osf.io/79n2h/>). The conditions of our ethics approval do not permit public

archiving of individual anonymised raw or summary MRI data. Readers seeking access to the data should contact the lead author (H.H.) or the local ethics committee at the Department of Medical Biotechnology and Translational Medicine, University of Milan. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. Specifically, requestors must complete a formal data sharing agreement, which is available by request.

Awake neurosurgery was performed in all patients, with the aid of the brain mapping technique, using functional borders to achieve total or supratotal resection for tumours distributed across the left hemisphere. All regions of the precentral gyrus for which motor evoked potentials of the hand could be evoked by direct electrical stimulation were preserved in all cases (Bello et al. 2014; Figure 3). Further, a new tool designed to assess and preserve eloquent regions controlling complex non-visually guided hand actions was used during awake brain mapping in these patients (see previous studies – Forna et al. 2019). The mean resection volume was 76.7ml (s.d. 71.3).

**Table 1: Demographic information**

Patient	Handedness	EHI	Age	Sex	Resection location	Resection volume (ml)	Education	Grade	HARDI
1	R	100	60	F	Parietal	29.76	13	HGG	x
2	R	100	42	M	Frontal	49.06	13	LGG	x
3	R	100	56	F	Frontal	10.36	17	LGG	x
4	R	100	28	F	Frontal	256.06	13	HGG	x
5	R	100	68	M	Frontal	91.14	8	HGG	
6	R	100	31	M	Parietal	31.7	17	HGG	x
7	R	100	46	M	Frontal	204.73	13	HGG	
8	R	100	51	M	Frontal	126.12	13	LGG	x
9	R	100	59	F	Frontal	38.4	13	HGG	x
10	R	100	49	F	Frontal	153.03	13	HGG	
11	R	100	61	M	Parietal	28.89	17	LGG	x
12	R	100	28	F	Occipital	15.11	17	LGG	x
13	R	60	37	F	Temporal	30.5	8	LGG	
14	R	100	19	M	Temporal	25.02	13	HGG	
15	MH (excluded)	15	27	M	Temporal	38.4	13	HGG	
16	L	-100	51	M	Temporal	66.1	13	LGG	
17	L	-60	30	F	Frontal	110.02	17	HGG	

Note: R: right-handed LH: left-handed, MH: mixed-handed; M: male, F: female; EHI Edinburgh handedness inventory, HGG high grade glioma, LGG low grade glioma, HARDI: high angular resolution diffusion imaging

## 2.2 Neuropsychological assessment

All patients underwent a comprehensive preoperative (1 week prior to surgery) and postoperative (1 month after surgery) neuropsychological assessment (non digital). This assessment included evaluation across cognitive domains including language, praxis, attention and executive function (for details see Puglisi et al. 2018). For the purpose of this study, and to exclude severe postoperative deficits that could affect the reliability of the postoperative assessment, we assessed changes between the pre- and postoperative timepoints for scores in visuospatial exploration (letter cancellation), visuoconstructional ability (Rey-Osterrieth Complex Figure), selective attention (Attentive Matrices) and auditory comprehension (Token Test). As hand selection requires a significant cognitive load (Rosenbaum, 1980; Liang et al. 2018), we compared these results with performance changes on selective attention and visuoconstructional tasks to evaluate whether changes in hand selection were associated with deficits in these domains.

### 2.2.1 Assessment of manual ability

Manual ability was evaluated in two domains: arm-hand motor skills and praxis. The Action Research Arm Test (ARAT) is a simple test used to assess upper extremity movements with the dominant hand. It consists of 19 motor actions that are grouped into four subtests assessing four actions: grasp, grip, pinch, and gross movement. All items are rated from 0 (the movement is not possible) to 3 (normal performance of the task). The total score on the ARAT ranges from 0-57, with a higher score indicating better performance (Yozbatiran et al., 2008). We used 57 as the cut-off for this test. Patients without motor, sensory or visual deficits were assessed also for coordination and fine movement control using the Movement Imitation test for ideomotor apraxia (De Renzi, 1980). It consists of twenty-four gestures of different complexity that are imitated by the patient, requiring independent movement of the hands. Each imitation trial is rated from 0 (impossible to replicate the movement) to 3 (correct imitation at first presentation). The total score ranges from 0-72, where a score of 52 is the cut-off for normal performance.

### 2.2.2 Assessment of hand preference: jigsaw puzzle task

At present the most commonly used inventory scales to assess handedness lack the sensitivity to evaluate subtle changes in manual behaviour (Brown et al. 2006; Flindall & Gonzalez, 2018). These questionnaires measure the overall result of the hand selection process over time, but do not provide data to understand the underlying mechanisms themselves. Grasp-to-construct tasks are a useful means by which to evaluate lateralised motor behaviour in an ecological context, providing a quantitative measure of the



interactions of each hand in both ipsilateral and contralateral space (Gonzalez et al. 2006,2007). Putting together a jigsaw puzzle is therefore a useful way of testing hand selection to evaluate whether changes in lateralised manual behaviour following neurosurgical removal of brain tumours.

During the neuropsychological assessment and while comfortably seated in front of a table, patients were asked to assemble two different jigsaw puzzles to evaluate spontaneous hand preference in a 'naturalised' setting (Gonzales et al. 2006). Each puzzle was of a standard size (17cm x 17cm) and made up of 25 equally sized pieces (Supplementary Video). The underside of the pieces were labelled with '1' or '2' to indicate the hemisphere in which they were to be presented (Figure 1). The pieces were distributed across each side of the tabletop with the same number of pieces on each side. The patient was seated exactly facing the middle of this distribution and provided with a central puzzle piece directly in front of them, for orientation. An image of the completed puzzle image was displayed opposite the patient for reference. The patients were asked to place each hand on the table face down and then to reproduce the puzzle as fast and as accurately as possible and were blinded to the purpose of the study (no instruction was given as to which hand to use). Patients were asked to take one piece at a time and replace it if they could not fit it into the puzzle. The patients' hands were video recorded by a camera position directly in front of the patient, tilted downward to provide a view of the action of both hands. Patients were given three minutes to complete each puzzle and then asked to stop, even if the puzzle was not completed. The order of presentation of each puzzle was counterbalanced between patients.

Performance on the two puzzles were scored offline using the video-recordings, by two neuropsychologists blind to whether performed pre- or post-operatively (see Supplementary Video). The performance was evaluated in two action phases: reach-to-grasp and manipulation. First, each video was analysed to record the hand used every time a piece of the puzzle was reached for and grasped (e.g.; Figure 1a). It was also recorded whether the hand used was reaching to grasp a piece within its hemisphere (e.g. right hand within right hemisphere, R, left hand within left hemisphere, L) or whether it reached to grasp within the opposite hemisphere (e.g. right hand into left hemisphere, Rx; left hand within right hemisphere, Lx). As the effort required to reach across hemisphere was higher, the last condition was given a higher weight (Elliott et al. 1993; Liang et al. 2018). We used the average across the two trials to create a final score of lateralised hand selection, calculated for the right hand as  $(R + (1.5 \times Rx))$  or left hand as  $(L + (1.5 \times Lx))$ . This was then used to create a lateralisation quotient, calculated as  $([R-L]/[R+L])$ . A score of -1 reflects selection solely of the left hand, a score of +1 reflects selection solely of the right, while a score of 0

reflects selection of both hands equally. When one hand would reach and grasp a puzzle piece, this was sometimes passed to the other hand for positioning. Thus, each video was also scored for the hand that rotated the puzzle piece into the appropriate configuration and then fit it into position (Figure 1b). This was a cooperative movement as the other hand generally played as a supportive role, by holding the puzzle in place. The final score for each hand was calculated based on the total number of manipulations performed by each hand and a similar lateralisation quotient of hand selection was created (average across the two trials). For each of the two scores, the proportion of right hand use out of the total grasps or manipulations was also calculated ( $R/(R+L)$ ).

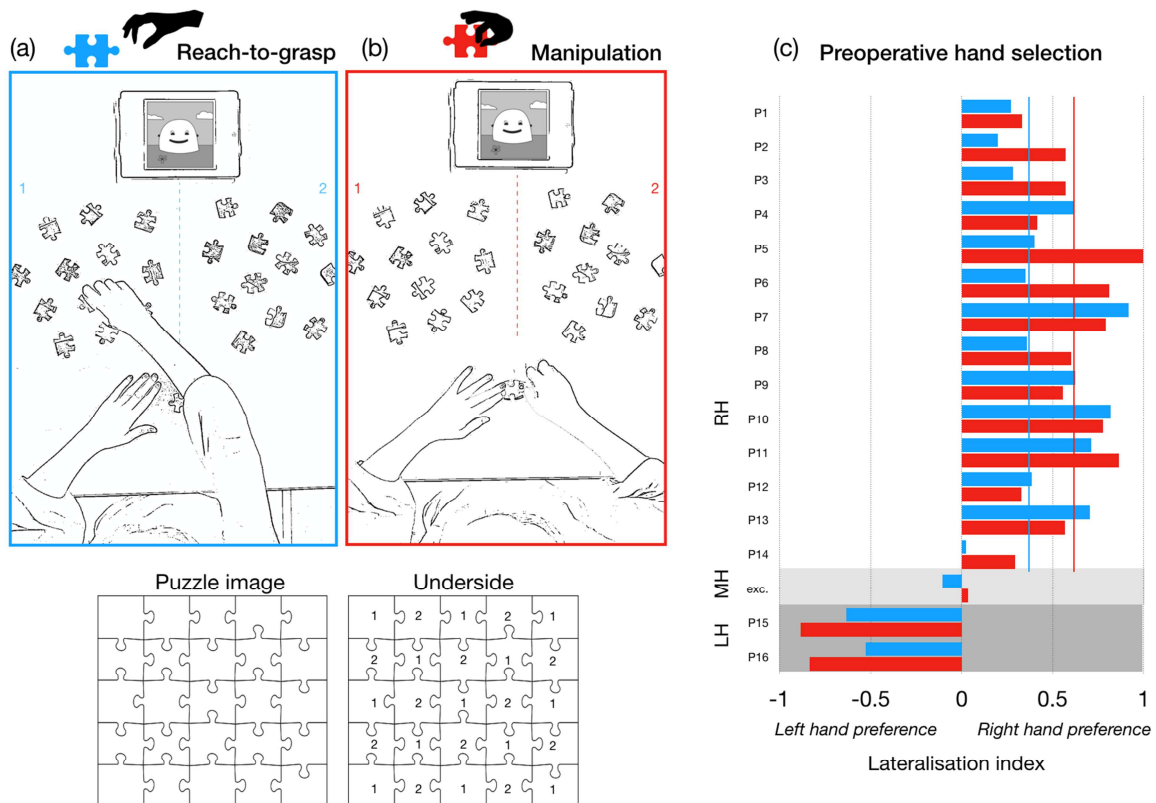


Figure 1. Photographs showing layout of puzzle task and hand movement during the (a) reach-to-grasp (blue) and (b) manipulation (red) phases, as well as the labelling of pieces in order to distribute them equally across hemispaces (see also Supplementary Video). (c) A bar graph shows hand selection in the preoperative time point for both phases of the puzzle task (lines in blue and red reflect median score for the right-handed patients). The direction of hand use is consistent with hand preference reported on the Edinburgh Handedness Inventory.

### 2.3 Neuroimaging acquisition

All patients underwent a clinical MR imaging sequence one day before surgery, and at the one-month follow-up. Preoperative MRI imaging was performed on a Philips Intera 3T scanner (Koninklijke Philips N.V. Amsterdam, Netherlands), and acquired for characterisation of lesion morphology and volume. A post-contrast gadolinium T1-MPRAGE

sequence was performed using the following parameters TE:2.7ms, TR:95.4s, FOV: 176 slices, isotropic voxel size of 1mm and a T2-FLAIR, as part of the clinical routine.

Nine patients also underwent a High Angular Resolution Diffusion Imaging (HARDI) sequence for clinical purposes, prior to surgery only, using an 8-channel head coil. A spin echo, single shot EPI sequence was performed with 73 directions collected using a b-value of 2000s/mm<sup>2</sup>, and seven interleaved non-diffusion weighted (b<sub>0</sub>) volumes (TE:96ms, TR 10.4ms). The acquisition had a matrix size of 128x128 with an isotropic voxel size of 2mm<sup>3</sup>.

### 2.3.1 Neuroimaging preprocessing and analysis

Volumetric analysis was used to define tumour volume using BrainLab software (Smartbrush). Resection cavities were delineated on the postoperative T1 and registered to a preoperative diffusion-weighted imaging map (Anisotropic Power, Dell'Acqua & Tournier, 2018) using the Clinical Toolbox in SPM (Rorden et al., 2012).

Diffusion imaging data was visually inspected for outliers, corrected for signal drift, reordered and corrected for head motion and eddy current distortions using ExploreDTI ([www.exploredti.com](http://www.exploredti.com), Leemans et al. 2009). Standard diffusion tensor models cannot show multiple fibre orientations within a voxel therefore are not suitable for evaluating fronto-parietal tracts (Thiebaut de Schotten et al. 2011). We used an advanced algorithm based on spherical deconvolution to model the fibre orientation distribution function (fODF), using a damped Richardson-Lucy algorithm (Dell'Acqua et al. 2010). The following settings were used for reconstructing the fODF:  $\alpha = 1.7$ , 300 iterations,  $\eta = 0.001$ ,  $\nu = 8$ , and an absolute threshold of 0.001. Deterministic tractography was calculated using a step size of 1mm, with a constraint to display streamlines between 15 and 200mm in length. We used a whole brain approach, seeding is performed from every voxel across the brain (3 runs), and the seeding position within the voxel was always randomised. Euler interpolation was used to track streamlines using an angle threshold of 45 degrees. All spherical deconvolution modelling and whole brain deterministic tractography was performed using StarTrack software (Dell'Acqua et al. 2012; [www.mr-startrack.com](http://www.mr-startrack.com)).

### 2.3.2 Tractography dissections

Virtual dissections of the three branches of the superior longitudinal fasciculus (SLFI-III) and the precentral component of the corticospinal tract were performed manually in both hemispheres using a ROI-based approach by the first author (H.H) using TrackVis software (<http://trackvis.org>). The regions of interest used to segment the SLF I-III are described in

detail in Thiebaut de Schotten et al. (2011) and Howells et al. (2018). The dorsal branch of the SLF (SLF I) connects the superior parietal lobule with the superior frontal gyrus, running anterior and parallel to the cingulum but distinct, separated by the cingulate sulcus (Thiebaut de Schotten et al. 2012). The middle branch (SLF II) connects the posterior inferior parietal lobule (angular gyrus) with the middle frontal gyrus including the frontal eye fields. The ventral branch (SLF III) connects the inferior frontal gyrus and ventral precentral gyrus with the anterior inferior parietal lobule (supramarginal gyrus) and intraparietal sulcus. For the purpose of this study, the corticospinal tract was defined as the streamlines extending from the precentral gyrus to the brainstem (Catani & Thiebaut de Schotten 2016). The postoperative MR with the delineated resection cavity was registered and overlaid on the preoperative diffusion tractography using the Clinical Toolbox in SPM and registration tools included in FSL. The number of streamlines intersecting with the resection cavity was identified and the proportion of these streamlines relative to the total number of streamlines of that tract was calculated as an indicator of disconnection (e.g. 120/600 streamlines ran within the resection cavity therefore 20% of the tract was disconnected). We used a cut-off of 50% to determine resection (>50% resected) as has been used in previous studies (Puglisi et al. 2019).

### 2.3.3 Estimation of tract resection

As we did not have access to individual tractography data for each patient, we used a disconnection approach to identify the most probable tracts to have been disconnected by the resection, of each patient. The use of atlas-based tract estimation tools can be challenging in patients with tumours that may displace or disconnect tracts, however in the case of large supratotal resections, tract-based lesion-symptom associations may be suitable, particularly when used in conjunction with tractography to provide some indicator of the reliability of the output. We used the online platform "Megatrack", a HARDI-based tractography atlas and lesion tool (<https://megatrackatlas.org>, Stones et al. OHBM 2019), to estimate the extent of disconnection of white matter tracts, based on the percentage of disconnected streamlines as a proportion of the total making up the fibre bundle of an estimated tract in a healthy adult. Although other tract atlases are available (e.g. Rojkova et al. 2016), this approach was relevant in this case, as one can produce averaged tract density maps for a healthy population based on specific demographic criteria. In this case, we used tract density maps for right-handed and left-handed populations separately to compare with the right- and left-handed patient lesions.

## 2.4 Statistical analysis

Shapiro-Wilk normality tests were performed and non-parametric tests were used where appropriate. Differences between pre- and post-operative scores were evaluated using paired samples t-tests or Wilcoxon rank-signed tests across neuropsychological tasks. Associations between and within neuropsychological tests were assessed using bivariate correlation analysis. The difference between the pre- and post-operative lateralisation quotient was calculated and used for subsequent analysis. Repeated measures were used to assess the interaction between clinical or demographic variables (age, sex, education level, resection volume and histology) and the extent of change of hand selection following surgery. As we hypothesised that fronto-parietal resections would have a significant impact on hand selection, we categorised patients into two groups: those with resections predominantly in the frontal or parietal lobe, and those with resections in the temporal or occipital lobe, and performed an independent t-test to assess the effect of resected lobe on hand selection shift. Univariate analyses were performed to evaluate the effect of resection of specific tracts on changes in neuropsychological performance on certain tests (puzzle - reach-to-grasp or manipulation phase, Rey figure, Attentive Matrices). Tests were reported as significant when  $p < 0.05$ .

### 3. Results

#### *3.1 Assessment of motor and cognitive abilities*

Upper limb motor skills. Motor assessment was performed to exclude alteration of motor ability of the dominant hand before and after surgery. The ARAT was used to test the ability of the dominant hand in performing four basic motor actions (i.e. grasp, grip, pinch, and gross movement). The task was fully accomplished (i.e. all actions were performed to achieve perfect scores) by all patients at both timepoints (Table 2).

Praxis ability. There was no significant change in score on the ideomotor apraxia test ( $t(16)=126$ ,  $p=0.126$ ), indicating no deficits were evident before or after surgery (Table 2).

Language comprehension. No patients experienced persistent postoperative aphasia, and their performance on the Token test for auditory comprehension, despite a decrease ( $t(15)=2.7$ ,  $p=0.014$ ), was within the range of normality in the postoperative phase (patients scored between 23.5 and 36; cut-off 22.5, maximum 36). All patients were therefore able to understand the instructions given for the task (Table 2).

Attentional processing. In line with the postoperative clinical course, a slight reduction in cognitive performance was observed in selective attention ( $t(15)=2.5$ ,  $p=0.023$ ). The difference in omitted letters between right and left hemifields in the cancellation test was assessed in the pre- and post-operative phases. There was no significant change in visual field exploration between the two timepoints ( $t(15)=-1.0$ ,  $p=0.3$ ). None of the patients showed hemispatial neglect (Table 2).

No patients experienced any postoperative sensory deficits. One patient presented with hemianopia in the immediate follow-up, which fully recovered subsequently (Patient 1).

### 3.2 Assessment of hand selection

Assessment of hand preference. Patients were asked to complete a self-rated handedness inventory (Edinburgh Handedness Inventory, EHI) before and one month after surgery to assess hand preference. Fourteen patients were right-handed (+60 on EHI), two patients were left-handed (-60 in EHI) and one patient was mixed-handed (+ 37.5 on EHI). No patients reported any change in the EHI score in the one month follow up.

Table 2: Neuropsychological scores before and after surgery

PUZZLE	PREOPERATIVE	POSTOPERATIVE	CHANGE
	Mean (SD)	Mean (SD)	Mean (SD)
REACH-TO-GRASP LAT	0.34 (0.43)	0.06 (0.48)	-0.27 (0.4)
CROSSING HEMISPACE LAT	0.69 (0.5)	0.17 (0.9)	-0.5 (0.8)
MANIPULATION LAT	0.42 (0.53)	0.25 (0.6)	-0.17 (0.5)
<b>COGNITIVE TESTS</b>			
IDEOMOTOR TEST (MAX 72)	71.5 (1.5)	70.7 (2.3)	0.7 (1.9)
ATTENTIVE MATRICES (MAX 60)	52.1 (8)	46.3 (13.5)	5.8 (9)
REY FIGURE (MAX 36)	33.2 (5.5)	31.3 (7.5)	1.9 (6)
CANCELLATION TEST (L-R)	0.25 (0.9)	0.68 (1.8)	-0.43 (1.67)
TOKEN TEST (MAX 36)	35.2 (1.8)	32.1 (5.2)	3.1 (4.5)

NOTE: Scores are mean (standard deviation). LAT: lateralisation quotient (see Section 2.2). A score of -1 indicates non-dominant hand use only; 0 indicates equal use of both hands, 1 indicates dominant hand use only.

Assessment of consistency of preoperative hand selection in the two phases of the puzzle task. Hand selection on the puzzle was compared with the patient's self-reported hand preference in the preoperative time point. All patients used their dominant hand more than the non-dominant hand for both phases of the puzzle (reach-to-grasp and manipulation; Figure 1c), with the exception of the mixed handed patient who showed an inconsistent hand

preference. This patient was excluded from subsequent neuropsychological analysis. We evaluated the consistency in the hand selected for both reach-to-grasp and manipulation phases. Shapiro-Wilk tests showed scores were normally distributed in the preoperative timepoint on both movement phases. A bivariate analysis showed a strong correlation between lateralisation quotients for hand selection for the two phases of the puzzle task in the preoperative phases ( $r^2=0.8$ ,  $p<0.001$ ). An ANOVA showed no effect of sex on lateralised preoperative hand selection in either phase (reach-to-grasp:  $F(1,14)=0.227$ ,  $p=0.6$ ; manipulation:  $F(1,14)=0.37$ ,  $p=0.6$ ).

Assessment of task consistency and competency. A comparison of hand selection, as measured by the lateralisation quotient, was conducted between trials (first vs second puzzle) in each timepoint. Lateralised hand selection was highly correlated between the two trials in the preoperative ( $r^2=0.8$ ,  $p<0.001$ ) and postoperative phase ( $r^2=0.6$ ,  $p<0.003$ ), indicating the test had good consistency for assessing hand selection in both reach-to-grasp and manipulation phases. We next compared the number of correct pieces placed at the end of the puzzle task between the two timepoints, in order to assess any potential postoperative difficulties in task completion. The mean number of pieces correctly placed was 14.9 out of 25 (s.d. 7.4) in the preoperative time point and 14.7 out of 25 (s.d. 7.3) in the postoperative time point. A paired samples t-test showed no significant difference between time points ( $t(15)=-0.249$ ,  $p=0.8$ ).

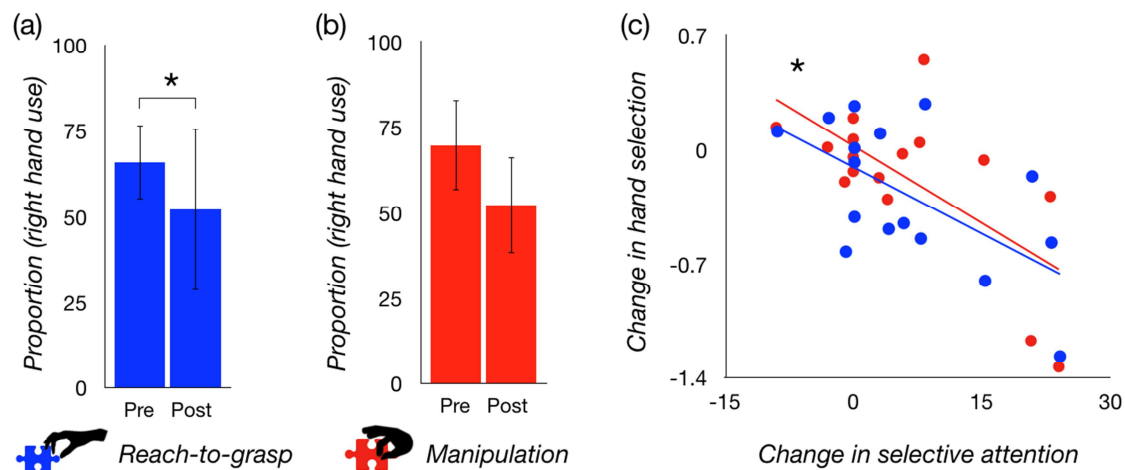


Figure 2. Changes in neuropsychological scores before and after surgery. The change in hand selection in the (a) reach to grasp and (b) manipulation phases of the puzzle. (c) A scatter graph showing the significant association between change in hand selection for each phase and change in score on the attentive matrices. A negative score indicates a shift to non-dominant hand use, or an improvement in the selective attention score. Note: \* reflects significance level of  $p<0.01$

Assessment of hand selection before and after surgery.

Scores were normally distributed for the preoperative and postoperative reach-to-grasp and preoperative manipulation phase but not the postoperative manipulation phase. A Wilcoxon signed-rank test showed there was a significant shift in hand selection following surgery in the reach-to-grasp ( $Z=-2.7$ ,  $p=0.006$ ; Figure 2a) but not the manipulation phase ( $Z=-1.3$ ,  $p=0.17$ ; Figure 2b).

A repeated measures ANOVA was used to assess the interaction between clinical or demographic variables and the change in hand selection before and after surgery. This showed no significant interaction between change in hand selection and education, sex, resection volume or age. The only significant interaction was between resected lobe and hand selection for both reach-to-grasp ( $F(1,14)=6.87$ ,  $p=0.02$ ) and manipulation phases ( $F(1,14)=5.06$ ,  $p=0.04$ ). A significant difference in hand selection before and after surgery emerged in patients with frontal or parietal resections, but not when resection affected the temporal or occipital lobes (Figure 3c).

We finally compared cognitive scores with hand selection on the puzzle task. Bivariate correlation analysis showed a significant association between change in selective attention performance and hand selection for reach-to-grasp ( $r^2=0.605$ ,  $p=0.01$ ) and manipulation ( $r^2=0.601$ ;  $p=0.014$ ; Figure 2c). The greater shifts toward non-dominant hand use were correlated with lower scores on the selective attention test. No significant correlations between change in visuoconstructional ability or auditory comprehension, and change in hand selection for reach-to-grasp or manipulation were observed.

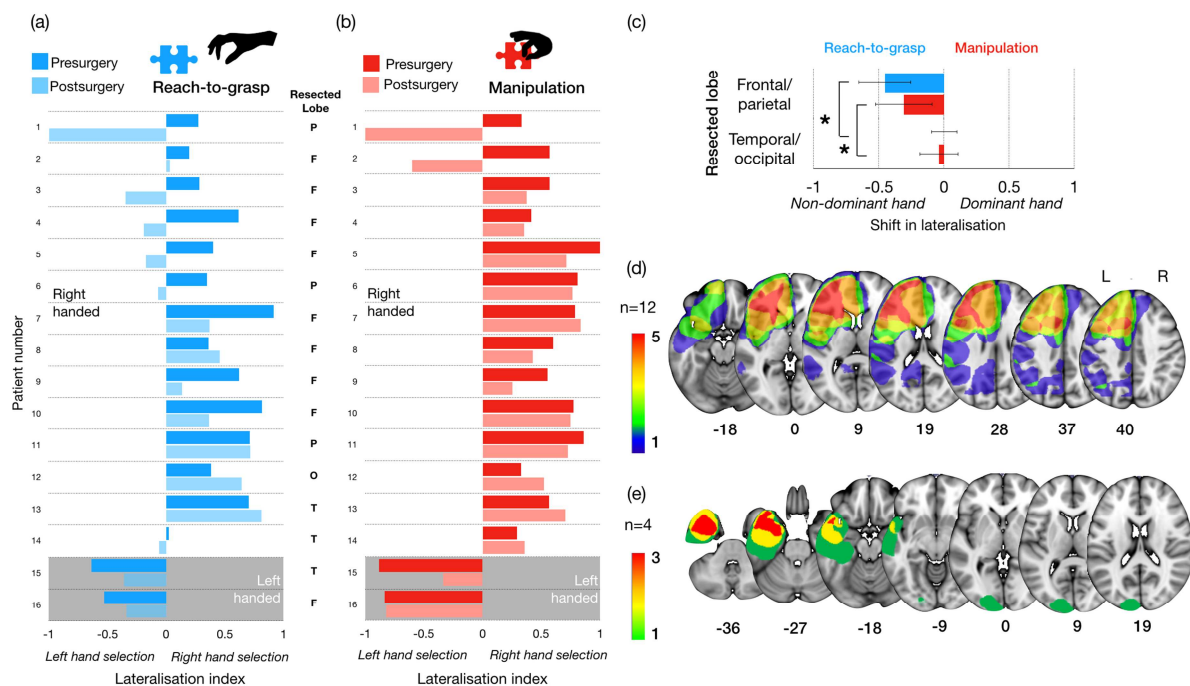




Figure 3. The individual scores for each patient on the puzzle task are shown in the pre- and post-operative phases for the (a) reach-to grasp and (b) manipulation phases. The lobe resected for each patient is also described F: frontal, P: parietal, O: occipital, T: temporal (c) Bar graph showing the shift in hand selection by resection group (d) Anatomical distribution of resections within the frontal and parietal lobe. The lesion location of the mixed handed patient is not included here (e) Anatomical distribution of resections within the temporal and occipital lobe. \* $p < 0.05$ .

### 3.3 Effect of resected region on hand selection

Table 3. Tractography measurements in right and left hemisphere

	TRACT MEASUREMENTS (L)	TRACT MEASUREMENTS (R)	TRACTOGRAPHY DISCONNECTION IN LEFT HEMISPHERE
TRACTS	Mean Volume <b>in ml</b> (SD)	Mean Volume <b>in ml</b> (SD)	
SLF I	11.47 (3.4)	14.44 (2.5)	5/9 cases
SLF II	13.37 (8.3)	13.17 (5.9)	4/9 cases
SLF III	7.72 (3.1)	12.03 (3.3)	4/9 cases
CST	11.46 (2.4)	9.53 (1.3)	0/9 cases

NOTE: SLF: superior longitudinal fasciculus, CST corticospinal tract

Using disconnectome tools, our results showed the precentral projections of the corticospinal tract were preserved in all patients, using estimations of trajectories of tracts using a healthy adult white matter atlas. The dorsal fronto-parietal tract (SLF I) was resected in 6/16 patients, the middle branch (SLF II) in 8/16 patients and the ventral branch (SLF III) in 7/16 patients.

The tractography performed in 9 patients confirmed the results of the atlas-based disconnectome analysis, showing that the dorsal branch of the superior longitudinal fasciculus (SLF I) was disconnected in 5/9 cases, the middle branch (SLF II) in 4/9 cases and the ventral branch (SLF III) in 4/9 cases (Table 3). The binary estimation of disconnection (resected/not resected based on >50% streamlines) calculated by the atlas-based disconnectome tools was in line with the estimated disconnection calculated with individual tractography in all 9 cases. The corticospinal tract was intact in all patients. We examined changes in hand selection in the two phases of the puzzle task (reach-to-grasp and manipulation) between patients with specific branches of the superior longitudinal fasciculus resected or preserved. We observed a trend to show greater shift in hand selection toward non-dominant hand use following resection of the SLF I or SLF I. No consistent result was associated with resection of the SLF III.

We performed univariate analysis to evaluate whether there was an interaction between estimated tract resection based on the disconnectome method, and shift in hand selection

on both reaching and manipulation phases (Figure 4b). Patients with the left dorsal fronto-parietal branch (SLF I) resected showed a significantly greater shift toward non-dominant hand use in the reach-to-grasp phase compared to patients submitted to a resection preserving the same tract ( $F(1,15)=21.8$ ,  $p=0.001$ ). This same results were observed for the manipulation phase ( $F(1,15)=5.6$ ,  $p=0.04$ ). Resection of the SLF II resulted in a shift in hand selection in the reach-to-grasp ( $F(1,15)=4.7$ ,  $p=0.05$ ) but not the manipulation phase ( $F(1,15)=2.6$ ,  $p=0.14$ ). Resection or preservation of the SLF III did not affect the hand selection in the reach-to-grasp phase ( $F(1,15)=2.4$ ,  $p=0.15$ ) but was significant for the manipulation phase ( $F(1,15)=9.1$ ,  $p=0.01$ ).

Additionally, we evaluated whether resection of these tracts was related to a change in cognitive performance on the selective attention and visuoconstructional tasks. Patients with resection of the SLF I showed a trend toward higher incidence of deficits on the selective attention task at 1 month following surgery ( $F(1,15)=4.3$ ,  $p=0.068$ ), but not the SLF II ( $F(1,15)=0.37$ ,  $p=0.5$ ) or SLF III ( $F(1,15)=0.36$ ,  $p=0.5$ ). No associations between resection of these tracts and visuoconstructional task performance before and after surgery was observed.

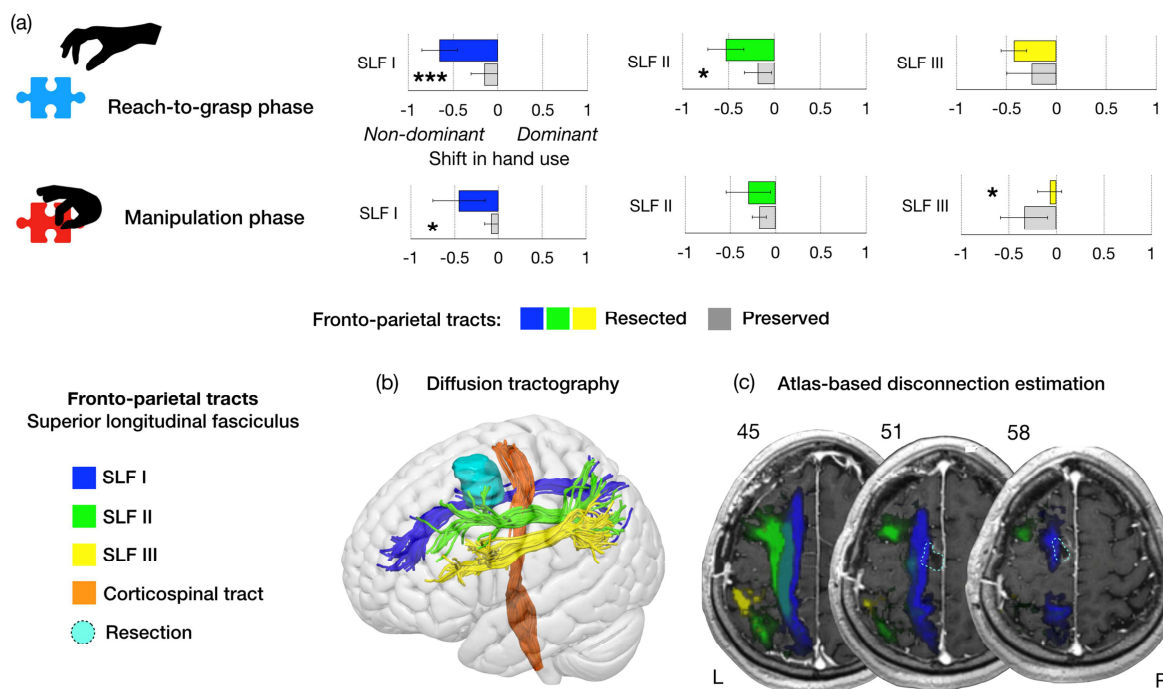


Figure 4. (a) Boxplots showing group differences in change in hand selection related to resection of specific tracts in the different phases of puzzle performance. (b) Preoperative diffusion tractography dissections of the four tracts in this patient are shown with an overlay of the resection cavity (cyan), showing the SLF I was resected (c) Megatrack atlas-based estimation of white matter disconnection shown on the postoperative T1 also indicated complete resection \*\*\* $p<0.001$ , \*\* $p<0.01$ , \* $p<0.05$

## 4 Discussion

In neurosurgical patients with left hemisphere brain tumours, we show that resection of fronto-parietal white matter pathways is associated with increased selection of the non-dominant hand for completing reach-to-construct tasks (jigsaw puzzles) requiring the use of both hands. Our results show that these changes in hand selection occurred following frontal and parietal resections, despite no primary deficits in motor ability. Patients preferentially selected the dominant hand (based on a self-reported handedness inventory) for both reach-to-grasp and manipulation phases of puzzle assembly before surgery, however there was a shift toward increased use of the non-dominant hand (or decreased dominant hand use) for this task in the postoperative phase. This hand selection shift was significantly correlated with the surgical resection of superior and middle fronto-parietal white matter connections (i.e. SLF I and II), but not the inferior fronto-parietal branch (SLF III) or corticospinal tract. Resections of comparable sizes in the temporal or occipital lobe did not produce this type of shift. Our results suggest that the relationship between brain structure and lateralised hand motor behaviour is reciprocal: forced alteration of spontaneous manual preference can affect structural hemispheric asymmetries (Sun et al. 2012), but also lesions altering brain structure can produce subtle shifts in lateralised motor behaviour.

Everyday interactions require complex highly skilled hand movements which are either performed unimanually, or more commonly, require bimanual cooperation. The decision to use one hand over the other to perform complex motor tasks is a distinct feature of our species, a lateralised behaviour referred to as hand preference. Hand-object interaction requires independent finger movements to be orchestrated based on the properties of the object and the goal of the action. Thus, lateralised hand use is unlikely to depend solely on asymmetry of neural structures in change of final motor output, for example the size of the precentral gyrus or corticospinal tract. A considerable body of work has indicated that cooperative interplay of both hemispheres is required for movement, and further that each hemisphere is responsible for different aspects of motor programming for complex actions of each hand (Sainburg et al. 2002). When considering grasping and hand-object manipulation, fronto-parietal connections are essential in providing the motor program with visual and somatosensory information required to achieve adequate hand shaping and control in both monkeys and humans (Borra et al. 2017; Turella & Lingnau 2014). Three parallel branches of the superior longitudinal fasciculus convey sensorimotor transformations between frontal and parietal regions, each of which has different patterns of structural asymmetry (Thiebaut de Schotten et al. 2011). This interhemispheric asymmetry has been associated with specific

aspects of upper limb kinematics in healthy adults, precisely for different phases of visuomotor processing needed for reach-to-grasp movements (Budisavljevic et al. 2016) and may have a genetic basis (Wiberg et al. 2019). We recently demonstrated further that hemispheric asymmetry of the dorsal fronto-parietal tract (SLF I) differs between self-reported right- and left-handers, with a greater left-lateralisation in right-handers, and right-lateralisation in left-handers (Howells et al. 2018). Asymmetry of the SLF I was also associated with manual specialisation between the hands, measured using relative unimanual performance between hands on a pegboard task. Taken together, the aforementioned studies indicate that lateralised motor behaviour, whether relating to hand selection or manual ability, is linked to the interplay of both hemispheres, each responsible for specific aspects of motor programming with each hand. In line with this hypothesis, unilateral lesions should result in alteration of lateralised motor behaviour related to a specific feature of motor programming by unbalancing interhemispheric interplay dependent on certain structural asymmetries. The neurosurgical setting thus provides an opportunity to observe the consequence of selective lesions. Our results indicate that neurosurgical resection of both frontal and parietal left hemisphere regions alters motor behaviour, shifting hand selection toward increased non-dominant hand use one month after the procedure. In particular, this was related to resection of those regions connected by the dorsal and middle branch of the superior longitudinal fasciculus (SLF I and II).

#### *4.1 Fronto-parietal resection affects hand selection but not motor ability*

A key result that emerged from our study is that the neurosurgical resections performed in premotor and parietal regions did not impair gross motor skills of the dominant hand, as all patients performed within the normal range on both basic motor and ideomotor apraxia tests (Figure 2). Preservation of these functions was due to the intraoperative cortical and subcortical electrical stimulation awake mapping procedure, used to identify eloquent structures during resection and hence producing functional borders to resection (Bello et al. 2014). In this case, patients use a dedicated object manipulation tool demonstrated to preserve praxis function (Rossi et al. 2018; Vigano et al. 2019; Fornia et al. 2019). Resection of fronto-parietal tracts in the left hemisphere did not impair motor ability itself, but rather caused a shift (and rarely a flip) in hand selection for reach-to-grasp movements: the dominant hand was still used primarily over the non-dominant hand in the postoperative timepoint, although to a lesser extent. This indicates that presurgical hand preference was still preserved, however the strength of its dominance over the other hand decreased. A prominent model of bilateral hemispheric interplay in control of hand movement indicates that the left hemisphere (in right-handers) is specialised for predictive control of limb dynamics, whereas the right hemisphere is specialised for impedance control and positional

stability in unanticipated perturbations (Sainburg, 2002). Both hemispheres contribute to the motor program with different competencies. Damage to the left hemisphere may thus interrupt the ballistic component or timing of movements which may affect the trajectory of the dominant hand. The hand selected for the task may therefore change to compensate and to ensure the goal of the task is still achieved. Notably, our results also showed that there was a similar shift toward right-hand use in the left-handers tested, following the left hemisphere resections. This may provide preliminary evidence to support the hypothesis that the left hemisphere is specialised for visually guided dominant hand grasping, in both left- and right-handers (Begliomini et al. 2018). Altogether this data supports the hypothesis that bilateral fronto-parietal tracts support complex hand movements, for which the balance of communication between hemispheres may support hand selection for goal directed actions (Budisavljevic et al. 2016; Howells et al. 2018). However, a second point arises from these results: as patients were still physically able to make goal-directed movements, the inclination to use the non-dominant, ipsilesional hand more (or dominant hand, less) may reflect the influence of a higher cognitive mechanism such as movement intentionality or executive function.

#### *4.2 Hand preference and online control of movement*

The dorsal fronto-parietal branch (SLF I) extends between superior frontal and anterior cingulate cortices, and the precuneus and superior parietal lobule and has been traced in both monkeys and humans (Petrides & Pandya, 1984; Thiebaut de Schotten et al. 2012). Despite running parallel to the cingulum, post-mortem studies have demonstrated that it is a distinct tract, separated by the cingulate sulcus (Yagmurlu et al. 2016; Komaitis et al. 2019). The frontal terminations of the SLF I include the preSMA, which codes for both contralateral and ipsilateral limb movements (Gallivan et al. 2013) and plays a critical role in translating higher level goals to action (Wang et al. 2019). Other cortical regions in the superior frontal gyrus including the frontal eye fields play an important role in attention and working memory (Boisgueheneuc et al. 2006). The SLF I connects these regions with the superior parietal lobule, crucial for orienting actions within space, using visual information to code target location and movement direction, transforming spatial targets into movement vectors (Goodale & Milner, 2018; Barany et al. 2014; Gallivan & Culham, 2015). The superior parietal lobule can directly influence motor output through M1, but also is connected with premotor cortex to form major relays for coordinating reach-related grasping movements (Monaco et al. 2011; Cattaneo et al. 2019). Notably, the function of the superior parietal lobule relates to online monitoring of one's own body - lesions in this region can cause disorders of self-awareness such as fading limb, alien hand or autotopagnosia (Wolpert et al. 1998; Herbet et al. 2019). The SLF I, bilaterally, likely conveys neural impulses for online

control of movement of both hands, and our results show that disconnecting this tract in the left hemisphere causes a shift toward non-dominant hand use when exploring peripersonal space. In a previous study, we reported handedness-related differences in hemispheric asymmetry of SLF I volume in healthy adults, a measurement likely reflecting enhanced speed of conduction (Howells et al. 2018; Drobyshevsky et al. 2005). Damage in the right hemisphere also causes hyperexcitability of parieto-motor connections in the left fronto-parietal network (Koch et al, 2008). Considering this evidence, one hypothesis may therefore be that hand selection, as measured by our test, is a reflection of enhanced top-down online monitoring of one hand, over the other. Thus, a shift in hand selection may reflect reduced monitoring of the dominant hand in this regard, or an upregulation in monitoring of the non-dominant hand that disturbs the other. Further investigation is however required to test this theory.

Resection of the ventral fronto-parietal branch (SLF III) connecting the inferior frontal gyrus and ventral precentral gyrus with the anterior inferior parietal lobule did not seem to affect hand selection in our patient cohort during the reach-to-grasp phase. In fact, our results unusually showed that patients without this tract resected had greater leftward shifts in hand selection during the manipulation phase, although this likely reflects the concomitant resection of other dorsal tracts. Given that structural asymmetry of the SLF III has been associated with both kinematics of reach-to-grasp movements and hand preference, this result was unexpected (Budisavljevic et al. 2016; Howells et al. 2018; Wiberg et al. 2019). Dorsal and ventral fronto-parietal networks may support segregated aspects of movement – the SLF I and II mediate online control and arm transport, whereas the SLF III connects regions more commonly linked to distal rather than proximal movement, such as for hand shaping or tool use (Davare et al. 2006). A possible explanation might be that the reach-to-construct paradigm used is best able to test online control of movement within peripersonal space, but may not be sensitive enough to detect subtle changes in skilled motor actions which may be supported by the SLF III. Dominant hand/arm selection for interactions with peripersonal space may be the precursor to hand preference, which is the final result of long-term practice with one hand over the other (e.g. writing). Hand preference does not always correspond with manual specialisation, i.e. the ability of one hand to perform better than the other on certain tasks. If manual specialisation and hand selection are supported by anatomically segregated circuits, this may explain why these two aspects are not always corresponding. This is an area that requires further study.

#### *4.3 Hand preference and attentional processing*

A recent combined magnetoencephalography-tractography study has also linked differences in structural asymmetry of the SLF I to selective attentional processes, measured in synchronisation of alpha and gamma band oscillations (Rhys Marshall et al. 2015). While the role of selective attention in action selection has been well described (Castiello, 1999), our results further show an association between selective attention and dominant or non-dominant hand selection. Patients with greater shift toward non-dominant hand use following surgery also had reduced selective attention ability, despite no impairment in visual search strategies in either hemispace. Further, our results also show that resection of the second branch of the SLF (SLF II) connecting the middle frontal gyrus with posterior inferior parietal lobule (the angular gyrus) was associated with changes in hand selection, with a similar trend for selective attention. Importantly, this tract connects neural regions within two important attention networks: the dorsal attention network (DAN; SLF I) and the ventral attention network (VAN; SLF III) (Corbetta & Shulman, 2002). Individual differences in structural asymmetry of the SLF II are associated with attentional biases in healthy adults, detected using behavioural tasks such as the line bisection task (Thiebaut de Schotten et al. 2011). Recent TMS-tractography combined studies have also demonstrated this tract also plays a key role in online monitoring and movement correction of actions (Koch et al. 2010; Rodrigues-Herreros et al. 2015). Thus, the SLF I and SLF II are likely to both be involved in top-down attentional processing as well as mediating online control of movement. Supporting this, there was a trend toward patients with resection of the SLF I and/or SLF II having greater declines in performance on the selective attention task in the postoperative phase. This suggests there may be a link between attentional processing and lateralised hand selection. Focusing on goal-relevant stimuli while ignoring distractors requires executive control to efficiently allocate attentional resources, which is theorised to be supramodal (Lavie et al. 2005; Spagna et al. 2015; Ptak et al. 2017). In 1980, Rosenbaum investigated reaction time for reaching, altering the pre-cues such as direction, distance and the hand to be used for the movement. He demonstrated that reaction time was reduced most substantially when hand selection was cued, indicating this decision making process has a considerable cognitive load. Executive control of attention therefore may extend also to allocating motor attention toward selection of one hand over another (Rushworth et al. 2003).

#### *4.4 Limitations*

Studying the relationship between clinical manifestations and lesions in patients with brain tumours is of great aid in that, unlike in situations of vascular insult, lesions are constrained, more focal and widely distributed, and it is possible to assess neuropsychological

performance before as well as after a neurosurgical intervention. However, there are a number of limitations that deserve discussion. First, it is challenging to assess whether or to what extent brain function is impaired in areas of diffuse tumour infiltration. In this study, the growth of a tumour may already have affected hand preference, which may explain why right hand preference was not as strong as expected based on previous studies (90% right-hand grasps in right-handers e.g. in Gonzalez et al. 2006). Further, the presence of masses of variable sizes in the brain means that white matter connections may be infiltrated or displaced prior to their removal, thus healthy adult disconnectome atlases may not be suitable for estimating the impact of surgery. To confirm that this approach was reliably estimating tract disconnection, we conducted the same analysis in a subset of patients for whom tractography was acquired for clinical purposes. Our results showed that the results of the disconnectome method matched exactly the results of the acquired tractography in all 9 patients. This indicates that it may be helpful to check the reliability of disconnectome approaches by using even small subsets of tractography patients. As brain tumours are a rare disease, the patient cohort tested was relatively small. With a larger patient cohort, we would have been able to conduct voxel-lesion symptom mapping and more sophisticated statistical analyses that would be better able to confirm our preliminary results (e.g. Foulon et al. 2018). Moreover, our evaluation of motor ability was relatively crude, and kinematic analysis would better be able to rule out the impact of subtle motor impairments and their effect on hand selection.

#### *4.5 Conclusions*

Handedness likely consists of a number of dimensions, each of which underlie lateralised motor behaviour for a circumscribed set of tasks. Given that hand preference does not have a one-to-one relationship with manual specialisation, the different items and skills required for different tasks designed to investigate this topic may yield different insights into preferred use of one hand for interaction with the immediate environment (Todor & Doane, 1977). We here confined the investigation of hand preference to a task involving completion of a jigsaw puzzle - requiring reaching to grasp pieces and manipulation into position. This task tests motor behaviour requiring the cooperation of different cognitive functions including motor planning but also mental rotation, working memory and spatial attention to name but a few. It would be intriguing to contrast these results with data collected from tasks requiring hand cooperation in different contexts, to dissociate whether changing the cognitive load can modulate hand as well as action selection.

To conclude, our results provide preliminary evidence to support the role of dorsal fronto-parietal tracts in lateralised hand selection for reaching and grasping movements. While



these dorsal white matter structures have already been associated with goal-directed hand movements in monkeys and humans, to our knowledge this study is the first to demonstrate that disrupting their structural asymmetry with unilateral lesions directly alters the choice of hand selected for these movements, even one month following surgery. It remains to study whether this hand selection is sustained over longer periods of time. This may provide intriguing avenues for future study within the field of motor control and attention, but also for understanding the importance of balance in the relative contributions of each hemisphere toward a single cognitive process.

## Competing interests

The authors have no competing interests to declare.

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Henrietta Howells: conceptualisation, methodology, investigation, analysis, writing. Guglielmo Puglisi: investigation, methodology, writing. Antonella Leonetti: investigation. Luca Vigano: writing, visualisation. Luca Forna: analysis, writing. Luciano Simone: analysis, writing. Stephanie J. Forkel: writing. Marco Rossi: investigation. Marco Riva: investigation. Gabriella Cerri: writing, funding acquisition. Lorenzo Bello: investigation

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