A DTI Investigation of Neural Substrates Supporting Tool Use

Recent functional neuroimaging and brain lesion studies have implicated a network of left hemisphere regions in human tool use: 1) posterior middle temporal cortex involved in conceptual knowledge of tools, 2) posterior inferior parietal cortex for representations of learned tool use gestures, and 3) anterior inferior parietal cortex, along with posterior inferior frontal and ventral premotor cortices, involved in grasping and manipulating objects. Here, we use diffusion tensor imaging (DTI) to investigate the anatomical connections that support this putative network. DTI scans were acquired from nineteen right-handed males and a deterministic tractography algorithm was used to identify connections between these regions implicated in tool use. Three of the resulting pathways were larger in the left than the right hemisphere. One connected posterior middle temporal cortex and the anterior inferior parietal cortex, a second connected posterior middle temporal cortex and the posterior inferior parietal cortex, and a third connected anterior inferior parietal cortex and the frontal lobe. In contrast, the connection between the posterior inferior parietal cortex and the frontal lobe was highly rightwardly asymmetric. Although further study is necessary to establish the functions of these pathways, we integrate our findings with previous evidence from functional neuroimaging and apraxia studies to suggest some possible functions.

Keywords: dorsal stream, inferior parietal lobe, neglect, spatial awareness, ventral stream, visual pathways

Introduction

Complex tool use is one of the most significant advancements in human evolution and a defining characteristic of our species (Gibson and Ingold 1993; Ambrose 2001; Stout and Chaminade 2007). Although many nonhuman primates display some form of tool use and mechanical problem solving, only human beings have developed a technological culture that revolves around tool use and tool production (Tomasello 1999). Understanding the neural basis for complex tool use is an important, but still unresolved, aspect of cognitive neuroscience.

Much of what we know about the neural basis of tool use is derived from the study of patients with ideomotor apraxia (IM), a disorder of skilled actions that is not caused by low-level perceptual or motor deficits (Buxbaum 2001). These studies have shown that a left hemisphere network including the temporal, parietal, and frontal lobes is involved in the planning and execution of tool-use gestures, integrating information from both ventral-stream object recognition, and dorsal-stream object localization, pathways (Heilman et al. 1982; Goldenberg and Haggmann 1998; Hodges 1999; Haaland 2000; Buxbaum 2001). Consistent with this evidence, recent functional neuro-imaging studies also describe a distributed network in the left cerebral hemisphere that is involved in tool use (Chao et al. 1999; Chao and Martin 2000; Creem-Regehr and Lee 2005; Johnson-Frey et al. 2005; Buxbaum et al. 2006). Using tasks to investigate areas involved in the planning of complex tool use, Johnson-Frey et al. (2005) reported activations in 1) posterior middle temporal cortex (MTG or middle temporal gyrus); 2) 2 distinct nodes in the inferior parietal lobe (IPL)—one anterior to the Sylvian fissure, in the anterior supramarginal gyrus (Ant. SMG), and another posterior to the Sylvian fissure, spanning the intraparietal sulcus (IPS), the posterior SMG, and angular gyrus (AG); and 3) the inferior frontal and ventral premotor cortices. Each of these regions has been linked with a distinct tool-use function.

Functional neuroimaging studies implicate the posterior MTG in storing semantic information about tools (Damasio and Geschwind 1984; Chao et al. 1999; Kellenbach et al. 2003; Creem-Regehr and Lee 2005; Johnson-Frey et al. 2005). This region is activated in tasks such as naming, categorization, and visual recognition of tools, and has thus been proposed to store information such as tool name, shape, and function (Chao et al. 1999; Johnson-Frey et al. 2005). This conclusion is supported by brain lesion data as damage to this region is associated with ideational apraxia and conceptual deficits of tool use (Goldenberg and Haggmann 1998; Hodges 1999; Buxbaum 2001). Additionally, damage to the left posterior temporal cortex is associated with loss of specific semantic knowledge (Geschwind et al. 1968; Damasio and Geschwind 1984; Hodges et al. 1992; Tranel et al. 1997). Thus, both functional neuroimaging studies and brain lesion data strongly support the hypothesis that this region stores semantic and conceptual information. Because this region is located just superior to the ventral-stream object recognition pathway in the inferior temporal cortex, it is well situated to associate the appearance of a tool with its name and function (Ungerleider and Haxby 1994).

Inferior parietal cortex is also critically involved in tool use. Neurological cases suggest this region is involved in the planning and execution of tool use gestures (Heilman et al. 1982; Goldenberg and Haggmann 1998; Hodges 1999; Haaland 2000; Buxbaum 2001). A recent functional neuroimaging study revealed 2 distinct inferior parietal nodes that are activated during tool-use planning and execution (Johnson-Frey et al. 2005), one located in the cortex of the SMG anterior to the Sylvian fissure (Ant. SMG) near the anterior portion of the IPS, and another located in the ventral bank of the IPS and including adjacent parts of posterior SMG and the AG. The anterior region is thought to be involved in integrating information during the planning of a tool-use gesture, and has been implicated in grasping and prehension, whereas the posterior

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region is involved in storing invariant spatio-temporal representations of learned actions (such as understanding that broad oscillations of the elbow are always required to swing a hammer) (Heilman et al. 1982; Buxbaum 2001; Johnson-Frey et al. 2005). Collectively, the inferior parietal cortex is involved in representing and processing information related to the grasping and use of tools. The fourth node in this network, which spans the ventral premotor cortex and adjacent posterior inferior frontal gyrus, is implicated in storing general motor programs underlying physical actions such as grasping and the manipulation of objects (Rizzolatti et al. 1988, 2002; Luppino and Rizzolatti 2000; Johnson-Frey et al. 2005). Recent functional neuroimaging studies of tool use report activations in both the posterior inferior frontal gyrus (Johnson-Frey et al. 2005; Buxbaum et al. 2006), and the ventral premotor cortex (precentral gyrus) (Chao and Martin 2000; Creem-Regehr and Lee 2005; Johnson-Frey et al. 2005). This general region of frontal cortex, spanning the ventral premotor cortex and the posterior inferior frontal gyrus, is likely to be involved in converting the planned tool-use gesture into a physical act, as it contains generalized motor programs that are required for the physical manipulation of any object, including tools (Leiguarda and Marsden 2000). DTI is a relatively new imaging technique that can be used to reconstruct major white matter fiber tracts in the brain (Catani et al. 2002; Mori and van Zijl 2002). Here, we use DTI to identify the anatomical connections that support the functionally identified network described above. We have the following 3 objectives: 1) determine if there are anatomical connections linking the regions that have been implicated in tool use in published functional neuroimaging and neuropsychological studies, 2) determine if there are asymmetries in the size of some of these pathways that parallel laterality effects observed in functional neuroimaging and neuropsychological studies, and 3) propose a model for tool use in which we ascribe specific functions for the pathways we describe.

Material and Methods

Subjects and Image Acquisition

Nineteen right-handed male subjects, aged 18-50 (mean: 23.75, SD: 7.1), were imaged with a Siemens Trio 3 Tesla MRI scanner. Subjects were restricted to right-handed males (determined by Waterloo Handedness Inventory) to limit potential pathway variability resulting from sex or handedness, as has been found in studies of language connectivity (Johnson-Frey 2004; Hagmann et al. 2006). All subjects gave written informed consent and the study was approved by the Emory University Institutional Review Board. Diffusion weighted images were collected using a Siemens Standard EPI single shot DTI sequence (echo time [TE] = 90, repetition time [TR] = 7700) with 12-diffusion directions, 1.7 × 1.7 × 2.0 mm voxels, 6 signal averages, 34 slices, with a diffusion weighting of b = 1000 and one volume of b = 0. Because 34 slices at 2.0 mm is not sufficient to cover the whole brain, the field of view (FOV) was manually positioned on a localizing image to ensure that the middle and inferior frontal, inferior parietal, and middle and inferior temporal cortices were included. A Transverse Electro-Magnetic head coil was used to improve the signal to noise ratio of the images. A T1-weighted MP-RAGE anatomical scan (TR = 2300 ms, TE = 4 ms, matrix = 256 × 256, FOV = 256, slice thickness = 1.0 mm) was also collected from each subject for anatomical localization of the fiber tracts. Total scanning time was approximately 30 min per subject including setup time (13 min for DTI, 7 min for T1).

Image Analysis

Images were analyzed with the Siemens DTI Task Card software (Wang 2006), which uses a deterministic tractography algorithm. The algorithm is based on the FACT tractography algorithm (Mori and van Zijl 2002), however, fibers are only initiated from the regions of interest (ROIs), and are not generated across the entire brain. When using a 2-ROI approach, fibers are generated from both ROIs, but retained only if they reach the second ROI. Tractography was conducted using the following parameters set in the DTI Task Card: number of samples per voxel length = 8, minimum FA threshold = 0.15, maximum turning angle between voxels = 15°, step length between calculations = 0.25 mm. ROIs were consistently drawn with a one-voxel border around the terminations to ensure that all relevant fibers were included.

To investigate the tool use network, 3 ROIs were defined anatomically in a single sagittal section in the white matter beneath the cortical region of interest, and used to track the pathways that are hypothesized to be involved with tool use. The sagittal slice was chosen based on the presence of all the necessary anatomical landmarks required to define the regions of interest. The first ROI was defined as the posterior MTG. The second ROI (Ant. SMG) was located in the anterior portion of the SMG. It was defined as being anterior to the upper limb of the Sylvian fissure and posterior to the postcentral sulcus. Dorsally, it was limited by the IPS, and ventrally by the Sylvian fissure. The third ROI (SMG/AG) was defined as being posterior to the upper limb of the Sylvian fissure, and anterior to the superior temporal sulcus (STS). Ventrally, it was limited by the longitudinal extension of the Sylvian fissure and dorsally by the IPS (ROIs shown in Fig. 1b). After defining these regions, 2-ROI tractography was used to define 2 pathways. The first connected the MTG and Ant. SMG ROI, shown in blue in Figure 1b. The second pathway connected the MTG and SMG/AG ROI, shown in pink in Figure 1b. The frontal ROI was not defined on the basis of its surface morphology because of the large anatomical region encompassing all of the activations described by functional neuroimaging studies of tool use. Instead, the frontal ROI was defined as follows. Single-ROI tractography was used to identify all projections from each parietal ROI into the frontal lobe. The union of the frontal lobe terminations from the 2 parietal ROI was used to define a fourth ROI in the precentral gyrus and posterior inferior frontal gyrus (Fig. 1a). Then, 2-ROI tractography was used to define connections between the frontal ROI and each of the parietal ROIs. The pathway connecting the Ant. SMG ROI and the frontal ROI is shown in yellow and the pathway connecting the SMG/AG ROI and the frontal ROI is shown in orange (Fig. 1d).

Transformation to Standard Space and Averaging

Tractography results were transformed into standard Montreal Neurological Institute (MNI) space and averaged using the following method. Each subject’s FA image was co-registered to all the others’ using first linear and then nonlinear registration with the ITK registration algorithm, included as a part of FSL’s TBSS tool (Smith et al. 2006). The FA image that required the least warping of all other images was used as a final target and this FA image was linearly registered to the MNI 152 standard brain. These registrations produced 2 transformation matrices, a nonlinear matrix between each subject’s diffusion space and the target space, and a common linear matrix between the target and the MNI standard brain. Individual subject’s tractography results were transformed into standard space using these matrices, and then averaged to produce a group result.

Plotting Functional Activation Coordinates

Peak parietal lobe activation coordinates from a recent functional imaging study (Johnson-Frey et al. 2005) that specifically examined a network underlying the planning of tool-use gestures were plotted in MNI space, after being converted from Talairach space (see http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). These were plotted along with tractography terminations to assess the degree of overlap. To aid in viewing the activation peaks in the figure, the coordinates were plotted above the surface of the brain at MNI coordinate (x = ±78), and thus the coordinates lie in a 2 dimensional plane.

Quantitative and Statistical Analysis

Pathway asymmetry was assessed by recording the volume of each pathway in 1.7 × 1.7 × 2 mm voxels. In cases where a pathway could
not be identified, the volume was considered zero. A paired t-test was used to test for pathway asymmetry.

Results
The MTG → Ant. SMG segment (blue) was identified in 17 of 19 subjects. There was clear overlap between the parietal terminations of this segment and the peak anterior parietal activation from a recent functional neuroimaging study of tool-use planning (Johnson-Frey et al. 2005). In 16 of the 19 subjects, the pathway could only be identified in the left cerebral hemisphere. In one subject, it was present in both hemispheres but was much larger on the left. Overall, this asymmetry was highly statistically significant in terms of absolute volume, with a mean of 4115 mm³ in the left hemisphere and 88 mm³ in the right hemisphere (t(18) = 6.98, P < 0.001) (Table 1, Figs 1C and 2, Supplementary Figs 1 and 3).

The MTG → SMG/AG segment (pink) was tracked bilaterally in all 19 subjects, and was also significantly leftwardly asymmetric in terms of absolute volume with a mean of 5521 mm³ in the left hemisphere and 4438 mm³ in the right hemisphere (t(18) = 2.12, P < 0.05). The parietal terminations of this segment were inferior and lateral to the peak posterior parietal activation from the study by Johnson-Frey et al., who reported

Table 1
Asymmetry statistics for the absolute volume of the 4 tool use segments

<table>
<thead>
<tr>
<th>Segment</th>
<th>No. of subjects with segment in right hemisphere</th>
<th>No. of subjects with segment in left hemisphere</th>
<th>Mean absolute volume (in mm³)</th>
<th>t(18) (volume)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AntSMG−&gt;MTG (blue)</td>
<td>1</td>
<td>17</td>
<td>4115</td>
<td>6.98 (P &lt; 0.001)**</td>
</tr>
<tr>
<td>SMG/AG−&gt;MTG (pink)</td>
<td>19</td>
<td>19</td>
<td>5521</td>
<td>2.12 (P &lt; 0.05)*</td>
</tr>
<tr>
<td>AntSMG−&gt;frontal (yellow)</td>
<td>15</td>
<td>19</td>
<td>3537</td>
<td>2.32 (P &lt; 0.05)*</td>
</tr>
<tr>
<td>SMG/AG−&gt;frontal (orange)</td>
<td>17</td>
<td>4</td>
<td>1012</td>
<td>-4.55 (P &lt; 0.001)**</td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.001.

Figure 1. (A) ROIs for DTI tractography. See text for anatomical landmarks. (B) Four segments were tracked using a deterministic tractography algorithm: 1) MTG → anterior SMG (Ant. SMG; blue); 2) MTG → SMG/AG (pink); 3) anterior SMG (Ant. SMG) → frontal (yellow); 4) SMG/AG → frontal (orange). Base figure reproduced from Duvernoy (1999) with permission. (C) Group average tractography results showing left and right hemisphere terminations of each segment in a sagittal slice (MTG → Ant. SMG = blue; MTG → SMG/AG = pink; Ant. SMG → frontal = yellow; SMG/AG → frontal = orange). Voxels in which segments are present in at least 2 individuals are shown. The peak parietal lobe activations from a recent functional neuroimaging study of tool-use planning are indicated by red and pink circles, and the region of maximal lesion overlap for visual neglect is indicated by the blue circle (Mort et al. 2003; Johnson-Frey et al. 2005). The anterior parietal terminations clearly overlap with the anterior parietal activation (red circle; Talairach coordinates: x = -50, y = -29, z = 33), however, the posterior parietal terminations are inferior and lateral to the posterior IPS activation found in the same study (pink circle; Talairach coordinates: x = -38, y = -52, z = 56). The right parietal terminations also clearly overlap with the region of maximal lesion overlap of visual neglect cases (blue circle, Talairach coordinates: x = 46, y = -44, z = 29).
activation centered in the IPS (Table 1, Figs 1C and 2, Supplementary Figs 1 and 3).

The Ant. SMG → frontal segment (yellow) was also tracked bilaterally in all 19 subjects, and was found to be significantly leftwardly asymmetric in terms of absolute volume with a mean of 3537 mm$^3$ in the left hemisphere and a mean of 1917 mm$^3$ in the right hemisphere ($t(18) = 2.32, P = 0.03$). Frontal projections from Ant. SMG were primarily found in the ventral premotor cortex (BA 6), but also extended superiorly to the level of the middle frontal gyrus (Table 1, Figs 1C and 2, Supplementary Figs 1 and 3).

The SMG/AG → frontal segment (orange) was tracked in the left hemisphere of 4 subjects and the right hemisphere of 17 subjects. Overall, it was rightwardly asymmetric in terms of absolute volume with a mean of 1012 mm$^3$ in the left hemisphere and a mean of 4447 mm$^3$ in the right hemisphere ($t(18) = -4.55, P < 0.001$). Frontal projections from SMG/AG were also primarily found in the premotor cortex (BA 6), but also extended anteriorly into the inferior frontal gyrus (BA 44). There was strong overlap between the parietal terminations of this segment and the region of maximal lesion overlap for visual neglect as reported by Mort et al. (2003) (Table 1, Figs 1C and 2, Supplementary Figs 1 and 3).

Finally, the surface area of pathway terminations exhibited asymmetries that paralleled those found for pathway volumes. This is further discussed in the Supplementary Material (Supplementary Fig. 4, Supplementary Table 1).

**Discussion**

We identified 4 distinct pathways connecting the ROIs described above. The pathway connecting the posterior MTG and the anterior SMG (MTG → Ant. SMG) was found to be almost completely leftwardly asymmetric. Two other pathways, the posterior MTG to SMG/AG (MTG → SMG/AG), and the anterior SMG to precentral gyrus (Ant. SMG → frontal), were also found to be significantly leftwardly asymmetric. On the other hand, the pathway connecting the SMG/AG and the frontal lobe (SMG/AG → frontal) was almost completely rightwardly asymmetric. Ant. SMG terminations clearly overlap with Ant. SMG activations reported in the neuroimaging studies of tool use by Frey et al., however, the SMG/AG terminations were inferior and lateral to SMG/AG activations reported in the same study (Johnson-Frey et al. 2005). The frontal lobe terminations of the parietal lobe were primarily located in ventral premotor cortex (BA 6), but also extended anteriorly to inferior frontal gyrus (BA 44). In order to understand the function that each of these segments has in tool use, the function of each of the cortical ROIs must first be understood (see Fig. 3, see Supplementary Fig. 2 for color version).

**Posterior MTG**

As discussed above, the MTG ROI is considered to be the semantic node of the tool-use network. Functional
neuroimaging studies (Chao et al. 1999; Creem-Regehr and Lee 2005; Johnson-Frey et al. 2005; Buxbaum et al. 2006) and brain lesion data strongly indicate that MTG is responsible for storing conceptual and semantic information about tools. Patients with lesions in the temporal cortex have been shown to lose specific semantic information (Geschwind et al. 1968; Damasio and Geschwind 1984; Hodges et al. 1992; Tranel et al. 1997) and also have conceptual deficits in tool use (such as using a comb to cut a piece of cake) (Goldenberg and Haggmann 1998; Hodges 1999; Buxbaum 2001). In addition to tool name and appearance, this region would also contain nonspatial information about the tool such as its function (i.e., "what is the tool used for?") (Goldenberg and Haggmann 1998; Buxbaum 2001), and characteristics such as weight, and fragility (Glover 2004). These representations in MTG are critical in distinguishing between "appropriate" tool use and "correct" tool use (Goldenberg and Haggmann 1998). For example, although it would be appropriate to cut a piece of cake using a comb, it would only be correct to use the comb to style one’s hair. Therefore, the cortex included in the MTG ROI is involved in identifying the object as a tool, and knowing its function and correct uses.

**Supramarginal gyrus/angular gyrus**

The SMG/AG ROI is primarily associated with stored memorial representations of invariant and critical features that are at the core of a meaningful gesture, such as the path of the gesture through space, the sequence of actions taken, or the pace at which the gesture is performed (Buxbaum 2001; Johnson-Frey et al. 2005). This would include the understanding that a broad oscillation of the elbow and a stationary shoulder angle are required in order to swing a hammer (Buxbaum 2001). Although both of these features are invariant aspects of the hammering gesture, they are both critical in distinguishing a swinging gesture from another gesture (Buxbaum 2001). Patients with lesions in the left IPL have difficulty with gesture recognition and also lack a superiority effect for learned actions over novel actions (Heilman et al. 1982; Buxbaum 2001). Patients without a superiority effect are as efficient at using a common tool like a hammer as they are at using a tool they have never seen before. These data support a memorial function for this region because these apraxic patients have lost the critical features of learned gestures that make them recognizable and accessible.

Additionally, functional neuroimaging studies have found this region to become activated when subjects explicitly imagine grasping objects based on object structure (Creem-Regehr and Lee 2005), and when viewing and naming pictures of tools but not other categories of objects (Chao and Martin 2000). These findings have led to the hypothesis that the representations stored in this region are involved in cognitive judgments regarding tools, such as mechanical problem solving (Goldenberg and Haggmann 1998; Buxbaum 2001), as well as in motor planning (Johnson-Frey et al. 2005).

**Anterior SMG**

In order to generate a motor plan for tool use, a variety of visual and cognitive information must be integrated and conveyed to the premotor cortex (Glover 2004). Based on its anatomical location and connectivity, we hypothesize that the anterior portion of the IPL (Ant. SMG) is ideally suited to perform this function. Given its anatomical location and connectivity, it is well positioned to integrate the following forms of visuospatial, proprioceptive, and cognitive information: 1) semantic and nonspatial information such as weight and fragility from the posterior temporal cortex (MTG → Ant. SMG), 2) invariant spatio-temporal representations of learned tool-use gestures from the posterior parietal cortex (SMG/AG), 3) dynamic spatial information about the gesture in relation to objects in the environment from the superior parietal lobe (SPL), and 4) proprioceptive information from the somatosensory cortex (Buxbaum 2001); see limitation 1). For example, when generating a plan to use a hammer to drive a nail into the wall, one uses knowledge about the hammer’s weight, function, and other nonspatial properties (from MTG), information about the hammering gesture itself (from SMG/AG) and dynamic computations about the locations of the hammer, the nail, the wall and one’s limbs (from SPL; Buxbaum 2001). Additionally, Ant. SMG has projections to the premotor cortex (Ant. SMG → frontal), which would allow it to provide the integrated tool-use plan to the premotor cortex where it can be put into action using the generalized motor representations stored there (Chao and Martin 2000; Rizzolatti et al. 2002; Johnson-Frey 2005). This hypothesis is consistent with data from recent functional neuroimaging studies that implicate the anterior IPL in explicit retrieval of tool use knowledge (Kellenbach et al. 2003; Johnson-Frey et al. 2005). This can be explained by the pathway linking Ant. SMG with the MTG (MTG → Ant. SMG), which would specifically allow Ant. SMG to access the semantic representations stored in the MTG. Also, the anterior portion of the IPS has been implicated in representing attributes required for the grasping and manipulation of tools (Binkofski et al. 1998; Chao and Martin 2000; Johnson-Frey et al. 2005). In humans, as in macaques (Leiguarda and Marsden 2000), there seems to be a direct parieto-frontal circuit that is involved in grasping and manipulation of tools, possibly in the form of the Ant. SMG → frontal pathway (Heilman et al. 1982; Chao and Martin 2000; Haaland 2000; Luppino and Rizzolatti 2000; Johnson-Frey et al. 2005). Data from apraxic patients support the idea that a parieto-frontal segment underlies the grasping and manipulation of tools, as lesions in the frontal lobe and its white matter connections to the parietal lobe are associated with deficits in the efficiency and accuracy of using a tool despite intact knowledge of how to use it (Heilman et al. 1982; Haaland 2000; Buxbaum 2001). These anterior lesions seem to cause a breakdown of parieto-frontal circuits that are involved in the grasping and manipulation of tools. In summary, the anterior IPL is primarily responsible for the integration of various types of tool use related information from surrounding regions and generating an integrated tool-use gesture that is conveyed to motor centers in the frontal lobe.

**Frontal Lobe (frontal)**

The frontal ROI includes all the white matter terminations in the inferior frontal cortex connecting with the inferior parietal cortex. The terminations lie mostly in the ventral premotor cortex (BA 6), in some cases extending into the inferior frontal gyrus. These regions of the brain are associated with storing general motor programs that underlie grasping and manipulation (Binkofski et al. 1999; Chao and Martin 2000; Luppino and Rizzolatti 2000; Rizzolatti et al. 2002; Johnson-Frey et al. 2005). As described earlier, lesions in the frontal lobe and its white matter connections to the parietal lobe are associated with
deficits in the efficiency and accuracy of grasping and manipulating a tool despite intact knowledge of how to use it (Heilman et al. 1982; Haaland 2000; Buxbaum 2001). We hypothesize that the premotor cortex is involved in converting planned gestures (from the Ant. SMG) into physical acts through putative motor circuits.

**Segments Tracked**

In addition to each region in the network having a specific function, we hypothesize that each of the pathways connecting the regions has a distinct function.

**Posterior MTG to Anterior SMG (MTG → Ant. SMG)**

The MTG → Ant. SMG segment (blue) most likely allows for the integration of ventral stream, semantic and nonspatial representations in the temporal lobe to the Ant. SMG, which is closely linked to the dorsal stream in the superior and posterior parietal lobes. This interaction is an important element of complex tool use as it is essential to combining semantic and nonspatial object characteristics, such as function, weight, fragility, and slipperiness, with both the dynamic spatial information about the environment (SPL) and invariant visuospatial representations (SMG/AG) (Glover 2004).

Take the use of a hammer, for example. Nonspatial information would be essential in distinguishing the strong grip required to lift a heavy-duty metal hammer from the lighter grip used to lift a plastic toy hammer of the same size. The MTG → Ant. SMG segment would provide the most efficient mechanism by which the nonspatial and semantic (ventral stream) information could be integrated with the spatial (dorsal stream) information of the SPL, and the invariant visuospatial representations of the posterior parietal lobe during the preparation of a gesture plan. A review of the literature revealed 12 functional neuroimaging studies of tool use that report peak activations that overlap with parietal terminations of this pathway (Binkofski et al. 1998; Chao and Martin 2000; Okada et al. 2000; Inoue et al. 2001; Grèzes and Decety 2002; Grèzes et al. 2003; Culham et al. 2003; Manthey et al. 2003; Bunzeck et al. 2005; Creem-Regehr and Lee 2005; Johnson-Frey et al. 2005; Lewis et al. 2005) and at least 10 studies that report peak activations that overlap temporal terminations of this pathway (Damasio et al. 1996; Mummery et al. 1998; Perani et al. 1999; Moore and Price 1999; Choi et al. 2001; Grèzes and Decety 2002; Grossman et al. 2002; Creem-Regehr and Lee 2005; Johnson-Frey et al. 2005; Tranel et al. 2005).

In our sample of right-handed males, this segment was found to be almost completely leftwardly asymmetric. This is an understandable finding, as the segment would primarily be involved in combining semantic information from the MTG, which has been shown to be left-lateralized (Price 2000; Kellenbach et al. 2003; Hickock and Poeppel 2004) with other information in the Ant. SMG. We hypothesize that the development of this connection increased the efficiency of tool-use behavior in human ancestors, and thus we predict that it is particularly well developed in humans relative to nonhuman primates.

**Posterior MTG → SMG/AG**

Unlike the parietal terminations of the MTG → Ant. SMG segment (blue), which overlap well with functional neuroimaging activations, the parietal terminations of the MTG → SMG/AG (pink) segment are inferior and lateral to the peak posterior parietal activations from recent functional neuroimaging studies (see Fig. 1C) (Chao and Martin 2000; Johnson-Frey et al. 2005; Buxbaum et al. 2006). The bulk of the functional neuroimaging activations are found within the ventral bank of the IPS, whereas the terminations of the segment are located on the lateral surface, inferior to the IPS, near the border of temporal and parietal cortex at the temporo-parietal junction. Therefore, the MTG → SMG/AG segment (pink) links the MTG with regions of the posterior parietal lobe that are not activated during the planning of tool-use gestures (Johnson-Frey et al. 2005). Due to these anatomical discrepancies, it is unlikely that this segment is directly involved in the tool use. However, it is possible that this segment is involved in conveying nonspatial tool-use information from the temporal lobe to the parietal lobe.

Given its leftward asymmetry, one possibility is that this segment is more involved in language functions, as the AG is often activated in semantic language studies (Price 2000).

**Anterior SMG to Frontal Lobe (Ant. SMG → frontal)**

The Ant. SMG → frontal segment (yellow) provides connections between the cortex involved in producing the tool use gesture plan in the Ant. SMG ROI and the premotor cortex (BA 6). As noted earlier, studies of IM apraxia have revealed that such a parieto-frontal pathway is critical for performing complex actions (Heilman et al. 1982; Haaland 2000; Buxbaum 2001). Additionally, prior anatomical studies in macaques have shown that a similar parieto-frontal pathway (SLF III, which links anterior parietal lobe to the precentral gyrus, and inferior frontal lobe) is involved in goal-directed, grasping actions (Petrides and Pandya 1984). We hypothesize that the segment is the human homologue of SLF III and performs a similar function, as it connects the gesture plan, which emerges in the anterior SMG by the confluence of ventral-stream and dorsal-stream processes (Buxbaum 2001), with premotor processes in the frontal lobe.

The final gesture for hammering a nail, for example, is a product of 1) semantic and nonspatial information such as function, weight and fragility of the hammer and nail (MTG), 2) invariant spatio-temporal representations associated with hammering a nail, such as a broad oscillation of the elbow and a stationary shoulder angle (SMG/AG), 3) dynamic spatial information (SPL) such as the 3-dimensional location of the nail, the handle of the hammer, and one’s hand and fingers (SPL), as well as 4) proprioceptive feedback (sensorimotor cortex) (Johnson-Frey et al. 2005; Buxbaum et al. 2006). The cortex included in the Ant. SMG ROI possibly conveys this integrated information to the premotor cortex in through this pathway. At least 12 functional neuroimaging studies of tool-use report peak activations that overlap with parietal terminations of this pathway (Binkofski et al. 1998; Chao and Martin 2000; Okada et al. 2000; Inoue et al. 2001; Grèzes and Decety 2002; Grèzes et al. 2003; Culham et al. 2003; Manthey et al. 2003; Bunzeck et al. 2005; Creem-Regehr and Lee 2005; Johnson-Frey et al. 2005; Lewis et al. 2005) and at least 10 studies report peak activations that overlap frontal terminations of this pathway (Grafton et al. 1997; Chao and Martin 2000; Okada et al. 2000; Beauchamp et al. 2002; Grèzes and Decety 2002; Manthey et al. 2003; Creem-Regehr and Lee 2005; Johnson-Frey et al. 2005; Rumia et al. 2004; Fridman et al. 2006). Although the Ant. SMG → frontal segment was found to be present bilaterally, it tended to be significantly larger on the left. Because the premotor cortex stores generalized motor
programs that underlie physical actions, this asymmetry may reflect handedness (Johnson-Frey et al. 2005). Because the subjects in our study were all right-handed, it is appropriate that the segment is leftwardly asymmetric.

**SMG/AG to Frontal Lobe (SMG/AG → frontal)**

The SMG/AG → frontal segment (orange) connects the SMG/AG and the posterior inferior frontal and ventromedial cortex (BA 6). This segment was found to be highly rightwardly asymmetric. Because tool-use representations of the posterior parietal lobe are left-lateralized (Heilman et al. 1982; Buxbaum 2001), it is unlikely that this pathway is directly involved in tool use. Additionally, as mentioned above, the parietal terminations of this segment are not in the same location as the posterior parietal activations identified by functional neuroimaging studies (Johnson-Frey et al. 2005). This segment was tracked in 17 subjects, 12 of which only had the segment in their right hemisphere. The frontal projections of the orange segment were also mostly present in the inferior precentral gyrus, but sometimes extended into BA 44. This segment is most likely involved in spatial awareness as right parietal and frontal lesions are associated with hemispatial neglect, in which the patient loses awareness of his/her left visual field (Mort et al. 2003; Hills et al. 2005). This is in contrast to parietal and frontal lesions in the left hemisphere, which cause IM apraxia (Heilman et al. 1982; Buxbaum 2001). Additionally, a recent intraoperative electrical stimulation study showed a direct involvement of a parieto-frontal pathway in hemispatial neglect (Schotten et al. 2005). The parietal terminations of this pathway showed strong overlap with a region of maximal lesion overlap of visual neglect cases as reported by Mort et al. (2003) (see Fig. 1C). An emerging idea to explain the evolution of this rightward asymmetry in spatial awareness is that the right hemisphere developed additional perceptive abilities due to selective pressures for tool making (Hodgson 2005, 2006). The right hemisphere is capable of processing both left and right visual fields, whereas the left hemisphere can only process the right visual field (Husain and Nachev 2007). The expanded perceptive abilities of right hemisphere allow it to compensate for deficiencies caused by lesions in the left IPL, however the left hemisphere cannot do the same. For this reason, lesions in the right IPL cause spatial neglect while lesions in the left IPL generally do not. It is understandable that this rightward asymmetry does not exist in nonhuman primates as they were not subject to similar evolutionary pressures from tool making, and thus did not undergo similar parietal reorganization (Hodgson 2005, 2006; Husain and Nachev 2007).

**The Functional Connectivity of Representations in SMG/AG**

Although we found pathways connecting the SMG/AG with both the MTG and the frontal lobe, the parietal terminations of both these pathways are located in a different region of the parietal lobe than the invariant spatio-temporal representations, as reported in various recent functional neuroimaging studies (Chao and Martin 2000; Johnson-Frey et al. 2005; Buxbaum et al. 2006). We thus hypothesize that both these pathways (MTG → SMG/AG, SMG/AG → frontal) are more directly involved in functions other than tool use (language and spatial awareness, respectively). Our inability to find strong pathways directly linking these invariant spatio-temporal memorial representations of the left SMG/AG with the left MTG or the left frontal lobe is an understandable finding. The spatio-temporal representations stored in the left posterior parietal lobe are invariant, and thus devoid of dynamic information about the plane and position of the gesture in relation to the objects in the environment (SPL), as well as nonspatial and semantic information about the object and tools (MTG) (Buxbaum 2001; Glover 2004). Without the integration of these invariant memorial representations with dynamic spatial information and nonspatial representations, these spatio-temporal representations are not sufficient to produce a complete motor plan. For example, although swinging a plastic toy hammer accesses the same memorial representation as a heavy-duty metal hammer, they involve very different actions. This difference occurs when the nonspatial and semantic characteristics of each hammer (such as its weight) are incorporated into the motor plan along with the invariant representations from the posterior parietal cortex. Therefore, it is likely that these spatially and temporally invariant representations in the posterior parietal lobe are integrated with these other forms of information in the anterior parietal lobe instead of being directly connected to semantic representations in the MTG or motor primitives in the frontal lobe.

**Correlation between Language and Tool Use**

Previously, we measured the size and degree of asymmetry in the arcuate fasciculus language pathway is the same subjects (Glasser and Rilling 2008). We divided the arcuate pathway into an STG and MTG projection because of their respective roles in phonological and lexical–semantic processing. To address the possibility that asymmetries in language pathways correlate with asymmetries in pathways involved in tool use, we tested for correlations between them (Table 2). Although there was no significant correlation between asymmetries in language and tool use pathways, the absolute size of the left MTG → AntSMG pathway was positively correlated with the absolute size of the MTG arcuate pathway at a marginal level of significance ($r = 0.41, P = 0.08$), but not with 4 other left hemisphere pathways. This observation leaves open the possibility that language and tool use pathways evolve in tandem to some degree. Also, the asymmetry of the MTG → SMG/AG pathway was significantly correlated with both the MTG Arcuate ($r = 0.49, P < 0.05$) and the STG Arcuate ($r = 0.59, P < 0.01$) pathways. This finding strengthens the hypothesis that this

<table>
<thead>
<tr>
<th>Segment (function)</th>
<th>MTG arcuate (lexical-semantic)</th>
<th>STG arcuate (phonological)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTG → Ant. SMG (tool use)</td>
<td>$r = -0.21, P = 0.40$</td>
<td>$r = -0.41, P = 0.08$</td>
</tr>
<tr>
<td>MTG → SMG/AG (language hypothesized)</td>
<td>$r = 0.01, P = 0.97$</td>
<td>$r = -0.41, P = 0.08$</td>
</tr>
<tr>
<td>Ant. SMG → frontal (tool use)</td>
<td>$r = -0.21, P = 0.40$</td>
<td>$r = -0.49, P &lt; 0.01$**</td>
</tr>
<tr>
<td>SMG/AG → frontal (spatial awareness)</td>
<td>$r = -0.19, P = 0.44$</td>
<td>$r = -0.20, P = 0.42$</td>
</tr>
</tbody>
</table>

Note: Here we relate 1) the asymmetries of the pathways, 2) the absolute size ($mm^3$) in the left hemisphere, and 3) the absolute size ($mm^3$) in the right hemisphere. *$P < 0.05$; **$P < 0.01$.
pathway is involved in language functions because it is the only pathway with an asymmetry correlated with that of the arcuate fasciculus. The results are shown in Table 2.

**The Involvement of Callosal Pathways in Tool Use**

Anatomical descriptions of the corpus callosum indicate that there is a fairly simple rostro-caudal mapping of callosal pathways to cerebral cortex. For instance, the splenium (a posterior region of the corpus callosum) interconnects mostly parietal, temporal, and occipital regions of the brain (Hofer and Frahm 2006). Damage to callosal pathways has been shown to be involved in both ideomotor and ideational apraxia (Watson and Heilman 1983). We hypothesize that callosal pathways are necessary to carry various information about the tool-use plan (such as semantic information from the left temporal regions and invariant spatio-temporal representations from the left posterior parietal lobe) from the left hemisphere to the right hemisphere. Damage to callosal pathways could prevent motor centers in the right hemisphere from accessing these 2 types of information and result in apraxia limited to the left hand. Watson and Heilman report this phenomenon in a patient with a total callosal disconnection that resulted in apraxia and apractic agraphia confined to the left hand. As the patient's condition improved, the splenium, but not the body, of her corpus callosum recovered, as did her ideational apraxia in the left hand (loss of conceptual information about skilled actions). This suggests that the premotor centers in the right hemispheric access conceptual information in the left temporal lobe via splenial connections that travel to the right temporal lobe. In other words, conceptual information in the left hemisphere travels to the right temporal lobe and then to the right frontal lobe via the SLF III pathway. As a consequence of this organization, damage to the splenium (connecting the left and right temporal lobes) led to ideational apraxia in the left hand of this patient. However, the recovery of the patient's splenium did not eliminate the dynamic IM apraxia in her left hand (intact knowledge of gestures, but diminished efficacy and efficiency in execution). As Watson and Heilman suggest, this is most likely due to the fact that the callosal pathways that convey information about invariant spatio-temporal representations from the left hemisphere to the right hemisphere did not regain function in this patient (Watson and Heilman 1983). Based on our model of tool use and callosal anatomy, spatio-temporal representations could cross hemispheres either via the anterior splenium, where callosal pathways would carry invariant spatio-temporal representations directly from the left parietal lobe to the right parietal lobe; or it could occur in the callosal body, where pathways would convey the completed gesture plan from the left premotor centers directly to right premotor centers. Because the splenium of this patient recovered, but her right hemisphere still could not access information about invariant spatio-temporal representations, we favor the latter possibility.

**A Note on Limitations of the Study**

The most obvious limitation of any purely anatomical study is the inherent problem of inferring function from structure. Although our review of the lesion and functional neuroimaging literature suggests that some of the segments we have tracked with DTI are likely involved in tool use, this may not be their exclusive function.

Instead, the brain most likely recruits these pathways during both tool use and related functions. A combined DTI/lesion or DTI/fMRI study is one way that structure–function relationships could be addressed more directly in future studies.

An additional limitation is that our DTI scans were originally collected for a study of human language pathways, and included only those regions of the brain inferior to the intraparietal sulcus. Therefore, we were not able to investigate connectivity between the SPL (which has been implicated in dorsal-stream object localization and dynamic spatial processing; Buxbaum et al. 2006) and other nodes of the tool use network.

**Conclusion**

In summary, we identify 4 pathways: 1) MTG → Ant. SMG (blue), 2) MTG → SMG/AG (pink), 3) Ant. SMG → frontal (yellow), 4) SMG/AG → frontal (orange). We suggest that the first of these pathways (MTG → Ant. SMG) allows for the integration of ventral-stream object recognition information with dorsal-stream object localization pathways. This pathway is almost completely leftwardly asymmetric. The second pathway (MTG → SMG/AG) is not likely directly involved in tool use, but may be involved in language, and is slightly leftwardly asymmetric. The third pathway (Ant. SMG → frontal) may provide a link between the integrated gesture plan and the premotor cortex; it is significantly leftwardly asymmetric. The fourth pathway (SMG/AG → frontal) is likely to be involved in spatial awareness and is found to be almost completely rightward asymmetric. The leftward asymmetry of the MTG → Ant. SMG and Ant. SMG → frontal pathways parallels the leftward laterality of functional neuroimaging studies of tool use, whereas the rightward asymmetry of the SMG/AG → frontal pathway parallels rightward laterality of lesions causing deficits in spatial awareness. Additionally, the existence of the pathways connecting the temporal and parietal lobes (especially MTG → Ant. SMG) suggests the integration of ventral- and dorsal-stream processes that have been hypothesized to be involved in complex human tool use (Johnson-Frey 2007). Future studies that compare these pathways in human, ape and monkey brains will shed light on the evolution of the neural substrates supporting human tool use.

**Supplementary Material**

Supplementary material can be found at: [http://www.cercor.oxfordjournals.org/](http://www.cercor.oxfordjournals.org/)

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