# Comparing brain connections in different species using diffusion weighted imaging

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Keywords: comparative anatomy, macaque, human, parietal cortex, prefrontal cortex, cingulate cortex, language

In: Johansen-Berg H & Behrens TEJ (Eds.) *Diffusion MRI: From quantitative measurement to in vivo neuroanatomy*, pp. 445-460. Amsterdam: Academic Press (2009)

**The anatomical connections of a brain area constrain the information it receives and the influence it exerts over other regions. A brain area's anatomical connections, therefore, determine its function. The recent advance in neuroimaging methods has led to a concerted effort to understand human brain function and the interactions that occur between human brain regions. Until recently, however, little has been known of the connections of human brain areas. Diffusion weighted imaging and tractography now provides a non-invasive method to estimate the probability that brain areas are interconnected and to compare such estimates with what is known of the connections of similar brain regions in other species. While there are clear limits to the type of evidence that can be provided by diffusion weighted imaging it has, nevertheless, begun to provide new insights into basic aspects of human connectional neuroanatomy.**

The advent of modern neuroimaging techniques in recent decades has led to a great advance in our understanding of human brain function. We now have a sense of how activity in many brain areas changes in tandem with cognitive, motor, and perceptual processes and we are beginning to understand how different areas interact with one another as behaviour unfolds. The functions and interactions of brain areas, however, are determined by their anatomical connections; the connections of a brain area constrain the information that it receives and the targets to which it can, in turn, convey information. Until recently, however, we have had little direct knowledge of the anatomical connections between human brain areas. Instead much of what is assumed about human brain connections is based on indirect inferences from studies conducted in animals, typically old world monkeys such as the macaque.

In animal models it is possible to inject tracer substances into the brain that are then taken up by axons and transported back to the cell body (retrograde tracers) or taken up by the cell body and transported along the length of the axon (anterograde tracers). The connections going to or from a brain area can then be established by looking at the distribution of the tracer in the brain at sites distant from the injection zone in a post-mortem histological analysis (Chapter 13). The tracers are normally actively taken up by neurons and transported along axons and so the initial injection must be made prior to death. Although such techniques can be used with monkeys they cannot be used with human subjects or indeed with other great apes such as the chimpanzee. The evolutionary divergence between old world monkeys, such as the macaque, and humans occurred many millions of years ago and so the obvious question to ask is whether what we have learned from difficult and painstaking tract tracing studies has any bearing on our understanding of human brain anatomy? This chapter reviews recent diffusion weighted imaging or diffusion tensor imaging (DTI) and tractography studies of the frontal lobes, the brain's language system, the motor system, and the parietal cortex. These are all areas that have all been thought to be different or special when the human brain has been compared to the brains of other primates (Passingham, 2008). An important general finding is that connection patterns in humans resemble those already seen in other primate species. Moreover, a better understanding of human brain connections can provide fresh perspectives on the functional contributions of human brain areas.

## Comparing DTI tractography with tract tracing techniques

The connections between one distant brain area and another are conveyed in bundles of white matter called fascicles. When an injection is made in one brain area the tracer is taken up and distributed in the axons of neurons projecting to or from that brain area. This means that it is possible to use tract tracing techniques to establish the routes taken by particular connections through the major white matter fascicles in the macaque monkey (Schmahmann and Pandya, 2006). A number of researchers have used diffusion weighted imaging and tractography approaches of one sort or another with macaque monkeys to test whether it is possible to visualize the same fascicles using these imaging techniques (Parker et al., 2002; Croxson et al., 2005; Schmahmann et al., 2007).

Schmahmann and colleagues (2007) have shown that it is possible to use diffusion spectrum imaging (DSI), a diffusion based technique with a high angular resolution, to identify the course taken by white matter fascicles in the monkey brain. They compared the fibre courses estimated by DTI-tractography with the fibre courses established in tracer injection studies. Schmahmann and colleagues were able to identify ten major projection pathways in this way using DTI-tractography. For example the extreme capsule (EC) pathway travels between the posterior and superior temporal lobe on the one hand and the ventral frontal lobe on the other hand while the third branch of the superior longitudinal fascicle (SLFIII) travels between the parietal cortex and the ventral frontal cortex (figure 1b).

*Figure 1 about here please*

The EC travels further forwards into the ventral prefrontal cortex (PFv) while SLFIII only reaches as far as the ventral premotor cortex (PMv). Few DTI-defined fibres in the SLFIII project anterior of the arcuate sulcus which lies on the border between PMv and PFv (figure 1b). Tractography algorithms are, however, only able to estimate the course and position of a pathway on the basis of the anisotropy in the diffusion signal (Chapter 15). When there is uncertainty about the principle direction of diffusion then it is difficult to estimate the direction taken by axons. It is, therefore, difficult to determine whether a given pathway reaches a particular part of cortex because such uncertainty increases as fibres approach and enter the cortex. Probabilistic techniques, however, have been developed to estimate the probability distribution on the principle diffusion direction at each voxel and with these techniques it is possible to estimate the probability of connections between a fascicle and a given cortical region (Behrens et al., 2003a; Parker and Alexander, 2005).

Using these probabilistic tractography techniques Croxson and colleagues (Croxson et al., 2005) investigated, in the macaque, the connections of the frontal lobe with other brain regions and several white matter fascicles including EC and SLFIII. Croxson and colleagues estimated a high probability of interconnection between EC and PFv but not between EC and PMv. By contrast SLFIII was found to have a high probability of connection with PMv but not PFv (figure 2). This pattern of connectivity is consistent with what is known from tract tracing studies. PMv has strong connections with the anterior inferior parietal cortex that are conveyed via SLFIII (Petrides and Pandya, 1984; Matelli et al., 1986; Cavada and Goldman-Rakic, 1989; Luppino et al., 1999; Fogassi et al., 2005; Petrides and Pandya, 2006; Schmahmann and Pandya, 2006) and such projections probably underlie the interaction of these brain areas during precise spatial movements such as those that are made during arm reaching and hand grasping (Toni et al., 2001; Verhagen et al., 2008). By contrast, in the macaque, PFv is not so strongly interconnected with the motor system and the parietal cortex but instead it has connections with posterior and superior parts of the temporal lobe, via not just EC but also another fascicle, the uncinate fascicle, giving it access to information about visual and auditory stimuli, particularly the identity as opposed to the spatial position of such stimuli (Webster et al., 1994; Carmichael and Price, 1995; Romanski et al., 1999b). Such connections may underlie the role of some parts of PFv in, on the one hand, the processing of complex sounds, such as vocalizations (Romanski et al., 2005) and on the other hand selecting objects to be the focus of attention (Rainer et al., 1998; Rushworth et al., 2005b).

*Figure 2 about here please*

## Using DTI-tractography to examine the connections of human ventral frontal cortex

The ventral frontal cortex of the human brain, at least in the left hemisphere, contains Broca's area. Broca's area is active during language tasks during functional magnetic resonance imaging (fMRI) studies and damage here is associated with the language problems of aphasia. Because, amongst mammals and even primates, language is a peculiarly human ability (Passingham, 2008) it has long intrigued scientists to integrate an understanding of Broca's area with an understanding of other aspects of frontal lobe function. In addition to using DTI-tractography to investigate connections in the macaque Croxson and colleagues (Croxson et al., 2005) also used it to investigate the same pathways in the human brain. Once again both EC and SLFIII were found to project to the ventral frontal cortex and once again there was a significant separation in the estimated connection patterns of the two pathways with sub-divisions of the frontal lobe. The boundary between regions of high EC and high SLFIII connection probability runs through the middle of Broca's area. In other words, Broca's area is not a single monolithic entity. The distinct connection patterns of its anterior and posterior parts suggest that something resembling the boundary between the prefrontal and premotor cortex of other primates, PFv and PMv, passes through Broca's area.

Posterior and anterior Broca's area are, respectively, usually taken to consist of the pars opercularis and the pars triangularis of the inferior frontal gyrus. There is an approximate relationship between the cytoarchitectonic areas 45 and 44 and the pars triangular and pars opercularis respectively. It is important to note, however, that when cortical boundaries are carefully established using cytoarchitectural and histochemical criteria they do not coincide exactly with the sulci that lie between pars opercularis and pars triangularis - the diagonal sulcus and the ascending branch of the lateral fissure (Amunts et al., 1999).

*Figure 3 about here please*

Because anterior Broca's area is more likely to be interconnected with EC it is more likely to be interconnected with the temporal lobe whereas pars opercularis is more likely to be interconnected with the anterior inferior parietal cortex. Connections to the temporal lobe and access to auditory and object identity information may underlie anterior Broca's area's pre-eminence in semantic computations (Dapretto and Bookheimer, 1999; Gough et al., 2005).

By contrast the posterior part of Broca's area is perhaps best understood within the context of the motor system. A probable connection with SLFIII means that this region communicates with anterior inferior parietal cortex. A number of neuroimaging studies have reported activity in both pars opercularis and the anterior inferior parietal lobule when human subjects observe and copy hand and mouth movements (Binkofski et al., 1999a; Binkofski and Buccino, 2006). It has recently also been demonstrated that even the macaque monkey brain contains a region with dysgrannular cytoarchitecture that resembles human area 44 (Petrides et al., 2005). It is situated at the bottom of the inferior arcuate sulcus so, like human 44, it is just posterior to PFv and anterior to the rest of PMv.

The existence of a connection pattern boundary within Broca's area has also been identified by a distinct DTI approach. Both Anwander and colleagues (2007) and Klein and colleagues (2007) looked for the similarities and differences in the DTI-defined connection patterns of all voxels in a Broca's area "seed region". The patterns of connection with the rest of the brain exhibited by all seed voxels were compared to establish whether clusters of similarly connected seed voxels could be identified. The "parcellation" method is explained in more detail in chapter 17. Its advantage is that it does not rely on identifying differences in the connexion patterns of a particular region or tract but instead the parcellations it defines are based on connection patterns with the whole of the rest of the brain. Both Anwander and colleagues and Klein and colleagues reported a major change in connection patterns between voxels in pars opercularis and pars triangularis (figure 4).

*Figure 4 about here please*

Broca's area has traditionally been regarded as a language area and its relationship with brain areas in non-linguistic primate species has been unclear. Diffusion weighted imaging studies, however, suggest that it is comprised of at least two component regions with radically distinct anatomical connections. Anterior Broca's area resembles the prefrontal cortex of other primates and its role in semantic processing may depend on interconnections with the temporal lobe. Posterior Broca's area resembles the premotor cortex of other primates. Its connections with the parietal cortex may underlie its motor role.

## Language and the arcuate fascicle in humans and other primates

There is concordance between studies that have focussed on EC and SLFIII and which distinguished between the connections of anterior and posterior Broca's area. There is, however, confusion about another major pathway, the arcuate fascicle (AF), long thought to be a core component of the human language system (Geschwind, 1970a, b). It has been considered the major pathway linking the posterior language area, Wernicke's area, in the superior temporal gyrus and Broca's area. A language disorder, conduction aphasia, is thought to follow from its damage and the consequent disconnection of Broca's area and Wernicke's area that ensues. It is agreed that the AF can be identified with DTI tractography (Catani et al., 2002; Catani et al., 2005 Catani et al., this volume) but the frontal cortical territories it interconnects have been disputed.

Several groups have reported connections between AF and Broca's area (Catani et al., 2005; Glasser and Rilling, 2008; Rilling et al., 2008). In the monkey, however, tract tracing studies studies suggest that AF carries few connections between the superior temporal gyrus and the homologue of Broca's area in the *ventral* frontal lobe, PFv (Petrides and Pandya, 1988, 2006). Instead the AF mediates connections between the superior temporal gyrus and more *dorsal* frontal lobe areas such as area 8 in and around the frontal eye fields. These connections are at the heart of the dorsal auditory stream (Romanski et al., 1999a). Information about the identity and locations of sounds is conveyed to the frontal lobe via two different routes from auditory association cortex in the superior temporal lobe. The dorsal route is thought to be important for auditory localization and it is certainly the case that area 8 and the frontal eye fields are important for other aspects of spatial orienting behaviour (Schiller and Chou, 1998). In other words, despite a widespread assumption to the contrary, AF's position in macaques means that its homologue in the human brain is unlikely to be strongly connected to Broca's area and it is unlikely to be important for human language.

The absence of strong AF-PFv connections in the macaque also indicates that it is necessary to carefully assess the evidence for AF connections with Broca's area in human DTI studies. It is certainly difficult to distinguish AF from the adjacent fibres of the superior longitudinal fascicle, particularly SLFIII (Makris et al., 2005). Frey and colleagues (in press) have reported that human AF resembles macaque AF and projects to area 8 and the posterior dorsal prefrontal cortex. In addition they argued that the AF has sometimes been confused with two other fascicles, the SLFIII and a part of the inferior longitudinal fascicle (ILF). A portion of the ILF runs between the superior temporal lobe and the inferior parietal cortex and SLFIII runs from adjacent inferior parietal cortex to posterior Broca's area. Together these two fibres have a course that resembles the supposed, but incorrect, trajectory of AF (figure 5 about here).

*Figure 5 about here please*

Although the position of AF, like that of EC, and SLFIII, is similar in the brains of humans and other primates there nevertheless appears to be some tantalizing evidence for inter-species differences in temporal-frontal connections. Rilling and colleagues (2008) used DTI to compare connections in macaques, chimpanzees, and humans. . They reported evidence for interconnection between the superior temporal cortex and area 45 in all three species but they reported better evidence of interconnection between middle and inferior temporal cortex and area 45 in humans. The report is couched in terms of a changing balance between the strength of EC and AF across species that may be difficult to sustain in the face of Frey's and Petrides' and Pandya's careful investigation of AF. The central observation of an increased connectivity between more middle and inferior temporal lobe cortex and PFv in the human is an exciting one that deserves further investigation.

## DTI suggests basic similarities in frontal lobe organization in man and other primates

Given the gulf between the behaviour of humans and other primates it has been tempting to look for differences in brain anatomy that might underlie such differences. There has been most interest in the possibility that frontal brain regions, particularly prefrontal cortex, may be different in humans. The interest in prefrontal cortex stems from its acknowledged role in complex and flexible behaviour. It is clear that human frontal cortex, in comparison with other brain areas, is proportionally larger than in other primates, even closely related primates such as the chimpanzee (Passingham, 2008). Nevertheless the basic pattern of frontal connections that is emerging from DTI studies of the human brain is one that would be familiar to a macaque neuroanatomist.

Differences between human and macaque prefrontal cortex connections have been the focus of some studies. Basic similarities in the connection plans of the two species are, however, just as prominent. Ramnani and colleagues (2006) compared prefrontal-cerebellum connections in humans and macaques. They looked at fibre pathways from cortex as they passed through the cerebral peduncle on their way to the pons before finally arriving in the cerebellum. They found evidence for connections between premotor cortex and the cerebral peduncle in both species. Particular emphasis, however, is given in the report to evidence that areas anterior to premotor cortex, in other words areas that one might initially suppose are prefrontal areas, are more likely to be interconnected with the cerebellum in humans than in macaque. There has been interest in the possibility that the cerebellum may have cognitive functions (Schmahmann, 1997). Given the prefrontal cortex's importance in higher order aspects of cognition, and given the expansion of prefrontal cortex in the human brain, it might then be argued that if the cerebellum is to contribute to cognition then its connections with the prefrontal cortex should increase.

One area traditional thought of as prefrontal that Ramnani and colleagues report as having a high probability of interconnection with the cerebellum is the posterior part of Broca's area. We have already seen, however, that this region, pars opercularis or area 44, is perhaps best thought of as a dysgrannular transition zone between premotor and prefrontal cortex, rather than prefrontal cortex proper, and that it has connections with areas such as anterior inferior parietal cortex that make it resemble PMv. In addition it is important to point out that even Ramnani and colleagues recognize that the dorsal prefrontal cortex of the macaque is thought to be interconnected with cerebellum (Middleton and Strick, 2001). In summary, even if there is evidence for greater cerebellar-prefrontal cortex connectivity in human as compared with macaque, the difference is not qualitative but one of degrees.

When other connections are considered the conclusion is the same: the basic pattern of prefrontal connectivity is similar in humans and macaques. Historically, some of the greatest interest in functional specialization within prefrontal cortex focussed on comparisons of ventral and dorsal sectors of lateral prefrontal cortex (Wilson et al., 1993). Functional dichotomies based on working memory specializations for object and for spatial information in ventral and dorsal prefrontal cortex have not stood the test of time (Rao et al., 1997; Rushworth and Owen, 1998). Nevertheless there is evidence that more ventral prefrontal neurons encode information about the identity and sensory features of objects while more dorsal prefrontal neurons encode information pertaining to the spatial direction, planning, and sequencing of actions (Rushworth, 2000 ; Hoshi and Tanji, 2004; Ninokura et al., 2004). Functional differences between these areas can be understood in terms of the stronger connections of ventral and dorsal prefrontal cortex with temporal and parietal cortex respectively (Cavada and Goldman-Rakic, 1989; Webster et al., 1994). In the monkey temporal cortex conveys information about objects and their identifies to the PFv not just via the EC but also via the uncinate fascicle (UF; Petrides and Pandya, 1988; Ungerleider et al., 1989) while parietal cortex interconnects with dorsal prefrontal and posterior frontal region via the various branches of the SLF and the fronto-occipital fascicle (Petrides and Pandya, 2006). Croxson and colleagues (2005) used DTI to examine the connections of EC, UF, and the second branch of the SLF, SLFII, with prefrontal cortex in human subjects. They reported a higher probability of SLFII connections with dorsal prefrontal cortex and a higher probability of EC and UF connections with PFv (figure 6).

*Figure 6 about here please*

The orbital frontal cortex is adjacent but ventral to ventrolateral prefrontal cortex. It is distinguished from the lateral surface by its possession of projections from the amygdala (Porrino et al., 1981; Ghashghaei et al., 2007). It is possible to compare the prefrontal cortex's connections with amygdala with its connections with temporal cortex because they run via different routes. Ungerleider and colleagues (1989) reported that transection of the UF near the insula, a lesion that would probably also transect the EC, did not prevent injected tracers crossing between the amygdala and prefrontal cortex. It is sometimes stated that amygdala connections run in the UF but it is clear that they take a route that mostly lies ventral to the striatum and that is medial to the route taken by temporal cortical connections (Schmahmann and Pandya, 2006). As in the macaque Croxson's and colleagues' (2005) DTI analysis of human prefrontal cortex connections found that orbital areas had a higher probability of interconnection with the amygdala than did adjacent areas (figure 6).

In the monkey some of the best evidence for regional differentiation in anatomical connectivity within the prefrontal cortex comes from comparisons between lateral orbitofrontal cortex and the more medial ventromedial frontal cortex. Connections with the temporal lobe sensory areas and perirhinal cortex are more prominent in the lateral orbitofrontal cortex while connections with visceromotor structures such as the hypothalamus and periaqueductal grey and with the subiculum of the hippocampal formation are more prominent in ventromedial frontal cortex (Carmichael and Price, 1995; An et al., 1998; Ongur et al., 1998; Ongur and Price, 2000; Kondo et al., 2003, 2005). Croxson and colleagues (2005) found that DTI evidence for temporal cortex connections via UF waned from lateral to medial orbitofrontal cortex in the human brain while evidence for amygdala and fornix mediated connections with the subiculum increased from lateral to medial frontal cortex (figure 6).

Although a host of cortical regions differ in the strength of their connections with ventromedial and lateral orbitofrontal cortex the first evidence for separation between these networks in the monkey emerged from an analysis of connections with the mediodorsal nucleus (MD) of the thalamus (Ray and Price, 1993). In the macaque medial MD, including the pars fibrosa (MDfi), is preferentially interconnected with the lateral orbitofrontal cortex while caudodorsal MD (MDcd) is interconnected with ventromedial frontal cortex. Lateral parvicellular MD (MDpc) is interconnected with the more ventral and the more dorsal parts of the lateral surface of prefrontal cortex while the central region of the lateral surface near the principal sulcus is interconnected with a limited region of MD at the border between MDfi and MDpc. Klein and colleagues (submitted) have used DTI to look at connection probabilities between macaque MD and the prefrontal and cingulate cortex and have reported the same pattern. In a second stage of the experiment Klein and colleagues then went on to estimate the connections of human MD using the same DTI tractography approach and once again they found evidence for the same pattern of connections (figure 7). Not only do such findings provide further evidence for similarities between the frontal lobes of macaques and humans but they also highlight the power of the DTI approach. For some time it has been clear that DTI might be used to estimate differences in the cortical connections of different thalamic nuclei (Behrens et al., 2003b; Johansen-Berg et al., 2005) but it is becoming increasingly clear that in some instances it can be used to identify differences in the connection probabilities of sub-components of individual thalamic nuclei.

*Figure 7 about here please*

In summary, to date, it seems that DTI studies have tended to confirm a pattern of anatomical connectivity in the human prefrontal cortex that is reminiscent of the pattern known from non-human primates. Despite prefrontal cortex's many shared features in different species some areas of relative expansion are likely to be found in the human brain in the future. Rather than expecting to find qualitative changes in connection patterns between species, however, it may be more realistic to expect to find new modules and subdivisions emerging and differentiating from within brain areas common to several primate species. Such a pattern of areal differentiation is certainly apparent in comparative and developmental studies of sensory systems. Comparisons of the visual systems of different monkey species suggest that some visual areas have duplicated during the course of speciation (Sereno and Tootell, 2005). In the rat local changes in the distribution of fibroblast growth factor can lead to duplication of barrel fields of the primary somatosensory cortex as well as the field's connections with particular thalamic nuclei (Grove and Fukuchi-Shimogori, 2003). DTI parcellation techniques (Johansen-Berg et al., 2004, chapter 17) may prove to be useful in identifying similar new areas, if they exist, in the human prefrontal cortex.

## Premotor cortex

Motor behaviour does not solely depend on the primary motor cortex but on a network of premotor regions that lie immediately anterior on both lateral and medial surfaces of the frontal cortex. Functionally these regions are characterized by their involvement in the selection and spatial planning of movements but anatomically they are distinguished by their connections with the ventral horn of the spinal cord and with the primary motor cortex (Dum and Strick, 1991; He et al., 1993; Luppino et al., 1994; He et al., 1995; Dum and Strick, 1996; Geyer et al., 2000).

The precise contribution made by each premotor region to motor behaviour is still the topic of debate but it is widely believed that each area's function is distinct. For example, in the monkey, the dorsal premotor cortex (PMd) and ventral premotor cortex (PMv), which lie on the lateral surface anterior to primary motor cortex, are particularly concerned with rule-guided action selection and with the spatial organization of movements respectively (Kurata and Hoffman, 1994; Jeannerod et al., 1995; Wise et al., 1997; Hoshi and Tanji, 2000). The supplementary motor area (SMA) and the pre-supplementary motor area (pre-SMA) on the medial surface are, amongst other things, important during the initiation and organization of sequences (Mushiake et al., 1991; Tanji, 2001). There are additional premotor regions within the cingulate cortex and at least some of these are concerned with reward guided action selection (Shima and Tanji, 1998; Kennerley et al., 2006). Although the areas are similar in that, with the exception of pre-SMA, they are connected to primary motor cortex and the spinal cord, they each have many distinct connections with specific sub-sections of parietal, prefrontal, and subcortical structures that mean that each has access to distinct types of information and is therefore able to carry out a distinct function.

In the premotor region on the lateral surface of the human brain there is evidence for more than one focus of activation in neuroimaging studies (Mayka et al., 2006). As in the macaque there is evidence for PMv and PMd specialization for spatial guidance of movement and rule guided action selection mechanisms respectively (Toni et al., 2001). Using the DTI parcellation approach Tomassini and colleagues (2007) found evidence for a change in connectivity between the dorsal and ventral parts of the lateral premotor cortex. The boundary was at the same approximate level as the horizontal extension of the inferior precentral sulcus, between the limits of the inferior and superior precentral sulci (see also chapter 17). Functional activations tend to cluster within the centres of the dorsal and ventral DTI-defined regions. As in the macaque there was a higher probability of connection between PMd and the superior parietal and dorsal prefrontal cortex while there was a higher probability of interconnection between the PMv and the inferior parietal cortex. The results suggest the cortex immediately anterior to the primary motor cortex is divided into two basic subdivisions, PMd and PMv, predominantly interconnected with superior and inferior parietal cortex respectively, across a wide variety of primate species including prosimians such as galagos or bushbabies (Wu et al., 2000), new world monkeys such as owl monkeys (Preuss et al., 1997; Stepniewska et al., 2006), and old world monkeys such as macaques (Matelli et al., 1986; He et al., 1993; Geyer et al., 2000; Dum and Strick, 2005).

The parcellation approach has also been used to investigate the medial premotor cortex. Johansen-Berg and colleagues (2004) reported a DTI connectivity-defined border between SMA and pre-SMA. Johansen-Berg and colleagues also obtained fMRI data from the same subjects during a repetitive movement and serial subtraction task and found that activations associated with the two tasks mapped onto the DTI-defined SMA and pre-SMA regions. Moreover individual differences in the fMRI-defined and DTI-defined boundaries were correlated across subjects. In the anterior cingulate cortex Beckmann et al., (submitted) found evidence for nine regions with distinct DTI-defined patterns of connectivity. Beckmann and colleagues also carried out a meta-analysis of fMRI activations reported in motor tasks and reported that their cluster 4, 5, and 6 (figure 8) are in approximately the same position. Beckmann's clusters 4, 5, and 6 are also in approximately the same positions as three motor regions as estimated from an earlier meta-analysis (Picard and Strick, 2001). There is evidence for a similar number of motor regions in the cingulate cortex in the macaque monkey (Strick et al., 1998) and at least two areas in the galago (Wu et al., 2000).

Prosimians, new world and old world monkeys possess several premotor regions that are distributed throughout the frontal lobe on both the lateral and medial surface and even in the cingulate cortex. Currently DTI suggests a similar organization in the human premotor system. More fine grained analyses may, however, provide evidence for additional sub-regions in the human.

*Figure 8 about here please*

## Comparing the parietal cortex in human and other primates

Beyond the language system and prefrontal cortex the parietal cortex is one of the brain regions most frequently held up as an example of major anatomical difference between humans and other primates. The region has been a focus of anatomical change during human evolution (Bruner et al., 2003) and, at least in some systems of nomenclature, the anatomical labels given to parietal areas in the human brain are considerably different to those assigned to the parietal cortex of other primates (figure 9a).

The principal anatomical division within the parietal cortex is between the inferior parietal lobule (IPL) and the superior parietal lobule (SPL). The two lobules are divided by the intraparietal sulcus (IPS). Brodmann (1909) identified two cytoartchitectonic areas, 39 and 40, respectively on the angular and supramarginal gyri in the posterior and anterior IPL of the human brain. Most of human SPL was classified as area 7 cortex. Areas 39 and 40, however, were absent from Brodmann's description of the monkey IPL and the IPL was designated area 7. A number of researchers have argued that human IPL is uniquely human and unlike the parietal cortex in other species (Glover, 2004; Husain and Nachev, 2007).

A close reading of Brodmann's original report, however, reveals that he was tentative about the possible relationships between area 7 and areas 39 and 40. Moreover, although widely used, Brodmann's cytoarchitectonic labels are not the only ones in existence. Other anatomists have been impressed by the similarities in the appearance of the parietal cortex in both humans and macaques and they have assigned the labels PF and PG to anterior and posterior IPL in both species (Von Economo, 1929; Von Bonin and Bailey, 1947). The most recent quantitative observer-independent methods for identifying cortical areas has suggested that 7 distinct regions can be identified within human IPL (Caspers et al., 2006). In subdividing IPL into 7 regions Caspers and colleagues exploited and extended the PF/PG naming system devised by von Economo.

Gregoriou and colleagues (Gregoriou et al., 2006) have also used a revised version of the same system in their recent analysis of macaque IPL cytoarchitecture.

One way to test for similarities in the IPLs of different primate species, humans and macaques, is to use DTI to look for connection patterns in the human parietal cortex that are characteristic of limited regions of macaque parietal cortex. Rushworth and colleagues (2005a) looked for connection patterns that were characteristic of three regions in the IPL and adjacent lateral bank of the IPS – anterior IPL, posterior IPL, and the lateral intraparietal (LIP) (figure 9). Unlike other lateral parietal areas LIP is interconnected with the superior colliculus (Lynch et al., 1985; Blatt et al., 1990; Clower et al., 2001; Gaymard et al., 2003; Lock et al., 2003). The connection is consistent with LIP's involvement in covert orienting and eye movements (Andersen and Buneo, 2002; Sugrue et al., 2005). Unlike other parietal areas the posterior IPL is interconnected with the parahippocampal gyrus via the inferior longitudinal fascicle (Seltzer and Pandya, 1984; Cavada and Goldman-Rakic, 1989; Suzuki and Amaral, 1994; Lavenex et al., 2002). The connection therefore links two brain areas involved in higher order visual processing and in which damage has been linked to visuospatial neglect (Mort et al., 2003). Unlike other parietal areas the anterior IPL and adjacent anterior IPS [anterior intraparietal (AIP) area] are interconnected with PMv via SLFIII (Matelli et al., 1986; Cavada and Goldman-Rakic, 1989; Petrides and Pandya, 2002). Such connections are consistent with these areas' roles in reaching and grasping (Binkofski et al., 1999b; Toni et al., 2001; Binkofski and Buccino, 2006; Davare et al., 2007; Davare et al., 2008).

The connection patterns of human anterior and posterior IPL resemble the connection patterns of macaque IPL. DTI tractography suggested that, as in the macaque, parahippocampal cortex was most strongly interconnected with posterior IPL and that PMv, via SLFIII, was most strongly interconnected with anterior IPL (figure 9). Unlike in the monkey, however, the area with the highest probability of interconnection with the superior colliculus was not on the adjacent lateral bank of the IPS. Instead it was an extensive region of the medial bank of the IPS (figure 9).

The similarities between the connection patterns of human and macaque IPL suggest human IPL is not without parallel in other primates. Despite the basic similarities in IPL organization in the two species some IPS regions have moved more superiorly and medially in the human brain. Area LIP, which lies immediately adjacent in the IPL in the macaque, appears to have expanded and to occupy part of the medial bank of the IPS in humans. Parallel FMRI studies of humans and macaques show that the key IPS area for eye movements is found on the medial bank in the human brain but on the lateral bank in the monkey brain (Koyama et al., 2004). Moreover, human fMRI studies suggest LIP has expanded into several distinct topographically mapped areas on the medial bank of the IPS (Sereno et al., 2001; Silver et al., 2005).

It is possible that the mid-portion of the IPL and the adjacent IPS has been especially well developed in the human brain. This region is active when human subjects are engaged in complex cognitive operations that are particularly well developed in humans, for example numerical processing (Simon et al., 2002) and task exploration and task switching (Daw et al., 2006; Jubault et al., 2007).

*Figure 9 about here please*

## Conclusions

In order to understand a brain system it is necessary not just to know about the activity patterns that occur within it but also to see how its component parts are interconnected. Information of this type can be derived from tract tracing experiments in animal models (Chapter 13). DTI does not constitute an *alternative* to such methods because it does not inform us about the direction of connections within the brain, it has a limited spatial resolution and is silent about the precise nature of the synaptic connection that is made between two areas (see for example Lacey et al., 2007). DTI is, however, an important *complement* to tract tracing methods and even already it has proved possible to compare DTI-based estimates of inter-regional connectivity across species and to compare DTI-based connectivity estimates with tract tracing studies. So far the picture of human brain connections that is emerging is reminiscent of the pattern seen in other primate species but evidence for human differences and specializations is beginning to emerge.

**Figures legends**

1. Sagittal sections through diffusion spectrum image of macaque monkey brain. (a) Fibres from the third branch of the superior longitudinal fascicle (SLFIII) are shown in blue. (b) Fibres from the extreme capsule (EmC in figure but referred to as EC elsewhere in this chapter) are shown in blue. Central sulcus – CS, intraparietal sulcus - IPS, lateral fissure – LS. Adapted from Schmahmann and colleagues (2007) with permission.

2. Probability of interconnection between the superior longitudinal fascicle (SLF) and the extreme capsule (EC) and the ventral prefrontal (PFv) and ventral premotor (PMv) cortex in the macaque monkey as estimated by DTI. While voxels in both SLF and EC have a high probability of interconnection with PFv EC voxels have a high probability of connection. The opposite is true when evidence for connection with PMv is considered; SLF voxels have a particular high probability of connection. Adapted from Croxson and colleagues (2005) with permission.

3. Probability of interconnection between the third branch of the superior longitudinal fascicle (SLFIII), the extreme capsule (EC) and anterior Broca's area (mostly consisting of area 45) and posterior Broca's area (mostly consisting of area 44) in the human brain as estimated by DTI. Anterior Broca's area resembles the macaque PFv because it has a high probability of connection with EC while posterior Broca's area resembles macaque PMv because of its high probability of connection with SLFIII. Adapted from Croxson and colleagues (Croxson et al., 2005) with permission.

4. When the connection probabilities of voxels within Broca's area with all other voxels in the brain are compared two principal patterns of connectivity emerge. Voxels with one pattern are mainly located in the posterior Broca's area approximately in the region of area 44 (green area) while voxels with the other pattern are located in anterior Broca's area approximately in area 45 (blue area). A third pattern (red) was associated with voxels in the most anterior and ventral area that approximately corresponds to area 47. A series of axial slices from a single example subject are shown on the left and a lateral surface reconstruction from the same subject is shown on the right [adapted from Anwawnder and colleagues (2007) with permission]. (b) Klein and colleagues were also able to sub-divide Broca's area into anterior and posterior regions on the basis of DTI-defined connectivity (left) in a manner that corresponded approximately with the known cytoarchitectonic positions of areas 44 and 45. Adapted from Klein and colleagues (2007) with permission.

5. Frey and colleagues examined the pathway taken by fibres from the superior temporal gyrus (red) into the frontal lobe (sagittal and axial views at top left and top right). A group of fibres (light blue) passed around the Sylvian fissure and continued on to area 8 in the frontal lobe (dark blue). Frey and colleagues identify this pathway as the arcuate fascicle (AF). The pathway came into close contact with the third branch of the superior longitudinal fascicle (SLFIII, orange) that then continued on to the posterior part of Broca's area. The region of overlap between the tracts is shown in white in the series of coronal sections at the bottom of the figure. DTI tracking algorithms can separate the two pathways and incorrectly suggest that there is a direct connection between the superior

temporal gyrus and Broca's area running dorsal to the Sylvian fissure. Adapted from Frey and colleagues with permission (Frey et al., in press).

6. Quantitative results of probabilistic tractography from five subcortical regions to the prefrontal cortex in the human brain (left hand side) and examples of a corresponding tract for each region run from a single seed point (right hand side). The prefrontal cortex has been divided into ten regions and the probability of connection with each of the ten regions is shown (CS - cingulate sulcus, CG - cingulate gyrus, PFom - medial orbitofrontal cortex, PFoc - central orbitofrontal cortex, PFol - lateral orbitofrontal cortex, PFvl - ventrolateral prefrontal cortex, PFdl+dm - dorsolateral and dorsomedial prefrontal cortex) (a) The majority of connections from anterior temporal lobe via the uncinate fascicle (UF) are with orbital PFC, with a greater bias to central orbital areas. (b) Connections from posterior and superior temporal lobe areas via the extreme capsule (EC) are mainly to the central/lateral orbital and ventrolateral PFC areas, whereas connections via the SLF, connecting with parietal areas, are most likely to be with the PFvl (for SLFII) and PFdl+dm (in the case of SLFIII), with very low probabilities to orbital areas (c,d). (e) The amygdala connections are most likely to be with PFom. Adapted from Croxson and colleagues (2005) with permission.

7. i) (top left) Coronal slice at level of rostral mediodorsal (MD) thalamus of the macaque monkey showing regions established in tract tracing studies to be connected with the orbital prefrontal cortex (yellow), the dorsal and ventral parts of the lateral surface (blue), the principal sulcus in the centre of the lateral frontal cortex (green), and ventromedial frontal

cortex and adjacent anterior cingulate cortex (purple). Adapted from Ray and Price (1993) with permission. (bottom left) Coronal MRI scan showing position of MD thalamus in macaque monkey. (ii) DTI-defined areas of high connection probability with different prefrontal regions in MD thalamus of an individual macaque. The same colour code is used as in part i of the figure. All of the DTI-defined regions resemble those found with tract tracing techniques in the same species with the possible exception of the purple region. This is because the purple region in the DTI study includes more posterior and dorsal the anterior cingulate cortex that are known to be interconnected with a wider swathe of MD thalamus than is the ventromedial frontal cortex alone. Lateral MD regions have been reported to connect with dorsal ACC while more medial MD connects with ventral ACC (Giguere and Goldman-Rakic, 1988). (iii) Axial (top) and coronal (bottom) views of DTI-defined areas of frontal connectivity in human MD (group average). Once again the colours correspond to the same frontal regions and the same basic pattern of connectivity is evident.

8. (a) DTI-based parcellation of human cingulate cortex (group mean image). Nine distinct patterns of connectivity can reliably be detected across subjects and these clusters map to discrete regions of cingulate cortex. Activation recorded in fMRI studies of motor tasks is found in a region corresponding to three of the clusters, 4, 5, and 6. (b) The same clusters, 4, 5, and 6 were found to have a high probability of connection with the premotor cortex and (c) the motor cortex. Adapted from Beckmann et al., (submitted) with permission.

9 (a) According to Brodmann (1909) the parietal cortex in the monkey (left) and human (right) is divided by the intraparietal sulcus (IPS, red arrow) into an inferior parietal lobule (IPL) and a superior parietal lobule (SPL). Area 7 occupies most of IPL in the monkey but the SPL in the human. Areas 39 and 40 occupy the IPL in the human brain but are not found in Brodmann's scheme for the monkey. (b) In the human brain, unlike what is known from track tracing studies in the macaque, DTI tractography estimated a high probability connection path between the superior colliculus and the medial bank of the IPS. A similar region is, however, active when people engage in covert orienting or make eye movements while fMRI data are collected. Despite this difference the human posterior IPL, like the macaque IPL, was found to have a high probability of interconnection with parahippocampal cortex via the inferior longitudinal fascicle (ILF), and the anterior IPL had a high probability of connection with the ventral premotor cortex via the third branch of the superior longitudinal fascicle (SLFIII). (c) In the macaque different parietal regions are distinguished by unique connections that are mediated by distinct white matter fascicles. LIP, posterior IPL, and anterior IPL are connected with the superior colliculus, the parahippocompal gyrus, and the ventral premotor cortex respectively (red, blue, and green respectively, left and centre). DTI tractography suggests an approximately similar relative pattern of connectivity in the human parietal cortex indicating that human IPL and monkey IPL have much in common (right). There are, however, some important differences, and the area with the highest probability of interconnection with the superior colliculus is displaced to a more medial location in the human brain.

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Figure 1

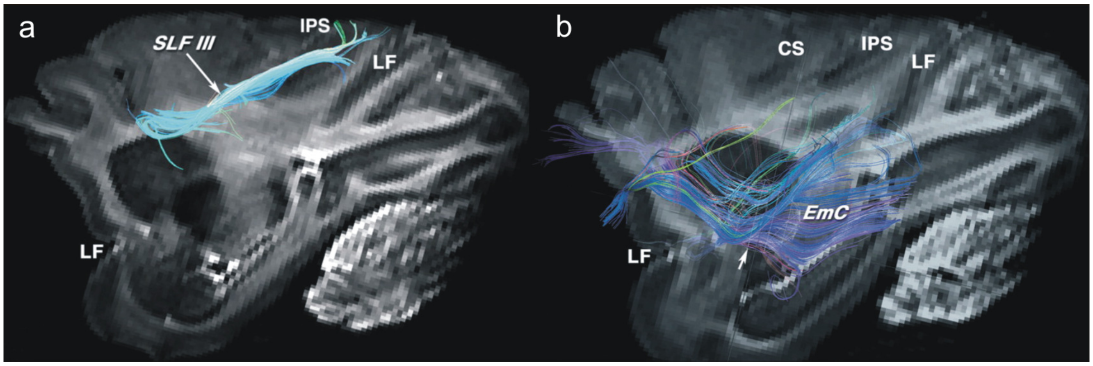


Figure 2

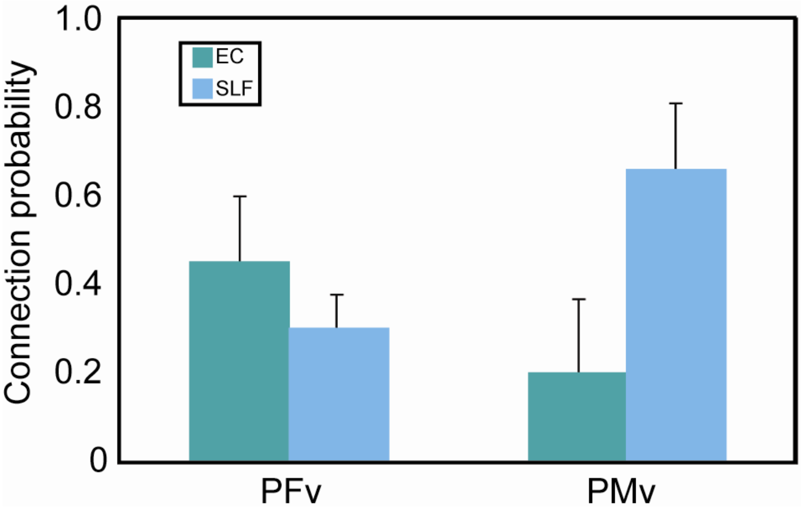


Figure 3

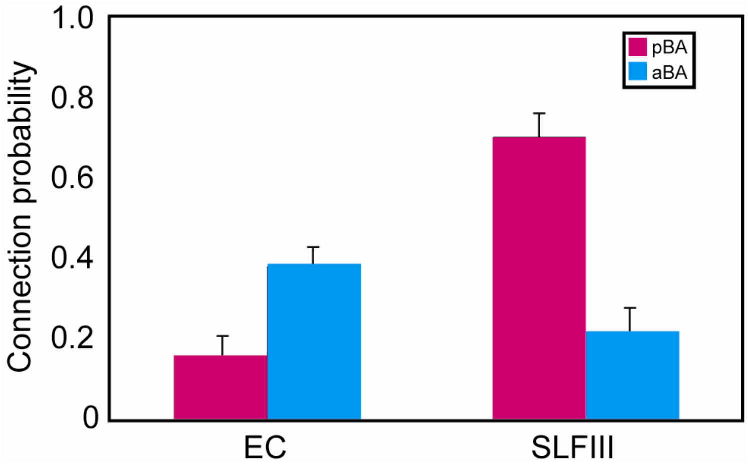


Figure 4

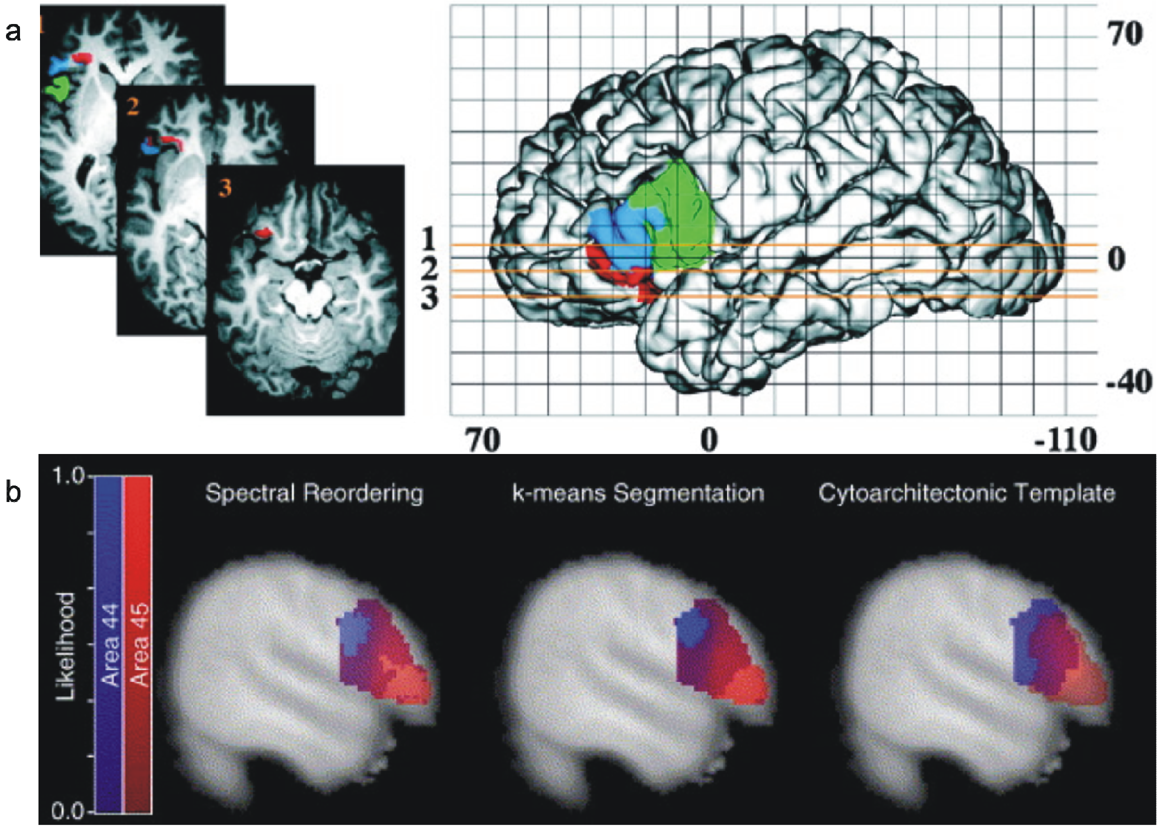

a
1
2
3
1
2
3
70
0
-40
70
0
-110
b
1.0
0.0
Likelihood
Area 44
Area 45
Spectral Reordering
k-means Segmentation
Cytoarchitectonic Template

Figure 5

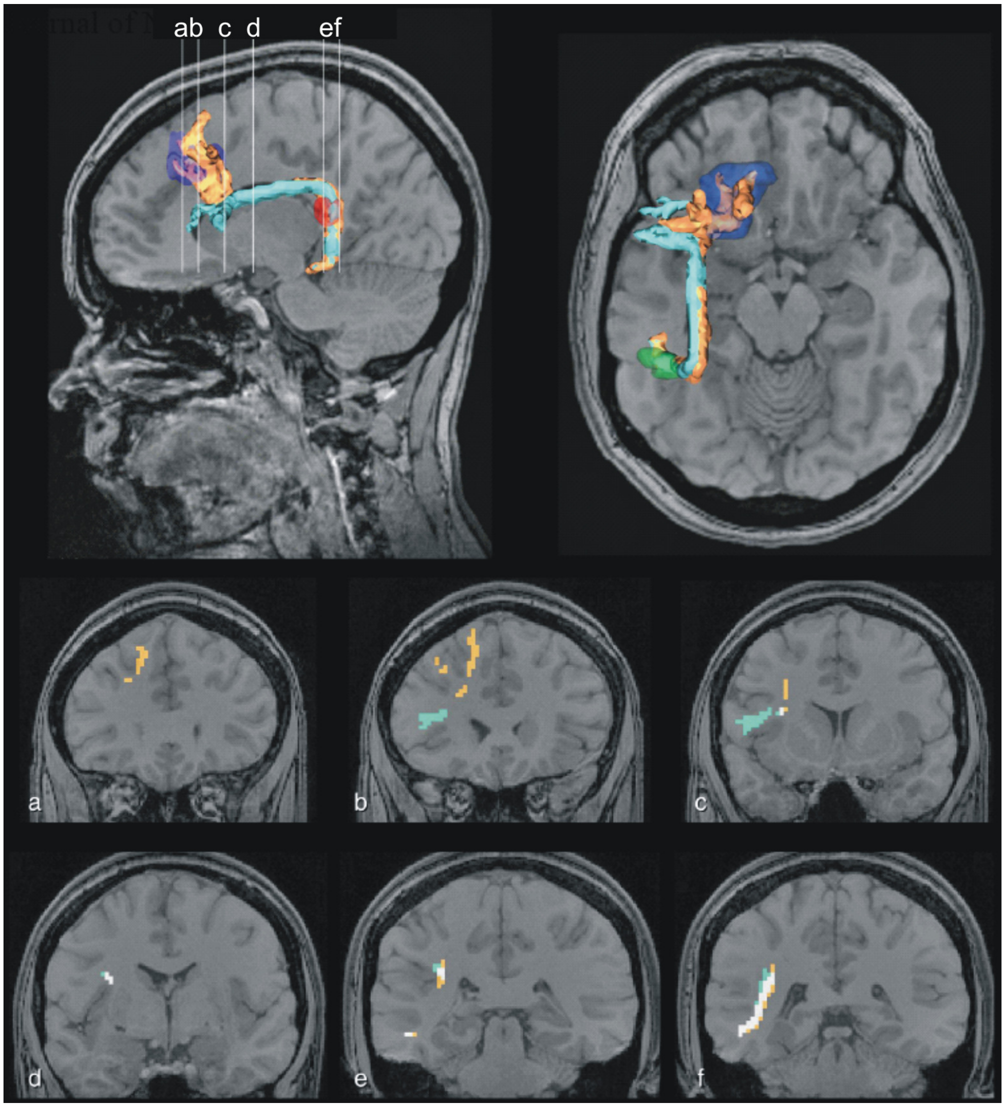
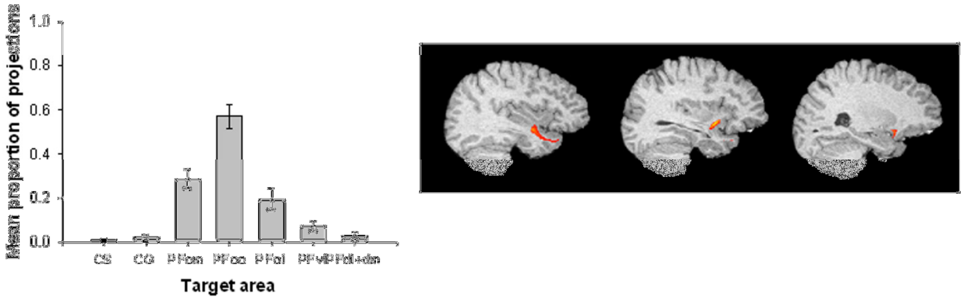
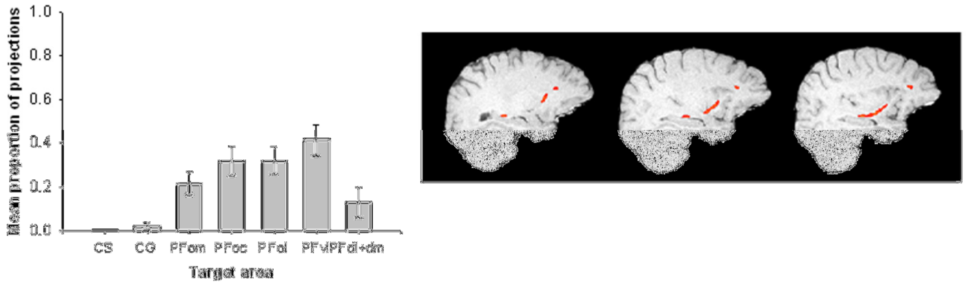


Figure 6

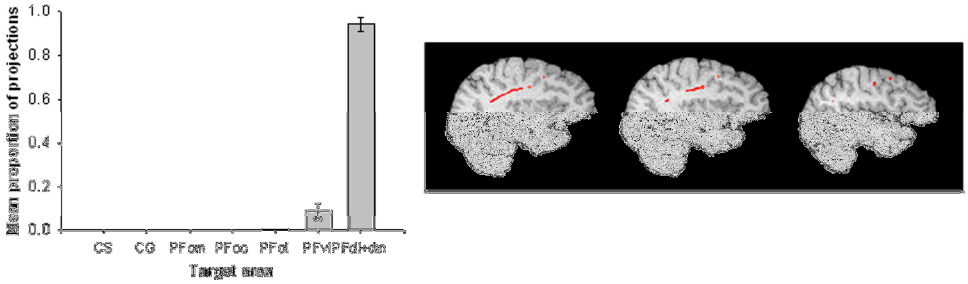
a UF



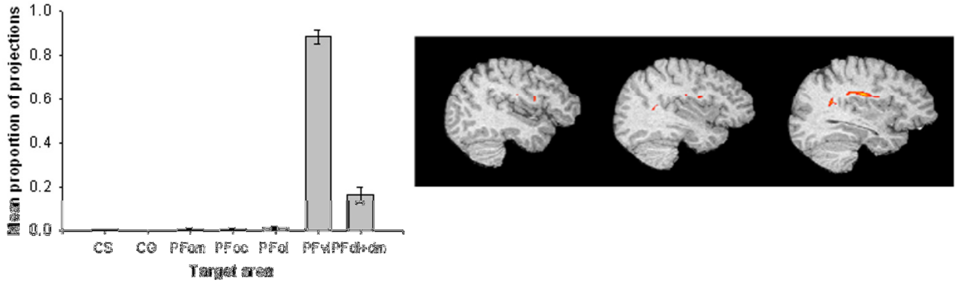
b EC



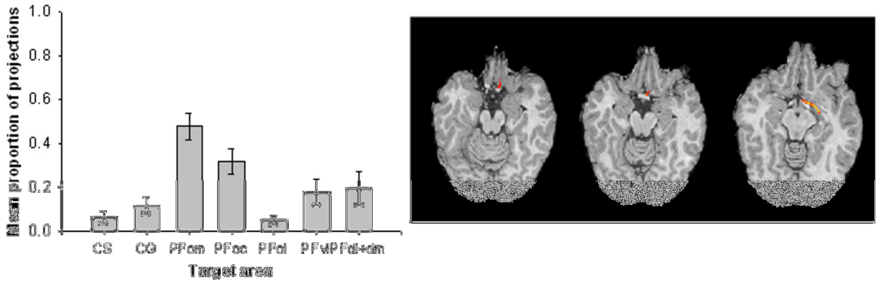
c SLF II



d SLF III



e Amygdala



# Figure 7

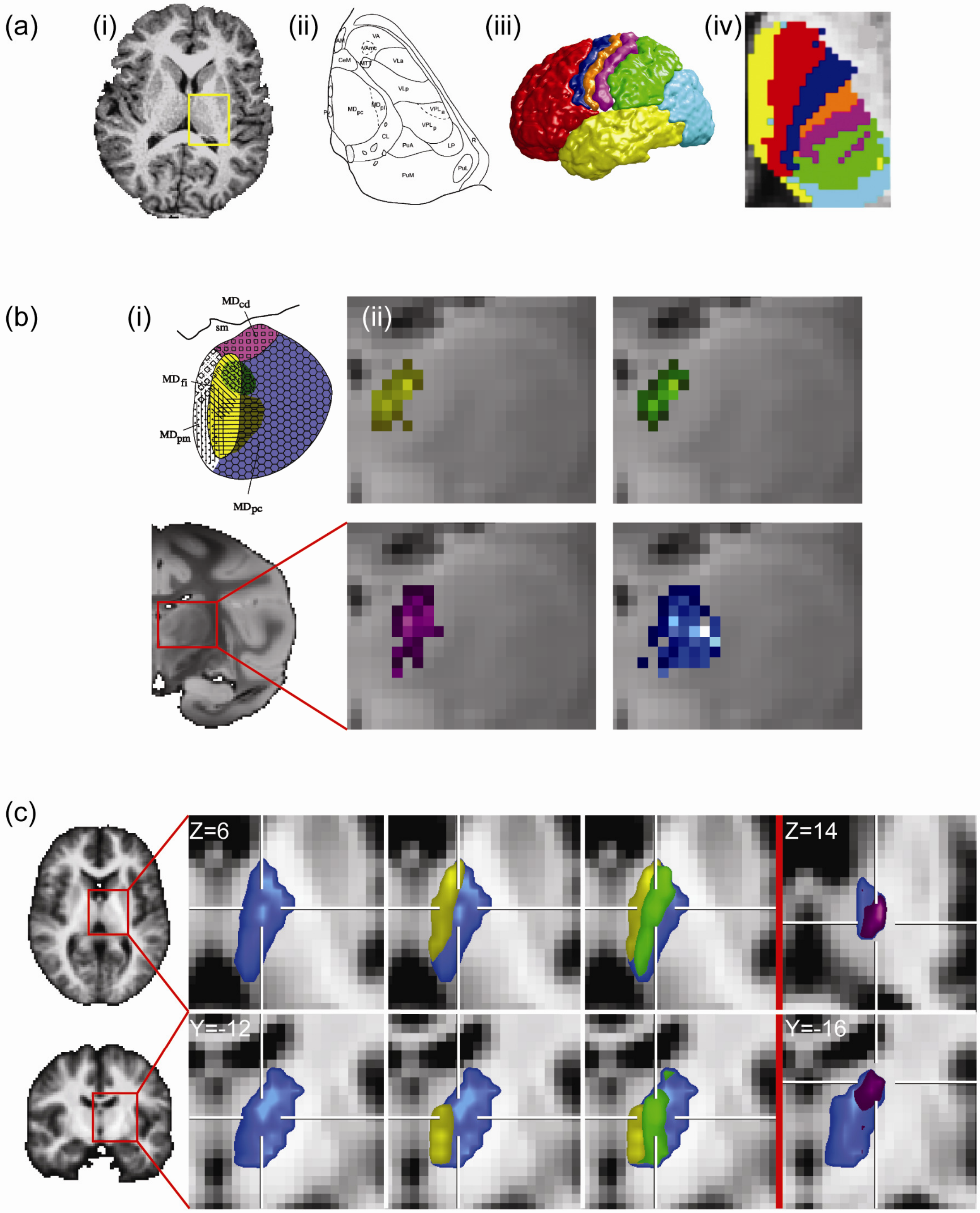

(a)
(i)
(ii)
AM
VA
VAmc
CeM
MTT
VLa
VLp
Pv
MD$_{pc}$
MD$_{pl}$
VPL$_a$
VPL$_p$
CL
PuA
LP
R
PuL
PuM
(iii)
(iv)
(b)
(i)
MD$_{cd}$
sm
MD$_{fi}$
MD$_{pm}$
MD$_{pc}$
(ii)
(c)
Z=6
Z=14
Y=-12
Y=-16

Figure 8

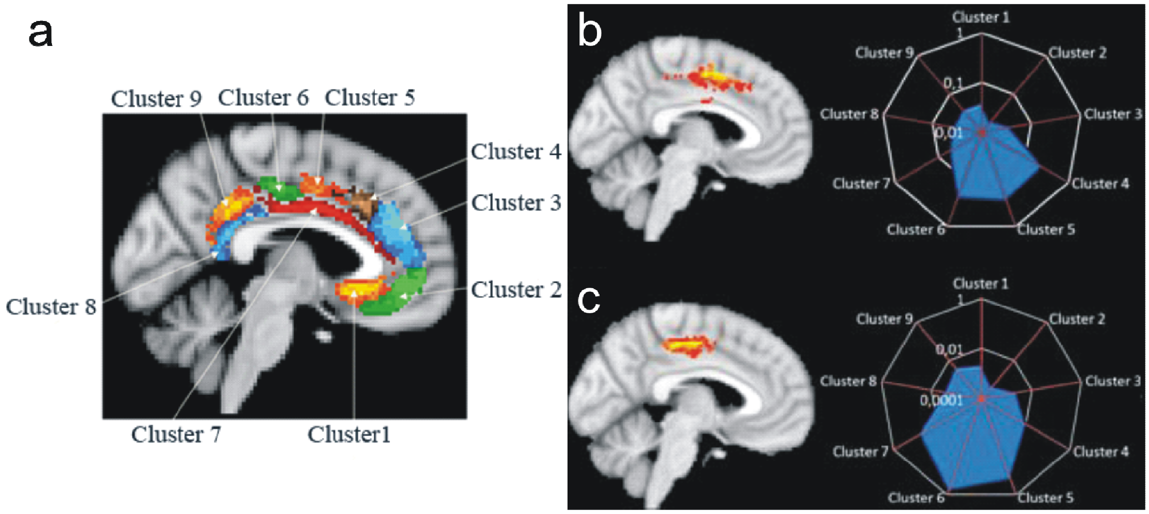
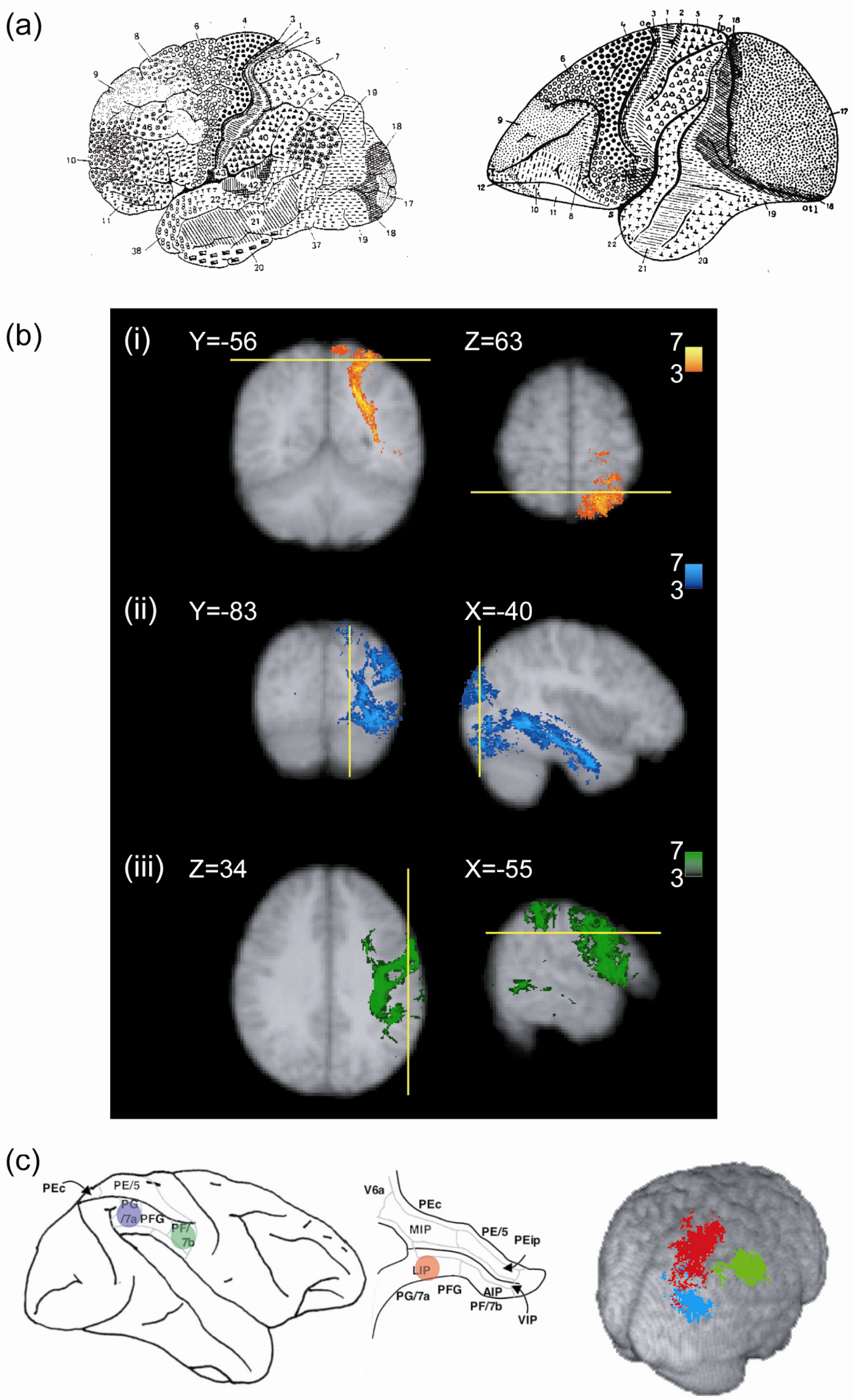

a
Cluster 9
Cluster 6
Cluster 5
Cluster 4
Cluster 3
Cluster 2
Cluster 8
Cluster 7
Cluster1
b
Cluster 1
1
Cluster 2
Cluster 3
Cluster 4
Cluster 5
Cluster 6
Cluster 7
Cluster 8
Cluster 9
0,1
0,01
c
Cluster 1
1
Cluster 2
Cluster 3
Cluster 4
Cluster 5
Cluster 6
Cluster 7
Cluster 8
Cluster 9
0,01
0,0001

Figure 9



(a)
8
6
4
3
1
2
5
7
9
46
10
45
44
40
39
19
18
17
43
42
41
22
21
38
20
37
11
12
(b)
(i) Y=-56
Z=63
7
3
7
3
(ii) Y=-83
X=-40
7
3
(iii) Z=34
X=-55
(c)
PEc
PE/5
PG/7a
PFG
PF/7b
V6a
PEc
MIP
PE/5
PEip
LIP
PG/7a
PFG
AIP
PF/7b
VIP