Chapter 14

Clinical studies of attention and learning

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Introduction

Clinical research and basic science exist and proceed synergistically; experimental manipulations that are developed to tease apart different cognitive and neural circuits within the healthy population become useful tools for quantifying the cognitive and neural basis of impairments within different clinical populations. Conversely, examination of how behaviour changes when specific neural circuits are impaired within those clinical populations feeds back into our understanding of what those circuits contribute to healthy cognition, leading to further refinement of neuroscientific methods and models. Tasks developed in this context also provide useful tools for examining how effective different pharmacological and psychological interventions are, both in cognitive and neural terms. In addition, they provide metrics by which individual differences within clinical populations may be examined, i.e. the mechanisms by which genetic, neural, and psychological factors interact with disease and treatment. This process yields information that has the potential to inform the development of interventions that are more targeted, not just to one disease or another, but also tailored to each individual in terms of their genetic makeup and the likely time-course that various discrete aspects of their disease are likely to follow. Whilst much of this potential is only just being realized, where attention and learning are concerned, clear progress has already been made; in particular, in understanding rule learning deficits and the impact that this has on various clinical populations in terms of poor adaptive behaviour, or 'executive dysfunction'.

Rule learning and the intradimensional/ extradimensional set-shifting task

Humans are remarkably adept at adapting rapidly when environmental conditions change. This behavioural flexibility is commonly described as being

under 'executive control'; that is to say, driven by conscious, wilful decision-making processes that guide the temporal organization of behaviour. There are, however, a number of phenomenologically distinct aspects to executive processing. One of the most important of these is the ability to identify and focus attention on just those types of object or feature that are of the most relevance to the task at hand, with deficits in this ability leading to an inflexible 'attentional set', i.e. the inability to switch the locus of attention away from previously relevant stimulus dimensions (e.g. Owen *et al.*, 1991; Roberts *et al.*, 1988; Dias *et al.*, 1996). Another is the ability to override habitual behaviours when feedback from the environment signals that the desired outcomes are no longer being achieved, with deficits in this ability leading to 'perseveration', i.e. the repetition of sub-optimal behaviours (e.g. Bechara *et al.*, 1994; Anderson *et al.*, 1999). Experimentally, perhaps the most influential tool that has been used to examine these two aspects of executive control is the CANTAB attentional set-shifting task (Roberts *et al.*, 1988) which assesses, at various points during the test, intra- and extra-dimensional set-shifting ability. An 'intra-dimensional shift' (ID) occurs when a participant is required to cease responding to one exemplar of a particular stimulus dimension (e.g. 'blue' from the dimension 'colour') and must begin responding to a new exemplar of that same dimension (e.g. 'red'). An 'extra-dimensional shift' (ED) occurs when a participant is required to switch responding to a novel exemplar of a previously irrelevant dimension (e.g. from 'blue' to 'squares' from the dimension 'shape'). When undertaking the CANTAB attentional set-shifting task, participants are required to select between one of two compound stimuli that are displayed on the screen. The compound stimuli each comprise two dimensions (in the original form of the task, these dimensions were 'stick' figures and solid shapes, although in subsequent versions 'colour', 'number', and 'shape' have also all been used. In the illustrative example below, the dimensions 'colour' and 'shape', which have been used in later versions of the task, will be used for clarity). For example, a participant may have to choose between a red square and a blue circle, but on the next trial the choice may be between a red circle and a blue square. During any given block of the task, there is a 'rule' and the participant has to discover it by a process of trial and error. Each 'rule' relates to just one exemplar of one of the two dimensions (thus, in the above example, 'blue' may be the current rule) and this rule determines which of the two compound stimuli is currently the 'correct' selection (in this case, the blue stimulus, regardless of whether that is a square or a circle). Therefore, at any point during the task, there is both a relevant (e.g. colour) and an irrelevant (e.g. shape) visual dimension. After every response, feedback is given to indicate whether the last selection was correct or incorrect and the participant has to learn to

apply the rule by a process of trial and error. Once the participant reaches a predefined criterion of a certain number of consecutive correct responses, the task moves on to a new block with a new rule. The participant is only made aware of this change of rule when he/she begins to receive negative feedback for making choices according to the previous rule. At the time of the rule change, one of a number of task manipulations may occur. In the simplest case, an entirely new stimulus set is displayed, using the same two familiar dimensions but with different exemplars from those dimensions (e.g. yellow triangles and orange hexagons, to continue the illustrative example above). If the rule defining which dimension is now correct does not change (i.e. it still relates to an exemplar from the previously relevant dimension – colour, in the example above) then this manipulation is termed an intra-dimensional shift. The participant is simply required to learn which of the two new exemplars from the previously relevant dimension is now 'correct'. By contrast, if the new rule relates to the previously irrelevant dimension (shape, in the example above), then the participant must also learn, not only that the rule has changed to a new exemplar, but also that the previously attended dimension (colour) is now no longer relevant. This manipulation is termed an extra-dimensional shift and requires the participant to adapt their entire 'attentional set' by switching the focus of their search away from the previously relevant dimension (colour) and towards the previously irrelevant dimension (shape). In a third type of manipulation, the compound stimuli may not change at all, but the current rule may reverse within the previously relevant dimension (e.g. from blue to red). This manipulation is termed a 'reversal' and the participant is required to stop responding to the previously correct exemplar and to 'reverse' their response to the other exemplar from within the same general dimension. The CANTAB attentional set-shifting task has made a number of important contributions to our understanding of attention and learning through its application in non-human primate studies and through investigations in human patients with frontal-lobe lesions. This research has demonstrated that ED switching and reversal learning are selectively impaired by lesions within the lateral prefrontal cortex (LPFC) and the orbitofrontal cortex (OFC), respectively (Dias *et al.*, 1996; Hornak *et al.*, 2004).

In terms of clinical applications, the IDED task has been a popular marker of executive dysfunction in various patient populations. In particular, the ED stage of the task (which requires a dimensional shift) has proven sensitive to cognitive impairments in schizophrenia (Pantelis *et al.*, 1997), ageing (Robbins *et al.*, 1998), Huntington's disease (Lawrence *et al.*, 1996), obsessive compulsive disorder (Veale *et al.*, 1996), and Parkinson disease (Downes *et al.*, 1989; Owen *et al.*, 1992), to name but a few. As a consequence, this manipulation has

been used extensively, both to assess executive dysfunction per se and to measure pharmacological efficacy in patients and healthy controls.

To some extent, the CANTAB task is limited by its own success, as the many clinical populations that are impaired on the task undoubtedly have quite diverse pathology and it seems unlikely, therefore, that they all suffer from the same basic impairment. In this respect, performance on the task should be considered to be a relatively non-specific marker of executive dysfunction, as it does not generally differentiate between the cognitive and neural circuits that are degraded in these different clinical populations (although for a counter example, see Owen *et al.*, 1993). The reason for this non-specificity becomes clear when the demands placed on the participant during the ED manipulation are considered in detail. The CANTAB attentional set-shifting task only examines the first (novel) ED shift to a previously irrelevant visual dimension (e.g. the first time that you shift from a colour such as 'blue' to a shape such as 'squares'), and this manipulation has multiple discrete cognitive components. For example, because only one dimension (e.g. colour) is relevant during the task *prior* to the ED switch (and therefore, the participant may never even have considered the alternative dimension—e.g. shape—as being a possibility), they must first identify it as being an option at all. Second, the participants must also work out that switching attention across object dimensions may be a relevant operation in the task. This difficulty in dimension identification is exacerbated further, because at the same time, they have to overcome the learning that has occurred during the previous stages of the task indicating that the dimension that they now have to switch to ('shape') was (previously) irrelevant. This type of prior learning, known as 'learned irrelevance', is well documented as biasing an individual's subsequent choices (Mackintosh, 1973). Finally, if the participant fails at this stage by responding continuously to exemplars from the previously rewarded dimension (as is typically the case), then picking an incorrect exemplar after an ED switch will lead to a partial, rather than a total, reward contingency. That is to say, because the stimuli are 'compound' (each made up of an exemplar from the two dimensions), half of the time, the participant's selection will lead incidentally to positive feedback. Thus, if a participant makes selections according to the rule 'blue', when the rule is in fact 'square', half of the time the blue shape that is selected will be a square and will result in a positive feedback. This is in direct contrast to both the ID shift and the reversal manipulation, where selecting an exemplar from the previously relevant dimension will *always* lead to an absolute reward contingency, i.e. only positive feedback (if the correct stimulus is chosen) or only negative feedback (if the incorrect stimulus is chosen). This means that after an ED shift, the participant not only has to process the task feedback correctly,

but they also have to make the more difficult judgement that a switch of attention is required because, depending on their disposition, positive feedback 50% of the time may be considered to be a quite reasonable reward. Given these difficulties of interpretation, it might be better to describe the CANTAB attentional set-shifting test as measuring general problem-solving ability, rather than set-shifting ability in particular. Moreover, whilst this task is sensitive to executive dysfunction across a broad range of clinical populations, the reasons why those populations show a deficit may differ and this may, in turn, relate to the exact pathology—i.e. which neural circuits are degraded and which cognitive processes are consequently impaired.

Notwithstanding these problems of cognitive heterogeneity, the CANTAB attentional set-shifting task is also not an ideal tool for delineating the neural circuits underlying cognitive flexibility on the basis of human neuroimaging data. This is because the task is built around just one instance of an ED switch and just a few instances of reversals. Although it is possible to examine changes in activity using fMRI or PET by comparing different stages of the task, there are too few 'events' to make the results meaningful. This is because the key processes (e.g. shifting attentional set) are likely to be transient and occur at only one point in time when attention is switched from one dimension to another (Konishi *et al.*, 1998; Nagahama *et al.*, 1999; Dove *et al.*, 2000; Cools *et al.*, 2002; Nakahara *et al.*, 2002; Monsell, 2003). For imaging studies, these transient events need to occur multiple times in order to be estimated separately from the noisy background of other task-related events. As an example, consider the comparison between imaging data acquired during the ED and ID blocks of the original task. The ED block will tend to involve more responses (because it is more difficult and takes longer to arrive at the correct solution) and, therefore, more feedback and a larger overall proportion of negative compared with positive feedback. A cross block comparison (ED vs. ID) would be most likely, therefore, to activate circuitry involved in (primarily negative) feedback processing as opposed to that specifically related to the switching of attention between (as compared with within) the different stimulus dimensions.

The behavioural effects of extradimensional switching beyond novelty

We have recently adapted the CANTAB attentional set-shifting task to make it more suitable for use in event-related fMRI studies (Hampshire and Owen, 2006). As a first step, it was necessary to demonstrate that the behavioural costs of ED switching existed beyond the first (novel) instance of a switch. To this

end, an attentional switching experiment was designed based upon the original CANTAB attentional set-shifting task (Roberts *et al.*, 1988), with similar visual dimensions—'stick' figures and solid abstract shapes—but using an extended stimulus set that allowed multiple occurrences of each of the key manipulations. In common with the original task, participants were required to optimize their behaviour by learning the rule that defined which of the two available compound stimuli was correct and the rule always related to just one visual dimension. Participants had to complete as many blocks as they could within the space of 20 min.

When the rule that defined which stimulus was correct switched between exemplars from the same visual dimension (e.g. from one 'stick' to another 'stick'), this was termed an 'intra-dimensional' rule change, whereas when the target switched between exemplars drawn from different visual dimensions (e.g. from a 'stick' to a solid abstract shape), this was termed an 'extra-dimensional' rule change. If the stimulus set *remained the same* between blocks, but the rule changed (e.g. from one 'stick' to another 'stick' or from one 'stick' to an abstract solid shape), this was termed a 'reversal'. If the stimulus set changed between blocks (for either ID or ED rule changes), this was termed a 'shift'. There were, therefore, four types of rule change, intradimensional shifts (ID; stimuli all change, shift required to one stimulus from the previously relevant dimension), intra-dimensional reversals (IDR; stimuli stay the same, shift required to the alternate stimulus from the previously relevant dimension), extra-dimensional shifts (ED; stimuli all change, shift required to one stimulus from the previously irrelevant dimension), and extra-dimensional reversals (EDR; stimuli stay the same, shift required to one stimulus from the previously irrelevant dimension), and these could all be examined, both at the first novel instance, and beyond novelty, when the visual dimensions and task manipulations were all familiar and the participant knew that they were relevant to the task.

The results showed that the ED shift effect was indeed robust beyond the very first shift, such that significantly more errors were made before the rule was derived when the target changed between the two visual dimensions, than when it changed within one visual dimension. A second analysis compared the first novel instances of the four types of rule change to those that occurred subsequently. The results demonstrated a significant effect of novelty, with participants making far more errors during the first occurrences of the four conditions than those subsequently. These findings demonstrate how important it is to consider the issue of novelty in these attentional set-shifting tasks—the first instances of the different task manipulations are behaviourally far more difficult than those required later on because the various visual

dimensions and task manipulations that make up the overarching schema required for optimal performance have to be initially acquired. This is particularly relevant to studies that take repeated measures from the same participant, as is often the case in drug trials. However, the results of this study also demonstrate that the ED effect is robust beyond novelty, confirming that this new variant of the task is likely to be of use for repeated measures designs, as well as fMRI studies.

IDED switching examined with fMRI

A further complexity of the CANTAB attentional set-shifting task design concerns how the experimenter knows exactly when the participant switches their attention between, or within, the two visual dimensions. This ambiguity exists because of the compound nature of the stimuli (e.g. each stimulus is made up of two components and either one of those components can be the reason that the stimulus is selected). Although it is possible to be certain that the participant is selecting one particular exemplar from one dimension after a number of repeated responses, it is not possible to determine which of the two component exemplars was actually the focus of attention (and selection) on the basis of any individual response. Whilst unimportant for behavioural studies, this uncertainty makes it impossible to synchronize the blood oxygenation level-dependent (BOLD) response with the attentional switch events in fMRI studies. The solution to this problem was to swap the two exemplars from which the compound stimulus pairs were composed after each and every response, whilst only giving feedback after every second response. This effectively forces the participants to make two (identical) selections of the same type before deciding to shift or stay on the basis of feedback (which only occurs after the second response). On the basis of these two responses, it is possible to determine exactly which exemplar has been selected (for details, see Hampshire and Owen, 2006). For the fMRI version of the task the visual dimensions were also changed from 'sticks' and abstract solid shapes to faces and buildings. This adaptation allows the posterior brain regions that are involved in processing the different exemplar dimensions to be examined (Kanwisher *et al.*, 1997; Epstein and Kanwisher, 1998) for attentional effects (as it turns out, 'sticks' and abstract solid shapes do not appear to be represented by anatomically distinct posterior regions, at least not at a level that is discernable with current fMRI methods).

Analyses of the behavioural data from 16 healthy young participants who undertook the fMRI task again demonstrated that the ED effect was robust beyond the first (novel) instance of the switch.

An important difference between these results and the original CANTAB attentional set-shifting task was that the fMRI analysis was focused on

discrete events (i.e. individual trials) as opposed to whole task blocks (which comprise many trials). Thus, the design of the task allowed these event types to be defined very specifically according to the current and previous foci of attention.

As in all of these attentional set-shifting tasks, the participant's behaviour varies between periods of trying to solve the current rule (when many mistakes are made) and periods of repeated responding according to the rule in order to reach the criterion for successfully demonstrating that they have acquired the rule successfully (when, typically, no mistakes are made). Once this criterion is reached, the next rule change occurs and the participant again begins trying to derive the new rule. Two types of event were contrasted during the period of time when the current rule was being derived. One was termed 'extra-dimensional' because the focus of attention switched between stimuli of different types (for example, from a face to a building) and the other 'intra-dimensional', because the focus of attention switched between stimuli of the same type (for example, from one face to another face). Whilst each of these events involved multiple switch components (for example, response suppression and attended stimulus change), unlike in the original CANTAB attentional set-shifting task, the only way in which they differed from one another was with respect to the allocation of attention between, or within, visual dimensions. Thus, the comparison of one with the other effectively isolated this extra-dimensional switching component in a way that is entirely impossible with any previous version of this task. This contrast activated a network of brain areas, including a region of the inferior frontal gyrus (IFG) spreading back into the anterior insula bilaterally and the pre-supplementary motor area (preSMA). This result both accords with, and extends, the findings of Dias *et al.* (1996) who reported that lesions of the lateral prefrontal cortex impaired attentional set-shifting in marmosets, whilst undertaking the primate version of the CANTAB attentional set-shifting task.

Two additional events were contrasted from the period immediately after the volunteer had passed the criterion of six consecutive correct responses and the rule changed. One of these events corresponded to the point in time that the stimulus set was changed and the volunteer selected a novel exemplar – effectively removing any response suppression component (because the previously relevant stimulus was no longer present to respond to). The other event was the reversal, modelled as the point in time when the participant first made a new selection within the same stimulus set on the basis of a change in the current rule. Whilst these two events had multiple components, subtraction of reversal minus stimulus set change allowed examination of the reversal aspect of attentional shifting specifically. That is to say, although both events involve a shift of response from one stimulus to another, in only one case did this also

require the inhibition of response to a previously available stimulus (note: although, arguably, these two condition also differ—unavoidably—in that one involves new stimuli and in the other the stimuli remain the same, since two faces and two houses remain present in all cases, the differences observed are unlikely to relate to any basic changes in the perceptual scene). A second quite distinct executive circuit was associated with reversal; this included the anterior portion of the lateral OFC, the posterior extent of the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortices (see Figure 14.1). These results again confirm and extend those of Dias *et al.* (1996) who reported that lesions of the orbitofrontal cortex lead to perseveration (or a failure of 'reversals') in non-human primates.

In addition, comparing neural activity during the reception of positive feedback with that observed during negative feedback identified a positive feedback related change in the medial OFC and the medial frontal wall, in line with previous reports of a role for this region in the processing of rewarding external feedback (Figure 14.1).

Interestingly, the anterior portion of the DLPFC, which has been widely implicated in attentional set-shifting, was active throughout the period of time when the rule was being derived, but this activity did not correlate disproportionately with any individual event type, suggesting that this region may play a more general (i.e. abstract) role in rule acquisition (Figure 14.1).

On the basis of these findings and previous research, we have suggested that at least four distinct neural circuits are active during, and contribute to performance of, this attentional set-shifting task. Thus, a 'ventrolateral frontal-lobe circuit' is centrally involved in disengaging attention from one dimension and refocusing attention on another. A 'medial orbitofrontal circuit' plays a key role in processing reward and presumably guiding responses made on the basis of that reward. A 'dorsolateral frontal-lobe circuit' is involved in problem solving at the most abstract level—perhaps maintaining the dimensions and manipulations that form the overarching task schema. Finally, a 'lateral orbitofrontal circuit' that also includes the posterior extent of the DLPFC and the posterior parietal cortices is crucial for suppressing previously learned but now inappropriate responses, as required by reversals.

The question that arises, therefore, is whether any of these circuits can be delineated in the various clinical populations that have been shown to be impaired at attentional set-shifting tasks, including the original CANTAB attentional set-shifting test. In addition, to what extent can disruption of one or more of these circuits be shown to be responsible for the pattern of deficits observed in any given population of patients? We now consider these questions in the context of recent data from obsessive compulsive disorder, healthy aging and Parkinson disease.

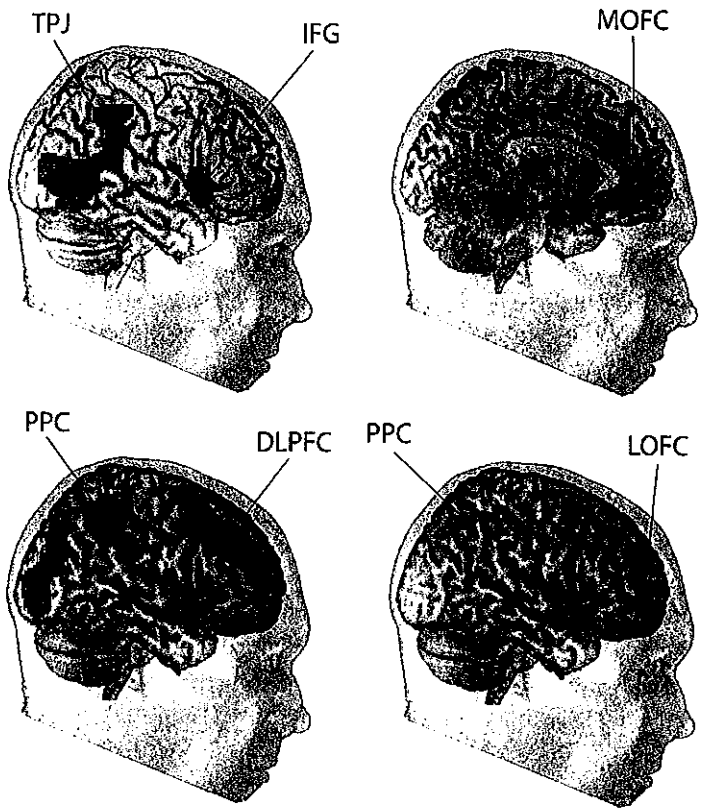

Fig. 14.1 Four cortical circuits that have been functionally dissociated in recent fMRI studies on attention and learning. Top left: activity during target detection in the posterior inferior frontal gyrus (IFG) and in a swathe of cortex centred on the temporal parietal junction (TPJ). Top right: medial orbitofrontal cortex (MOFC) activity during the reception of positive feedback. Bottom left: activity during rule learning. A dorsal network is recruited including the dorsolateral prefrontal cortex (DLPFC) and a swathe of posterior cortex spreading along the dorsal visual stream to the parietal cortex. Bottom right: activity during reversal learning. The lateral orbitofrontal cortex (OFC) posterior parietal cortex (PPC) and a region at the posterior extent of the middle frontal gyrus are all activated at the point of reversal.

The IDED task and obsessive compulsive disorder

Obsessive-compulsive disorder (OCD) is a 'dysexecutive syndrome' that is characterized by repetitive thoughts and behaviours. Previous research has implicated the OFC as being central to OCD (Hollander *et al.* 1996), although the causal relationship between OFC function and OCD is poorly understood. Initial pilot data, in which a group of patients and matched controls undertook

the adapted IDED task described above (Hampshire and Owen, 2006), indicated that OCD patients were disproportionately impaired during reversal learning *beyond novelty*. This result accords well with the findings of the fMRI validation study in healthy volunteers (Hampshire and Owen, 2006), which showed that the lateral OFC was recruited when a reversal was performed. On this basis, it seemed likely that the fMRI task described above would be a suitable tool for investigating the causal relationship between the lateral OFC circuit and the set-shifting deficits that have been reported previously in OCD. This was recently confirmed by Chamberlain *et al.* (2008) who used the task developed by Hampshire and Owen (2006) to demonstrate that not only OCD patients, but also their unaffected first degree relatives have abnormally reduced activation within the lateral OFC circuit during reversal learning.

The implications of this finding are that reduced activity within the lateral OFC circuit can be considered to be an endophenotype (Gottesman and Gould, 2003) of OCD, i.e. a neurological marker of the unknown genetic factors that predispose an individual towards developing OCD. The nature of the OCD deficit also refines our understanding of the contribution made by this circuit, not only to rule learning per se, but to adaptive behaviour in general, i.e. it appears to be the case that hypoactivity within the lateral OFC circuit is associated with a form of cognitive inflexibility that is characterized by repetitive thoughts and behaviours. For future research, activation within the OFC circuit during reversal learning may be a useful clinical marker, both for disease susceptibility and treatment efficacy. An interesting related question is what the difference is between the OCD patients and their first degree relatives that leads to the (behavioural) executive deficit only being expressed in the former group? One clue is evident from the response time data; the first degree relatives were slower to respond during the stage of the task when the rule was being derived compared with both controls and patients, suggesting perhaps that they deliberated more when choosing which response to make. Further research is required, however, to fully elucidate the cognitive and neural basis of the factors which modulate the expression of OCD.

Self-organized attentional switching in (healthy) aging

As people progress from adulthood into old age there are changes throughout the brain at the molecular, cellular, and structural level, with concomitant changes in cognitive ability. The brain undergoes a global decline in terms of thinning of the cerebral cortex (Uylings and de Brabander, 2002; Salat *et al.*, 2005), reduction in grey matter (Good *et al.*, 2001), sulcal depth (Rettmann *et al.*, 2006), increased ventricular volume (Resnick *et al.*, 2000), dysmorphology of neurons, and loss of dendritic spines (Raz and Rodrigue, 2006).

However, not all regions in the brain show similar levels of age-related decline. Studies of the ageing brain have demonstrated that areas of the frontal cortex, along with their associated top down executive control processes, are particularly prone to the neurodegenerative effects of age.

It has previously been demonstrated that, in terms of executive deficits, the largest difference between old and young participants is in their ability to carry out the ED switch stage of the original CANTAB attentional set-shifting task (Robbins *et al.*, 1998). On this basis, it seems likely that switching attention between object dimensions may be one of the most vulnerable aspects of age-related degeneration, manifesting itself as impaired cognitive flexibility in older participants. Furthermore, it seems likely that this cognitive impairment relates to the disproportionate degeneration of frontal-lobe systems. It is not clear, however, which frontal-lobe circuits are responsible for age-related deficits on this task and which of the various cognitive processes that have been shown to be recruited during ED shifting are (relatively speaking) conserved or impaired.

Behaviourally, when the effects of ageing on performance of the fMRI task described above (Hampshire and Owen, 2006), were examined, older participants showed no increase in *perseverative behaviour*, either to the recently rewarded objects (i.e. at the stimulus level) or to the recently relevant visual dimension (i.e. at the dimensional level) (Hampshire *et al.*, 2008b). This fails to confirm previous suggestions that the effects of ageing on attentional set-switching ability reflect a specific deficit in switching attention between dimensions, as indexed by *perseveration* to the previously relevant dimension at the point of shift (Robbins *et al.*, 1998). In line with the observed lack of perseveration in the elderly participants, lateral and medial regions of the orbitofrontal cortex, which have previously been shown to activate during inhibitory control and reward processing, respectively (Hampshire and Owen, 2006), appeared to be functionally intact in the elderly participants.

However, these older participants did show a deficit of a more general kind; specifically, a global loss of efficient problem solving strategy (used while trying to derive the rules) was apparent (as indexed by a disordered search between possible rules) and there was a concomitant decrease of neural activity in the IFG and the preSMA. Interestingly, comparison of ID switches with non-switches also revealed an age-related decrease in this circuit. The dorsolateral prefrontal cortex circuit was also impaired during problem solving.

These results demonstrate that the executive impairment observed within the normal ageing population differs both in behavioural and neural terms to that observed in the OCD group. Such dissociations are not possible using the standard (behavioural) form of this task. The lowered activity within the

IFG-preSMA circuit in the older group was concomitant with a general decrease in efficient strategy during the solution search phase of the task. More specifically, when trying to acquire the rules guiding the shifts, older participants tended to repeatedly check those exemplars that had already been eliminated. This deficit did not reflect a total loss of strategy, however, (that is to say, it did not reflect a complete failure to understand the basic task requirements) as older participants still showed an overall cost of ED switching which would only be evident if the basic task instructions are being followed (as opposed to truly random responding). The IFG has been implicated in attentional control, responding selectively to task relevant and attentionally demanding inputs (Rao *et al.*, 1997; Freedman *et al.*, 2001; Everling *et al.*, 2002; Duncan, 2006; Hampshire *et al.*, 2007; Hampshire *et al.*, 2008a). On the basis of these results, we have proposed, therefore, that the primary age-related deficit in these tasks reflects a failure to bias or 'tune' attentional processing between competing representations in modality-specific posterior regions in order to maintain their relevance to current behavioural goals (Hampshire *et al.* 2008b). Interestingly, in the original CANTAB attentional set-shifting task—where the ED shift only occurs once in the entire test—such a deficit would most likely manifest as an inefficient approach to the identification and elimination of those parameters and dimensions that could be relevant during the forthcoming novel ED shift. This would result in an overall reduction in cognitive flexibility which is indeed what has been observed in that task (Robbins *et al.* 1998).

Rule learning and Parkinson disease

In recent years, increasing emphasis has been placed on the cognitive and behavioural symptoms that often accompany the primary motor deficits in Parkinson's disease (PD). Executive dysfunction is often particularly prominent in early PD (Foltynie *et al.*, 2004; Muslimovic *et al.*, 2005) and has important implications for treatment and quality of life (Aarsland *et al.*, 2000; Schrag *et al.*, 2000). PD patients as a group are impaired on the CANTAB attentional set-shifting task (Downes *et al.*, 1989; Owen *et al.*, 1992) and it has proved to be a useful tool for both characterizing patient deficits and for assessing treatment efficacy (e.g. Lange *et al.*, 1992; Owen *et al.*, 1992; 1993; 1995).

In a recent study, we compared PD patients and age-matched controls while undertaking the fMRI task involving faces and houses described above. Behaviourally, the most notable deficit was in terms of the rate at which the PD patients acquired the task. Specifically, they found it difficult to learn how to approach the task at the most general level, took longer during the training phase outside the scanner and still performed poorly in the first of the two

blocks of the scanning acquisition itself, despite extensive pre-training. In contrast, by the second block of scanning acquisition, the patients and the age-matched controls were performing at the same level. In contrast to previous studies that have suggested a specific ED shifting deficit in PD (e.g. Downes *et al.*, 1989; Owen *et al*, 1993), these results—using a version of the tasks that involves multiple ED and ID shifts—suggest a rather general 'task-level' learning deficit in the PD group. When the fMRI data from the two groups was compared, an abnormal decrease in activity was observed in the patients in the right DLPFC and the anterior cingulate cortex, concomitant with a role for this circuitry in the problem solving processes that are intrinsic to learning any task of this sort.

PD is a heterogeneous disorder, however, with marked variability in individual susceptibility to executive dysfunction (Lewis *et al.*, 2003). The neurological basis of PD lies in dopamine (DA) depletion, and frontostriatal circuits are known to be modulated by levels of DA (Lange *et al.*, 1992; Owen *et al.*, 1995). On this basis, it seems likely that executive deficits, where they are observed, are also caused by abnormal DA levels, a suggestion supported by the observation that dopaminergic medication modulates both executive behaviour and DLPFC function in PD (Lange *et al.*, 1992; Cools *et al.*, 2001). One gene that is likely to account for some of the variability in susceptibility to executive dysfunction in PD is the COMT val^{158}met polymorphism. The COMT gene plays a particularly important role in metabolizing DA within the frontal lobes and the two commonly occurring polymorphisms produce marked differences in frontal-lobe DA levels (Karoum *et al.*, 1994; Gogos *et al.*, 1998; Lewis *et al.*, 2001; Mazei *et al.*, 2002; Chen *et al.*, 2004).

In a recent study (Williams-Gray *et al.* 2008), PD patients in the two COMT val^{158}met homozygous groups were scanned while performing the fMRI attentional set-shifting task described above (Hampshire and Owen, 2006). The behavioural results revealed a novel dissociation between the strategies adopted by the two patient groups. As described above, typically, healthy participants preferentially shift attention within, rather than between, stimulus dimensions, and consequently identify the correct target with fewer errors when an ID shift is required rather than when an ED shift is required. Amongst the PD patients, a similar (i.e. normal) pattern was observed in the val/val homozygote group. However, the met/met homozygote group performed equivalently in terms of number of errors whether an ID or ED shift was required, indicating that they had not formed an attentional 'set' to the previously relevant stimulus dimension, but rather treated each new stage of the task as though it were an entirely independent problem. This alternative strategy, although 'abnormal', was not detrimental in terms of the overall number of errors;

however, it was associated with increased response time when the rule was being derived. Moreover, this poorly formed 'attentional set' in the met/met group was concomitant with under-activation within the dorsolateral frontal cortex and the posterior parietal cortex, regions that have been shown previously to be necessary for rule acquisition.

Finally, examination of the effects of L-Dopa medication revealed an interaction between dose and COMT genotype, both in terms of task performance and BOLD response. Thus, in the val/val group, increasing levels of L-Dopa medication had a detrimental effect on performance by increasing the number of errors made whilst searching for the target stimulus. In contrast, in the met/met group, there was no significant effect of L-Dopa dose on performance. The imaging data revealed similar results; there was a significant interaction between genotype and the relationship between L-Dopa dose and BOLD activation in frontal and parietal areas, such that higher L-Dopa doses had a greater negative impact on activation in val/val than in met/met homozygotes.

This study demonstrates that executive function (and dysfunction) in PD is critically determined by a combination of both genetic and pharmacological influences on dopaminergic levels within the frontal lobes. These data can be accommodated by the well-established hypothesis of an 'inverted U-shaped relationship' between dopamine levels and prefrontal function (e.g. either too little or too much dopamine is bad for prefrontal functioning; for discussion, see Williams-Gray *et al.* 2008). According to this model, in healthy controls, an increasing number of met alleles is associated with improved prefrontal function as predicted by the left-hand side of the inverted U-shaped curve. The findings in PD suggest that they are, conversely, on the right hand side of the curve where an increasing number of met alleles is associated with impaired prefrontal function. It is well known that in the early stages of PD, the prefrontal cortex is in 'hyperdopaminergic state' providing a pathophysiological mechanism for this shift rightwards on this hypothesized inverted U-shaped curve. The inverted U model also suggests that the effect of dopaminergic medication (L-Dopa) will differ according to an individual's pre-existing position on the curve. In line with this, we observed a greater detrimental effect of L-Dopa medication in PD val homozygotes who are expected to be nearer the peak of the curve than in PD methomozygotes who are already near the base of the curve, suggesting a floor effect in the latter group. These findings have important implications for understanding the neurobiological basis of attentional control, and highlights the risk of medication-induced cognitive dysfunction in certain genotypic groups of PD patients, which may ultimately impact on clinical practice.

Conclusions

Using fMRI and a task that can independently measure the effects of various different cognitive demands, it has been possible to functionally define several of the anatomical components which underpin human executive processing (see Figure 14.1). These circuits facilitate different aspects of performance during tests of attention and learning. When differentially degraded, dissociable forms of executive dysfunction are observed, yielding clinically-specific patterns of impairment within different pathological conditions and abnormal BOLD activity. In this way, a number of distinct executive circuits have been delineated including a ventral prefrontal circuit that appears to be involved in disengaging and refocusing attention (e.g. between different stimulus dimensions in an attentional set-shifting task) a DLPFC/posterior parietal circuit that appears to be involved in learning and maintaining the overarching task schema, a lateral OFC circuit, that appears to enable behaviour to adapt when response-outcome contingencies change and a medial OFC circuit that processes reward.

Using this framework, we have begun to dissociate the neural correlates of attention and learning deficits in PD patients, OCD patients, and in the healthy aging population. In the latter case, the findings suggest that a re-evaluation is required regarding the underlying basis of age-related cognitive inflexibility—dimensional perseveration and an associated ED shifting deficit do not provide an adequate explanation for the deficits observed. In the case of OCD, neuroimaging analysis has allowed a 'vulnerability marker' to be identified, for the first time, in first degree relatives. This endophenotype lends insight into the causal relationship between OFC function and OCD pathogenesis and could form a useful neurological marker for the efficacy of pharmacological interventions in this population. Finally, in the case of PD, it has been possible to begin to unravel the complex relationship between activity within the affected executive circuit, inheritable (genetic) factors, and medication—raising the real possibility of generating individually tailored interventions that take each patient's genetic vulnerability to both disease- and drug-related executive dysfunction into account.

Importantly, the results of this clinical work feed back into the basic science by allowing new hypotheses to be generated and tested about how these various cortical circuits—and their pharmacological and genetic influences—operate during healthy cognitive functioning. For example, by studying genetic sub-groups of patients with PD, we have shown that an increasing number of met alleles is detrimental to performance on set-shifting tasks and is associated with impaired prefrontal function (Williams-Gray *et al.* 2008). If, as we have

argued, these results reflect the relative positions of these two sub-groups on the hypothesized inverted U-shaped curve, then a direct prediction that follows about the general population is that healthy met homozygotes will be *better* at attentional set-shifting than healthy val homozygotes (i.e. the exact opposite to the pattern observed in PD). That is to say, because the genetic predisposition of healthy met homozygotes generates more optimal operating levels of dopamine within the prefrontal cortex and because the prefrontal cortex is crucial for set-shifting performance, their baseline performance should be better. Our recent results in healthy volunteers suggest that this is indeed the case (Fallon, Hampshire, Owen *et al.* in preparation). By extension, a hypothesis that remains to be tested is that healthy val homozygotes would benefit more on such tasks from dopaminergic intervention (because they are improving from a lower baseline) than healthy met homozygotes (who would be 'pushed' beyond their point of optimal performance on the inverted U-shaped curve).

In summary, we have tried to illustrate, through example, how the relationship between basic science and clinical research is synergistic—the cognitive and neural circuits that have been defined through studies of attention and learning in the healthy population become tools for understanding how and why performance breaks down in various pathological conditions. In contrast, the impaired performance of well-studied clinical populations with known genetic, pharmacological or neurological disorders can be used to generate and test new hypotheses about how attention and learning are instantiated in the healthy brain, leading to advances in cognitive models, as well as the tools that are developed to test those models.

Abbreviations

ED	Extra-dimensional shift
ID	Intra-dimensional shift
EDR	Extra-dimensional reversal
IDR	Intra-dimensional reversal
PD	Parkinson disease
OCD	Obsessive-compulsive disorder
DA	Dopamine
LPFC	Lateral prefrontal cortex
OFC	Orbitofrontal cortex
MOGC	Medial orbitofrontal cortex
LOFG	Lateral orbitofrontal cortex
TPJ	Temporal parietal junction

PPC	Posterior parietal cortex
preSMA	Pre-supplementary motor area
IFG	Inferior frontal gyrus
DLPFC	Dorsolateral prefrontal cortex
fMRI	Functional magnetic resonance imaging
BOLD	Blood oxygenation level dependent
PET	Positron emission tomography

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