Understanding cognition and action in Parkinson's disease and related neurodegenerative disorders

Contents:

Abbreviations:
BCNI – medical research council Behavioural and Clinical Neuroscience Institute
BDI - Beck Depression inventory
BNF – British National Formulary
BOLD – Blood Oxygen Level Dependent MRI signal (not a blood test)
CBU – Medical Research Council Cognition and Brain Sciences Unit
CRF – Wellcome Trust Clinical Research Facility, Addenbrookes' Hospital
HSB – Herchel-Smith Building (clinical suite)
MRI – magnetic resonance imaging
PD – Parkinson's disease
PIS – patient information sheet
SSRT – Stop signal reaction time task
WBIC – Wolfson Brain Imaging Centre

Research Team:

Professor James B. Rowe (PI, CI and medically qualified), Department of Clinical Neurosciences.

Dr Laura Hughes, Department of Clinical Neurosciences and MRC Cognition and Brain Sciences Unit, University of Cambridge.

Dr Roger A Barker (medically qualified), Department of Clinical Neurosciences and Cambridge Centre for Brain Repair, University of Cambridge.

Prof Trevor W Robbins, Department of Experimental Psychology, University of Cambridge.

Dr Luca Passamonti (medically qualified), Department of Clinical Neurosciences, University of Cambridge

Dr Claire O'Callaghan, Department of Psychiatry, University of Cambridge

Dr Rong Ye, Department of Clinical Neurosciences, University of Cambridge

Dr Negin Holland (medically qualified), Department of Clinical Neurosciences, University of Cambridge

Frank Hezemans, Medical Research Council Cognition and Brain Sciences Unit, University of Cambridge.

General background

Neurodegenerative diseases are major cause of worldwide morbidity and mortality (Griffiths and Rooney, 2006). Parkinson's disease (PD) is a common disorder characterised by dysfunction of the frontal lobes and their connections, reducing quality of life for patients and carers due to motor, cognitive and neuropsychiatric problems (Schrag et al., 2000). PD affects 1.6% of Europeans over 65 years (de Rijk et al., 2000; de Rijk et al., 1997) and is often associated with cognitive impairment or dementia (Williams-Gray et al., 2007a). Unfortunately, treatment options for PD using dopaminergic drugs or deep-brain stimulation emphasise the motor disorder and may leave unchanged or even worsen key cognitive functions (Cools et al., 2001, 2003).

There is therefore an urgent need to understand the non-dopaminergic deficits and non-motor symptoms in PD. It is premature to study the clinical efficacy of many drug or behavioural manipulations in PD. Conversely, advances in molecular biology are remote from an understanding of the complex behavioural problems associated with PD. Our approach is to study the important cognitive, structural and neuro-pharmacological features of PD at intermediate levels called 'endophenotypes'. These endophenotypes include systems dominated by a handful of neurochemical modulators (blue) linked to a set of core cognitive systems (yellow). They characterise cognitive and behavioural patterns in PD that result from cell loss in frontal cortico-subcortical circuits (Alexander et al., 1990) and loss of neuromodulatory projections from the brainstem to cortex and striatum. These include noradrenaline NA, serotonin (5HT) and acetylcholine (ACh) as well as dopamine (DA).

The cognitive endophenotypes of PD and FTD have features in common with frontal lobe injury (Owen et al., 1992; Robbins et al., 1994) affecting attentional control (working memory, planning and rule-switching) and reward based behaviours. In PD, the cognitive deficits depend on an interaction between the task, disease severity, genotype and treatment (Foltynie et al., 2004; Rowe et al., 2008c; Williams-Gray et al., 2008; Williams-Gray et al., 2007b). Depending on medication, PD patients are impaired at planning, switching from one task to another, risk taking paradigms, gambling and inhibition (Cools et al., 2001, 2003; Foltynie et al., 2004; Owen et al., 1990; Rowe et al., 2008c; Swainson et al., 2000; Voon and Fox, 2007).

In health, correct actions are made or inhibited according to contexts (rule)

and goals (reward). There is a complex relationship between actions, rules, and goals in the brain. Whereas reward representation is associated with orbitomedial frontal cortex, anterior cingulate and ventral striatum (Bechara et al., 1998; O'Doherty et al., 2001; Shidara and Richmond, 2002), cognitive 'rule' functions are often associated with lateral prefrontal cortex (Aron et al., 2004a; Manes et al., 2002; Sakai and Passingham, 2003). We have recently shown how these lateral and ventromedial systems can interact, and how action- and rule-selection processes overlap (Rowe et al., 2008b; Rowe et al., 2008c).

The 'motor system' is also affected directly by musical rhythms, even in the absence of movement (Grahn and Rowe, 2009). This raises the possibility of rhythmic facilitation of the motor systems, at least in some individuals. Trained musicians for example have enhanced activation and connectivity in the motor system in response to passive listening to rhythms (Grahn and Rowe, 2009).

The impact of PD on these cognitive and motor processes is less well understood. Using the framework of endophenotypes we will study the cognitive and behavioural control in PD. Focussing on the selection and inhibition of rules and actions. Serotonergic, noradrenergic and cholinergic modualtions will be studied with functional magnetic resonance imaging (fMRI). With this neuroimaging one gains sensitivity to the effects of disease and interventions together with insight into the neural mechanism of disease and pharmacological probes. Neuroimaging is therefore a useful supplement to behavioural studies, to understand both the heterogeneity of disease and the functional anatomy or neurocognitive mechanism of drugs.

Note on v3

Several studies have now been successfully conducted under early versions of this ethics protocol. The results confirm that in Parkinson's disease, functional brain systems show enhanced activity and connectivity in response to drugs that modulate the serotonergic and noradrenergic systems (Borchert et al., 2016; Kehagia et al., 2014; Ye et al., 2014a, b). This enhanced prefrontal function after serotonergic and noradrenergic drugs was associated with behavioural improvements in response inhibition. These studies are further supported by recent work in healthy people confirming that noradrenergic drugs influence the organisation of large-scale brain networks (van den Brink et al., 2016). Together, these results provide initial evidence that prefrontal networks are responsive to serotonergic and noradrenergic drugs, and that these effects can improve motor control and behaviour in Parkinson's disease.

However, further work is now needed to establish what other processes may be improved by these drugs in Parkinson's disease and related disorders. In particular, it has become clear that the "Parkinson's plus" syndrome called Progressive supranucelar palsy (PSP) has even more severe – and early – loss of noradrenaline than Parkinson's disease, together with cognitive deficits in domains that are linked to noradrenaline. This v3 therefore includes additional studies of PSP, and modifications of the PSP studies proposed in the earlier versions of the protocol.

Finally, as we aim to provide a more detailed understanding of these behavioural symptoms, under v3 we will also include a measure of the possible burden or stress that these symptoms may place on caregivers. Anecdotally, our studies to date have suggested that when people with Parkinson's and related disorders exhibit high levels of impulsivity or reduced motivation, this can contribute to caregiver burden or stress. Under v3 we will include a validated questionnaire (the Zarit Burden Inventory) to assess possible caregiver burden, allowing us to quantify the broader impact of these symptoms. (Please see Page 32 for a copy of the questionnaire).

No clinical trials are included in this protocol.
It is possible that these studies will support or motivate future clinical trials in PD. However, these studies use either no pharmacological intervention, or selective agents intended to probe serotonergic, noradrenergic and cholinergic cognitive systems in the context of PD and related disorders.

Our principal outcome measures are the neurocognitive architectures of action and behavioural control. We do not expect that these studies will produce clinically significant outcome effects from the single dose regimes, nor symptomatic benefits in patients at the doses/regimens used. Our primary outcome measures do not include clinical assessment scales, or patient based symptom ratings.

From the MHRA clinical trials algorithm and MHRA mock examples, these studies are not clinical trials. Also, in line with the precedent of local studies using MRI and behaviour to study citalopram and atomoxetine in PD and other neuropsychiatric disorders, these are not clinical trials. Confirmation will be sought from the MHRA that these studies are not clinical trials, but their judgement on a preliminary protocol for the atomoxetine studies was that it was not a clinical trial.

Related protocols

This study includes populations, tasks and imaging procedures and psychopharmacological interventions that have also been included in separate recent or current research protocols underway in Cambridge. The particular synthesis of these factors is novel, requiring new and coordinated research protocol and study documentation. Comments, questions and suggestions of the REC prior to a favourable opinion on these other protocols and their documentation have been considered in drawing up the present protocol and documentation.

Participation in this study is not contingent on participation in any of these other studies. The related protocols include:

06/Q0102/96 Functional magnetic resonance imaging (fMRI) brain scanning of response selection in Parkinson's disease

09/H0302/84 An investigation of the cognitive effects of atomoxetine in Parkinson's disease

07/H0308/191 Neurochemical modulation of cognitive biases: A behavioural study of the effect of acute atomoxetine vs. citalopram on contextual and affective biases in cognition .

07/Q0102/3 Diagnosis and prognosis markers in Progressive Supranuclear Palsy (PSP), Corticobasal degeneration (CBD) and Frontotemporal degeneration (FTD)

However, individual participation in this study is not dependent on these other studies, and the study team would liaise with the managing clinical team to prevent any burden that might otherwise arise from invitation to take part in multiple studies.

Study specific background

Behavioural control: inhibiting actions.

We are often required to inhibit responses. We can restrain an action before it is made e.g. when traffic lights go green we don't drive if there are still children crossing. This inhibition of an action before it is made ('restraint') is characteristic of the Go-No-go paradigm. Alternatively we might 'cancel' an action after it is initiated e.g. if a child runs across the crossing after we have initiated driving. This 'cancellation' forms the basis of the 'stop signal reaction time task (the time needed to stop on 50% of trials is known as the 'stop signal reaction time', SSRT).

These two forms of response inhibition are anatomically and neurochemically distinct across many species (Eagle et al., 2008; Robbins, 2007). Essentially, No-go inhibition is modulated by serotonin while the SSRT is modulated by noradrenaline. The inferior frontal cortex is activated in association with both forms of inhibition and lesions here or in its basal ganglia connections impair response inhibition (Aron et al., 2004b; Rieger et al., 2003). Noradrenaline modulates action cancellation in humans. Recent work has shown that atomoxetine may exert its effects by increasing neural gain, which is the capacity for brain systems to optimise their processing to support cognition and motor behaviour (Warren et al., 2016). Changes in neural gain mediate response urgency during motor behaviour, by influencing the threshold for when an action is initiated (Murphy et al., 2016). These results suggest that modulation of neural gain is a mechanism that might support action cancellation, and that this can be modified by atomoxetine.

The noradrenergic reuptake inhibitor atomoxetine increases noradrenergic neurotransmission in healthy volunteers and improves response cancellation (SSRT) without affecting sustained attention or working memory (Chamberlain et al., 2006). Serotonin also modulates action restraint behaviour and activation. For example, acute tryptophan depletion (ATD) may reduce No-go activation in inferior frontal cortex (Rubia et al., 2005) while the selective serotonin uptake inhibitor (SSRI) Citalopram may enhance it (Del-Ben et al., 2005). The effects of serotonergic modulations depend on individual differences in trait serotonergic function (figure 1), which is reduced in PD.

Response inhibition has received little attention in PD, perhaps because of the coexistence of bradykinesia. However impulsivity can occur even in bradykinetic PD patients (Frank et al., 2007; Rowe et al., 2008c) and is not affected by dopaminergic therapies (Inase et al., 1997; Overtoom et al., 2003; Rowe et al., 2008c). Poor inhibitory control in PD may instead result from depletions of noradrenaline and serotonin: at post mortem, PD patients have 60-80% loss of NA in frontal cortex and 40-60 % loss of serotonin (Scatton et al., 1983). Poor response inhibition may be particularly harmful if coupled with abnormal reward-motivated behaviours including gambling, which can be exacerbated by available dopaminergic therapies (Molina et al., 2000; Voon et al., 2006).

Moreover, PSP causes an even more severe loss of noradrenaline, from early degeneration of the locus coeruleus (Williams et al., 2007). PSP is also associated with executive function cognitive deficits, inflexible thinking and impulsivity. We propose that these cognitive and behavioural changes may reflect reversible loss of noradrenaline.

Cognitive control: changing and inhibiting rules.

Normal behaviour depends on the context or 'rules' which relate actions to outcome or reward. Some rules are very stable e.g. it is all right to undress in private but not in

public. Other rules are transient or arbitrary e.g. a driving instruction to turn left at the next traffic lights. Cognitive flexibility is essential to change from one rule to another in an environment with changing reward contingencies and unpredictable outcomes.

The prefrontal cortex is closely associated with rule processes (Sakai, 2008). We have studied how healthy individuals and those with PD or frontal brain injury are able to choose, maintain or make transitions between rules (Rowe et al., 2008b; Rowe et al., 2008c; Rowe et al., 2007)]. The effects of neurological disease are sometimes only manifested as changes in network connectivity in fMRI data (Rowe et al., 2007). Such analyses of connectivity are therefore included in the current proposal. Moreover, the selection of rules is associated with the same pattern of neural responses as the selection of actions themselves (Rowe et al., 2008a). Changing and inhibiting rules may also have anatomical and neurochemical similarities with inhibiting actions.

Cognitive rules may change in different ways. Subjects may change from a rule based on one dimension of stimuli (e.g. shapes) to a rule based on a different dimension (e.g. lines: an extradimensional shift, EDS). EDS is abnormal in PD and frontal brain injury (Lange et al., 1992; Owen et al., 1993; Owen et al., 1991), and modulated by noradrenergic projections to cortex (Lapiz and Morilak, 2006; McGaughy et al., 2008; Mehta et al., 2004). Interestingly, the relatively preserved noradrenergic function in frontotemporal dementia (Yang and Schmitt, 2001) may explain why these patients are not impaired on EDS nor improved by methylphenidate (Rahman et al., 2006; Rahman et al., 1999). Alternatively, one can reverse a rule and learn to make the opposite response to a stimulus. Reversal is typically indicated by negative feedback (punishment) to a previously correct (rewarded) response. Reversal learning requires inhibition of the old rule. It is impaired with frontal cortical lesions, PD and bv-FTD (Daum et al., 1991; Hornak et al., 2004; Lange et al., 1992; Owen et al., 1993; Owen et al., 1991; Rahman et al., 2006; Rahman et al., 1999). Unlike EDS, reversal learning is most associated with serotonergic and cholinergic systems: in monkeys, serotonin depletion from PFC impairs reversal learning but not EDS (Clarke et al., 2004; Clarke et al., 2005) while acute tryptophan depletion impairs human reversal learning (Evers et al., 2005; Murphy et al., 2002).

Rule inhibition and EDS can be studied using compound visual discriminations. The Hampshire paradigm (Hampshire and Owen, 2006) includes the type of reversal learning and EDS that has successfully been studied during fMRI and PD patients ‘on’ and ‘off’ dopaminergic therapy (Cools et al., 2007; Swainson et al., 2000). fMRI reveals separate systems for reversal and EDS (Hampshire and Owen, 2006). In brief, subjects view two side-by-side images of overlapping faces and houses, and choose one of them according to the current ‘rule’, or explore the different possibilities if they have no rule in mind. After each pair of trials they get positive or negative feedback. I have recently studied a different rule task (Rowe et al., 2008c) that required subjects to shift between opposite rules. This was associated with focal activation of the left inferior frontal gyrus. However, there was no effect of PD or dopaminergic therapy, suggesting that it was not dependent on dopaminergic neurotransmission (figure 4). This begs the question of whether serotonergic modulation instead influences reversal learning and rule inhibition in PD. Early studies suggested that escitalopram does not improve reversal learning in healthy individuals (Wingen et al., 2007). However, both this study relied on behavioural measures and evaluated small groups. Larger groups are required including neurophysiological indices of the response to citalopram.

The reversal of cognitive set is also influenced by cholinergic projections to frontal cortex. In animal models depletion of prefrontal cortical acetylcholine impairs serial reversals (Cabrera et al., 2006; Roberts et al., 1992). In humans, cholinesterase

inhibitors like rivastigmine enhance cortical cholinergic transmission and are often used in Alzheimer's disease and Parkinson's Disease Dementia. However, the frequent executive dysfunction on non-demented patients must be distinguished from later Parkinson's Disease Dementia (Williams-Gray et al., 2007a). In the context of non-demented patients with PD, we would therefore like to also study the neurocognitive mechanisms of reversal (set inhibition) with and without facilitation of cholinergic neurotransmission.

Neglecting and Selecting rules.

Luria (1966) observed that patients with frontal lobe injury could describe what they were supposed to do yet make no attempt to do it. This type of "rule neglect" has been noted in some normal individuals, and results from a failure to construct a task model from known rules, facts and experience (Duncan et al., 2008). It confounds many tests of executive function (Duncan et al., 1996; Duncan et al., 1997). It has been suggested that goal neglect is a feature of the executive dysfunction in PD (Owen et al., 1992; Owen et al., 1993) contributing to the deficits in switching between cognitive tasks in complex paradigms (Cools et al., 2003; Downes et al., 1989; Owen et al., 1993). The presence of goal neglect in PD would have important implications for re-interpreting rule-switching deficits in PD and would open new possibilities for non-drug therapy such as 'goal management training' (Levine et al., 2007). Neglecting rules has an impact on behaviour. It means that the wrong responses are chosen even when the subject "knows" the simple way in which to choose the right action (Duncan et al., 1996; Duncan et al., 2008). When performing a simple task in the context of many rules, errors are higher and reaction times longer than if that task had be modelled alone. The behavioural cost of rule neglect, is proportional to activity in prefrontal cortex and intraparietal sulcus (Dunmontheil et al., 2008). The scale of rule neglect in neurodegenerative disease is not known.

In the previous studies of the inhibition and neglect of rules, there have been defined correct rules. However, frontal lobes have also been implicated in action selection when there is no defined rule (Norman and Shallice, 1980) through the action of a 'supervisory attentional system'. Free selection of actions, colours, objects or rules are all associated with activation of prefrontal cortex (Fahn et al., 1987; Forstmann et al., 2008; Frith et al., 1991; Rowe et al., 2002; Rowe et al., 2006; Rowe et al., 2004; Wiese et al., 2005). Critical to these paradigms, there is no specified correct response or feedback. Nonetheless, behavioural analyses indicate a structured pattern of responses i.e. non- randomness. Healthy subjects tend to inhibit repetitions of the same actions (Baddeley et al., 1998). PD patients in the 'off' state show less non-randomness: when treated effectively with dopaminergic medication these patients' responses become non-random again but now they have excess repetitions, the opposite of healthy subjects. The medication has driven the patients even further from normality on this simple test of voluntary action. The degree of non-randomness is determined in part by the prefrontal cortex in healthy subjects (Jahanshahi et al., 2000).

Baddeley suggested that response selection depended in part on working memory in the central executive (Baddeley et al., 1998). However, an alternative explanation is that subjects impose transient pragmatic rules to determine their actions, consistent with the hypothesis that prefrontal cortex is essential for rules based behaviours (Mansouri et al., 2007). Stable rule representations will enable a subject to 'exploit' a response strategy, whereas unstable rules will lead to 'exploration' of new responses, in the absence of external evidence of the need to change. A critical role for dopamine in stabilising neuronal activity has been proposed before in the context of working memory, PD and schizophrenia (Cohen et al., 2002;

Cools, 2006; Durstewitz et al., 1999) and suggested by preliminary work in my group (figure 5c). However, before making premature inferences about the role of dopamine or other neurotransmitter systems, one must understand better the way in which implicit rules may influence seemingly voluntary actions. This will be addressed in the proposed program of investigations.

Action and rhythm in PD

The studies above have focussed on voluntary actions. We are also interested in automatic activations of the motor system, and the role of the 'motor system' for non-motor functions. These are relevant to PD. Perception of certain regularities (a beat, or pulse) in auditory sequences produces robust activation and greater coherence within motor systems (Grahn & Brett, 2007; Grahn & Rowe, 2009). Interestingly, auditory sequences can also affect gait kinematics in some patients with neurological motor disorders (Molinari et al., 2003; Thaut et al., 2001), but the underlying neurobiological mechanism is unknown. In Parkinson's disease, steady auditory beat presentation can ameliorate freezing, asymmetry, lack of fluidity, and other aspects of gait and speech production disorders in certain neurological patient populations (Bernatzky et al., 2004; Thaut et al., 2001). However, it is unknown whether all Parkinson's disease patients respond to a steady beat, and what the important characteristics of the auditory sequences are. In addition, no one to our knowledge has assessed the affects that auditory sequences may have on non-motor functions. We propose to assess the effects of a variety of auditory stimuli (from simple rhythms to musical excerpts) on simple cognitive and motor tests in Parkinson's disease patients. In addition, fMRI will be used to characterize the motor network response to these sequences in Parkinson's patients and healthy controls, to clarify how any benefits of auditory sequence listening may be neurally mediated.

The role of noradrenaline in Parkinson's disease and PSP (v3)

The underlying causes of cognitive and personality changes, including impulsivity, in Parkinson's disease and PSP are likely to be multi-factorial. However, there is converging evidence that alterations in the noradrenergic system may play a fundamental role in determining cognitive and behavioural symptoms.

In animal models and in patients with Parkinson's disease (Borchert et al., 2016; Kehagia et al., 2014; Ye et al., 2015, 2016) there is evidence that changes in noradrenaline transmission mediate impulsivity, decision making and response control, and that these abilities can be improved by medications enhancing noradrenaline (i.e., atomoxetine). We therefore believe that the noradrenergic system is an attractive target for effective treatment of impulsivity and other cognitive changes in both Parkinson's disease and PSP. This is further supported by evidence that PSP leads to early loss of neurons in the locus coeruleus, the major source of noradrenergic inputs to the forebrain (Williams et al., 2007).

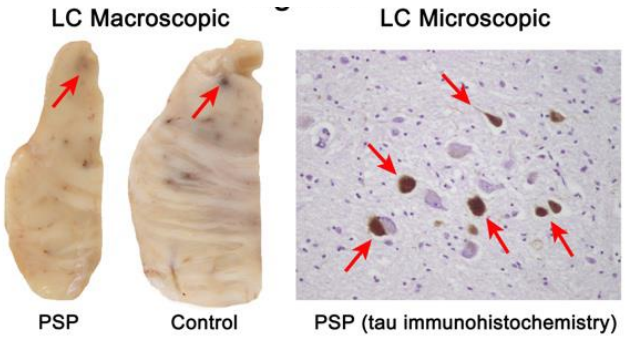

Figure. Left panel. *At the macroscopic post mortem examination, a PSP patient show a paler locus coeruleus (LC) (red arrows) reflecting reduced intracellular neuromelanin.* ***Right panel.*** *We have also evidence that tau pathology (red arrows) is present in the LC in PSP. Together this data support the notion that the noradrenergic system is impaired in PSP and may be a key target for noradrenergic therapy.*

Experimental protocol:

General procedures: recruitment, power, randomisation, imaging

Several linked experiments are proposed, using functional neuroimaging to study the selection and inhibition of actions and rules, in the context of neurodegenerative disease. Some use pharmacological interventions with citalopram, atomoxetine, rivastigmine or placebo, with MRI-based neurophysiological outcome measures. Neuroimaging methods focus on (1) analysis of regional activations and (2) the coupling within hypothesis driven structural models of brain networks. The specific hypotheses tested in each experiment derive directly from the previous discussion of the neurobiology of response and rule inhibition.

Recruitment. Patients with Parkinson's disease (UK PD Brain bank diagnostic criteria) will be recruited via the very large PD Research Clinic at the University Centre for Brain Repair, lead by collaborator Professor Roger Barker. PD patients will be Hoehn and Yahr stage 1.5 – 3 with known medication, stage, and prior cognitive performance (MMSE>25/30, TOL, fluency) with no dementia and be English speaking. If known, genotype for common modulatory polymorphisms will also be recorded for post-hoc comparisons (COMT, BDNF, SERT). Healthy controls subjects will be recruited initially from the PD research database and the MRC-CBU volunteer panel. The Cambridge BioResource managers may be approached for future healthy controls if separate ongoing studies indicate a need for genotypic matching of patients to controls, in terms of common polymorphisms. Racial background will not be used for inclusion or exclusion criteria.

Patients with PSP will be recruited from the specialist clinic for PSP and related disorders at Cambridge, led by Prof James Rowe, according to international consensus diagnostic criteria (Höglinger et al., 2017).

Participant age will be between 45 and 80 years old. The age cut off at 80 years is precautionary on two fronts. (1) the risk of side effects in pharmacological studies may increase with advanced age, and (2) the risk of latent cerebrovascular disease or severe atrophy alongside Parkinson's disease increases with advanced age. The proposed threshold at 80 years is a compromise that should allow our sample to be representative of the general Parkinson's disease population, while at the same time reducing the frequency of significant latent comorbidities.

Inclusion criteria summary:
Idiopathic Parkinson's disease, PSP, CBS or healthy control
Spouse, relative or close friend who identifies as a caregiver to the study participant
PD: Hoehn and Yahr stage 1.5-3; PSP: Golbe stage 1-5.
Age 45-80 for patients and controls (no age restriction for caregivers)
English speaking
Right handed

Exclusion criteria summary:
Lack of mental capacity
Clinically significant current depression
Contraindications to MRI as per 3T or 7T protocols
Distressing reaction to l-dopa withdrawal (for withdrawal study only)
Contraindication to pharmacological challenges:
Ischemic heart disease or cardiac rhythm abnormalities,
other significant non-ischemic cardiac disease,

uncontrolled hypertension,
adverse drug reactions to proposed drugs or closely related drugs,
major psychiatric disorders including mania or schizophrenia
recent or current asthma or COPD (rivastigmine only)
recent or current gastric or duodenal ulceration (rivastigmine only)
epilepsy
warfarin/monoamine oxidase inhibitor (citalopram-atomoxetine study)
known hepatic or renal failure (moderate or severe)

Design and randomisation. The non-pharmacological studies are repeated measures designs (within group) suitable for general linear modelling (ANOVA based t- and F- tests), with normative data from healthy controls, also suitable for general linear modelling of contrasts with patients. Drug withdrawal studies will be cross over studies. The pharmacological studies of PD patients will be crossover studies. Each patient will be studied on 2 or 3 days, and receive both placebo and drug(s).

The order of drug/placebo administration will be randomly permuted within blocks of 6, in order of recruitment. We have chosen random permutation, not serial randomisation, to ensure approximate equality of order effects and practice effects for each drug/session. Failure to do so with low subject numbers would have a high risk of unequal confounding effects of practice. Moreover, in the unlikely event of study termination before all subjects were completed, the balanced design imposed by random permutation increases the utility of a smaller dataset. The permutation, packaging and labelling of drugs for the pharmacological studies will be performed independent of the study team, either by a member of the University, Medical School or external drug supplier.

Power. Computing power, reproducibility and power-cost tradeoffs for fMRI studies is complex. In the first series of experiments conducted under v1 and v2, we draw on empirical data and simulations that converged on n~20 as optimal (Mumford and Nichols, 2007; Thirion et al., 2007). For the Go-No-go studies for example, if the BOLD-MRI response in inferior frontal cortex of older subjects is half the size identified in the CIMBI young cohort (to 0.5%) and the inter-subject variance increased to 0.75%, then simulation and empirical studies indicate that n=20 gives 80-90% power to detect an effect at α=0.05 (Desmond and Glover, 2002; Murphy and Garavan, 2004). Attrition may arise from participant dropout during or between scanning, or from technical problems. I have recently performed a comparable phMRI study of placebo, citalopram plus two other drug interventions, in collaboration with the Danish Centre for Integrated Molecular Brain Imaging. Only 2 out of 24 subjects withdrew before completing all four pharmacological MRI sessions. Withdrawals were due to inconvenience and loss of interest. There were no adverse incidents. This success rate reflects careful subject selection, information and care throughout. Death or loss of consent capacity is not likely during the short period of participation by any one subject. Based on previous neuroimaging of clinical populations, I estimate 10% attrition within each study.

In subsequent studies of PD, the heterogeneity of PD, and the variability of response to drugs, leads us to seek larger studies sample size. For example, in Borchert et al 2016 and Ye at al 2016, 34<n<38 subjects were used, enabling better characterisation of which patients responded positively and which do not. Under v3 of this ethics protocol, for experiment 10, we therefore seek n=30 patients in each group.

Imaging. To enhance the interpretability and reproducibility of fMRI, we have adopted recommendations for best practice for pharmacological MRI studies (Carter et al., 2008; Iannetti and Wise, 2007) including (1) use of tasks and controls that engage relevant psychological processes; (2) assessment of baseline brain perfusion-

MRI on each session; (3) use of standardised unbiased pre-processing and data preparation methods; (4) focus on regionally specific effects with clear hypothesis testing.

The studies will use structural and functional magnetic resonance imaging (phMRI) with BOLD-sensitive echo-planar imaging at the dedicated Wolfson Brain Imaging Centre (WBIC) and MRC Cognition and Brain Sciences Unit (CBU) MRI suites. Their approved standard operating procedures will apply.

Both sites have high performing Siemens Tim PRISMA MRI scanners operated by clinical radiographers, with fully functional stimulus delivery and response monitoring systems. In addition, the WBIC houses a 7T Terra MRI scanner. There is extensive experience here of scanning PD & PSP patients and pharmacological MRI. At the CBU, only non-drug studies or studies on and off dopamine medications will be performed. At the WBIC, studies may also include pharmacological MRI with rivastigmine, atomoxetine, citalopram, or dopamine withdrawal, using either the 3T or 7T scanner.

MRI scanning will include several sequences, to investigate brain function (BOLD weighted EPI functional MRI sequences) and structure (MPRAGE, T2 and DWI) and perfusion (ASL). Each sequences lasts 4-25 minutes, with total EPI time less than 60 minutes, and total time in-scanner less than 90 minutes.

fMRI data pre-processing will use statistical parametric mapping software with semi-automated processing pipelines, with quality control assessments at each step. Data will be coregistered, sinc-interpolated to correct for acquisition delay, realigned, segmented and normalised using optimised iterative algorithms with linear and non-linear transformations and smoothed with Guassian kernels. Two-step random effects analyses of within and between subjects variance will be done for each study, adjusting for motion artifacts at the first stage and non-sphericity at the second stage. Contrasts of effects of task, group or drug effects will create SPM(t) and SPM(F) maps, corrected for multiple comparisons. Supplementary analysis procedures are described in each experiment where applicable. Structural data analysis will use voxel based mophometrics of grey and white matter regional volumes in SPM software, and tract based statistics of diffusion metrics in FSL software.

Additional behavioural tests: In addition to MRI scanning, supplementary tests will include the Unified Parkinson's Disease Rating Scale, visual acuity, MMSE, Beck depression inventory, national adult reading test, verbal fluency. Selected tests from the standardised computerised battery of cognitive function may be used, for example of reaction times, response inhibition, attention and the IDED test, lasting up to 45 minutes post scanning. These are simple short (5-15 minute) computer based tests using simple pictures and button press responses, testing attention and motor reactions.

General procedures: safety, comfort and consent

The safety of our participants is paramount. Participants will have no contraindications to MRI, and for the pharmacological studies, they will also have no contraindications to citalopram, atomoxetine or rivastigmine on the relevant experiments. A preliminary checklist for contraindications will be used at the recruitment stage, with further secondary safety checks immediately prior to drug administration and scanning. The screening checklists are provided separately with this application. Some subjects may require an ECG, and this is made clear in the PIS.

Volunteers will be screened via questionnaire to ensure they have no history of relevant medical problems (e.g. significant cardiac disease, uncontrolled hypertension, adverse drug reactions to these or closely related drugs, and relevant psychiatric

disorders), and are not taking other medications which might interact adversely.

Pharmacological challenges. For the pharmacological studies, we are using oral preparations of commonly used drugs, taken once on the morning of the assessment day. These are used in the NHS out-patient setting for adults and children, without supervision of first dose effects. It is therefore not necessary that a doctor be present with the participant throughout the assessment period and scanning. However, a named qualified doctor will be available on the same research site throughout each session, and contactable by telephone or bleep. The medical supervisor would however meet all participants prior to drug challenges, to ensure safety procedures have been correctly followed, and to answer any medical questions that may arise. By default, this will be Dr James Rowe (consultant neurologist) but the medical supervisory role may delegated to an appropriately qualified clinical research fellow or registrar attached to the study. An out of hours 24 hour telephone contact number will be provided in case of any symptoms following participation.

For studies of Atomoxetine, we use a standard oral dose (40 mg) which is at the lower end of the clinical dose range (40-100 mg). In adult clinical trials of atomoxetine with long term use, the most commonly observed adverse events (occurring in 5−10% of subjects) included: constipation, dry mouth, nausea, decreased appetite, dizziness, insomnia, and urinary retention. These data for occurrence of adverse events refers to longer term administration - the actual likelihood of adverse events in a single dose study is considerably lower. Atomoxetine is generally well−tolerated, and unlikely to cause serious adverse events provided that standard exclusion criteria are applied, such as concurrent medication with mono-amine oxidase inhibitors, current psychiatric illness and uncontrolled hypertension. This dose of atomoxetine has been well tolerated in psychopharmacological studies run at our institute and by members of the research team (e.g., Chamberlain et al., 2009), and has recently been approved for a new study of PD cognition out-of-scanner. Over the last 8 years, over 100 patients have received this dose of atomoxetine in acute studies, and there have been no serious adverse effects, and no significant changes in pulse rate or blood pressure, versus placebo.

Citalopram is one of the most widely used antidepressant medications. In comparable research studies, it has been used extensively in oral and intravenous preparations in healthy volunteers. We propose to use oral 20 mg, the standard starting dose in most out-patient neuropsychiatric settings (clinical range 20-60 mg). Although citalopram is only contraindicated in patients with mania, we would as a precaution also exclude patients with epilepsy, significant cardiac disease, concurrent monoamine oxidase inhibitors or warfarin.

For rivastigmine, we will use an oral dose of 3 mg. This compares with 3 mg per day in the introductory period of clinical dosage, and a maximum 12 mg per day in clinical use. Previous single dose studies have used 3 mg. Rivastigmine is licensed for use in PD and Alzheimer's disease, but the licence extends only to the treatment of dementia. Our subjects do not have dementia. The BNF lists no contraindications for our participants (breastfeeding only). Based on the cautions associated with rivastigmine, we would exclude patients with recent or current asthma or COPD, cardiac rhythm abnormalities, recent or current symptoms suggestive of gastric or duodenal ulceration, or epilepsy.

Cardiac safety. An ECG is not part of routine clinical use of atomoxetine or citalopram, even when doses above 40 mg are used. No ECG abnormalities were detected in elderly PD patients in a recent trial of Atomoxetine that used doses up to 100 mg, mean 90 mg (Marsh et al, Movement disorders, 2009). Given the range of participants in the study – in terms of age and comorbidity – we propose to review the ECG in subjects who have risk factors for cardiovascular disease, including

hypertension, a personal or family history of heart disease, or relevant concurrent medications. An ECG is not required in participants with none of these factors. If review of the ECG is indicated, and if an ECG is not available from within the last two years, a new ECG will be performed at the CRF or the clinical suite of the Herchel-Smith building in the department of Clinical Neurosciences and reviewed by a supervising physician. An ECG from within two years of the study date would be reviewed instead if available. An ECG is not obligatory in clinical practice prior to rivastigmine therapy but it is commonly performed. For participants intended to receive rivastigmine therefore, we will routinely review the ECG if available within the last 2 years, or perform a new ECG at the CRF or HSB.

Blood tests. For pharmacological studies, a blood test will be performed prior to scanning. This is to measure drug levels, to ensure correct randomisation and for post-hoc analysis using drug levels as covariates. Up to 10 ml (two teaspoons) will be taken, and the PIS refers to this and the associated minor discomfort. Blood will be taken by a qualified doctor, nurse or phlebotomist. Blood will be processed for storage of serum, not whole blood. Extracted DNA will be used to genotype for polymorphisms (natural variations) in the Noradrenaline transporter, in experiment 10.

Capacity. All participants will be required to have the capacity to provide informed consent. We do not include vulnerable persons such as those PD patients with severe cognitive problems. Consent procedures include enough information and enough time to make a decision to participate, and we stress the voluntary nature of participation and ability to withdraw. We have written our information sheets and consent sheets so as to be complete, but concise and comprehensive for the lay participant.

Neuropsychological evaluation. The supplementary cognitive testing requires subjects to sit using a computer or paper and pencil and thus could potentially cause fatigue. Subjects will perform the cognitive testing battery for no more than 2 hours. Breaks will be included throughout the session, and subjects will be reminded that they can take a break at any time by asking the researcher. The procedures used in this experiment will neither be physically stressful nor impinge on the safety of the participants. The images and feedback that are presented are also not emotional and have not caused any distress in related studies of patients or healthy controls. Testing will stop if a patient reports excessive frustration or appears tired.

Protection of participants. MRI scanning at both WBIC and CBU uses independent qualified radiographers. They are experienced at ensuring participant comfort throughout scanning. One of their roles is to be an independent assessor of the participant comfort and mood, and terminate scanning at the request of the participant or if they judge there to be pain, distress or anxiety.

Subjects may be invited to participate in one, two or three different testing sessions. This will be made clear to them at the outset verbally and in the PIS. It will also be made clear to all subjects that they may withdraw during or in between sessions at any time without needing to give a reason, and without harming their usual care. We will coordinate with other PD research studies (associated with the PD research clinic) to prevent participation in multiple pharmacological studies, or burdensome inclusion in multiple studies even when these do not include MRI or pharmacological interventions.

Other Ethical Considerations:

Several areas have been considered above regarding safety, comfort, consent and power calculations to use sufficient but not excessive numbers of participants. We

will also arrange appropriate insurance cover, and make these arrangements known to participants through the PIS.

In addition, we follow standard good research practices within our departments, to ensure confidentiality of electronic and hard copy data, in keeping with the Data Protection Act. Hard data are kept locked, and electronic data are anonymised and encrypted. We collaborate with other members of the University and the CBU, and we require similar adherence to DPA and confidentiality by collaborators. Anonymised data may also be shared outside of these departments, provided it is used for non-commercial research purposes, as part of our commitment to "open data" as required by the Medical Research Council and Wellcome Trust. Raw data will be stored long term within the department of clinical neurosciences (currently the WBIC and Herchel-Smith Building) and the CBU.

Conflict of interest. No commercial company is directly involved in this study, and there is no conflict of interest. The tablets are prepared independently from commercially available branded Strattera atomoxetine, citlopram, or Exelon rivastigmine without sponsorship. There is no commercial financial support or influence from a commercial organisation.

Psychiatric state. None of our participants have dementia, and the recruitment process excludes those with known current depression. However, during the course of the study, participants will undertake screening tests such as the MMSE and the BDI. If a participant scores significantly outside the normal range, we would treat this as any other abnormal finding, and inform the GP (with the subjects consent). However, the MMSE is not a diagnostic tool for dementia, and there are many reasons why a participant might score low on a given day. Clinical judgment from an experienced cognitive neurologist (Dr Rowe) would be used in deciding the appropriate response to a low MMSE score.

Regarding the BDI, it is extremely unlikely that suicidal patients would be selected. If an unexpectedly suicidal patient were to be assessed, and complete question 9 with a rating of 2 or 3, this would be counted as an abnormal result, and with the subject's permission, the GP would be notified. It should be noted that the BDI is not a diagnostic tool for depression, and does not replace a clinical diagnostic approach by the patient's NHS doctors (GP and neurologist), nor does it replace the clinical diagnostic criteria for depression. Furthermore, the standard cut-off values for research ratings of depression using the BDI are based on physically fit depressed patients and are not necessarily applicable to patients with PD. This is because the BDI, like many questionnaire assessments of depression symptoms, includes PD-related physical symptoms (eg. fatigue, sexual interest and sleep change) that may inflate the score in the absence of depression. The BDI is used in our study as an index of our case mix in relation to other studies of Parkinson's Disease, that by convention use BDI or similar ratings. It is not a clinical outcome measure or diagnostic tool.

Reimbursement to subjects. Participants will be reimbursed at standard rates for behavioural and imaging studies at the CBU and WBIC (£6 perhour for behavioural tests, 10 per hour for MRI studies, plus travel expenses). We have spoken with the Pension Credit Support line and the Benefits Enquiry Line regarding the issue of benefits entitlements. Pension Credit would not be affected by a single reimbursement from this study. The reimbursement would not be considered as income (as a single payments related to research study participation). A similar response was given for Housing Benefit and Council Tax benefit. Attendance allowance and Disability Living Allowance are not means tested, and would not be affected by study reimbursement. We mention this in the PIS.

Experimental details.

Experiment 10 (v3)
We have shown that response control and action selection could be improved by atomoxetine in Parkinson's disease (PD). Given the great deficit in noradrenaline in PSP and related disorders, experiment 10 will include both PD and PSP. This experiment will establish a role for atomoxetine in modulating a broad range of motivated behaviours, including response inhibition and other cognitive abilities that support motivation include sustaining effort, reward sensitivity and flexibly adapting behaviour. These abilities can be affected in PD and PSP. This experiment will determine whether these abilities are modulated by atomoxetine, leading to improvements in motivated behaviour.

In conjunction with the cognitive and behavioural tasks, we will establish individual differences in response to atomoxetine by using pupillometry, exploiting the fact that pupil diameter is controlled by noradrenaline. In an exploratory analysis we will examine the effect of natural variations in the noradrenaline transporter (NET) gene. Pupillometery is a measure of changes in pupil size, performed non-invasively using a remotely set up camera. Pupil size is a reliable indicator of noradrenaline brain function (Joshi et al., 2016), which will provide a measure of how well an individual is responding to atomoxetine. In other disorders, genetic variations in the NET gene have been shown to predict how well an individual responds to atomoxetine therapy (Ramoz et al., 2009). As part of this experiment, we will extract DNA from a blood test to determine whether variations in the NET gene affect how patients respond to atomoxetine.

Methods:
30 PD patients will be recruited from the PD research clinic lead by Prof Barker, or by self referral (eg in response to the charity Parkinson's UK website information on active PD research studies in the UK) and 30 PSP patients from the Disorders of Movement and Cognition Clinic led by Prof Rowe or self referral, and 30 healthy controls. The procedure for recruiting PD patients, including inclusion and exclusion criteria, as well as safety procedures, will be the same as the preceding experiments, as outlined in the "Experimental Protocol" section of this document. For PSP patients, inclusion and exclusion criteria, and safety procedures, would be the identical, except they would meet core diagnostic criteria for probable or possible PSP (Höglinger et al., 2017), rather than PD

There are two practical and ethical issues that are specific to PSP patients. Firstly, PSP patients may have difficulty writing. In line with the Experiment 8 in this protocol and our companion study "Diagnosis and prognosis markers in Progressive Supranuclear Palsy (PSP), Corticobasal degeneration (CBD) and Frontotemporal degeneration (FTD) (Protocol 07/Q0102/3), we would still require a witnessed signature on consent forms, but would ask patients with PSP to tick boxes on the consent form rather than provide initials. Secondly, patients with PSP may have selective deficits in speech and drawing that can impact their MMSE score, which is used to establish the study inclusion criteria of no dementia. In line with Experiment 8 and our companion study (Protocol 07/Q0102/3), for patients with PSP the criterion will be changed to a clinical diagnosis of dementia.

In this experiment, participants will not undergo task-based functional MRI scanning while performing a task. However at the baseline visit they will complete an imaging

session that will include key sequences used in the preceding experiments to investigate brain function (BOLD weighted EPI functional MRI sequences at rest) and structure (MPRAGE, T2, field maps and DWI). The scanning will take place at the dedicated WBIC unit under the same procedures outlined earlier in this protocol.

In a double-blind randomised crossover design, 30 PD and 30 PSP patients will undergo three sessions. Session one will comprise the baseline neuroimaging and basic measures of cognition and motor function (including MMSE and UPDRS). This visit will take about 1.5 hours.

Sessions two and three will be on separate days, at least 6 days apart. These will involve computerised tasks assessing motivation, following either a single dose of atomoxetine or placebo. Participants will be randomised to receive atomoxetine on session two or three. As in the preceding experiments, 40 mg of atomoxetine will be used, and patients will not need to withdraw from their regular medications. The computerised tasks will measure a range of abilities relating to motivation, including response inhibition, reward processing, behavioural flexibility and effort. These tasks have been piloted in patients, and they do not require computer proficiency and do not involve complex motor responses. Each task is preceded by detailed instructions and practice trials, to ensure participants are comfortable before commencing. Changes in pupil dilation will be recorded during tasks.

As in the preceding experiments, there will be resting time after the atomoxetine/placebo is administered. After 2 hours atomoxetine reaches its active levels in the brain, at this point we will take blood samples (10 ml, or about two teaspoons). The blood samples will be used to measure atomoxetine levels and also to extract DNA for the NET genotyping. The computerised tasks will then take approximately 2 hours, including regular breaks. Age-matched controls will undergo neuroimaging and the motivation tasks with pupillometry, providing a control comparison group on these measures.

Caregiver burden assessment:
If a close relative, friend or spouse is identified as a caregiver to the study participant, they will be invited to complete the Zarit Burden questionnaire (Zarit et al., 1987). This questionnaire asks individuals to rate the frequency of burden or stress that they may feel in association with caring for a person with a neurological illness. Caregivers will be under no obligation to participate, however if they are interested in participation, they will be provided with an information sheet and we would seek informed consent to their involvement in the study. The questionnaire is included on Page 32 of this protocol.

Data Sharing Plan

Neuroimaging and behavioural data will be made available to other national and international research groups using a controlled release process. Only anonymised data will be shared. This will maximise the scientific research impact of our studies, while maintaining the necessary security for PiD in keeping with the Data Protection Act. We note that such sharing of data is increasingly a condition of research funding, including Parkinson's UK, Wellcome Trust and Medical Research Council (the main funders of this study), and PPI focus groups with patients and healthy research

participants has shown that such maximised use of data is indeed demanded. This does not conflict with the individual participants right for anonymity and protection of personal data, but instead reflects the national trend and changing expectations over the last decade.

As part of their participation in the study, participants will be asked to provide written informed consent (such consent is obviously a condition of our inclusion of a participant in the study). During the consent procedures, it is made clear that their anonymised data – and only anonymised data - will be made available to other national and international research groups.

Neuroimaging data will be made available in the international standard of unprocessed 'DICOM' files. This improves comparability and replicability. Meta-data would include technical descriptions of the neuroimaging sequences used. To ensure the anonymity of the neuroimaging data we will remove of any identifying information (including but not limited to name, surname, address, date of birth, NHS number). We may make available anonymised values from questionnaires and summary performance data from neuropsychological tasks. A minimal set of clinical and demographic information may be shared (e.g., age in years, sex, diagnostic group, disease duration and severity summary scores, drug levels). No personally identifiable information would be shared or linked to the open dataset. We will achieve this by using a unique study identification number for the data. The open data will be hosted initially at University of Cambridge High Performance Hub for Informatics, and Dementias Platform UK imaging portal. These are curated by data mangers to preserve the integrity and anonymity of hosted data. Sharing of data with other research sites will be subject to conditions including (i) not to be used for commercial purposes (ii) not for third-party sharing (iii) that no attempt will be made to undermine anonymity or to identify participants (iv) and that local curation will adhere to the recipients' national standards for data curation to preserve anonymity. Researchers wishing to receive data would be required to agree to the terms and conditions before gaining access to the data. Such measures are in place already for large scale cohorts of Cambridge participants for example in the "Cambridge Centre or Ageing and Neuroscience (CamCAN)" and "16/EE/0351 7Tesla MRI Scanning in dementia" and "16/EE/0084 Cognitive Neuroscience with 7Tesla MRI Scanning in Healthy Individuals".

Note regarding the PIS

We have written a 'modular' PIS, that clearly explains the proposed research to any given participant. The PIS includes two front pages with general information about the study, and summary information on the number of sessions and medication, together with a summary of medico-legal issues.

Each potential participant would also be given the relevant supplementary sheets, regarding medication (A to E) and a full statement regarding confidentiality, complaints and insurance (sheet F). We believe that this modular approach is most easily accessible for lay participants, allowing them to locate and focus on the relevant information necessary to provide informed consent.

All PIS forms include my name and contact details as principal investigator. A second contact person may also be included, where that person is a clinical research fellow or post-doctoral research fellow closely associated with the study and likely to have direct contact with the participant during their screening or assessment sessions.

Screening Form (by telephone, then checked before medication)

"Have you had an opportunity to read the volunteer information sheet that I sent to you? Do you have any questions about the study? We need to ask you a few questions to see if you would be suitable for the experiment. Your answers will be treated confidentially. You don't have to answer any questions if you do not wish to."

Volunteer Name ……..

Date of Birth …… Age…… Approximate Weight: ……

Handedness……

Contact phone numbers……..

Availability. Do you work at the moment? What hours do you work? Do you have access to transport to get into Cambridge? We advise that you do not drive on the test days.
……. ……..

Health & Safety screening
If participant answers 'yes' to any of the following questions, details will be collected and a physician will be consulted to determine whether it is safe to include the participant in the study.

Your Health:
Which medications do you take regularly?
……..…….
……..
……
Do you take other medications on an "as needed" basis? Y N
……..…….
Have you taken other medications in the last 14 days?
……..…….
Have you ever taken antidepressant medication? Y N if so which
……when……

Do you have any allergies? Y N ……
Do you have a history of fainting or collapse? Y N ……
Do you have any of the following?
heart conditions Y N ……
slow/irregular heart beat Y N ……
high blood pressure Y N ……
asthma or emphysema or chronic bronchitis
Y N ……
migraine Y N ……
epilepsy or fits Y N ……
depression or anxiety Y N ……
diabetes Y N ……...
glaucoma Y N ……
stomach ulcers Y N ……
liver/kidney failure Y N ……
other significant illness Y N……

Family History:
As far as you know, has any family member suffered from the following?
heart disease, angina? Y N ……
anxiety or depression Y N ……
……

Blood sample (if relevant):
Would you mind giving a small blood sample? Y N
……..

Drugs & Alcohol:
How much alcohol do you drink if at all? ……
Do you smoke? Y N ……/day

MRI contraindications (if applicable):
Do you have any metal in your body eg.
Bone pins or plates Y N ……
Or a heart pacemaker? Y N
False teeth, braces, bridges Y N ……
Metal splinters or shrapnel Y N ……..
Have you ever done any metal- or lathe- work? Y N
Do you suffer from claustrophobia? Y N ……
…….. ……...

With glasses (if needed) can you read normally? Y N
If you need glasses, please bring them with you on the day.

If volunteer answers 'no' to all questions (except glasses), volunteer may proceed with the study.
If volunteer answers 'yes' to any question, a physician will be consulted before volunteer may proceed with the study.

Suitable for inclusion in study? Y N

Is a ECG required? Y N
(Hypertension, Diabetes or Personal or family history of heart disease)

Physician consulted (where applicable):

Date:

Signature:

BDI – personal information would be replaced by a unique alphanumeric identifier

BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

_____ Subtotal Page 1

Continued on Back

11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have much greater difficulty in making decisions than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

For Experimenter Use Only:

Participant # _____ Date _____ Experiment _____ Time _____

Music Questionnaire

1) Handedness: Right Left Ambidextrous

2) Do you have normal hearing? Yes No

If not, please describe…….

3) Do you enjoy listening to music? Yes No

4) How much time do you spend listening to music a week (hours)? ……..

5) How would you rate your rhythm ability on a scale of 1 to 10 (1 not good, 10 very good)? ……

6) What types of music do you listen to? ……...

……..

7) Do you have any formal music training (for either voice or an instrument)? Yes No

If yes, which instrument(s) ……..

Please list the number of years for each instrument above ……

What type of training did you receive?

___School/Band ___Friends/Family

___Private Lessons ___Self Taught

___Church ___Other (Please explain)

8) Are you currently studying and/or performing music? Yes No

If yes, how many hours a week do you practice and/or perform? ……

9) Do you have any formal dance training? Yes No

If yes, what style(s)? ……

Please list the number of years for each style ……

What type of training did you receive?

___School ___Friends/Family

___Private Lessons ___Self Taught

___Other (Please explain)

10) Are you currently studying and/or performing dance? Yes No

If yes, how many hours a week do you practice and/or perform? …….

11) Have you ever noticed a change in your symptoms when listening to music? Yes No

If yes, what symptoms changed, and how did they change? ……. …..

……

……

(Music Questionnaire v1.0, 24/2/2010)

Caregiver questionnaire (Zarit Burden Inventory)

Caregiver Burden Scale

Caregiver's name: _____ Date: _____

The following questions reflect how people sometimes feel when they are taking care of another person. After each question, circle how often you feel that way: never, rarely, sometimes, frequently, or nearly always. There are no right or wrong answers.

	Never	Rarely	Sometimes	Frequently	Nearly always
1. Do you feel that your relative asks for more help than he or she needs?	0	1	2	3	4
2. Do you feel that because of the time you spend with your relative, you do not have enough time for yourself?	0	1	2	3	4
3. Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?	0	1	2	3	4
4. Do you feel embarrassed over your relative's behavior?	0	1	2	3	4
5. Do you feel angry when you are around your relative?	0	1	2	3	4
6. Do you feel that your relative currently affects your relationship with other family members or friends in a negative way?	0	1	2	3	4
7. Are you afraid about what the future holds for your relative?	0	1	2	3	4
8. Do you feel your relative is dependent on you?	0	1	2	3	4
9. Do you feel strained when you are around your relative?	0	1	2	3	4
10. Do you feel your health has suffered because of your involvement with your relative?	0	1	2	3	4
11. Do you feel that you do not have as much privacy as you would like, because of your relative?	0	1	2	3	4
12. Do you feel that your social life has suffered because you are caring for your relative?	0	1	2	3	4
13. Do you feel uncomfortable about having friends over, because of your relative?	0	1	2	3	4
14. Do you feel that your relative seems to expect you to take care of him or her, as if you were the only one he or she could depend on?	0 0	1 1	2 2	3 3	4 4
15. Do you feel that you do not have enough money to care for your relative, in addition to the rest of your expenses?	0	1	2	3	4
16. Do you feel that you will be unable to take care of your relative much longer?	0	1	2	3	4
17. Do you feel you have lost control of your life since your relative's illness?	0	1	2	3	4
18. Do you wish you could just leave the care of your relative to someone else?	0	1	2	3	4
19. Do you feel uncertain about what to do about your relative?	0	1	2	3	4
20. Do you feel you should be doing more for your relative?	0	1	2	3	4
21. Do you feel you could do a better job in caring for your relative?	0	1	2	3	4
22. Overall, how burdened do you feel in caring for your relative?	0	1	2	3	4

Total score: _____

References

Alexander, G.E., Crutcher, M.D., DeLong, M.R., 1990. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res 85, 119-146.

Armstrong, M.J., Litvan, I., Lang, A.E., Bak, T.H., Bhatia, K.P., Borroni, B., Boxer, A.L., Dickson, D.W., Grossman, M., Hallett, M., 2013. Criteria for the diagnosis of corticobasal degeneration. Neurology 80, 496-503.

Aron, A.R., Monsell, S., Sahakian, B.J., Robbins, T.W., 2004a. A componential analysis of task-switching deficits associated with lesions of left and right frontal cortex. Brain 127, 1561-1573.

Aron, A.R., Robbins, T.W., Poldrack, R.A., 2004b. Inhibition and the right inferior frontal cortex. Trends Cogn Sci 8, 170-177.

Baddeley, A., Emslie, H., Kolodny, J., Duncan, J., 1998. Random generation and the executive control of working memory. Q J Exp Psychol A 51, 819-852.

Bechara, A., Damasio, H., Tranel, D., Anderson, S.W., 1998. Dissociation Of working memory from decision making within the human prefrontal cortex. J Neurosci 18, 428-437.

Borchert, R.J., Rittman, T., Passamonti, L., Ye, Z., Sami, S., Jones, S.P., Nombela, C., Vazquez Rodriguez, P., Vatansever, D., Rae, C.L., Hughes, L.E., Robbins, T.W., Rowe, J.B., 2016. Atomoxetine Enhances Connectivity of Prefrontal Networks in Parkinson's Disease. Neuropsychopharmacology 41, 2171-2177.

Bymaster, F.P., Katner, J.S., Nelson, D.L., Hemrick-Luecke, S.K., Threlkeld, P.G., Heiligenstein, J.H., Morin, S.M., Gehlert, D.R., Perry, K.W., 2002a. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology 27, 699-711.

Bymaster, F.P., Zhang, W., Carter, P.A., Shaw, J., Chernet, E., Phebus, L., Wong, D.T., Perry, K.W., 2002b. Fluoxetine, but not other selective serotonin uptake inhibitors, increases norepinephrine and dopamine extracellular levels in prefrontal cortex. Psychopharmacology (Berl) 160, 353-361.

Cabrera, S.M., Chavez, C.M., Corley, S.R., Kitto, M.R., Butt, A.E., 2006. Selective lesions of the nucleus basalis magnocellularis impair cognitive flexibility. Behav Neurosci 120, 298-306.

Carter, C.S., Heckers, S., Nichols, T., Pine, D.S., Strother, S., 2008. Optimizing the Design and Analysis of Clinical Functional Magnetic Resonance Imaging Research Studies. Biol Psychiatry.

Chamberlain, S.R., Del Campo, N., Dowson, J., Muller, U., Clark, L., Robbins, T.W., Sahakian, B.J., 2007. Atomoxetine improved response inhibition in adults with attention deficit/hyperactivity disorder. Biol Psychiatry 62, 977-984.

Chamberlain, S.R., Muller, U., Blackwell, A.D., Clark, L., Robbins, T.W., Sahakian, B.J., 2006. Neurochemical modulation of response inhibition and probabilistic learning in humans. Science 311, 861-863.

Clarke, H.F., Dalley, J.W., Crofts, H.S., Robbins, T.W., Roberts, A.C., 2004. Cognitive inflexibility after prefrontal serotonin depletion. Science 304, 878-880.

Clarke, H.F., Walker, S.C., Crofts, H.S., Dalley, J.W., Robbins, T.W., Roberts, A.C., 2005. Prefrontal serotonin depletion affects reversal learning but not attentional set shifting. J Neurosci 25, 532-538.

Cohen, J.D., Braver, T.S., Brown, J.W., 2002. Computational perspectives on dopamine function in prefrontal cortex. Curr Opin Neurobiol 12, 223-229.

Cools, R., 2006. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. Neurosci Biobehav Rev 30, 1-23.

Cools, R., Barker, R.A., Sahakian, B.J., Robbins, T.W., 2001. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. Cereb Cortex 11, 1136-1143.

Cools, R., Barker, R.A., Sahakian, B.J., Robbins, T.W., 2003. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. Neuropsychologia 41, 1431-1441.

Cools, R., Lewis, S.J., Clark, L., Barker, R.A., Robbins, T.W., 2007. L-DOPA disrupts activity in the nucleus accumbens during reversal learning in Parkinson's disease. Neuropsychopharmacology 32, 180-189.

Daum, I., Schugens, M., Channon, S., Polkey, E., Gray, J., 1991. T-maze discrimination and reversal learning after unilateral temporal or frontal lobe lesions in man. Cortex 27 613-622.

de Rijk, M.C., Launer, L.J., Berger, K., Breteler, M.M., Dartigues, J.F., Baldereschi, M., Fratiglioni, L., Lobo, A., Martinez-Lage, J., Trenkwalder, C., Hofman, A., 2000. Prevalence of Parkinson's disease in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 54, S21-23.

de Rijk, M.C., Tzourio, C., Breteler, M.M., Dartigues, J.F., Amaducci, L., Lopez-Pousa, S., Manubens-Bertran, J.M., Alperovitch, A., Rocca, W.A., 1997. Prevalence of parkinsonism and Parkinson's disease

in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. J Neurol Neurosurg Psychiatry 62, 10-15.
Del-Ben, C.M., Deakin, J.F., McKie, S., Delvai, N.A., Williams, S.R., Elliott, R., Dolan, M., Anderson, I.M., 2005. The effect of citalopram pretreatment on neuronal responses to neuropsychological tasks in normal volunteers: an FMRI study. Neuropsychopharmacology 30, 1724-1734.
Desmond, J.E., Glover, G.H., 2002. Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses. J Neurosci Methods 118, 115-128.
Downes, J.J., Roberts, A.C., Sahakian, B.J., Evenden, J.L., Morris, R.G., Robbins, T.W., 1989. Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. Neuropsychologia 27, 1329-1343.
Duncan, J., Emslie, H., Williams, P., Johnson, R., Freer, C., 1996. Intelligence and the frontal lobe: the organization of goal-directed behavior. Cognit Psychol 30, 257-303.
Duncan, J., Johnson, R., Swales, M., Freer, C., 1997. Frontal Lobe Deficits after Head Injury: Unity and Diversity of Function Cognitive Neuropsychology, 14, 713 - 741
Duncan, J., Parr, A., Woolgar, A., Thompson, R., Bright, P., Cox, S., Bishop, S., Nimmo-Smith, I., 2008. Goal neglect and Spearman's g: competing parts of a complex task. J Exp Psychol Gen 137, 131-148.
Dunmontheil, I., Thompson, R., Duncan, J., 2008. Involvement of prefrontal cortex in learning and executing multiple task rules. Experimental Psychology Society UK.
Durstewitz, D., Kelc, M., Gunturkun, O., 1999. A neurocomputational theory of the dopaminergic modulation of working memory functions. J Neurosci 19, 2807-2822.
Eagle, D.M., Bari, A., Robbins, T.W., 2008. The neuropsychopharmacology of action inhibition: cross-species translation of the stop-signal and go/no-go tasks. Psychopharmacology (Berl) 199, 439-456.
Evers, E.A., Cools, R., Clark, L., van der Veen, F.M., Jolles, J., Sahakian, B.J., Robbins, T.W., 2005. Serotonergic modulation of prefrontal cortex during negative feedback in probabilistic reversal learning. Neuropsychopharmacology 30, 1138-1147.
Fahn, S., Elton, R., atmotUPsDRSD, C., 1987. Unified Parkinson's Disease Rating Scale. In: Fahn, S., Marsden, C., Calne, D. (Eds.), Recent developments in Parkinson's disease. MacMillan, New York, pp. 153-163.
Foltynie, T., Goldberg, T.E., Lewis, S.G., Blackwell, A.D., Kolachana, B.S., Weinberger, D.R., Robbins, T.W., Barker, R.A., 2004. Planning ability in Parkinson's disease is influenced by the COMT val158met polymorphism. Mov Disord 19, 885-891.
Forstmann, B.U., Wolfensteller, U., Derrfuss, J., Neumann, J., Brass, M., Ridderinkhof, K.R., von Cramon, D.Y., 2008. When the choice is ours: context and agency modulate the neural bases of decision-making. PLoS ONE 3, e1899.
Frank, M.J., Samanta, J., Moustafa, A.A., Sherman, S.J., 2007. Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. Science 318, 1309-1312.
Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modelling. Neuroimage 19, 1273-1302.
Frith, C.D., Friston, K., Liddle, P.F., Frackowiak, R.S., 1991. Willed action and the prefrontal cortex in man: a study with PET. Proc R Soc Lond B Biol Sci 244, 241-246.
Grahn, J.A., Rowe, J.B., 2009. Feeling the beat: premotor and striatal interactions in musicians and nonmusicians during beat perception. J Neurosci 29, 7540-7548.
Griffiths, C., Rooney, C., 2006. Trends in mortality from Alzheimer's disease, Parkinson's disease and dementia, England and Wales, 1979-2004. Office of national Statistics: Health Statistics Quarterly 30,, 6-14.
Hampshire, A., Owen, A.M., 2006. Fractionating Attentional Control Using Event-Related fMRI. Cereb Cortex.
Höglinger, G.U., Respondek, G., Stamelou, M., Kurz, C., Josephs, K.A., Lang, A.E., Mollenhauer, B., Müller, U., Nilsson, C., Whitwell, J.L., 2017. Clinical diagnosis of progressive supranuclear palsy: The Movement Disorder Society criteria. Movement Disorders.
Hornak, J., O'Doherty, J., Bramham, J., Rolls, E.T., Morris, R.G., Bullock, P.R., Polkey, C.E., 2004. Reward-related reversal learning after surgical excisions in orbito-frontal or dorsolateral prefrontal cortex in humans. J Cogn Neurosci 16, 463-478.
Iannetti, G.D., Wise, R.G., 2007. BOLD functional MRI in disease and pharmacological studies: room for improvement? Magn Reson Imaging 25, 978-988.
Inase, M., Li, B.M., Tanji, J., 1997. Dopaminergic modulation of neuronal activity in the monkey putamen through D1 and D2 receptors during a delayed Go/Nogo task. Exp Brain Res 117, 207-218.
Jahanshahi, M., Dirnberger, G., Fuller, R., Frith, C.D., 2000. The role of the dorsolateral prefrontal cortex in random number generation: a study with positron emission tomography. Neuroimage 12, 713-725.
Joshi, S., Li, Y., Kalwani, R.M., Gold, J.I., 2016. Relationships between pupil diameter and neuronal activity in the locus coeruleus, colliculi, and cingulate cortex. Neuron 89, 221-234.

Kehagia, A.A., Housden, C.R., Regenthal, R., Barker, R.A., Müller, U., Rowe, J., Sahakian, B.J., Robbins, T.W., 2014. Targeting impulsivity in Parkinson's disease using atomoxetine. Brain 137, 1986-1997.
Lange, K.W., Robbins, T.W., Marsden, C.D., James, M., Owen, A.M., Paul, G.M., 1992. L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. Psychopharmacology (Berl) 107, 394-404.
Lapiz, M.D., Morilak, D.A., 2006. Noradrenergic modulation of cognitive function in rat medial prefrontal cortex as measured by attentional set shifting capability. Neuroscience 137, 1039-1049.
Levine, B., Stuss, D.T., Winocur, G., Binns, M.A., Fahy, L., Mandic, M., Bridges, K., Robertson, I.H., 2007. Cognitive rehabilitation in the elderly: effects on strategic behavior in relation to goal management. J Int Neuropsychol Soc 13, 143-152.
Litvan, I., Agid, Y., Calne, D., Campbell, G., Dubois, B., Duvoisin, R.C., Goetz, C.G., Golbe, L.I.M., Grafman, J.P., Growdon, J.H.M., Hallett, M.M., Jankovic, J.M., Quinn, N.P.M., Tolosa, E.M., Zee, D.S.M., 1996. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): Report of the NINDS-SPSP International Workshop*. Neurology 47, 1-9.
Manes, F., Sahakian, B., Clark, L., Rogers, R., Antoun, N., Aitken, M., Robbins, T., 2002. Decision-making processes following damage to the prefrontal cortex. Brain 125, 624-639.
Mansouri, F.A., Buckley, M.J., Tanaka, K., 2007. Mnemonic function of the dorsolateral prefrontal cortex in conflict-induced behavioral adjustment. Science 318, 987-990.
McGaughy, J., Ross, R.S., Eichenbaum, H., 2008. Noradrenergic, but not cholinergic, deafferentation of prefrontal cortex impairs attentional set-shifting. Neuroscience 153, 63-71.
Mehta, M.A., Goodyer, I.M., Sahakian, B.J., 2004. Methylphenidate improves working memory and set-shifting in AD/HD: relationships to baseline memory capacity. J Child Psychol Psychiatry 45, 293-305.
Molina, J.A., Sainz-Artiga, M.J., Fraile, A., Jimenez-Jimenez, F.J., Villanueva, C., Orti-Pareja, M., Bermejo, F., 2000. Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment? Mov Disord 15, 869-872.
Mumford, J.A., Nichols, T.E., 2007. Power calculation for group fMRI studies accounting for arbitrary design and temporal autocorrelation. Neuroimage.
Murphy, F.C., Smith, K.A., Cowen, P.J., Robbins, T.W., Sahakian, B.J., 2002. The effects of tryptophan depletion on cognitive and affective processing in healthy volunteers. Psychopharmacology (Berl) 163, 42-53.
Murphy, K., Garavan, H., 2004. An empirical investigation into the number of subjects required for an event-related fMRI study. Neuroimage 22, 879-885.
Murphy, P.R., Boonstra, E., Nieuwenhuis, S., 2016. Global gain modulation generates time-dependent urgency during perceptual choice in humans. Nature Communications 7, 13526.
Norman, D., Shallice, T., 1980. Attention to action: willed and automatic control of behaviour. Center for human information processing, University of California, San Diego.
O'Doherty, J., Kringelbach, M.L., Rolls, E.T., Hornak, J., Andrews, C., 2001. Abstract reward and punishment representations in the human orbitofrontal cortex. Nat Neurosci 4, 95-102.
Overtoom, C.C., Verbaten, M.N., Kemner, C., Kenemans, J.L., van Engeland, H., Buitelaar, J.K., van der Molen, M.W., van der Gugten, J., Westenberg, H., Maes, R.A., Koelega, H.S., 2003. Effects of methylphenidate, desipramine, and L-dopa on attention and inhibition in children with Attention Deficit Hyperactivity Disorder. Behav Brain Res 145, 7-15.
Owen, A.M., Downes, J.J., Sahakian, B.J., Polkey, C.E., Robbins, T.W., 1990. Planning and spatial working memory following frontal lobe lesions in man. Neuropsychologia 28, 1021-1034.
Owen, A.M., James, M., Leigh, P.N., Summers, B.A., Marsden, C.D., Quinn, N.P., Lange, K.W., Robbins, T.W., 1992. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. Brain 115, 1727-1751.
Owen, A.M., Roberts, A.C., Hodges, J.R., Summers, B.A., Polkey, C.E., Robbins, T.W., 1993. Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. Brain 116, 1159-1175.
Owen, A.M., Roberts, A.C., Polkey, C.E., Sahakian, B.J., Robbins, T.W., 1991. Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. Neuropsychologia 29, 993-1006.
Rahman, S., Robbins, T.W., Hodges, J.R., Mehta, M.A., Nestor, P.J., Clark, L., Sahakian, B.J., 2006. Methylphenidate ('Ritalin') can ameliorate abnormal risk-taking behavior in the frontal variant of frontotemporal dementia. Neuropsychopharmacology 31, 651-658.
Rahman, S., Sahakian, B.J., Hodges, J.R., Rogers, R.D., Robbins, T.W., 1999. Specific cognitive deficits in mild frontal variant frontotemporal dementia. Brain 122 (Pt 8), 1469-1493.

Ramoz, N., Boni, C., Downing, A.M., Close, S.L., Peters, S.L., Prokop, A.M., Allen, A.J., Hamon, M., Purper-Ouakil, D., Gorwood, P., 2009. A haplotype of the norepinephrine transporter (Net) gene Slc6a2 is associated with clinical response to atomoxetine in attention-deficit hyperactivity disorder (ADHD). Neuropsychopharmacology 34, 2135-2142.
Rieger, M., Gauggel, S., Burmeister, K., 2003. Inhibition of ongoing responses following frontal, nonfrontal, and basal ganglia lesions. Neuropsychology 17, 272-282.
Robbins, T.W., 2007. Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. Philos Trans R Soc Lond B Biol Sci 362, 917-932.
Robbins, T.W., James, M., Owen, A.M., Lange, K.W., Lees, A.J., Leigh, P.N., Marsden, C.D., Quinn, N.P., Summers, B.A., 1994. Cognitive deficits in progressive supranuclear palsy, Parkinson's disease, and multiple system atrophy in tests sensitive to frontal lobe dysfunction. J Neurol Neurosurg Psychiatry 57, 79-88.
Roberts, A.C., Robbins, T.W., Everitt, B.J., Muir, J.L., 1992. A specific form of cognitive rigidity following excitotoxic lesions of the basal forebrain in marmosets. Neuroscience 47, 251-264.
Rowe, J., Hughes, L., Eckstein, D., Owen, A.M., 2008a. Rule-Selection and Action-Selection have a Shared Neuroanatomical Basis in the Human Prefrontal and Parietal Cortex. Cereb Cortex 18, 2275-2285.
Rowe, J., Stephan, K.E., Friston, K., Frackowiak, R., Lees, A., Passingham, R., 2002. Attention to action in Parkinson's disease: impaired effective connectivity among frontal cortical regions. Brain 125, 276-289.
Rowe, J.B., Eckstein, D., Braver, T., Owen, A.M., 2008b. How does reward expectation influence cognition in the human brain? J Cogn Neurosci 20, 1980-1992.
Rowe, J.B., Hughes, L., Ghosh, B.C., Eckstein, D., Williams-Gray, C.H., Fallon, S., Barker, R.A., Owen, A.M., 2008c. Parkinson's disease and dopaminergic therapy--differential effects on movement, reward and cognition. Brain.
Rowe, J.B., Sakai, K., Lund, T.E., Ramsoy, T., Christensen, M.S., Baare, W.F., Paulson, O.B., Passingham, R.E., 2007. Is the prefrontal cortex necessary for establishing cognitive sets? J Neurosci 27, 13303-13310.
Rowe, J.B., Siebner, H., Filipovic, S.R., Cordivari, C., Gerschlager, W., Rothwell, J., Frackowiak, R., 2006. Aging is associated with contrasting changes in local and distant cortical connectivity in the human motor system. Neuroimage 32, 747-760.
Rowe, J.B., Stephan, K.E., Friston, K., Frackowiak, R.S., Passingham, R.E., 2004. The Prefrontal Cortex shows Context-specific Changes in Effective Connectivity to Motor or Visual Cortex during the Selection of Action or Colour. Cereb Cortex 6, 6.
Rubia, K., Lee, F., Cleare, A.J., Tunstall, N., Fu, C.H., Brammer, M., McGuire, P., 2005. Tryptophan depletion reduces right inferior prefrontal activation during response inhibition in fast, event-related fMRI. Psychopharmacology (Berl) 179, 791-803.
Sakai, K., 2008. Task set and prefrontal cortex. Annu Rev Neurosci 31, 219-245.
Sakai, K., Passingham, R.E., 2003. Prefrontal interactions reflect future task operations. Nat Neurosci 6, 75-81.
Scatton, B., Javoy-Agid, F., Rouquier, L., Dubois, B., Agid, Y., 1983. Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain Res 275, 321-328.
Schrag, A., Jahanshahi, M., Quinn, N., 2000. What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry 69, 308-312.
Shidara, M., Richmond, B.J., 2002. Anterior cingulate: single neuronal signals related to degree of reward expectancy. Science 296, 1709-1711.
Stephan, K.E., Kasper, L., Harrison, L.M., Daunizeau, J., den Ouden, H.E., Breakspear, M., Friston, K.J., 2008. Nonlinear dynamic causal models for fMRI. Neuroimage 42, 649-662.
Swainson, R., Rogers, R.D., Sahakian, B.J., Summers, B.A., Polkey, C.E., Robbins, T.W., 2000. Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. Neuropsychologia 38, 596-612.
Thirion, B., Pinel, P., Meriaux, S., Roche, A., Dehaene, S., Poline, J.B., 2007. Analysis of a large fMRI cohort: Statistical and methodological issues for group analyses. Neuroimage 35, 105-120.
van den Brink, R.L., Pfeffer, T., Warren, C.M., Murphy, P.R., Tona, K.-D., van der Wee, N.J.A., Giltay, E., van Noorden, M.S., Rombouts, S.A.R.B., Donner, T.H., Nieuwenhuis, S., 2016. Catecholaminergic Neuromodulation Shapes Intrinsic MRI Functional Connectivity in the Human Brain. The Journal of Neuroscience 36, 7865.
Voon, V., Fox, S.H., 2007. Medication-related impulse control and repetitive behaviors in Parkinson disease. Arch Neurol 64, 1089-1096.
Voon, V., Hassan, K., Zurowski, M., de Souza, M., Thomsen, T., Fox, S., Lang, A.E., Miyasaki, J., 2006. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. Neurology 67, 1254-1257.

Warren, C.M., Eldar, E., van den Brink, R.L., Tona, K.-D., van der Wee, N.J., Giltay, E.J., van Noorden, M.S., Bosch, J.A., Wilson, R.C., Cohen, J.D., Nieuwenhuis, S., 2016. Catecholamine-Mediated Increases in Gain Enhance the Precision of Cortical Representations. The Journal of Neuroscience 36, 5699.
Wiese, H., Stude, P., Nebel, K., Forsting, M., de Greiff, A., 2005. Prefrontal cortex activity in self-initiated movements is condition-specific, but not movement-related. Neuroimage 28, 691-697.
Williams, D.R., Holton, J.L., Strand, C., Pittman, A., de Silva, R., Lees, A.J., Revesz, T., 2007. Pathological tau burden and distribution distinguishes progressive supranuclear palsy-parkinsonism from Richardson's syndrome. Brain 130, 1566-1576.
Williams-Gray, C.H., Foltynie, T., Brayne, C.E., Robbins, T.W., Barker, R.A., 2007a. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 130, 1787-1798.
Williams-Gray, C.H., Hampshire, A., Barker, R.A., Owen, A.M., 2008. Attentional control in Parkinson's disease is dependent on COMT val 158 met genotype. Brain 131, 397-408.
Williams-Gray, C.H., Hampshire, A., Robbins, T.W., Owen, A.M., Barker, R.A., 2007b. Catechol O-methyltransferase Val158Met genotype influences frontoparietal activity during planning in patients with Parkinson's disease. J Neurosci 27, 4832-4838.
Wingen, M., Kuypers, K.P., Ramaekers, J.G., 2007. Selective verbal and spatial memory impairment after 5-HT1A and 5-HT2A receptor blockade in healthy volunteers pre-treated with an SSRI. J Psychopharmacol 21, 477-485.
Yang, Y., Schmitt, H.P., 2001. Frontotemporal dementia: evidence for impairment of ascending serotoninergic but not noradrenergic innervation. Immunocytochemical and quantitative study using a graph method. Acta Neuropathol 101, 256-270.
Ye, Z., Altena, E., Nombela, C., Housden, C.R., Maxwell, H., Rittman, T., Huddleston, C., Rae, C.L., Regenthal, R., Sahakian, B.J., Barker, R.A., Robbins, T.W., Rowe, J.B., 2014a. Improving response inhibition in Parkinson's disease with Atomoxetine. Biological Psychiatry 77, 740-748.
Ye, Z., Altena, E., Nombela, C., Housden, C.R., Maxwell, H., Rittman, T., Huddleston, C., Rae, C.L., Regenthal, R., Sahakian, B.J., Barker, R.A., Robbins, T.W., Rowe, J.B., 2014b. Selective serotonin reuptake inhibition modulates response inhibition in Parkinson's disease. Brain 137, 1145-1155.
Zarit, S.H., Anthony, C.R., Boutselis, M., 1987. Interventions with care givers of dementia patients: comparison of two approaches. Psychology and Aging 2, 225.
Ziv, J., Lempel, A., 1977. A Universal Algorithm for Sequential Data Compression. IEEE Transactions on Information Theory 23, 337-343.