Brain mechanisms underlying option generation for behaviour



Yuen Siang Ang

Brasenose College

Nuffield Department of Clinical Neurosciences

University of Oxford

To my wife, who encouraged me to pursue my dreams, and the memory of my beloved mother, who helped shape me into who I am today.

In science, I am a magician who gets to wield Harry Potter's wand to create miracles; a sportsman who gets to fence with mysteries and problems of the universe; an artist that gets to paint the future of the world.

DECLARATION

This dissertation is the result of my own work and includes nothing that is the outcome of work done in collaboration except as declared in the Preface and specified in the text.

It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Oxford or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Oxford or any other University of similar institution except as declared in the Preface and specified in the text

In accordance with the Nuffield Department of Clinical Neuroscience guidelines, this thesis does not exceed 50,000 words, and it contains less than 150 figures.

Signed: 

Date: 29 April 2018

Yuen Siang Ang

University of Oxford

ABSTRACT

Brain mechanisms underlying option generation for behaviour (Yuen Siang Ang, Brasenose College)

This thesis examines the highly interlinked fields of voluntary action, apathy and option generation. Substantial research have now implicated the medial frontal cortex in voluntary actions, but the exact roles of each region remain unclear. Seeking clarity on this is important because the lack of self-generated behaviour is characteristic of apathy, a debilitating condition prevalent in neurodegenerative diseases and occurring to varying degrees in healthy individuals. Unfortunately, the conceptualization of apathy is currently unclear. Proposals of its underlying cognitive mechanisms have also mostly focused on deficits in selecting between options and learning outcomes during feedback. Intriguingly, the possibility that an inability to self-generate options may contribute to apathy has never been examined. This is because neuroscientific research on option generation is sparse.

Here, a major contribution was the advancement of our understanding of option generation for behaviour. As there was no suitable objective measure available in the current literature, a simple, quantitative and culture-free task to assess option generation was first developed. The task was then administered to patients with Parkinson's disease and utilised in two pharmacological studies of dopamine agonist (cabergoline) and antagonist (haloperidol). These provided the first direct evidence that dopamine modulates option generation for behaviour in humans, specifically in the aspects of fluency (generating many options) and uniqueness (how different each option is from others). The ability to generate options was also found to associate with apathy in the healthy population. Besides that, the multidimensional structure of apathy was examined via the development and rigorous validation of a new questionnaire known as the Apathy Motivation Index. Finally, a functional neuroimaging experiment in healthy individuals revealed that the pre-supplementary motor area plays a key role in planning during volitional decisions of what action to execute. Together, these findings have provided new insights and point to new directions for future work in this field.

ACKNOWLEDGEMENTS

Pursuing a PhD (or DPhil in Oxford) was something I have never seriously considered until the final years of my undergraduate degree. Even then, I remembered being apprehensive at this notion. This was not because I disliked science. In fact, I was already madly passionate about scientific research then! The main source of discouragement came from the numerous horrifying reports and personal anecdotes surrounding graduate school, particularly on how supervisors essentially exploit PhD students as cheap labour to further their own career without giving a hoot about their life or death.

I decided to take a risk after much consideration and ended up at Oxford with Masud. For the believers, I must have been born under a lucky star. Because Masud is the loveliest advisor every graduate student can literally wish for. He is patient, nurturing and always willing to listen. Coming from a physics background, I remembered being very unfamiliar with cognitive neuroscience when I first started and would knock on his office door in the old Tinburgen building every other day to ask him about – what I now know – are really basic stuff. Yet, he was always ready to answer all my (silly) questions with a smile. He takes a real interest in my personal development, giving much valuable advice to help improve my writing skills, presentation techniques and critical thinking ability. I am immensely grateful to Masud for making my DPhil journey such a wonderful and enjoyable one.

The best thing Masud did, however, was to create a wonderful environment where many brilliant individuals gathered together to work on research. I'll like to thank: Sanjay, for teaching me experimental task design and data scrutiny; Matt, for passing to me his knowledge on fMRI analysis; Sean, for all the wise advice on statistics; Pat, for the guidance on the wonderful AMI-related work; Kinan, Laura, Edwin and Raquel, for always being so upbeat and positive about everything; Campbell, for showing me how to perfectly balance work and family; Liv, Annika, Ellie, Ayat and Dan, for helping out with all the data collection on the AMI and testing of participants; Lisa, Youssuf and Sean, for the mamma mias and fun times out; and Tanja, for the interesting late-night discussions on imaging. Besides that, there are a few people that I had only a short overlap with and wished I had more time to know better: Annie, Trevor, Kathrin and Nahid, who made me feel right at home when I first joined the lab.

Outside of the lab, I would like to thank my secondary supervisor and college advisor, Chris Kennard, for looking after my welfare all these time and giving me plenty of useful advices on my research and career development. My transfer and confirmation examiners, Nick Yeung, Kate Watkins and Chrystalina

Antoniades, also gave me important guidance to ensure that my DPhil projects were progressing on the right track.

Despite these amazing academic supports, it was never easy doing a higher degree in a foreign country. Gratefully, there was the fantastic company of several fellow Singaporeans, especially Koon Hwee, Shiyu and Choon Boon. I will miss all the home-cooked food, mahjong, At Thai, Opium Den, Zheng, board games, TV series, movies, SG Day and all.

Finally, I would like to extend my gratitude to A*STAR. Without the fellowship from them, this amazing experience in Oxford would not have been possible.

CONTENTS

1 General Introduction 1
1.1 Voluntary Action 2
1.1.1 Timing of self-initiated actions ('when') 2
1.1.2 Volitional action selection ('what') 10
1.1.3 To act or not to act ('whether') 17
1.1.4 Summary 20
1.2 Apathy: a disorder of self-generated behaviour 21
1.2.1 Conceptualisations of apathy 21
1.2.2 Neural correlates of apathy 26
1.2.3 Cognitive mechanisms underlying apathy 30
1.2.3.1 Impairments in effort-reward analysis 30
1.2.3.2 Deficiencies in feedback learning 34
1.3 Option generation for self-generated behaviour 38
1.3.1 Defining options and option generation 38
1.3.2 Investigations of option generation 42
1.4 Summary and directions for this thesis 47
2 Characterising Apathy in Health and Disease 50
2.1 Introduction 50
2.2 Validating the Apathy Motivation Index (AMI) in healthy people 53
2.2.1 Exploratory factor analysis (EFA) 53
2.2.1.1 Procedure 53
2.2.1.2 Results 56
2.2.2 Confirmatory factor analysis (CFA), construct validity and reliability 59
2.2.2.1 Procedure 59
2.2.2.2 Results 63
2.2.3 Classification of apathy-motivation subtypes 69
2.2.3.1 Latent profile analysis (LPA) 69
2.2.3.2 Results 71
2.3 Multidimensional apathy in Parkinson's disease (PD) 78

2.3.1 Procedure 78
2.3.2 Results 80
2.3.2.1 Internal reliability, validity and diagnostic accuracy of the AMI 80
2.3.2.2 Selective impairment of apathy domains 80
2.3.2.3 Association of apathy domains with depression and anhedonia 83
2.4 Discussion 85
2.4.1 Healthy population 85
2.4.2 Parkinson's disease (PD) 89
2.5 Conclusion 91
3 Option Generation and Apathy in Healthy Population 93
3.1 Introduction 93
3.2 Procedure 99
3.2.1 Participants 99
3.2.2 External measures 100
3.2.3 Experimental setup 100
3.3 Option Generation Task 101
3.3.1 Description 101
3.3.2 Quantifying creativity 103
3.3.3 Results 107
3.4 Motor Execution Control Task 111
3.4.1 Description 111
3.4.2 Results 111
3.5 Externally-cued Action Control Task 114
3.5.1 Description 114
3.5.2 Results 114
3.6 Option Selection Control Task 118
3.6.1 Description 118
3.6.2 Results 118
3.7 Option Generation Task with obstacles 122
3.7.1 Description 122

3.7.2 Results 122
3.8 Discussion 126
3.8.1 Apathy is associated with reduced option generation 126
3.8.2 Only fluency contributed to the prediction of motivation level 128
3.9 Conclusion 129
4 Influence of Dopamine on Option Generation and Apathy in Parkinson's Disease 131
4.1 Introduction 131
4.2 Procedure 135
4.2.1 Participants 135
4.2.2 External measures 136
4.2.3 Experimental tasks 138
4.2.4 Statistical analysis 140
4.3 Results from option generation task 141
4.3.1 No effect of repeated testing was found 141
4.3.2 Apathy in PD did not relate to fluency or creativity 141
4.3.3 Dopamine modulates the balance between fluency and uniqueness 143
4.3.4 Dopamine increases uniqueness for a given fluency 147
4.3.5 Results were similar even when not correcting for mirror paths 148
4.3.2 Increased fluency ON dopamine is not due to improved motor deficits 152
4.4 Results from control tasks 154
4.4.1 Motor execution control task 154
4.4.2 Externally-cued action control task 156
4.4.3 Option selection control task 158
4.5 Discussion 162
4.5.1 Dual effects of dopamine on fluency and uniqueness 162
4.5.2 Deficits in option generation did not contribute to apathy in PD 164
4.6 Conclusion 165

5 Effect of Dopamine Agonist and Antagonist on Option Generation 167
5.1 Introduction 167
5.2 Study 1: Cabergoline 171
5.2.1 Methods 171
5.2.1.1 Participants 171
5.2.1.2 External measures 171
5.2.1.3 Experimental tasks 172
5.2.1.4 Statistical analysis 174
5.2.2 Results from option generation task 175
5.2.2.1 No effect of repeated testing was found 175
5.2.2.2 Dopamine modulates the balance between fluency and uniqueness 175
5.2.2.3 Cabergoline increases uniqueness for a given fluency 177
5.2.2.4 Results were similar even when not correcting for mirror paths 178
5.2.3 Results from control tasks 181
5.2.3.1 Motor execution task 181
5.2.3.2 Externally-cued action control task 181
5.2.3.3 Option selection control task 182
5.2.3.4 Cabergoline's improvement in fluency was specific to option generation 182
5.3 Study 2: Haloperidol 187
5.3.1 Methods 187
5.3.1.1 Participants 187
5.3.1.2 Experimental tasks 187
5.3.1.3 Statistical analysis 187
5.3.2 Results from option generation task 188
5.3.2.1 No effect of haloperidol on option generation task 188
5.3.2.2 Haloperidol increased uniqueness for a given fluency 190
5.3.2.3 Results were similar even when not correcting for mirror paths 190

5.3.3 Results from motor execution control task 193
5.3.4 Results from option generation task with obstacles 193
5.4 Discussion 196
5.4.1 Pharmacological mechanisms for findings in cabergoline are unclear 196
5.4.2 Limitations may explain unexpected pattern of results in haloperidol 198
5.5 Conclusion 200
6 Neural Mechanisms Underlying Planning of Voluntary Action 201
6.1 Introduction 201
6.2 Methods 206
6.2.1 Participants 206
6.2.2 External measures 207
6.2.3 Task design 207
6.2.4 Behavioural analysis 212
6.2.5 Functional imaging and analysis 212
6.2.5.1 Data acquisition 212
6.2.5.2 Image preprocessing 213
6.2.5.3 First-level statistical analyses 215
6.2.5.4 Second-level statistical analyses 216
6.3 Results 216
6.3.1 Behavioural data 216
6.3.2 Functional imaging data 219
6.3.2.1 Main effect of PLAN > PRESS 219
6.3.2.2 Activations for PLAN TWO FREE > PLAN NO FREE 221
6.3.2.3 Activations for PLAN ONE FREE > PLAN NO FREE 223
6.3.2.4 Activations for PLAN TWO FREE vs. PLAN ONE FREE 225
6.3.2.5 Activations for PRESS TWO FREE vs. PRESS NO FREE 227
6.3.2.6 Activations for PRESS ONE FREE vs. PRESS NO FREE 229
6.3.2.7 Activations for PRESS TWO FREE vs PRESS ONE FREE 231
6.3.2.8 Degree of increase in activation does not correlate with motivation 231

6.4 Discussion 232
6.4.1 Pre-SMA plays a role in freely selecting actions 232
6.4.2 Activation of posterior parietal cortex 235
6.5 Conclusion 237
7 General Discussion 238
7.1 Summary 238
7.1.1 Premise for thesis 238
7.1.2 Apathy in health and disease 240
7.1.3 Dopamine modulates option generation for behaviour 242
7.1.4 Pre-SMA plays a key role in planning freely selected actions 245
7.2 Greater perspicuity on the relationship between apathy and depression is required 247
7.3 Should the option generation task be framed in terms of creative cognition instead? 249
7.4 Role of serotonin in option generation? 252
7.5 Conclusion 254
8 References 256

LIST OF TABLES

Table

2.1 EFA on preliminary 51-item scale 54
2.2 Apathy Motivation Index (AMI) 58
2.3 Participant characteristics 61
2.4 Descriptive statistics of related measures 62
2.5 Proposed cut-offs for moderate and severe apathy on the AMI 65
2.6 Correlation between AMI and other measures 67
2.7 Latent Profile Analysis (LPA) model fit indices 72
2.8 Overall sample means and AMI conditional means 74
2.9 Descriptive statistics of related measures in PD and controls 79
4.1 Demographics and measures for PD patients and controls 137
4.2 Correlations between LARS and task variables in PD patients 142
4.3 Results from linear mixed model analysis in PD patients 150
5.1 Results from linear mixed model analysis in cabergoline 180
5.2 Results from linear mixed model analysis in haloperidol 191
6.1 Main effect of Plan > Press 219
6.2 Activations for PLAN TWO FREE > PLAN NO FREE 221
6.3 Activations for PLAN ONE FREE > PLAN NO FREE 223
6.4 Activations for PLAN TWO FREE < PLAN ONE FREE 225
6.5 Activations for PRESS TWO FREE > PRESS NO FREE 227
6.6 Activations for PRESS ONE FREE > PRESS NO FREE 229
6.7 Correlations between difference in activation and AMI 231

LIST OF FIGURES

Figure

1.1 Illustration of the two major components of the Bereitschaftspotential (BP) 3

1.2 Sagittal view of the human brain, highlighting regions in the medial frontal wall implicated in voluntary action 8

1.3 Activations found by Lau and colleagues (2004) 13

1.4 Pre-SMA activations reported by Nachev and colleagues (2005) 16

1.5 Activations reported by Brass and Haggard (2007) 19

1.6 Reciprocal connections between medial frontal and subcortical structures in the basal ganglia 29

1.7 T-maze barrier choice task to assess effort-based decision making 32

1.8 Schematic model of decision making based on the framework of Sinha et al. (2013) 37

1.9 Examples of output from a design fluency task 45

2.1 Apathy Motivation Index (AMI) factor model 64

2.2 Correlation coefficients between AMI subscales and established measures of depression, anhedonia and fatigue 68

2.3 Distribution of apathy along the AMI subscales and conditional response means of the 4-class solution 75

2.4 Relationships between apathy subtypes and depression, anhedonia and fatigue. 77

2.5 Validity and diagnostic accuracy of the AMI in PD 81

2.6 Comparison of apathy domains in PD against controls 82

2.7 Association of apathy domains with depression and anhedonia in PD and controls 84

3.1 Conceptual framework for making decisions to initiate actions 96

3.2 Illustration of the option generation task 102

3.3 Uniqueness metric 105

3.4 Visualisation of similarity subspace and pairwise distance matrix 106

3.5 Results from the option generation task in healthy people 109

3.6 Examples of path options produced by individuals 110

3.7 Illustration of the motor execution control task 112

3.8 Results from motor execution control task 113

3.9 Illustration of the externally-cued action control task 116
3.10 Results from the externally-cued action control task 117
3.11 Illustration of the option selection control task 120
3.12 Results from the option selection control task 121
3.13 Illustration of the option generation task with obstacles to paths 124
3.14 Results from the option generation task with obstacles to paths 125
4.1 Results from option generation task 145
4.2 Effect of dopamine on fluency and uniqueness of option generation 146
4.3 Results from the linear mixed effects (LME) model analysis in PD patients..... 149
4.4 Dual effects of dopamine on option generation 151
4.5 Correlation plots for disease severity on option generation..... 153
4.6 Result from motor execution control task 155
4.7 Result from externally-cued action control task..... 157
4.8 Result from option selection control task 159
4.9 Comparison of fluency per minute for different tasks in PD patients..... 161
5.1 Option generation task performance in healthy elderly people on cabergoline and placebo..... 176
5.2 Results from the linear mixed effects (LME) model analysis in cabergoline study 179
5.3 Result from motor execution control task 183
5.4 Result from externally-cued action control task..... 184
5.5 Result from option selection control task 185
5.6 Comparison of fluency per minute for different tasks in cabergoline 186
5.7 Option generation task performance in healthy young people on haloperidol and placebo 189
5.8 Results from the linear mixed effects (LME) model analysis in haloperidol study 192
5.9 Results from the motor execution control task in haloperidol study..... 194
5.10 Results from the option generation task with 0 and 4 barriers in haloperidol study 195
6.1 Regions of interest in this study 205
6.2 Illustration of the fMRI task 209
6.3 Behavioural results..... 218
6.4 Results of main effect PLAN > PRESS 220

6.5 Results of contrast PLAN TWO FREE > PLAN NO FREE 222
6.6 Results of contrast PLAN ONE FREE > PLAN NO FREE..... 224
6.7 Results of contrast PLAN TWO FREE < PLAN ONE FREE 226
6.8 Results of contrast PRESS TWO FREE > PRESS NO FREE..... 228
6.9 Results of contrast PRESS ONE FREE > PRESS NO FREE 230

List of Abbreviations and Acronyms

ACC	Anterior Cingulate Cortex
ACE	Addenbrooke's Cognitive Examination
AD	Alzheimer's Disease
AES	Apathy Evaluation Scale
AIC	Akaike's Information Criterion
ANOVA	Analysis of Variances
BA	Behavioural Activation
BDI	Beck's Depression Inventory
BIC	Bayes Information Criterion
BLRT	Bootstrap Likelihood Ratio Test
BP	Bereitschaftspotential
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
DAS	Dimensional Apathy Scale
DLPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalogram
EFA	Exploratory Factor Analysis
EM	Expectation Minimization
ES	Emotional Sensitivity
fMRI	Functional Magnetic Resonance Imaging
FWE	Family Wise Error
GDS	Geriatric Depression Scale
GLM	General Linear Model
LARS	Lille Apathy Rating Scale
LME	Linear Mixed Effects
LMRT	Lo-Mendell-Rubin test
LPA	Latent Profile Analysis
LPC	Lateral Premotor Cortex
LRT	Likelihood Ratio Test
MFIS	Modified Fatigue Impact Scale
OFC	Orbitofrontal Cortex

PCC	Posterior Cingulate Cortex
PD	Parkinson's Disease
PET	Positron Emission Tomography
pre-SMA	Presupplementary Motor Area
RMSEA	Root Mean Square Error of Approximation
RPE	Reward Prediction Error
SD	Standard Deviation
SHAPS	Snaith Hamilton Pleasure Scale
SM	Social Motivation
SMA	Supplementary Motor Area
SPM	Statistical Parametric Mapping
SRMR	Standardised Root Mean Square Residual
SSRI	Selective Serotonin Reuptake Inhibitor
UPDRS	Unified Parkinson's Disease Rating Scale
VS	Ventral Striatum
VTA	Ventral Tegmental Area

1 General Introduction

In this chapter, I will provide an overview of the interlinking fields of voluntary action, apathy and option generation (Mogenson et al., 1980). Voluntary action has important links to pathological apathy, a debilitating disorder of motivation characterised by the lack of self-generated behaviour (Marin, 1991). Unfortunately, the mechanisms underlying apathy are currently unclear. Considerations from a decision-making perspective suggest that impairments in generating options may be an important contributory factor (Sinha et al., 2013). Nonetheless, examinations of this possibility are hindered by the sparse and problematic research on option generation. Therefore, this thesis chiefly aims to advance our understanding of the brain mechanisms underlying option generation, a hugely neglected aspect of cognitive neuroscience research that lies within the intersection of voluntary action and apathy.

1.1 Voluntary Action

The generation of voluntary actions is considered to be a vital feature of human behaviour (Kalis et al., 2008; Haggard, 2008). Conceptually, voluntary actions are generated endogenously without any external agent. This distinguishes them from externally guided actions, which are produced in response to environmental stimuli or events. Voluntary action may be operationalised as choosing 'when' to execute a particular action, selecting 'what' predefined movement to perform, or deciding 'whether' or not to perform an action (Brass and Haggard, 2008). Each of these aspects will be briefly discussed below.

1.1.1 Timing of self-initiated actions ('when')

Research into the neural mechanisms underlying voluntary movement was inspired by a seminal electrophysiological study by Kornhuber and Deecke (1965), which revealed that a negative cortical wave or *Bereitschaftspotential* (BP) precedes self-paced internally generated movements in humans. The BP comprises two major components that likely arise from different cortical areas and reflect different processes (**Figure 1.1**; Shibasaki and Hallett, 2006). The early BP begins ~1000–2000ms before movement and slowly increases in negativity, bilaterally symmetrically with maximum amplitude at position Cz, located very close to the SMA (supplementary motor area). The late BP, on the other hand, sets in as a steep rise in negativity ~500ms prior to action and achieves maximal amplitude at the contralateral primary motor cortex with precise somatotopy.

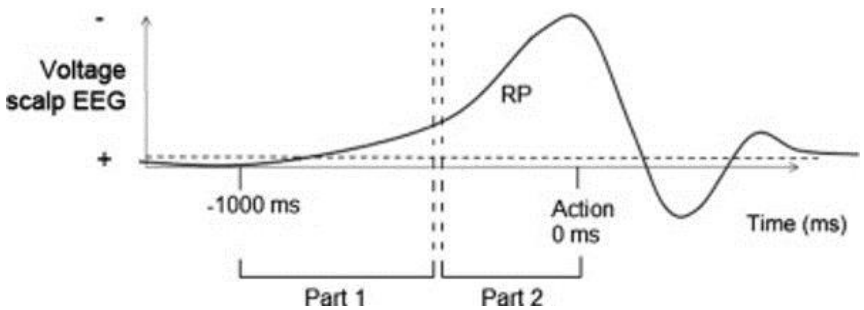


Figure 1.1 Illustration of the two major components of the Bereitschaftspotential (BP). The early BP (Part 1) begins ~1000–2000ms before movement as a slowly increasing negative wave. At ~500ms prior to action, the late BP then sets in and steeply rises in negativity until the peak amplitude (Part 2). Note that RP is the same as BP and is short for readiness potential. Image adapted from Verbaarschot et al. (2015).

Accurately localizing the source of the BP is extremely challenging (Neshige et al., 1988; Shibasaki and Hallett, 2006), with different source characterization approaches yielding slightly mixed findings. Many studies have found EEG (electroencephalogram) sources in the frontal medial wall including the SMA (Ball et al., 1999; Cui et al., 1999; Cunnington et al., 2003; Knösche et al., 1996; Praamstra et al., 1996), but some have also shown the contrary and suggested no contribution of SMA to the BP (Böcker et al., 1994; Bötzel et al., 1993). It is currently agreed that the BP likely starts in medial frontal regions, and subsequently cascades to premotor and motor regions (Haggard, 2008; Shibasaki and Hallett, 2006).

The BP's distinct waveform led to suggestions that the early component is involved in preparatory processes during voluntary actions whereas the late portion is for motor execution instead (Ball et al., 1999; Barrett et al., 1986; Shibasaki et al., 1980). If that is true, then cortical activity preceding self-paced and externally-paced movements should differ. This was verified by studies observing that the early BP was present when individuals decided by themselves when to move, but absent when movements had to be made according to external tones (Cunnington et al., 1995; Jahanshahi et al., 1995; Papa et al., 1991).

Given the preferential role of BP in voluntary action, Libet et al. (1983) examined whether that was related to conscious intention to act by asking participants to self-initiate hand movements. Crucially, at the same time, they watched a dot rotate quickly around a clock face and had to note and report the moment of desire to act. This urge began ~200ms before action execution whereas BP appears ~500ms prior

to movement onset, suggesting that BP causes both the movement and conscious intent to act.

However, there were many criticisms of Libet's paradigm (see e.g. Breitmeyer, 1985; Gomes, 1998, 2002; Klein, 2002; Pockett, 2002; Trevena and Miller, 2002; Brass and Haggard, 2008). For example, some argued that explicitly instructing participants to attend to awareness of the urge to act forces them to assign discretely separable onset times for 'wanting to move' and 'actual movement', even if they were not actually experienced as distinct events. This was indeed reported by several participants, suggesting that conscious intention may have been artificially imposed in the paradigm. Critics were also not convinced by the investigators' attempt to control for temporal judgment errors (Gomes, 2002, 1998; Klein, 2002). They used timing discrepancies in judging awareness of an external tactile stimulus to correct for any potential error in awareness of intrinsic intent to act, even though there was no evidence that they were equivalent.

Despite these issues, Libet and coworkers' results have been replicated by others (Brass and Haggard, 2007; Haggard and Eimer, 1999; Keller and Heckhausen, 1990; Lau et al., 2004). Furthermore, using fMRI (functional magnetic resonance imaging), greater activations in the pre-SMA (pre-supplementary area rather than the SMA proper) was observed when participants attended to their intention rather than action (Lau et al., 2004). This suggests an important role for the pre-SMA in the generation of voluntary movements, which is generally consistent with findings from other lines of research.

In primates, electrophysiological recordings have suggested a preferential role of the SMA and ACC (anterior cingulate cortex) in deciding when to act in the absence of external cues. Okano and Tanji (1987) recorded from monkeys performing a simple button-pressing task and found that a significantly larger proportion of SMA cells than LPC (lateral premotor cortex) fired earlier prior to movement onset. Most of these SMA neurons exhibited exclusive or preferential activity changes when the task was self-paced compared to externally-cued, suggesting that the SMA was involved in the preparation of self-initiated movements. These findings were largely consistent with a similar study conducted by Romo and Schultz (1987). However, Thaler et al. (1988) argued that the mixing of self-initiated and externally triggered trials in those studies meant that the monkeys might not be initiating movements by themselves, but were simply responding by treating the absence of a cue as an external trigger. Thus, they adopted a block design instead and similarly found that SMA activity in monkeys appeared earlier during voluntary relative to externally guided movements. These results were valid even when the movement involved a complex motor sequence (Mushiake et al., 1991).

Similar patterns were observed for the ACC. Single cell recordings of monkeys performing a self-paced key press task revealed a larger proportion of long lead cells that fired >500ms before movement onset in the ACC compared to the PCC (posterior cingulate cortex). Furthermore, these ACC neurons fired significantly earlier than those in the PCC, indicating a close relationship between the ACC and self-initiated movements (Shima et al., 1991).

If the SMA and ACC are indeed important for self-initiated actions, then lesions of these regions should be expected to impair such movements. This was confirmed in a series of well-controlled studies by Thaler and colleagues (1995). Monkeys with bilateral removal of either the SMA or ACC were poor at initiating self-paced movements on an arm-raising task, but performed normally when a tone was provided to prompt them. Crucially, the animals were tested in the dark thereby removing all visual cues that could serve as external triggers. These findings also cannot be attributed to paralysis or akinesia. The effects appeared to be specific to the medial frontal cortex as LPC lesions had little impact on the monkeys' attempts to initiate actions by themselves. However, many of these attempts were not successful at obtaining the reward, suggesting that this region was involved in controlling the amplitude and velocity of the motor action instead (Kurata and Hoffman, 1994). Together, these results indicate an important role for the SMA and ACC in self-initiated actions (Eccles, 1982; Goldberg, 1985).

Findings from functional imaging studies in humans are slightly mixed though. Many have implicated the pre-SMA, SMA and/or ACC in initiating voluntary movements (Figure 1.2; Rao et al., 1993, 1997; Wessel et al., 1997; Deiber et al., 1999; Jenkins et al., 2000; Cunnington et al., 2002; Debaere et al., 2003; Brass and Haggard, 2007). However, Remy et al. (1994) found the contrary, with auditory-cued finger movements activating the SMA and self-paced actions not. This likely arose because ten participants performed the internally-guided movements while only three completed the externally-guided action, which makes a comparison between both conditions very difficult.

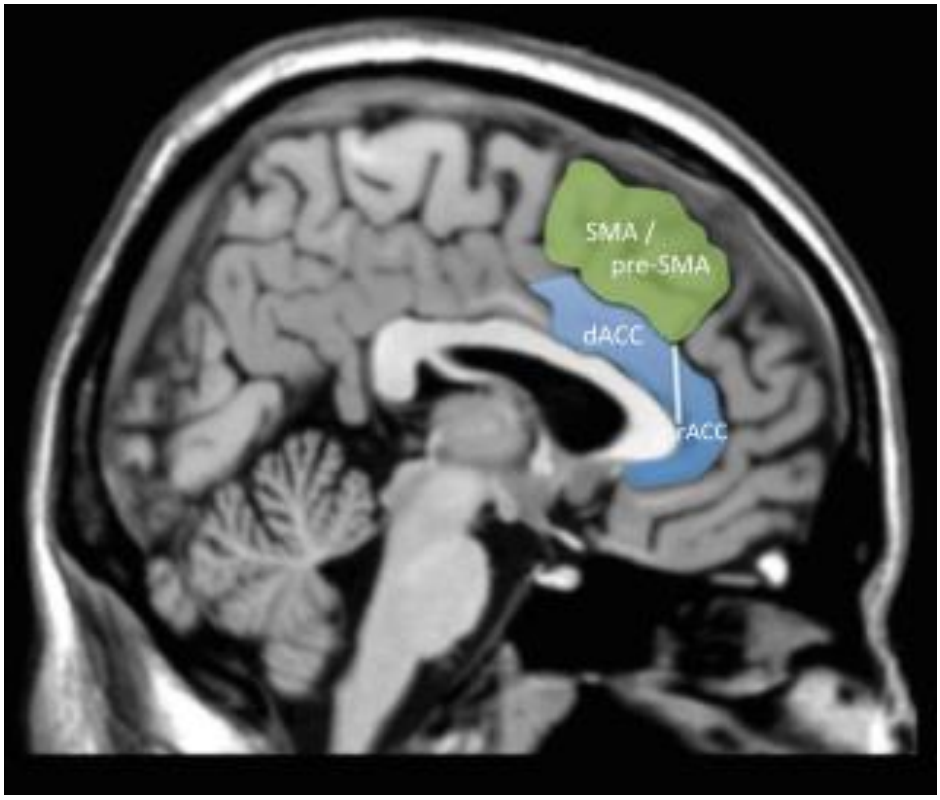


Figure 1.2 Sagittal view of the human brain, highlighting regions in the medial frontal wall implicated in voluntary action. Anatomical outlines of: SMA (supplementary motor area) and pre-SMA (presupplementary motor area) are shown in green; dorsal anterior cingulated cortex (dACC) and rostral anterior cingulated cortex (rACC) in blue. Figure adapted from Lieberman and Eisenberger (2015).

On the other hand, Jahanshahi et al. (1995) observed that similar structures including the SMA and ACC were activated in *both* the self-initiated and externally-guided states of a finger tapping task, suggesting no preferential involvement of any brain region in voluntary movements. This might be because the movement rate in the external mode was yoked to the internal condition, which was constant at once every 3 seconds and thus might have allowed stimulus anticipation and motor preparation to occur. To examine this possibility, two independent experiments were conducted in which internal movements now had to be generated at random intervals in order to ensure the yoked external movements were unpredictable (Deiber et al., 1999; Jenkins et al., 2000). As might be expected based on previous studies, both investigations reported greater activations of the pre-SMA and ACC when the self-initiated condition was compared to the externally-triggered mode.

One recent theory also proposed that the posterior parietal cortex, particularly the inferior parietal lobule, is responsible for generating the subjective experience of 'wanting to move' (Desmurget and Sirigu, 2009). Evidence for this comes from a direct electrical stimulation experiment on patients undergoing brain surgery (Desmurget et al., 2009). Intriguingly, stimulation of the inferior portion of the posterior parietal cortex resulted in patients reporting an intention to move certain parts of the body, e.g. lips, hands and chest. Crucially, desire to move was not reported when no current was applied, suggesting that conscious intention was a direct consequence of the electrical stimulation. Furthermore, the investigators argued that this reported desire

to move was not due to sensory feedback from contractions of muscles, as parietal stimulation did not result in any muscle activity.

Summarizing these findings, activity in the medial frontal wall appears to be strongly involved in the decision of 'when' to generate a movement. It might be more accurate to say, though, that this region is important for voluntary action in general – because it is also implicated in deciding 'what' movement to execute.

1.1.2 Volitional action selection ('what')

In 'what' experiments, movement is typically initiated in response to an external cue, but there is free choice between responses. Playford et al. (1992) compared participants moving a joystick either freely in any direction or in a single predetermined direction and found greater activation of the DLPFC (dorsolateral prefrontal cortex) during the unrestricted condition. Using a similar task, Deiber and colleagues (1991) demonstrated that free selection was associated with pre-SMA activity instead, although it must be noted that their two conditions were not matched in preparatory time for movement. A follow-up work addressed this potential confound and reported specific involvements of the pre-SMA and ACC in internal movement selection (Deiber et al., 1996). Another study that examined word generation and finger movement also reported increased activity in the DLPFC and ACC when free choice is allowed (Frith et al., 1991). Intriguingly, Van Oostende et al. (1997) did not find any difference in brain activation areas between free-selected and externally-guided finger movement.

One criticism of these early works is that participants are often told to freely select between actions without using rules or strategies (e.g. 'do not choose in a systematic pattern'), but such instructions in a block design paradigm may lead to efforts at generating a random sequence of responses instead (Brass and Haggard, 2008). In other words, random sequence generation might have been investigated instead of intentional action selection. To reduce this likelihood, recent studies have opted to randomly mix internally-guided trials with externally-guided ones. They similarly uncovered a preferential role for the DLPFC, pre-SMA and ACC, in volitional action selection (Cunnington et al., 2006; Lau et al., 2004; Mueller et al., 2007; Rowe et al., 2005; Thimm et al., 2012; van Eimeren et al., 2006).

It had been questioned, however, whether the DLPFC is truly involved in internal response generation or simply reflects the greater attentional demand needed for action selection when the response is not fully specified by external parameters (Lau et al., 2004). Alternatively, greater DLPFC activations might have arisen because free selection tasks impose larger working memory demands than a single repetitive movement task (Lau et al., 2004). Support for this interpretation comes from many studies in monkeys and humans that have implicated this region in working memory (Cohen et al., 1997; D'Esposito et al., 2000, 1998; Goldman-Rakic, 1995, 1992; Mottaghy et al., 2003; Mull and Seyal, 2001; Owen, 1997; Owen et al., 1998).

To resolve this issue, Lau and colleagues (2004) conducted an elegant event-related fMRI investigation in which participants had to move a small cursor to select from a given set of fractal images presented on a computer screen. There were three trial types. In the 'non-routine unspecified' condition, the cursor took the form of a

cross and selection was made freely. On the other hand, during the 'non-routine specified' mode, the cursor appeared as the target fractal that the individual had to search for and select. Finally for the 'routine specified' condition, the cursor was a white square and the participant had to choose the fractal enclosed within a big white circle. Analyses of the reaction times suggested that the attentional demands for both non-routine conditions were similar and that for routine was lowest. Furthermore, novel stimuli were used on every trial minimizing demands on working memory.

The investigators found that the activity of the DLPFC was greater on both non-routine modes compared to routine (Figure 1.3; Lau et al., 2004). Crucially, these activations did not differ from each other, even though one allowed free selection and another was externally guided. This suggested that the DLPFC is linked to attention for response selection but not internal response generation. Instead, the two non-routine conditions were distinguished by the pre-SMA, which showed greater activation when there is free choice.

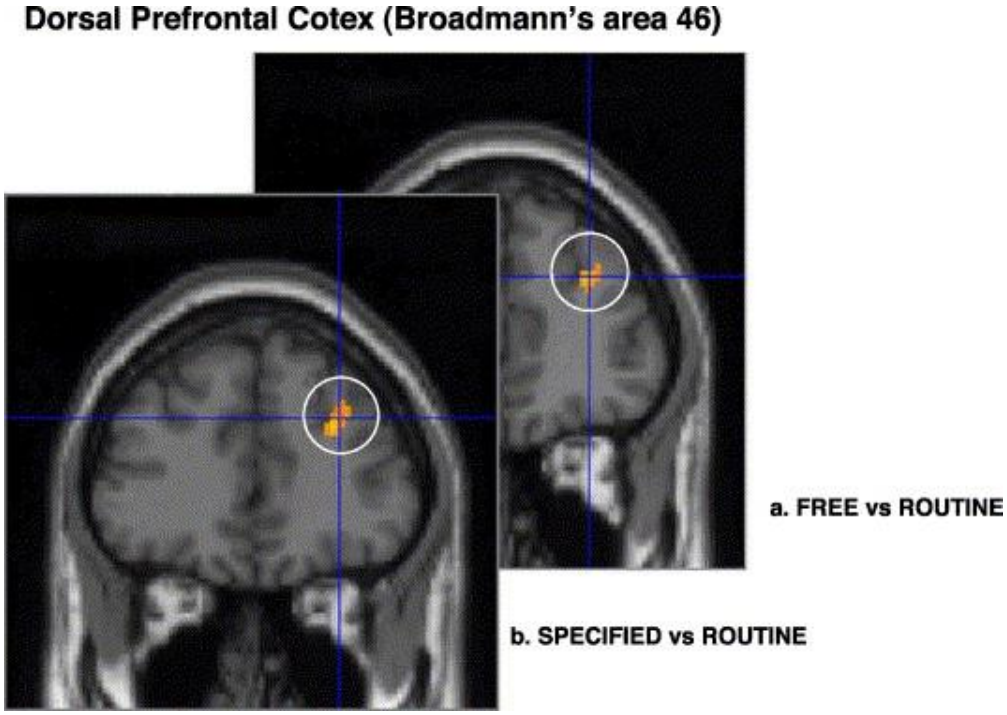


Figure 1.3 Activations found by Lau and colleagues (2004). Similar activations for the dorsolateral prefrontal cortex (DLPFC) were found when contrasting both the 'non-routine unspecified' (FREE) and 'non-routine specified' (SPECIFIED) against the 'routine specified' (ROUTINE) condition. This suggests that the DLPFC was linked to attention for response selection rather than internal response generation, as one allowed free selection while the other was externally instructed. Adapted from Lau et al. (2004).

A bigger controversy perhaps is the alternative interpretation that activity in the pre-SMA and ACC simply reflects conflict resolution (Botvinick et al., 2001) and not intentional selection processes. On this view, selecting in favour of a particular action requires the inhibition of competing alternatives. This competition is elevated in a free choice scenario because unlike externally-guided trials, there is no bias towards any one action thereby leading to presumably similar activation levels in the available choices. In line with this view, numerous studies have implicated the medial frontal cortex in conflict processing (see e.g. Rushworth et al. (2004) for review).

To clarify this, Lau et al. (2006) modified the Erikson Flanker task (Eriksen, 1995) to include a free condition displaying 'OOOOO', which required participants to decide by themselves whether to press a '<' or '>' arrow. The ACC was activated when contrasting the incongruent and congruent modes, indicating that this region was involved in response conflict. On the other hand, the pre-SMA distinguished between the free and congruent conditions. This led the investigators to conclude the pre-SMA was associated with intentional selection – a finding that must be interpreted with caution as their behavioural data suggested that the free selection mode was similar in conflict level to the incongruent condition, but much higher than the congruent condition. This means that the pre-SMA was activated not solely due to greater volition in choice, but also to higher response conflict. Surprisingly, they did not report any comparison of the free and incongruent modes, which would be relatively matched in conflict level but differ in degree of selection freedom.

Nachev and colleagues (2005), in contrast, developed a novel saccadic paradigm to independently manipulate volition and conflict. First, participants were asked to plan an eye movement towards one of two fixed targets either by themselves or via external direction (volition). They then had to follow through the original plan, or cancel it and rapidly saccade to the alternative target (conflict). These researchers found that the caudal pre-SMA responded exclusively to volition while the rostral pre-SMA was activated solely to conflict (**Figure 1.4**). No involvement of the ACC was observed, although it should be noted that conflict in this task is purely motoric and may involve brain regions different from conflict in cognitive tasks such as the Eriksen Flanker.

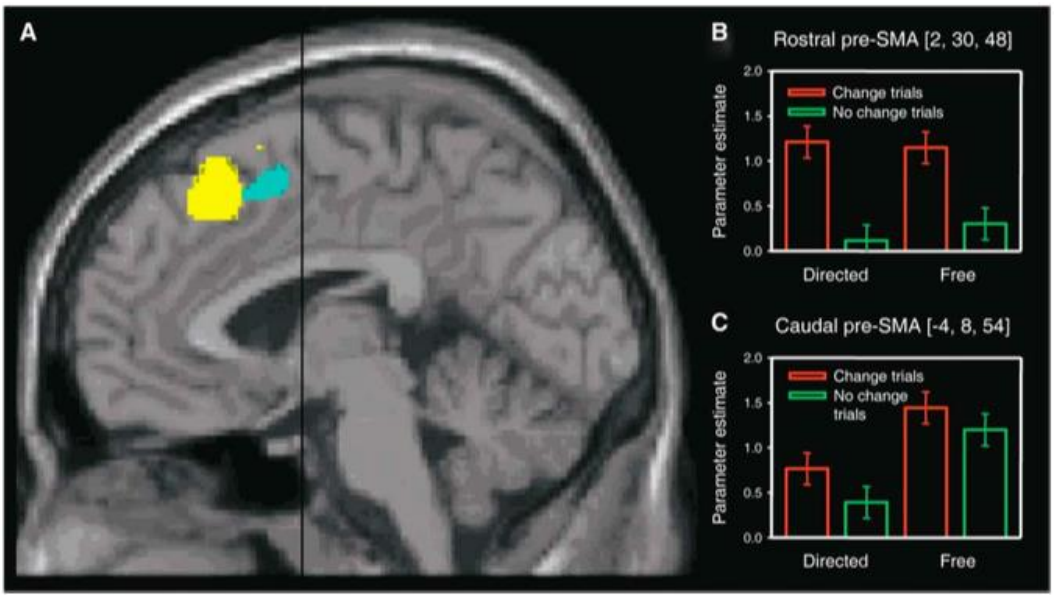


Figure 1.4 Pre-SMA activations reported by Nachev and colleagues (2005). (A) The rostral (in yellow) and caudal pre-SMA (in blue) are involved in conflict and volition respectively. (B) The rostral pre-SMA was activated for change trials in which the original action plan had to be cancelled and an alternative action has to be executed. This was regardless of whether the initial action was freely selected or externally directed, suggesting that this area responded solely to conflict. (C) On the other hand, the caudal pre-SMA exhibited greater activity when the action was freely selected compared to being externally directed. There was no effect of whether or not the action plan had to be changed later, suggesting that this region was involved exclusively in volition. Adapted from Nachev et al. (2005).

Attempts have also been made recently to dissociate the neural correlates relating to timing of self-initiated movement and volitional action selection. Krieghoff et al. (2009) designed a task in which participants had to first decide 'what' button to press either internally or externally. They then decide 'when' to make the movement out of two possible timings. These investigators found greater activations of the rostral cingulate zone and superior frontal gyrus for 'what' and 'when' respectively. Another study adapted the Libet paradigm so that participants spontaneously made a key press with either his left or right finger instead of one fixed finger. Using a multivariate approach, the researchers reported that deciding on 'when' to act was associated with the pre-SMA, whereas information relating to 'what' finger to move was decoded in the frontopolar cotex and precuneus (Soon et al., 2008). These results suggest that the 'when' and 'what' aspects of voluntary action may be functionally dissociated, although the exact locations require greater clarification.

Taking these findings together, the medial frontal cortex is consistently activated during intentional action. However, deciphering the exact roles closely neighbouring neural substrates within this region play remains a major challenge.

1.1.3 To act or not to act ('whether')

Unlike the 'when' and 'what' components, research on 'whether' to execute an action or not has been largely neglected. To investigate this, Brass and Haggard (2007) administered a modified version of the Libet task within the fMRI scanner, where participants had to self-initiate a key press at any time within a six-second window on each trial. Crucially, they could also choose to abort the motor plan and

intentionally withhold the key press. In both trial types, the time when they experienced intent to act had to be reported on a clock face. Intentional inhibition was associated with greater activations of a specific region in the medial frontal cortex anterior to the pre-SMA and dorsal to the rostral cingulate zone, suggesting the presence of a distinct neural correlate for self-control (Figure 1.5). However, one caveat of this study is that the reported activations were at uncorrected thresholds of $p<0.001$ and did not account for multiple comparisons (Poldrack et al., 2008). Moreover, it is difficult to tell whether endogenous inhibition really occurred in trials without a key press. Participants could have simply decided not to press on that trial and thus, not prepare any motor plan that has to be cancelled later.

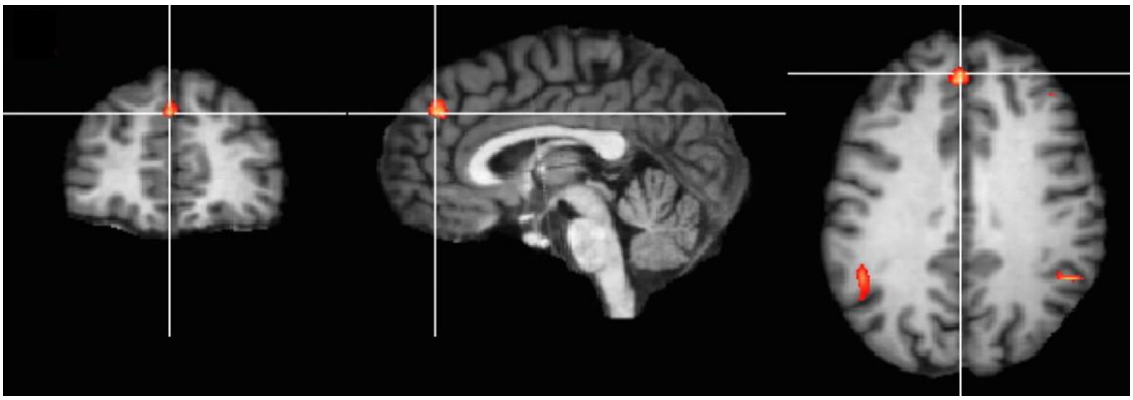


Figure 1.5 Activations reported by Brass and Haggard (2007). A specific region in the medial frontal cortex anterior to the pre-SMA and dorsal to the rostral cingulate zone was reported to be activated during intentional inhibition, suggesting this area was involved in whether or not to execute an action.

To overcome these limitations, Kühn and colleagues (2009) designed a task in which individuals watched a marble roll down a ramp. On ~40% of the trials, they had to make a key press as quickly as possible in order to stop the marble from falling off the ramp and shattering into pieces. Delayed responses were punished by loss of monetary reward. This induced in the participants a prepotent response to press the key whenever they saw the rolling marble. On another ~30% of trials, they decided whether to stop its motion or allow it to continue rolling without any implications of reward. Because the tendency now is to make a key press rather than not, as opposed to Brass and Haggard (2007), the investigators were confident that endogenous inhibition was taking place in the experiment. As in the previous study, they found similar activations in the dorso-frontomedian cortex during inhibition of intentional actions.

These two studies suggest that a specific region in the medial frontal wall, which is dissociable from those involved in internal selection and timing of action initiation, is important in the voluntary inhibition of planned actions.

1.1.4 Summary

The concept of voluntary action is not unitary, comprising of decisions on 'when' to initiate an action, 'what' action to execute and 'whether' or not to perform an action. Findings from various lines of research have consistently implicated the medial frontal cortex (e.g. pre-SMA and ACC) in these aspects of intentional movement, but there remains a lack of consistency on the exact locus of activations. More work will have to be conducted in order to clarify the neural basis of how

humans generate actions by themselves. This is important because a deficit of self-generated behaviour is considered to be a core feature of a debilitating disorder of motivation known as apathy (Levy and Dubois, 2006; Marin, 1991).

1.2 Apathy: a disorder of self-generated behaviour

Apathy is a complex neuropsychiatric syndrome characterised by reductions in goal-directed behaviour (Levy and Dubois, 2006; Marin, 1991). It is prevalent in neurodegenerative and psychiatric diseases e.g. Alzheimer's, Parkinson's and schizophrenia, significantly lowering the quality of life for these patients and their caregivers (den Brok et al., 2015; Evensen et al., 2012; Levenson et al., 2014; Pagonabarraga et al., 2015). Apathy also occurs to varying degrees in the healthy population, negatively impacting their everyday life in areas such as education and employment (Ang et al., 2017; Vansteenkiste et al., 2004, 2005). While these have been increasingly recognized in the clinical literature, there is no official diagnostic criterion for apathy as yet within the DSM-V (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) because of a lack of consensus on its conceptualization.

1.2.1 Conceptualisations of apathy

For more than a decade, apathy had been treated as a unitary syndrome arising from the "loss of motivation not attributable to emotional distress, intellectual impairment, or diminished level of consciousness" (Marin, 1991). Accordingly, various instruments were developed based on this description e.g. Apathy Evaluation Scale (Marin et al., 1991), Apathy Scale (Starkstein et al., 1995), apathy module of the

Neuropsychiatric Inventory (Cummings et al., 1994), Apathy Inventory (Robert et al., 2002), Dementia Apathy Interview and Rating (Strauss and Sperry, 2002) and Structured Clinical Interview for Apathy (Starkstein et al., 2005).

A psychological interpretation like lack of motivation, however, is unclear and incapable of describing clinical apathy objectively. Therefore, Levy and Dubois (2006) developed a theoretical account that defines apathy as a "quantitative reduction of self-generated voluntary and purposeful behaviour" instead. On this view, the disorder may arise from deficits occurring at any stage of goal-directed behaviour. Importantly, three sub-components were proposed, paving the way for research efforts into the multidimensional nature of apathy.

Accoriding the Levy and Dubois' conceptual framework, emotional-affective apathy arises from an inability to utilize emotional and affective signals for modulating behaviour. These patients would exhibit signs of blunted affect and loss of interests in activities previously enjoyed. Cognitive apathy, on the other hand, stems from deficits in executive functioning that interfere with plans to execute a task. Thus, affected individuals may default in organizing plans and maintaining goals for the future. Finally, auto-activation apathy broadly (and vaguely) describes people who have difficulty in generating actions internally, but are relatively normal when prompted to act by external agents or environment. These patients are likely to remain inert most of the time without any spontaneous speech or action. One reason for this might be due to the lack of motivation to make self-generated actions (Mogenson et al., 1980). Indeed, many caregivers of patients with apathy often report that they will not perform

actions voluntarily, but have no problem doing so when being asked to (i.e. externally-cued, Nobis and Husain, 2018).

This triadic theory of apathy led Radakovic and Abrahams (2014) to develop the Dimensional Apathy Scale (DAS). An exploratory factor analysis of this measure in the healthy population found three subscales that maps closely to Levy and Dubois's hypothesis, namely behavioural/cognitive inhibition, executive and emotional apathy. This makes the DAS a possible instrument for assessing multidimensional apathy. However, a confirmatory factor analysis has never been conducted in an independent sample to validate the factor structure, thereby reducing the reliability of this instrument.

In an alternative account, Sockeel et al. (2006) developed the Lille Apathy Rating Scale (LARS) based on their clinical experience and found a four factor structure of apathy instead. Other than emotional blunting, loss of intellectual curiosity and lack of action initiation – which relate respectively to the triadic framework of emotional-affective, cognitive and auto-activation apathy – the LARS also identified a new domain arising from the extinction of self-awareness. Patients suffering from this would not able to evaluate their own behaviour and adjust it to social requirements. One caveat of the LARS is, like the DAS, the proposed four-factor structure is based on an exploratory factor analysis and, to the best of my knowledge, has not been validated via a confirmatory factory analysis.

Some evidences also suggest that social apathy, which is characterised by poor engagement in and withdrawal from social interactions, might be an important separate domain or axis of apathy (Stuss et al., 2000). Support for this comes from an

exploratory factor analysis on the clinical version of the AES, which revealed the presence of a specific "social indifference" factor (Ahearn et al., 2012). Other factor analyses studies based on using the Geriatric Depression Scale to create an apathy scale have also yielded social withdrawal as a distinct subscale (Hollocks et al., 2015; Kim et al., 2013).

These studies highlight the rapid evolution in conceptualisations of apathy. While initially thought to be a unitary syndrome, apathy is now accepted to be multidimensional in nature. However, different methodologies have led to multifarious theories. As a result, the concept of apathy remains far from clear. This problem is further exacerbated by overlaps between apathy and other disorders that too present altered motivation e.g. depression and anhedonia.

A major challenge in describing apathy is distinguishing it from depression. Both conditions are often comorbid in different diseases and have overlapping symptoms such as a lack of self-initiated action and reduced goal-directed behaviour (Kirsch-Darrow et al., 2011, 2006). However, various studies have shown that apathy and depression – as defined by established questionnaires – can occur independently of each other (Kirsch-Darrow et al., 2011, 2006; Oguru et al., 2010; Pluck and Brown, 2002; Ziropadja et al., 2012). Factor analyses using the Apathy Scale and Beck's Depression Inventory also found that the two represent different constructs (Kirsch-Darrow et al., 2011). Furthermore, two recent studies acquiring functional resting state connectivity demonstrated that apathy and depression in Parkinson's disease (PD) are associated with different brain network dysfunctions (Baggio et al., 2015; Dan et al.,

2017). These emerging evidences strongly suggest that apathy may be a discriminable construct to depression.

Anhedonia is a core symptom of depression characterised by reduced interest or pleasure from stimuli previously perceived as rewarding. However, some studies suggest that it may also be related to apathy. PD patients with higher levels of apathy were reported to exhibit greater anhedonia (Pluck and Brown, 2002) and items used in clinical instruments to assess both symptoms often overlapped (Leentjens et al., 2008; Lieberman, 2006), although another study did not find any relationship between these two conditions (Isella et al., 2003).

Recently, it has been proposed that anhedonia can be subdivided into two components. The first is consummatory anhedonia, which refers to deficits in ability to experience pleasure. Anticipatory anhedonia, on the other hand, refers to an inability to link pleasure with particular actions (Gard et al., 2006). It has long been established that positive reinforcement is essential to maintain goal-directed behaviour (Everitt and Robbins, 2005). Given this relationship between motivation and reward, Jordan et al. (2013) posited and subsequently demonstrated that anticipatory, but not consummatory, anhedonia is correlated to apathy. This suggests that rather than responsiveness to rewards, apathy may be linked to reduced pursuit of goals.

An important issue though is that these studies reporting links between apathy and depression or anhedonia did not take into account the multidimensional nature of apathy. Seeking perspicuity on domains within apathy and establishing how each aspect is related to other comorbid symptoms in various diseases may be important for guiding the selection of therapeutic strategies. Besides this, another crucial

element pivotal to developing effective treatment paradigms is the understanding of brain mechanisms underlying apathy.

1.2.2 Neural correlates of apathy

Several studies utilizing a range of neuroimaging techniques in different neurodegenerative disorders have consistently linked apathy to disruptions of frontal or subcortical brain regions such as parts of the basal ganglia, or fronto-striatal circuits (for a recent review, see Le Heron et al., 2017).

In PD, resting state fMRI analyses have revealed that higher levels of apathy were related to reduced functional connectivity between the striatum and medial frontal areas including the ACC and OFC (orbitofrontal cortex) (Baggio et al., 2015; Dan et al., 2017; Skidmore et al., 2013). This is in line with investigations using structural MRI, which showed that greater severity of apathy associated with reduced frontal (Reijnders et al., 2010) and striatal volume (Carriere et al., 2014). Using PET (positron emission tomography), decreased metabolism in the ventral striatum (VS) (Robert et al., 2014), ACC and OFC (Huang et al., 2013) have also been observed to correlate with greater apathy. Moreover, apathetic PD patients show lower activations than those without apathy in the ventromedial prefrontal cortex, striatum, amygdala and midbrain when they performed a spatial search task for monetary reward (Lawrence et al., 2011).

Similar patterns of findings were observed in Alzheimer's disease (AD). Most of the studies utilized PET and SPECT (single-photon emission computed tomography), demonstrating associations between apathy in AD and reduced metabolism or

perfusion in various regions such as the ACC, OFC, VTA (ventral tegmental area) and DLPFC (Benoit et al., 2004; Holthoff et al., 2005; Kang et al., 2012; Lanctôt et al., 2007; Marshall et al., 2007; Migneco et al., 2001; Robert et al., 2006; Rosen et al., 2005; Schroeter et al., 2011). Apathy was also linked to gray matter atrophy in the ACC, OFC, DLPFC, caudate nucleus and putamen (Bruen et al., 2008; Tunnard et al., 2011) and reduced fractional anisotropy in the left anterior cingulum, which connects components of the limbic system including the ACC (Hahn et al., 2013; Kim et al., 2011).

A few studies have investigated the structural correlates of apathy in frontotemporal dementia and reported correlations of decreased gray matter volume in the ACC, OFC, insula and striatum with levels of apathy (Eslinger et al., 2012; Rosen et al., 2005; Zamboni et al., 2008), which generally agree with findings from PD and AD.

Finally, focal lesions of the anterior cingulate (Anderson et al., 2003; Mega and Cohenour, 1997; Tengvar et al., 2004) and basal ganglia involving the caudate nucleus or nucleus accumbens (Bhatia and Marsden, 1994; Gerace et al., 2013; Maeda et al., 2012; Phillips et al., 1987), thalamus (Engelborghs et al., 2000; Ghika-Schmid and Bogousslavsky, 2000; Krolak-Salmon et al., 2000; Nishio et al., 2011; Perren et al., 2005) and globus pallidus (Adam et al., 2013; Mega and Cohenour, 1997) have been clinically related to the development of apathy. In extreme cases, akinetic mutism occurs where patients exhibit complete loss of spontaneous speech and action despite being physically capable of doing so (Adam et al., 2013).

All these findings strongly link apathy to disruptions of the medial frontal cortex and subcortical structures in the basal ganglia (**Figure 1.6**). In particular, the ACC and VS, which receive strong monosynaptic dopaminergic inputs from the VTA, appear to be consistently identified across diseases (Le Heron et al., 2017). It is unclear how these areas are related to specific domains of apathy, but consideration of their functional properties may lead to insights on the cognitive mechanisms giving rise to the syndrome.

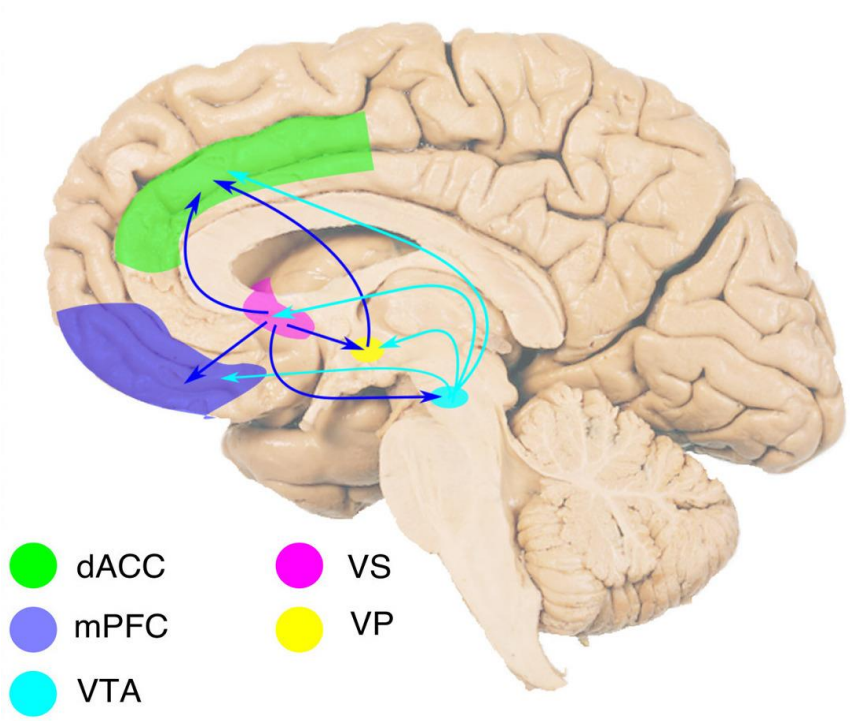


Figure 1.6 Reciprocal connections between medial frontal and subcortical structures in the basal ganglia. dACC: dorsal anterior cingulate cortex; mPFC: medial prefrontal cortex; VTA: ventral tegmental area; VS: ventral striatum; VP: ventral pallidum. Disruptions of these regions have been strongly linked to apathy. Adapted from Le Heron et al. (2017).

1.2.3 Cognitive mechanisms underlying apathy

1.2.3.1 Impairments in effort-reward analysis

A prominent, recent hypothesis postulates that impaired motivation may arise from deficits in analyzing the effort costs and reward benefits of performing actions. Specifically, it states that apathetic patients would exhibit reduced tendencies to engage in effortful behaviour either because they attribute a higher cost to performing the action, or are less incentivised by the reward, or both (Le Heron et al., 2017; Sinha et al., 2013). Support for this comes from many studies demonstrating that the ACC and VS, which have been consistently implicated in clinical apathy across diseases, encode the subjective value of whether it is worth exerting effort for reward in a task (Apps and Ramnani, 2014; Bonnelle et al., 2016; M. M. Botvinick et al., 2009; Burke et al., 2013; Chong et al., 2017; Croxson et al., 2009; Kennerley et al., 2009; Klein-Flugge et al., 2016; Kurniawan et al., 2010; Massar et al., 2015; Prévost et al., 2010; Schmidt et al., 2012; Scholl et al., 2015; Skvortsova et al., 2014; Vassena et al., 2014).

Recently, Bonnelle et al. (2015) developed a cost-benefit decision-making task that asked healthy people with a range of motivation levels to decide whether or not to exert a particular amount of effort for a certain magnitude of reward. By analyzing the pattern of choices, they estimated the extent to which every individual discounts effort from reward and reported that apathy in the healthy population was related to a greater subjective estimate of effort costs. Intriguingly, using the same task, Le Heron et al. (2018) found that apathy in PD occurs due to reduced incentivisation by reward instead. This is consistent with oculomotor findings that apathetic PD patients

exhibited lower sensitivity to monetary incentives, as indexed by their change in pupillary dilatation to reward magnitude (Muhammed et al., 2016) and peak saccadic velocity towards the rewarded target (Adam et al., 2013). Another study in schizophrenia required patients to choose between exerting no effort for a fixed small reward or exerting a certain amount of effort for a larger reward, and observed that apathy is related to both higher effort cost estimation and lower reward incentivisation (Hartmann et al., 2015). These findings strongly suggest that deficits in subjective valuations of effort-reward contribute to apathy. Importantly, apathy in different populations may arise from one of at least three ways: over-valuing effort costs, under-valuing reward offered, or a combination of both.

Much work on rodent models of effort-based decision making have now provided insights on the neurochemical regulation of motivation (see reviews by e.g. Chong et al., 2016; Salamone et al., 2016, 2018). In a classic T-maze procedure, rodents have to make a choice between two arms with different effort-related challenges and reinforcement densities (Figure 1.7, Salamone et al., 1994). One arm would contain a vertical barrier that they had to surmount in order to obtain a high density of food reinforcement (e.g. 4 pellets), while the other allows unobstructed access but offers less food in return (e.g. 2 pellets). The administration of dopamine D1 and D2 antagonists and depletion of nucleus accumbens dopamine significantly altered the rats' choices, reducing their selection of the high effort/ high reward side and increasing frequency towards the low effort/ low reward arm (Cousins et al., 1996; Denk et al., 2005; Mott et al., 2009; Salamone et al., 1994; Schweimer et al., 2005; Yohn et al., 2015).

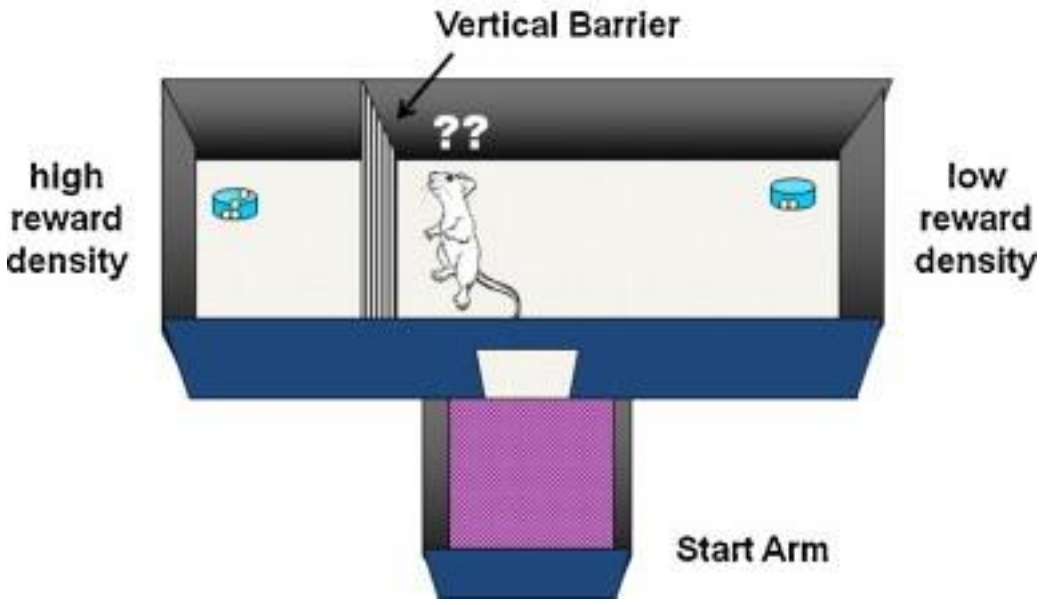


Figure 1.7 T-maze barrier choice task to assess effort-based decision making. Rats could choose to climb over a barrier in order to obtain a high density of food reinforcement, or settle for a low reward density that has no obstruction. Adapted from Markou et al. (2013).

Another commonly used procedure requires the rats to choose whether to respond on a fixed ratio lever pressing schedule for preferred food, or consume lab chow that is freely available within the chamber. At baseline, they typically opted to obtain food via lever pressing and consume little amounts of chow. However, D1 and D2 antagonists and neurotoxic depletions of accumbens dopamine have been found to shift their response allocation such that lever presses for food are reduced and consumption of chow is increased (Cousins et al., 1994, 1993; Farrar et al., 2010; Koch et al., 2000; Nowend et al., 2001; Salamone et al., 2002, 1991; Sink et al., 2008; Worden et al., 2009). In a progressive ratio version of this task, the number of operant responses to obtain the preferred food is incremented gradually over sequential trials. Similarly, dopamine antagonism was observed to reduce the maximum amount of effort the rat was willing to exert for the better reward (Randall et al., 2014, 2012; Schweimer and Hauber, 2005). Importantly, the low-effort biases in the T-maze and lever pressing tasks were not due to reductions in appetite, primary food motivation or motor performance (Cousins et al., 1996; Koch et al., 2000; Nowend et al., 2001; Randall et al., 2012; Salamone et al., 2002; Sink et al., 2008). The ACC, amygdala, ventral pallidal gamma-aminobutyric acid and adenosine have also been implicated in effort-reward decisions (Farrar et al., 2010, 2008, 2007; Floresco and Ghods-Sharifi, 2007; Font et al., 2008; Mott et al., 2009; Schweimer et al., 2005; Schweimer and Hauber, 2005; Walton et al., 2005, 2003, 2002; Worden et al., 2009).

However, the influence of serotonin on effort processing is less clear. Denk et al. (2005) observed that administration of a serotonin synthesis blocker has no effect on rats' preferences on the T-maze barrier task. Yet, other studies have found that the

selective serotonin reuptake inhibitor (SSRI) fluoxetine significantly reduced effort expenditure for preferred food in lever pressing paradigms (Sanders et al., 2007; Yohn et al., 2016). In humans, a recent study reported that chronic administration of the SSRI escitalopram improved willingness to exert effort in order to obtain a monetary reward (Meyniel et al., 2016). Crucially, this effect was specifically due to a reduction in effort cost and not an increase in weightage of the reward. This led the investigators to suggest that SSRIs might help to improve apathy by decreasing the perceived cost of action and promoting behavioural activation. Nonetheless, further investigations will be needed to examine this as previous studies have found contradictory effects of SSRI treatments on apathy. Several work have suggested that SSRIs can induce apathy (Barnhart et al., 2004; Padala et al., 2012; Sansone and Sansone, 2010; Wongpakaran et al., 2007), while others have reported that apathy may be improved instead (Mikami et al., 2013; Yuen et al., 2014).

1.2.3.2 Deficiencies in feedback learning

Another theory posits that apathetic patients may be deficient in monitoring and processing outcome-related information during feedback. They are unable to differentiate actions leading to beneficial outcomes from those that are unfavourable and thus do not properly modulate subsequent behaviour (Cohen and Ranganath, 2007; Le Heron et al., 2017). This proposal is based on a large literature implicating the ACC and VS in signaling reward prediction error (RPE) – the difference between expected and actual reward – during reinforcement learning. RPEs are important for updating the value of performing a particular action in future. A positive RPE indicates

that a larger reward than expected was received, thus increasing the action value. Conversely, a negative RPE implies that a smaller reward than anticipated was obtained thereby decreasing the action value (Carter et al., 1998; Hayden et al., 2011; Holroyd and Coles, 2008; Jahn et al., 2016; Jocham et al., 2009; Kolling et al., 2016; Lockwood et al., 2016; Matsumoto et al., 2007; McClure et al., 2003; O'Doherty et al., 2003; Rushworth and Behrens, 2008; Schultz, 2013; Schultz and Dickinson, 2000).

Martinez-Horta and colleagues (2014) tested this hypothesis by conducting electrophysiological recordings of apathetic and non-apathetic PD patients performing a gambling task. Apathy was associated with the blunting of feedback-related negativity – an event-related potential thought to reflect RPE signals derived from dopaminergic projections to the ACC (Walsh and Anderson, 2012) – after monetary gains and losses, suggesting impaired incentive processing in these patients. Another study using fMRI to investigate neural responsivity to gaining monetary rewards also reported lower activations in an extensive circuit including the ACC, striatum, amygdala and midbrain for apathetic compared to non-apathetic PD patients (Lawrence et al., 2011). Thus, the syndrome of apathy might be in part caused by an inability to learn the rewarding values of actions during outcome processing, thereby making them not worth performing in future.

In fact, these two proposed theories can be subsumed under 'impairments in decision-making' (Sinha et al., 2013). To achieve a goal, an individual has to first generate possible options for behaviour before evaluating them, acting on a chosen one and assessing the outcome (Figure 1.8). Therefore, an inability to weigh the effort

costs and reward benefits affects how options are selected and acted upon, while deficits in learning impair outcome assessment during feedback after action.

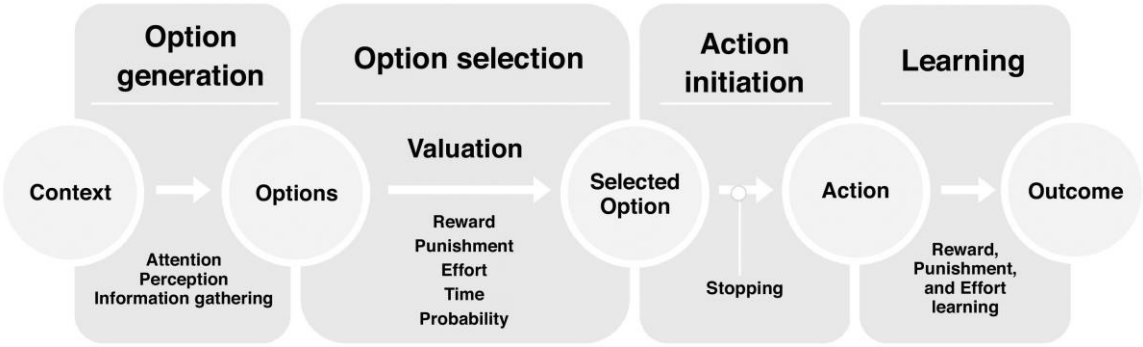


Figure 1.8 Schematic model of decision making based on the framework of Sinha et al. (2013). Initiating actions involves first generating possible courses of action (*option generation*); then evaluating and selecting from self-generated options and/or those prompted by external events, cues or rewards in the environment (*option selection*); developing motor plans to initiate behaviour (*action initiation*) and finally, the outcome is assessed (*learning*). For simplicity, this has been conceptualised as a serial process. Figure adapted from Nobis and Husain (2018).

On this perspective, an inability to self-generate options for behaviour might also lead to a paucity of actions characteristic of apathy. Intriguingly, research on option generation, especially in cognitive neuroscience, is sparse. As a result, our understanding of this phase of decision-making and how it might contribute to apathy is little.

1.3 Option generation for self-generated behaviour

1.3.1 Defining options and option generation

A major problem lies in the lack of an operational definition of an option, with at least three different notions of varying levels of abstractness being proposed or assumed by theoretical and empirical studies.

At the lowest level of abstraction, variations in kinematic parameters of the same primitive action have been assumed to result in distinguishable options. Several studies by Raab and colleagues showed handball and basketball players different scenes of an actual game and asked them to generate options for the next move by imagining they were the person with the ball. These investigators considered passes to the same player or shots at the opposing goal as distinct options, as long as they varied in trajectories. In other words, a loop throw at 30 degrees and at 45 degrees were deemed to be different even if the start and end point of the trajectory is the same (Johnson and Raab, 2003; Raab et al., 2009; Raab and Johnson, 2007).

A more abstract use of options may be observed in problem-solving tasks that typically allow a range of actions to be performed. For example, Klein et al. (1995)

presented chess players with different situations and required them to verbalize all the actions he was considering as the next move. Thus, options in this case would be steps to solve a problem i.e. possible chess moves deliberated by the participant out of all legal moves. Of course, executing the variety of chess moves could be argued simply as a variation in kinematics of the same primitive action. However, the mental representations in both scenarios are different because to the chess player, the nuances in angle or direction of movement are not what qualify the action as an option.

At the highest level of abstraction, options are construed as a series of temporally extended primitive actions. This commonly occurs in work on hierarchical reinforcement learning (Botvinick et al., 2009; Holroyd and Yeung, 2012). For example, driving a car might involve shifting the gear, stepping on the gas pedal and then turning the steering wheel etc. It is this sequence of primitive actions that would define the option of 'driving' when faced with a problem of how to get to work. An alternative option might be 'cycling', which would comprise a set of entirely different series of primitive actions to achieve.

Integrating these different units of representation, options could be construed as elements of action within a hierarchical decision-making structure (Kalis et al., 2013). In an unconstrained situation such as deciding what to do on a weekend, one might start with highly abstract options like sightseeing or exercising. Once that has been decided on say, exercising, more concrete options can be developed for what exercises to perform, which might include running, swimming or boxing. Down at the

finest level, the kinematics of the primitive movement may be considered e.g. how big a stride to make during a run.

Conceptualizing options in this way means that the process of option generation could also occur at the various corresponding levels. A crucial aspect, however, is that generating options is not equivalent to listing all possible manners of reaching the end-state. An option is an action representation that has been deliberated and might be decided on. For instance, skiing is a possible form of exercise on a weekend, but it is unlikely to be considered by an individual living in a hot tropical country and thus, would not qualify as an option even though it is a possibility. With this notion established, how then, might options be generated?

An influential account in operations research posits that hypothesis and/or solution generation relies on a complex search process through long term memory (Keller and Ho, 1988). It speculates that when a problem or goal is identified, knowledge in memory will be organized coherently into a cognitive network around nodes representing relevant information. Elements of the scenario and imposed constraints would trigger certain nodes, spreading the activations along its connections throughout the network. Presumably, solutions get generated when the level of activation in relevant nodes is of sufficient strength. Computer simulations based on this theory provide some support by showing that different solutions may be generated depending on the pattern of network activation (Lange et al., 2012; Thomas et al., 2008). Empirical studies asking people to generate solutions for a parking problem have also found that providing different contextual cues biases their output towards unique categories, suggesting that different starting nodes were likely

to have been triggered (Adelman et al., 1995; Gettys et al., 1987). It has been recognized, however, that such a memory-based model is insufficient for explaining how novel or unique solutions – or indeed, options – may be generated (Goel, 2010).

A dominant psychological account of creative cognition known as *geneplore* (generate and explore) states that originality in ideation proceeds in two stages. Preliminary structures, akin to nodes activated beyond a particular threshold, are first generated and then explored through associations or random recombination to create novel output (Finke et al., 1992). Thus, this may be viewed as an extension of the memory-based model rooted purely in association retrieval. It must be noted, however, that creative ideation may not be entirely similar to option generation. In creative ideation, novelty is the primary consideration whereas option generation focuses on candidate actions for goal-directed behaviour. This means that asking an individual to think creatively about what to do on a weekend might lead to products that he would not never consider acting on but are novel to him e.g. tightrope walking.

Nevertheless, these two processes still share a similar generative component. Thus, option generation likely involves similar cognitive mechanisms of long term memory retrieval and association recombination exploration. However, the brain mechanisms remain largely unknown due to the lack of objective and well-controlled empirical paradigms.

1.3.2 Investigations of option generation

Studies of option generation have typically focused on decision-making settings that are very specific, such as sports (Johnson and Raab, 2003; Raab et al., 2009; Raab and Johnson, 2007), chess (Klein et al., 1995) and car parking (Adelman et al., 1995; Del Missier et al., 2015; Gettys et al., 1987). These complex scenarios have the advantage of affording a wider range of possible options and are consequently more relevant to real life option generation. However in these domains, individuals may still be limited by their understanding of and familiarity with the domain being tested (Channon and Crawford, 1999; Kaiser et al., 2013).

A recent fMRI investigation by Kaiser et al. (2013) reported the anterior prefrontal cortex as the neural basis of option generation. The participants first saw simple hypothetical real world scenarios on each trial, e.g. "You win an expensive Porsche. What could you do?" They were then shown the word 'generate' and had eight seconds to think of as many options as they could. Crucially, the subjects pressed a button each time an option is generated instead of explicitly producing it. While this design helps to prevent excessive head motion, it also makes it difficult to track whether an individual was attending to the task. Furthermore, in a control condition, the investigators made participants read and memorize, in eight seconds, two to four options that were presented in succession e.g. "I can take it for a spin with my other half" or "I can sell it to earn money". This means that the 'generate' and 'control' conditions are not matched in terms of visual processing, language processing and working memory. Therefore, their findings need to be interpreted with caution.

Another study investigated the relationship between frontal and non-frontal lobe lesions to option generation in hypothetical social predicaments e.g. how to deal with new neighbours that have noisy dogs (Channon and Crawford, 1999). Patients with damage to the frontal lobe produced significantly fewer options in two minutes than those with non-frontal lesions. However, working memory might have affected their performance as the experimenters had to provide up to three prompts in order to help them recall details of the presented situation. Besides this, all of the statements produced were counted as options even if they simply represented abstract thoughts (e.g., "people should not keep dogs in flats") or actions that an individual was highly unlikely to consider due to legal issues (e.g., "shoot the dogs" or "kill the neighbours"). Thus, this paradigm may not be an accurate measure of option generation.

Peters and coworkers (2017) adopted a similar approach, but allowed unlimited time for responding. They found that patients with ventromedial frontal lesions generated significantly fewer options than those with frontal damage sparing this region, but only after removing statements of abstract thoughts and are unrealistic. In line with these results, other studies have reported that patients with damage to the prefrontal cortex exhibit significant difficulties in ill-structured open-ended scenarios despite showing no deficits in most cognitive domains (Burgess, 2000; Eslinger and Damasio, 1985; Goel et al., 1997).

The prefrontal cortex has also been implicated in neuropsychological tools of verbal and design fluency, which may serve as proxies of option generation. Verbal fluency tests ask participants to generate as many words as possible that begin with a

particular letter (e.g. 'F') or fall within a specific category (e.g. animals; Thurstone, 1938). Reduced fluency was commonly reported to occur after damage to the frontal lobe (Alvarez and Emory, 2006; Baldo et al., 2001; Baldo and Shimamura, 1998; Benton, 1968; Martin et al., 1990; Miceli et al., 1981; Milner, 1964; Pendleton et al., 1982; Perret, 1974; Robinson et al., 2012; Stuss et al., 1998; Tucha et al., 1999; Uslaner et al., 2006), although this deficit may not be frontal-specific as it has also been reported for posterior impairments (Coslett et al., 1991; Henry and Crawford, 2004; Stuss et al., 1998).

In design fluency tasks, subjects may be required to produce as many nonsense drawings as possible that do not resemble and are not developed based on real objects, create as many novel figures as they can using only four lines (Figure 1.9), or generate as many figures as possible by connecting at least two out of five dots arranged in a particular configuration (Jones-Gotman and Milner, 1977; Regard et al., 1982; Ruff et al., 1994). Similar to verbal fluency, impaired performance has been generally associated with dysfunction of the frontal lobe (Baldo et al., 2001; Jones-Gotman and Milner, 1977; Ruff et al., 1994; Tucha et al., 1999).

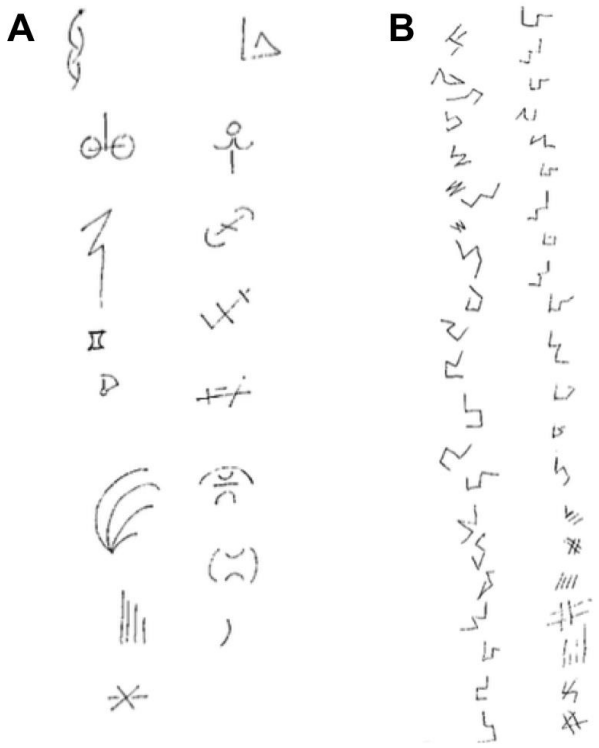


Figure 1.9 Examples of output from a design fluency task. Participants were required to produce as many novel figures as they can under a time constraint using only four lines. (A) Drawings produced by a healthy control. (B) Drawings generated by a patient with frontal lobe lesions, which shows a remarkable degree of preserveration. Figure modified from Jones-Gotman and Milner (1977).

One difficulty with interpreting these tasks is that options may be generated, but just not executed. In other words, these tasks cannot distinguish between option generation and action initiation. Performance may also be influenced by working memory ability, education and culture.

Another challenge in interpreting fluency tests is that the novelty of generated items is conflated with processing speed: individuals may choose to produce many simple items, or a few complex items. One way of dealing with this issue is to analyse the generated options qualitatively. For example, the novelty and uniqueness of a generated item can be quantified by its uncommonness in a standard corpus, or as its distance from other items (Jones and Mewhort, 2007). Using similarity metrics, search strategies in verbal fluency tasks can be modeled (Hills et al., 2015), but the space of options is again constrained by individuals' vocabularies. Moreover, verbal output is by nature discrete and the space of words is highly non-homogeneous.

The Alternate Uses Test (Guilford, 1967; Torrance, 1991) – a classical measure of divergent thinking – may also be used to assess option generation ability. In this task, participants are required to generate within a time limit as many alternate uses as they can for common objects such as a brick or shoe. Besides the number of valid responses (i.e. fluency), another main metric for evaluating performance is the novelty of the outputs (i.e. originality), which highlights an aspect of options that previously discussed paradigms do not address. Functional neuroimaging (Carlsson et al., 2000; Chávez-Eakle et al., 2007; Fink et al., 2009; Gibson et al., 2009; Gonen-Yaacovi et al., 2013; Jung et al., 2010; Moore et al., 2009) and lesion (Abraham et al., 2012; de Souza et al., 2010; Shamay-Tsoory et al., 2011) studies have consistently implicated

prefrontal regions for both fluency and originality in this task. However, this task suffers from the same problems that were already pointed out for verbal and design fluency tests. Furthermore, the assessment of originality relies on subjective third-party ratings that may not be reliable (Dietrich and Kanso, 2010).

Notwithstanding the limitations, all these studies strongly suggest an important role for the prefrontal cortex in the generation of many options (fluency) and the creativity of these options. The neurochemical modulation of option generation, on the other hand, is unknown.

A recent theoretical model of creative cognition by Boot and colleagues (2017) proposed a key role for dopamine in fluency and creativity. It was hypothesized that prefrontal dopamine and the mesocortical dopaminergic pathway facilitates persistence and fluency in generating many responses, while striatal dopamine and the nigrostriatal pathway enhances flexibility in thinking of original and novel products. Although there is currently no direct evidence for this proposal, the theory offers a useful starting point for investigating dopamine as the key neurotransmitter of option generation – which this thesis will pursue.

1.4 Summary and directions for this thesis

In this chapter, I have first provided evidences from a wealth of literature implicating the medial frontal cortex in voluntary action, specifically in decisions of 'when' to initiate a movement, 'what' actions to execute and 'whether' or not to perform a movement. Nonetheless, the specific role played by closely neighbouring

structures in this region remain unclear. Clarifying the neural basis of how humans generate actions by themselves is important because the lack of self-generated behaviour is characteristic of clinical apathy – a debilitating disorder of motivation that has only been recently recognized. The conceptualization of apathy is still under debate, although researchers now generally agree that it is multidimensional in nature. More surprisingly, the construct of apathy has never been examined in the healthy population. Mechanistically, investigations into the neural correlates of apathy have provided a fairly consistent picture by regularly implicating disruptions of the medial frontal cortex and subcortical basal ganglia structures, particularly the ACC and VS, across neurodegenerative diseases. Consideration of the functional properties of these regions led to proposals of underlying cognitive mechanisms centered on deficits in selecting between options and learning outcomes during feedback. Intriguingly, the possibility that an inability to self-generate action options may also contribute to apathy has barely been considered. This stems from a general lack of research on option generation and challenges in developing an objective way to specifically measure this process.

Chapter 2 will describe the development and rigorous validation of a new tool suitable for measuring apathy in healthy people and patients with neurodegenerative diseases – the Apathy Motivation Index (AMI). This instrument forms the basis for assessing apathy in later empirical investigations that will be discussed in chapters 3 and 6.

In chapter 3, I will introduce a simple new paradigm that measures option generation in an objective quantifiable manner. This task is used to explore the

relationship between the ability to self-generate options and apathy in the healthy population.

Chapter 4 will survey the same question but with a focus on clinical apathy in PD instead. I will also investigate the influence of dopamine levels on option generation by comparing the performance of PD patients after taking versus withdrawing from their dopaminergic medication.

Chapter 5 further pursues the role of dopamine in option generation via two pharmacological manipulation studies in the healthy population, specifically cabergoline (D2 receptor agonist) and haloperidol (D2 receptor antagonist).

In chapter 6, I will attempt to clarify, partially, the neural basis of how humans self-generate actions. This is achieved by conducting a functional neuroimaging study that investigates the brain areas implicated in the planning of freely selected actions.

Finally, the thesis will conclude with a general discussion of how all of the empirical findings together advance our understanding of brain mechanisms underlying option generation, a hugely neglected aspect of cognitive neuroscience research that lies within the intersection of voluntary action and apathy.

2 CHARACTERISING APATHY IN HEALTH AND DISEASE

2.1 Introduction

Apathy is a disorder of motivation characterized by reduced action initiation and goal-directed behaviour (Levy and Dubois, 2006; Marin, 1991). Although it is very common in several neurological and psychiatric disorders such as Parkinson's disease (PD), it is also apparent to varying degrees in healthy people. A lack of motivation can significantly diminish the quality of life for patients and their caregivers, and affect the everyday life of healthy individuals particularly in education and employment opportunities (Barone et al., 2009; Bonnelle et al., 2016; Kiang et al., 2003; Kirsch-Darrow et al., 2006; Landes et al., 2001; Muhammed and Husain, 2016; Pagonabarraga et al., 2015; Vansteenkiste et al., 2004, 2005).

Theoretical accounts have proposed that apathy is a multidimensional construct which actually covers motivation within dissociable domains: cognitive, emotional/affective and behavioural (Levy and Dubois, 2006; Marin et al., 1991). Self-report and clinical administered measures have now been developed to characterize apathy in clinical samples based on this multidimensional construct, specifically the Lille Apathy Rating Scale (LARS, Sockeel et al., 2006) and Dimensional Apathy Scale (DAS, Radakovic and Abrahams, 2014). However, currently there is no validated assessment of apathy in healthy people. As a result, the mechanisms underlying variability in apathy are still poorly understood. It is also unknown whether different domains of apathy can be identified in healthy people, and whether they might be dissociable across individuals.

Besides that, despite the high prevalence of apathy in PD, it is unclear whether all domains of apathy are affected. Only two previous studies have examined this using the DAS, albeit with mixed results. Santangelo et al. (2017) reported greater emotional apathy but preserved executive motivation in PD compared to controls, while Radakovic and colleagues (2017) found the opposite instead with preserved emotional motivation and greater executive apathy.

While apathy is a common syndrome associated with altered motivation, it is also frequently comorbid with other states which may have symptoms of reduced motivation, particularly depression, anhedonia and fatigue (Muhammed and Husain, 2016; Pagonabarraga et al., 2015; Pluck and Brown, 2002; Skorvanek et al., 2015). In clinical disorders such as PD, it is now established that apathy is frequently linked to depression, with many overlapping symptoms including loss of interest and lack of

initiative (Kirsch-Darrow et al., 2011). However, there is also evidence that apathy and depression may be separable, particularly in the domain of affect (Kirsch-Darrow et al., 2011, 2006). Thus anhedonia, or loss in pleasure derived from activities one used to enjoy, is correlated with apathy in PD (Pluck and Brown, 2002) and items used in the assessment of both symptoms are often overlapping (Leentjens et al., 2008; Lieberman, 2006). Recently fatigue – the feeling of exhaustion caused by the exertion of effort, which is unrelated to actual exertion of energy by muscles – has also been shown to associate with apathy in clinical disorders such as PD and multiple scelerosis (Cochrane et al., 2015; Skorvanek et al., 2015).

Despite these evidences of links between apathy and depression, anhedonia and fatigue in neurological conditions, it remains to be established whether different apathy domains in PD relate specifically to these syndromes. Furthermore, are there similar specific links in the healthy population?

Here, I first adapted the LARS (Sockeel et al., 2006), a semi-structured interview of clinical apathy, to produce and validate a novel self-report measure of assessing apathy in healthy people: the Apathy Motivation Index (AMI). The most rigorous psychometric procedures were then used to dissect out the different factors comprising the AMI and determine whether other comorbid states are related to distinct domains of apathy. It was hypothesized that after developing this new index, distinct subtypes of apathy in the general population would be identified and differentially associated with depression, anhedonia and fatigue.

Following that, the AMI was applied to examine the multidimensional profile of apathy in PD. This was achieved by first establishing the reliability and validity of the

AMI in PD by comparing the measurement of apathy using the AMI to the LARS. Next, I assessed whether there are differences in apathy dimensions in patients with PD compared to healthy controls, and whether the different domains of apathy exhibit differential associations with depression and anhedonia.

2.2 Validating the Apathy Motivation Index (AMI) in healthy people

2.2.1 Exploratory factor analysis (EFA)

2.2.1.1 Procedure

505 healthy people were recruited from the local communities via online adverts and posters (211 males, 271 females, 23 gender undisclosed, mean age=28.7 years, SD=14.9, range=16–85, N=27 age undisclosed). They gave written informed consent and the study was approved by the University of Oxford ethics committee. Methods were carried out in accordance with the relevant guidelines and regulations.

The initial item validation was adapted from the LARS (Sockeel et al., 2006). To create a comparable measure suitable for the general population, a team of clinical neurologists and university researchers developed, based on their experience with clinically apathetic patients, novel items to specifically reflect each domain of the LARS. Items from the clinical LARS that were deemed to be applicable to healthy people were also adapted. This gave rise to a preliminary 51-item scale that all participants completed (Table 2.1), which was also used in Chapter 3.

Table 2.1: EFA on preliminary 51-item scale

Item	In the last 2 weeks…	Loadings on factor		
		1	2	3
1	I felt bad when I heard an acquaintance had had an accident or illness.	0.486	0.055	0.154
2	I didn't like to laze around.	0.053	0.561	-0.108
3	If a new restaurant opened locally, I'd want to try it out.	-0.033	-0.051	0.429
4	If I realized I'd been unpleasant to someone, I felt terribly guilty afterwards.	0.724	-0.067	-0.088
5	I liked to have a busy schedule.	-0.057	0.456	0.192
6	I started conversations with random people.	-0.124	0.039	0.537
7	I usually got up in the morning even if I didn't have to go to work.	0.097	0.413	-0.148
8	When I didn't manage to do something, I tried to find other solutions.	-0.016	0.479	0.118
9	I enjoyed spending time with my friends.	0.046	-0.042	0.517
10	If I couldn't do something, I accepted help from others.	0.024	0.001	0.375
11	I got things done when they need to be done, without being reminded by others.	0.002	0.656	-0.021
12	I made decisions firmly and without hesitation.	-0.285	0.576	0.110
13	If someone had asked me "Would you like to visit every continent in the world?" I'd have said yes.	-0.025	-0.005	0.243
14	When I had something I needed to do, I did it straightaway so it was out of the way.	-0.021	0.750	-0.240
15	I changed my mind during an argument when I realised the other person might be right.	0.297	0.071	0.068
16	I liked being in charge.	-0.158	0.235	0.197
17	If I had made a list of my attributes, my ability to push myself to achieve would have been one of them.	-0.031	0.532	0.098
18	I laughed out loud when listening to a comedy show.	0.101	-0.053	0.317
19	I enjoyed visiting new places.	0.006	0.030	0.500
20	When I couldn't find something (e.g. a document), I went to a lot of trouble looking for it.	0.214	0.164	-0.022
21	Based on the last 2 weeks, I'd say I care deeply how my loved ones think of me.	0.462	0.024	0.024
22	If I didn't achieve my goals for the day, I got annoyed.	0.307	0.121	-0.052
23	I felt sad or upset when I heard bad news.	0.559	-0.091	0.028
24	If I had to RSVP to an invitation, I did it promptly, without needing a reminder.	-0.001	0.406	0.124
25	I suggested activities for me and my friends to do.	0.002	-0.059	0.624
26	I enjoyed choosing what to do from a range of activities.	-0.140	0.122	0.601
27	I enjoyed doing things with people I'd just met.	-0.125	0.023	0.655
28	I was easily able to decide to do things by myself,	-0.038	0.559	0.215

	without needing someone to push or encourage me.			
29	I started conversations without being prompted.	-0.105	0.019	0.574
30	When I listened to music, it could affect me deeply.	0.169	-0.110	0.191
31	I enjoyed trying out products, tools or recipes that I was unfamiliar with.	0.062	-0.010	0.388
32	After having taken a decision, I wondered if I'd made the wrong choice.	0.512	-0.280	-0.012
33	When I decided to do something, I was motivated to see it through to the end.	0.033	0.622	-0.028
34	If I hadn't seen a close friend for a while, I got in touch by phone/internet.	0.095	-0.020	0.429
35	When I finished doing something, I took stock of the situation to identify what was going well and what wasn't.	0.168	0.419	0.024
36	I enjoyed learning new things at work.	0.106	0.262	0.281
37	I was pleased when I received unexpected invitations from friends.	0.188	-0.107	0.454
38	I would say I've been quite interested in life.	-0.004	0.372	0.306
39	When I decided to do something, I was easily able to make an effort.	-0.037	0.642	0.049
40	I felt awful if I said something insensitive.	0.779	0.020	-0.128
41	I've been feeling there is so much to do in life and I want to try everything.	0.072	0.113	0.345
42	When someone told me a joke I laughed easily.	0.161	0.035	0.320
43	Getting something done by 9am gave me a sense of satisfaction.	0.264	0.342	-0.089
44	If, during a discussion, I realised I was in the wrong, I admitted it – at least to myself.	0.251	0.114	0.086
45	I've been going out with friends on a weekly basis.	-0.052	-0.099	0.538
46	I found it annoying when I was in the middle of doing a task at work and I had to stop to do something else.	0.237	0.073	-0.114
47	I wished I had more spare time for hobbies and leisure activities.	0.163	0.077	-0.041
48	If I thought of something I needed to do, I wrote it down so I wouldn't forget.	0.142	0.241	0.011
49	I tried out new ways of doing things at work or home.	0.089	0.253	0.167
50	I felt anxious when I was waiting to hear important news (e.g. exam result or job interview).	0.359	-0.063	0.013
51	I was easily 'moved' by films/TV programs.	0.286	-0.164	0.189

Participants were asked to self-rate each item on a five-point Likert scale by deciding how true that statement was based on the past two weeks of their life. The scale ranged from 0 – 4 (with 0 = 'completely untrue', 4 = 'completely true'). An "N/A" option was also available for items that were not applicable. Each item was scored so that a higher rating indicated more motivation (i.e. less apathy).

An exploratory factor analysis (EFA) with promax rotation was conducted in MPlus (Muthen and Muthen, 1998) to examine the latent structure of this 51-item apathy questionnaire. The exploratory-derived solutions were assessed by scree plot (Cattell, 1966) and two absolute fit indices: Root Mean Square Error of Approximation (RMSEA) and Standardised Root Mean Square Residual (SRMR). A value of RMSEA and SRMR less than 0.08 is generally considered to be reasonable (Hu and Bentler, 1999).

2.2.1.2 Results

A simple three-factor structure was the most parsimonious account of the data. This structure had good model fit (RMSEA=0.051 with 90% confidence interval of 0.048–0.053, SRMR=0.05) and was supported by scree plot, which showed the characteristic "elbow" or plateau in eigenvalues after 3 factors. After the EFA, twenty-one items were excluded, as their loadings were less than 0.40 (Table 2.1).

Next the six highest loading items for each factor were retained to form a revised 18-item Apathy Motivation Index (AMI, also used in Chapter 6). These three factors were labeled according to their common themes as (1) *behavioural activation* (BA): tendency to self-initiate goal-directed behaviour (e.g. I get things done when they need to be done, without requiring reminders from others), (2) *social motivation*

(SM): level of engagement in social interactions (e.g. I start conversations without being prompted), and (3) *emotional sensitivity* (ES): feelings of positive and negative affection (e.g. I feel awful if I say something insensitive). Each of the six questions for the three subscales is shown in Table 2.2. The EFA loadings for each subscale were good (BA: 0.56–0.75; SM: 0.54–0.66; ES: 0.46–0.78).

At this point, it was decided that each item in the AMI should be negatively scored instead so that a higher score indicates greater apathy. The "N/A" option was also removed.

Table 2.2: Apathy Motivation Index (AMI)

Item	Subscale	Statement
1	ES	I feel sad or upset when I hear bad news.
2	SM	I start conversations with random people.
3	SM	I enjoy doing things with people I have just met.
4	SM	I suggest activities for me and my friends to do.
5	BA	I make decisions firmly and without hesitation.
6	ES	After making a decision, I will wonder if I have made the wrong choice.
7	ES	Based on the last two weeks, I would say I care deeply about how my loved ones think of me.
8	SM	I go out with friends on a weekly basis.
9	BA	When I decide to do something, I am able to make an effort easily.
10	BA	I don't like to laze around.
11	BA	I get things done when they need to be done, without requiring reminders from others.
12	BA	When I decide to do something, I am motivated to see it through to the end.
13	ES	I feel awful if I say something insensitive.
14	SM	I start conversations without being prompted.
15	BA	When I have something I need to do, I do it straightaway so it is out of the way.
16	ES	I feel bad when I hear an acquaintance has an accident or illness.
17	SM	I enjoy choosing what to do from a range of activities.
18	ES	If I realize I have been unpleasant to someone, I will feel terrible guilty afterwards.

Note: BA=Behavioural Activation. SM=Social Motivation. ES=Emotional Sensitivity. Participants have to rate, based on the last two weeks, how true each statement is ('completely untrue', 'mostly untrue', 'neither true nor untrue', 'quite true', or 'completely true'). Each item is negatively scored such that a higher score indicates greater apathy (4 = 'completely untrue', 0 = 'completely true') and level of apathy is assessed by taking the mean rating of the items within the subscale.

2.2.2 Confirmatory factor analysis (CFA), construct validity and reliability

2.2.2.1 Procedure

Data from a new group of 479 healthy people recruited via online adverts and Prolific Academic (www.prolific.ac) was used for the analysis (for demographic information see **Table 2.3**). Exclusion criteria were self-reported neurological or psychiatric disorder. All participants gave electronic informed consent and the study was approved by the University of Oxford ethics committee. 63 of these participants also completed the AMI a second time between 6–8 days after initial completion to assess test-retest reliability.

Participants completed the AMI to confirm the proposed three-factor structure. In addition, they were also asked to complete a set of established related measures to assess construct validity (noted below). Descriptive statistics of these additional measures are provided in **Table 2.4**.

- **Apathy Evaluation Scale (AES,** Marin et al., 1991**)**. The AES is an 18-item scale that measures apathy as a single construct. Each item was scored on a 4-point Likert scale, with a higher total score indicating greater apathy (1–4: 1='very true', 4='not true at all' for positively scored items).
- **Dimensional Apathy Scale (DAS,** Radakovic and Abrahams, 2014**)**. The DAS is a 24-item scale that assesses apathy on three different subscales, namely executive, emotional and behavioural/cognitive initiation. Each item was rated on a 4-point Likert scale, with a higher score indicating greater apathy (0–3: 0='Almost Always', 3='Hardly Ever' for positively scored items).

- Beck's Depression Inventory (BDI, Beck et al., 1996). The BDI is a 21-item scale that measures the severity of depression. Each item relates to a symptom of depression, e.g. hopelessness, and was scored on a 4-point Likert scale (0–3: 0=least severe, 3=most severe). A higher total score indicates higher depression.
- Snaith Hamilton Pleasure Scale (SHAPS, Snaith et al., 1995). The SHAPS is a 14-item scale that assesses hedonic tone, or ability to experience pleasure. While responses were made on a 4-point scale, for simplicity, Snaith and colleagues scored each item in a binary manner (0–1: 0=either 'Strongly Agree' or 'Agree', 1=either 'Strongly Disagree' or 'Disagree'). I followed Pluck and Brown (2002) and Franken et al. (2007) and scored responses using a 4-point Likert style instead (1–4: 1='Strongly Disagree', 4='Strongly Agree') with higher scores reflecting greater hedonic tone. Conversely, lower scores indicated higher levels of anhedonia.
- Modified Fatigue Impact Scale (MFIS, Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). The MFIS is a 21-item scale that measures how fatigue affects daily life, with each item being rated on a 5-point Likert scale (0–4: 0='Never', 4='Almost Always'). A higher score indicates a greater impact of fatigue on the individual.

Table 2.3: Participant characteristics.

Characteristic	
Age	Mean=29.7 (10.7) years old, Median=27.0, range=18–74 (N=2 undisclosed)
Male: Female	230:249 (48% male)
Education level	Primary/ Elementary school (N=1, 0.2%)
	Secondary/ Middle school (N=33, 6.9%)
	Post-secondary non-tertiary education (N=139, 29.0%)
	Bachelor's Degree (N=179, 37.4%)
	Master's Degree (N=101, 21.1%)
	Doctor of Philosophy (N=26, 5.4%)
Employment	Student (N=188, 39,2%)
	Full-time employed (N=160, 33.4%)
	Part-time employed (N=56, 11.7%)
	Self-employed (N=29, 6.1%)
	Unemployed (N=19, 4.0%)
	Housework at home (N=10, 2.1%)
	Long-term disabled (N=6, 1.3%)
	Retired (N=11, 2.3%)

Table 2.4: Descriptive statistics of related measures.

Measure	Mean	SD	Median	Range
Apathy Evaluation Scale				
Total	33.1	8.6	32	18–60
Beck Depression Inventory				
Total	11.2	10.2	8	0–53
Dimensional Apathy Scale				
Executive	9.3	4.7	9	0–23
Emotional	9.1	4.0	9	0–23
Behavioural/Cognitive	10.5	4.3	10	0–21
Total	28.9	9.2	28	3–61
Snaith Hamilton Pleasure Scale				
Total	48.7	5.7	49	23–56
Modified Fatigue Impact Scale				
Physical	12.4	8.7	11	0–36
Cognitive	14.3	8.5	14	0–40
Psychosocial	3.0	2.2	3	0–8
Total	29.7	17.7	29	0–84

A confirmatory factor analysis (CFA) was conducted in MPlus (Muthen and Muthen, 1998). Model fit was assessed using RMSEA, SRMR and Comparative Fit Index (CFI). While a CFI of at least 0.90 is normally taken to indicate an acceptable model (Hu and Bentler, 1999), it should be noted that this index calculates the fit difference between a null independence model (i.e. zero correlation between all observed variables) and the hypothesized model. This means that for a model with low item inter-correlations, the CFI may be lowered even if it describes the data adequately. Thus, it has been suggested that in the event of substantial low inter-correlations, the CFI criterion could be relaxed to >0.80 (Benjamini and Hochberg, 1995). Approximately 65% of the inter-correlations in our data were low (<0.20), hence, we adopted the relaxed CFI cut-off of 0.80 while ensuring that the cut-offs for RMSEA and SRMR were <0.08.

2.2.2.2 Results

The three-factor structure of the 18-item AMI (**Table 2.2**) was confirmed, and had good model fit indices (RMSEA=0.076 with 90% confidence interval of 0.068–0.083, SRMR=0.071, CFI=0.83). This model is schematically illustrated in **Figure 2.1**. Each item on the AMI was scored from 0–4, with a higher score indicating greater apathy. Cut-offs for moderate and severe apathy on the AMI are proposed to be respectively >1 SD and >2 SD above the mean (**Table 2.5**). While SM correlated significantly with BA and ES components of motivation, BA did not correlate significantly with ES.

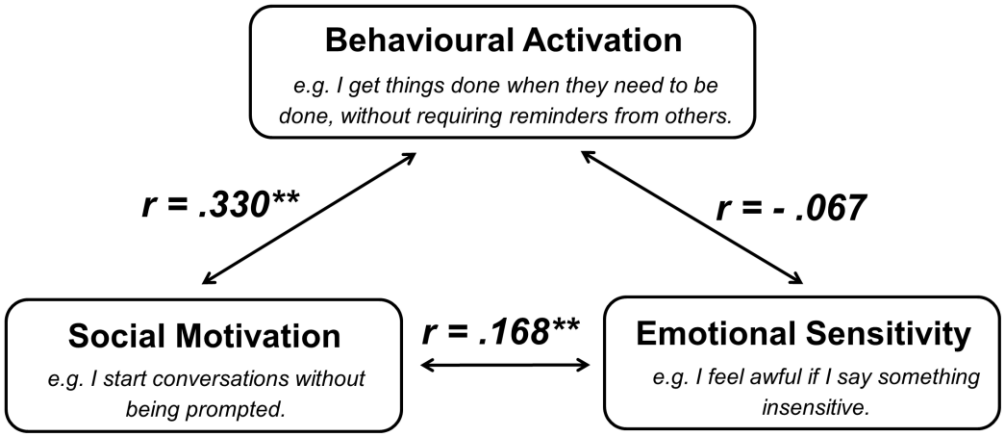


Figure 2.1 Apathy Motivation Index (AMI) factor model. The factor analysis identified three distinct subscales, namely behavioural activation (BA), social motivation (SM) and emotional sensitivity (ES). BA relates to an individual's tendency to self-initiate goal-directed behaviour, SM examines a person's engagement of social interactions and ES probes an individual's feelings of positive and negative affection. While SM correlated with BA and ES, BA did not associate with ES. (**: $p<0.01$).

Table 2.5: Proposed cut-offs for moderate and severe apathy on the AMI.

AMI subscale	Mean (SD)	Proposed cut-off	
		Moderate	Severe
Behavioural Activation	1.58 (0.76)	≥2.34	≥3.10
Social Motivation	1.69 (0.74)	≥2.43	≥3.17
Emotional Sensitivity	1.05 (0.63)	≥1.68	≥2.31
Total	1.44 (0.47)	≥1.91	≥2.38

Note: Every AMI subscale consists of 6 items that is each scored from 0–4. Mean values and proposed cut-off scores for each subscale are given above. A higher mean rating indicates greater apathy on that subscale. Mean score based on ratings from 479 healthy people.

To assess internal reliability, Cronbach's coefficient alpha values were calculated for both the total score and subscales. They showed adequate values, indicating acceptable internal consistency ($\alpha_{overall}$=0.77, α_{BA}=0.79, α_{SM}=0.75, α_{ES}=0.75). Test-retest reliability coefficients for the scale and subscales were also satisfactory, indicating stable responses across time ($r_{overall}$=0.83, r_{BA}=0.88, r_{SM}=0.84, r_{ES}=0.72).

To examine construct validity, correlational analyses between the overall and subscale scores of the AMI and other related measures were conducted. The Benjamini and Hochberg method was used to control for false discovery on multiple comparisons (Benjamini and Hochberg, 1995). Key correlational results are briefly summarized in text (details in **Table 2.6** and **Figure 2.2**). AMI *total score* showed positive correlations with existing assessments of apathy: DAS total (r=0.62, p<0.01) and AES (r=0.61, p<0.01). It was also positively associated with the BDI (ρ=0.26, p<0.01) and MFIS total (r=0.19, p<0.01). Finally, the AMI total score was negatively correlated with the SHAPS (r=-0.46, p<0.01), indicating that apathetic people experience greater anhedonia. Overall, these findings indicated that the AMI had good construct validity.

Table 2.6: Correlation between AMI and other measures.

	Apathy Motivation Index			
	Behavioural Activation	Social Motivation	Emotional Sensitivity	Total
Dimensional Apathy Scale [a]				
Executive	**0.59 ****	**0.14 ****	**-0.12 ***	**0.34 ****
Emotional	0.07	**0.22 ****	**0.57 ****	**0.41 ****
Behavioural/Cognitive	**0.49 ****	**0.53 ****	0.08	**0.57 ****
Total	**0.57 ****	**0.42 ****	**0.23 ****	**0.62 ****
Apathy Evaluation Scale [a]				
Total	**0.55 ****	**0.51 ****	**0.11 ****	**0.61 ****
Beck Depression Inventory [b]				
Total	**0.35 ****	**0.29 ****	**-0.17 ****	**0.26 ****
Snaith Hamilton Pleasure Scale [a]				
Total	**-0.22 ****	**-0.41 ****	**-0.29 ****	**-0.46 ****
Modified Fatigue Impact Scale [a]				
Physical	**0.26 ****	**0.14 ****	**-0.19 ****	**0.13 ****
Cognitive	**0.41 ****	**0.11 ***	**-0.20 ****	**0.18 ****
Psychosocial	**0.31 ****	**0.31 ****	**-0.11 ***	**0.28 ****
Total	**0.36 ****	**0.16 ****	**-0.20 ****	**0.19 ****

Note: [a]=Pearson correlation. [b]=Spearman correlation. Correlations of $p<0.05$ after correcting for multiple correlations are in bold. * $p<0.05$, ** $p<0.01$.

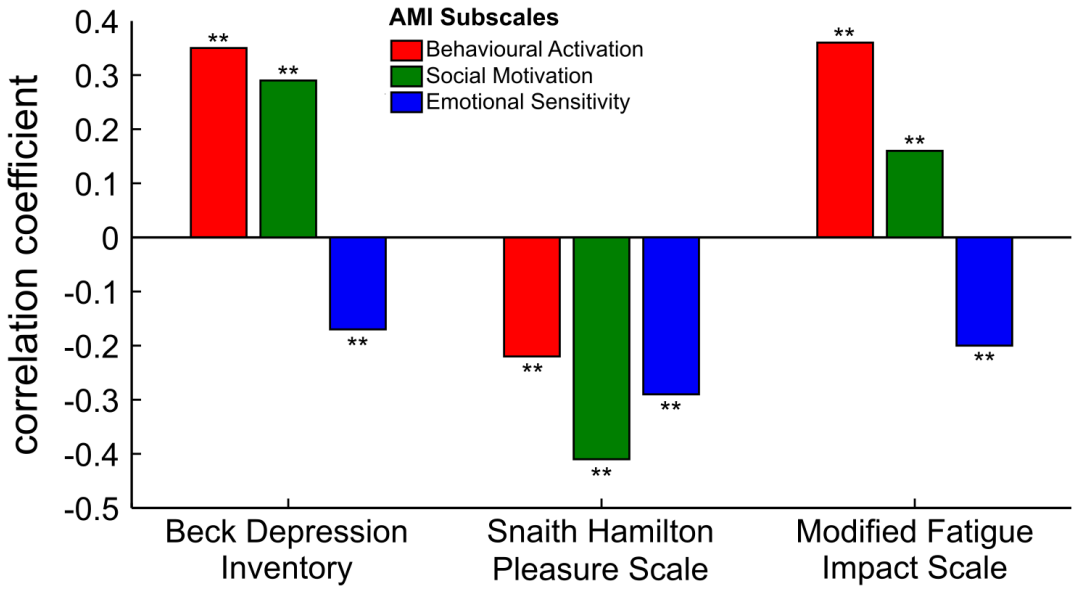


Figure 2.2 Correlation coefficients between AMI subscales and established measures of depression, anhedonia and fatigue. BA and SM correlated positively with BDI and MFIS, indicating that individuals that were more apathetic on these subscales also had higher levels of depression and fatigue. In contrast, the ES scale was negatively correlated with depression and fatigue. All three subscales were negatively correlated with the SHAPS (lower scores indicate higher levels of anhedonia), suggesting that higher apathy was associated with lower hedonia.

2.2.3 Classification of apathy-motivation subtypes

2.2.3.1 Latent profile analysis (LPA)

To examine whether distinct profiles of apathy could be identified and how these are differentially predictive of comorbid states (depression, anhedonia and fatigue), I conducted a latent profile analysis (LPA, McLachlan and Peel, 2000) using the data acquired for CFA.

LPA is a model-based or probabilistic clustering technique used to estimate unobserved constructs within a given set of observed variables. Specifically, it assumes that different *latent* classes of individuals make up the observed sample, and that those belonging to the same class would respond to a set of continuous variables in a similar manner i.e. same probability distribution. Within each class, the variables are assumed to be independent and normally distributed. A latent profile model for the observed responses to the set of variables, x_i (i = 1, 2, …, n) may thus be expressed as:

$$f(x_i \mid \theta) = \sum_{j=1}^{K} \pi_j f_j(x_i \mid \theta_j)$$

where π_j is the probability of belonging to class j (j = 1, 2, …, K) and f_j is a class-specific normal density function with parameters $\theta_j = (\mu_j, \sum_j)$ representing respectively the mean vector and covariance matrix. Solving for the maximum likelihood of the complete data is difficult and requires an iterative estimation algorithm like expectation maximization (EM). EM first starts by initializing the model parameters with random guesses. It then iterates and repeats between two steps (E-

step and M-step) until a convergence criterion is reached. In the E-step, the expectation for the complete likelihood is calculated by using the current parameterization. This expected likelihood function is then maximized in the M-step to obtain a new estimate of the model parameters.

In practice, the number of classes is often not known a priori. Thus, a set of models with different number of classes have to be considered and compared via posterior fit statistics. The Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) are absolute fit indices that recognize there is a cost to improving fit of the model by adding parameters. Lower values for these indices generally indicate better fit. They capture model fit with the maximum log likelihood value (L_m) and impose a penalty term that could depend on the number of parameters (d) and/or sample size (n):

$$AIC = -2L_m + 2d$$

$$BIC = -2L_m + d \ln n$$

Likelihood ratio tests (LRT) can also be used to compare relative fit between two nested models. However, the traditional LRT is not suitable for nested latent class models as the regularity conditions for an asymptotic chi-squared difference distribution are not met (Aitkin and Rubin, 1985). The Lo-Mendell-Rubin test (LMRT) overcomes this by utilizing an analytically-derived distribution of the log-likelihood difference (Lo et al., 2001). Alternatively, the bootstrap likelihood ratio test (BLRT) derives the distribution of the likelihood ratio test statistic empirically using a bootstrap resampling method (McLachlan and Peel, 2000). Both the LMRT and BLRT provide a p-value that signals whether a model with (K-1) classes should be rejected in

favour of that with *K* classes. A small *p*-value (<0.05) indicates that the solution with *K* classes fit better.

I investigated models with one to five classes and determined the optimal number of classes for the sample with the AIC, sBIC (sample-size adjusted BIC), LMRT and BLRT.

2.2.3.2 Results

The 4-class model was the most appropriate (**Table 2.7**). An iterative comparison of models one class apart (i.e. 1- versus 2-class, then 2- versus 3-class etc.) with LMRT and BLRT *p*-value revealed that the 4-class model had the best fit. Furthermore, the 4- and 5-class models had the lowest AIC and sBIC values.

Table 2.7: Latent Profile Analysis (LPA) model fit indices.

Number of Classes	1	2	3	4	5
AIC	3086	3020	3000	2968	2966
sBIC	3092	3030	3014	2986	2988
LMRT *p*-value	-	<0.001	0.29	0.02	0.36
BLRT *p*-value	-	<0.001	<0.001	<0.001	0.19

Note: AIC = Akaike Information Criterion, sBIC = sample-size adjusted Bayesian Information Criterion, LMRT = Lo-Mendell-Rubin Test, BLRT = Bootstrapped Likelihood Ratio Test. For AIC and sBIC, the smaller the value the more optimal is the model fit. For LMRT and BLRT of *K* classes, a small *p*-value (<0.05) indicates that the solution with *K* classes fit better than that with *K*-1 classes.

To interpret each class, we compared the conditional response means with the overall sample means on each AMI subscale (Table 2.8, Figure 2.3). We then labeled these classes according to their profile on apathy subtypes:

- Class 1 consisted of 57 individuals (11.9%) and was labeled **"emotionally apathetic"** as their mean ES subscale was higher than that of the overall sample mean.
- Class 2 contained 121 individuals (25.3%) and was labeled **"behaviourally/socially apathetic"** due to a higher mean BA and SM subscale score than the overall sample mean.
- All conditional response means for Class 3 were lower than the overall sample mean, thus this class of 291 individuals (60.8%) was referred as **"generally motivated"**.
- Class 4 consisted 10 individuals (2.1%) who had substantially higher conditional response means than the overall sample means on every subscale. Accordingly, they were referred to as **"generally apathetic"**.

Table 2.8: Overall sample means and AMI conditional means.

Subscale	Overall Sample Mean (*N*=479) (SD)	Class 1: Emotionally Apathetic (*N*=57) (SD)	Class 2: Behaviourally/Socially Apathetic (*N*=121) (SD)	Class 3: Generally Motivated (*N*=291) (SD)	Class 4: Generally Apathetic (*N*=10) (SD)
Behavioural Activation	1.58 (0.76)	1.07 (0.55)	2.17 (0.69)	1.41 (0.65)	2.33 (0.76)
Social Motivation	1.69 (0.74)	1.56 (0.57)	2.53 (0.47)	1.32 (0.49)	3.00 (0.54)
Emotional Sensitivity	1.05 (0.63)	2.06 (0.36)	1.03 (0.46)	0.79 (0.41)	2.75 (0.36)

Note: Every AMI subscale consists of 6 items that is each scored from 0–4. A higher mean rating indicates greater apathy on that subscale.

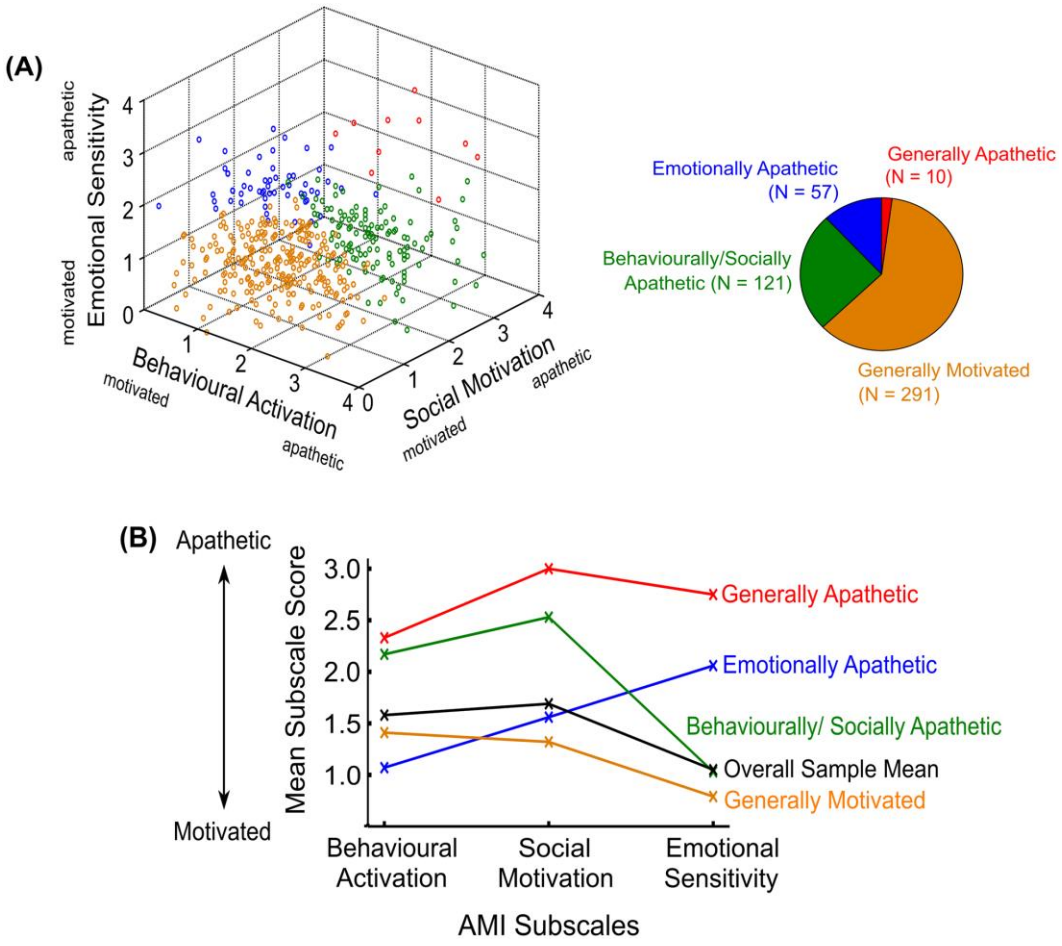


Figure 2.3 Distribution of apathy along the AMI subscales and conditional response means of the 4-class solution. The AMI consists of three subscales: Behavioural Activation, Social Motivation and Emotional Sensitivity. Every subscale contains 6 items that is each scored from 0–4, with a higher mean score indicating greater apathy. **(A)** 3D scatterplot illustrating the distribution of each healthy individual's mean rating along the three AMI subscales. The four classes were labeled generally motivated (orange), behaviourally/socially apathetic (green), emotionally apathetic (blue), and generally apathetic (red). **(B)** Conditional response mean value greater than overall sample means (black line) indicates apathy on that AMI subscale.

ANOVA was used to examine differences among the four apathy-motivation subtypes on independent measures of depression, anhedonia and fatigue (**Figure 2.4**). Significant differences were found between classes for all three measures (BDI: $F(3,475)=14.7$, $p<0.001$; SHAPS: $F(3,475)=29.9$, $p<0.001$; MFIS: $F(3,475)=8.63$, $p<0.001$).

Post-hoc comparisons showed that the behaviourally/socially apathetic class were significantly more depressed and fatigued than the emotionally apathetic and generally motivated classes. The generally motivated class also experienced greater fatigue than the emotionally apathetic class (**Figure 2.4A and 2.4C**). For anhedonia, the generally motivated class experienced more pleasure than each of the other classes. The emotionally apathetic people were also more hedonic than the generally apathetic class (**Figure 2.4B**).

All post-hoc comparisons were significant at $p<0.05$ (Emotionally apathetic: BDI mean=8.0, SD=8.8, SHAPS mean=47.6, SD=5.6, MFIS mean=20.9, SD=14.0; Behaviourally/socially apathetic: BDI mean=16.2, SD=11.8, SHAPS mean=45.7, SD=5.8, MFIS mean=34.9, SD=17.6; Generally motivated: BDI mean=9.7, SD=9.0, SHAPS mean=50.4, SD=4.9, MFIS mean=29.3, SD=17.3; Generally apathetic: BDI mean=12.8, SD=13.0, SHAPS mean=42.3, SD=6.6, MFIS mean=29.3, SD=26.7). Together, these results suggest that different subtypes of apathy are differentially predictive of depression, anhedonia and fatigue.

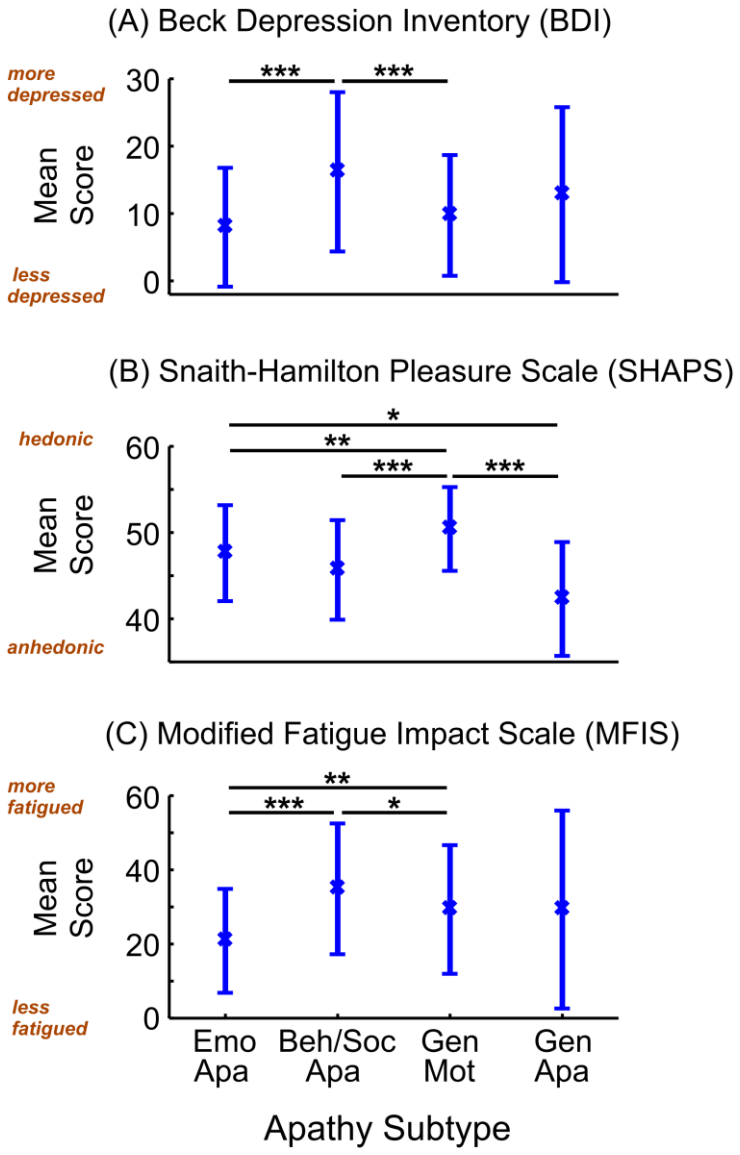


Figure 2.4 Relationships between apathy subtypes and depression, anhedonia and fatigue. The four apathy-motivation subtypes were predictive of different associations with depression (A), anhedonia (B) and fatigue (C). The behaviourally/socially apathetic experienced the greatest depression and fatigue while the generally motivated were the most hedonic (* p<0.05, ** p<0.01, *** p<0.001).

2.3 Multidimensional apathy in Parkinson's disease (PD)

2.3.1 Procedure

102 patients with PD (79 males, 23 females, mean age=67.7 years, SD=8.1) were recruited from Neurology clinics and 147 healthy age and gender matched controls (104 males, 43 females, mean age=66.1 years, SD=8.5) from a volunteer database. The Unified Parkinson's Disease Rating Scale was used to assess severity of the disease (UPDRS-III mean=27.0, SD=13.2, *N*=13 missing) while cognitive ability was examined via Addenbrooke's Cognitive Examination (ACE mean=89.4, SD=9.1, *N*=16 missing). All patients and controls had no history of other neurological or psychiatric conditions, gave written informed consent, and the study was approved by the local ethics committee.

In addition to the **AMI** (patients *N*=102, controls *N*=147) and **SHAPS** (patients *N*=84, controls *N*=67), patients also completed (descriptive statistics of these measures are provided in **Table 2.9**):

- **Lille Apathy Rating Scale (LARS,** patients *N*=87, Sockeel et al., 2006**)**. The LARS is a clinical interview assessment of apathy with a total score ranging from -36 to +36. A higher score indicates greater apathy.
- **Geriatric Depression Scale Short Form (GDS-15,** patients *N*=80, controls *N*=87, Yesavage and Sheikh, 1986**)**: The GDS-15 is a 15-item scale that assesses depression as a unidimensional construct. Each item is scored in a binary manner (0–1), with higher scores indicating greater levels of depression.

Table 2.9: Descriptive statistics of related measures in PD and controls.

Measure	PD		Controls	
	Mean (SD)	Range	Mean (SD)	Range
Apathy Motivation Index [a]				
Behavioural Activation	1.71 (0.79)	0.33 – 3.83	1.21 (0.67)	0.00 – 3.00
Social Motivation	1.85 (0.87)	0.00 – 4.00	1.64 (0.76)	0.00 – 3.83
Emotional Sensitivity	1.09 (0.56)	0.17 – 3.00	1.22 (0.66)	0.00 – 4.00
Total	1.55 (0.60)	0.28 – 3.28	1.36 (0.40)	0.44 – 2.56
Geriatric Depression Scale [b]				
Total	4.41 (3.58)	0 – 15	2.66 (3.31)	0 – 14
Lille Apathy Rating Scale [c]				
Total	-21.3 (7.4)	-34.0 – 0.0	-	-
Snaith Hamilton Pleasure Scale [d]				
Total	48.3 (5.0)	35 – 56	49.4 (5.2)	36 – 56

[a]: PD *N*=102, controls *N*=147; [b]: PD *N*=80, controls *N*=87; [c]: PD *N*=87; [d]: PD *N*=84, controls *N*=67

2.3.2 Results

2.3.2.1 Internal reliability, validity and diagnostic accuracy of AMI

Cronbach's alpha values for the AMI total and subscales were good ($\alpha_{overall}$=0.86, α_{BA}=0.79, α_{SM}=0.80, α_{ES}=0.66). Moreover, the AMI total score correlated positively with the LARS overall score (r=0.51, p<0.001, **Figure 2.5A**), demonstrating good construct validity. An ROC analysis was also conducted to evaluate the diagnostic accuracy of the AMI against the LARS. 37 apathetic and 50 non-apathetic patients were identified based on the LARS cut-off of >-22 and the area under curve was 0.82, indicating good diagnostic accuracy (**Figure 2.5B**).

2.3.2.2 Selective impairment of apathy domains

Patients had a higher total AMI score than controls (t(163)=2.9, p=0.005), indicative of greater apathy overall. Next I examined if patients have greater apathy in particular domains, or were simply more apathetic in general.

A mixed ANOVA with group as the between-subjects factor (patients vs. controls) and AMI subscales as within-subjects factor (BA vs. SM vs. ES) revealed a significant interaction effect (F(1.8,448)=14.1, p<0.001). Post hoc comparisons showed that PD patients exhibited higher levels of behavioural (p<0.001) and social (p<0.05) apathy relative to controls. Emotional apathy, however, did not differ between the two groups (p=0.11). These findings suggest that PD is associated with elevated levels of behavioural and social apathy, but does not affect emotional apathy (**Figure 2.6**).

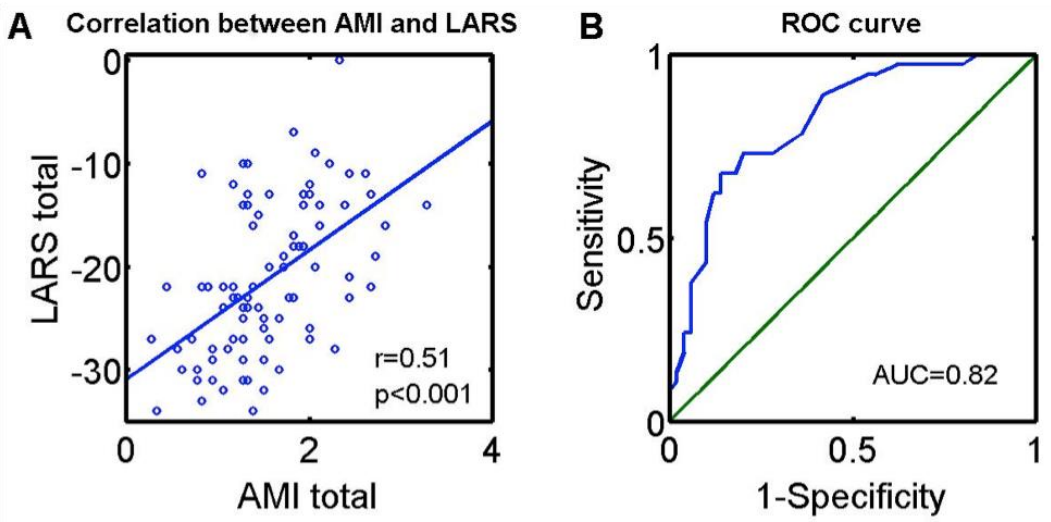


Figure 2.5 Validity and diagnostic accuracy of the AMI in PD. (A) There was a significant positive correlation between the AMI and LARS, an established clinical interview measure of apathy. (B) An ROC curve analysis performed by adopting the LARS as the gold standard found that the AMI has good diagnostic accuracy for clinical apathy.

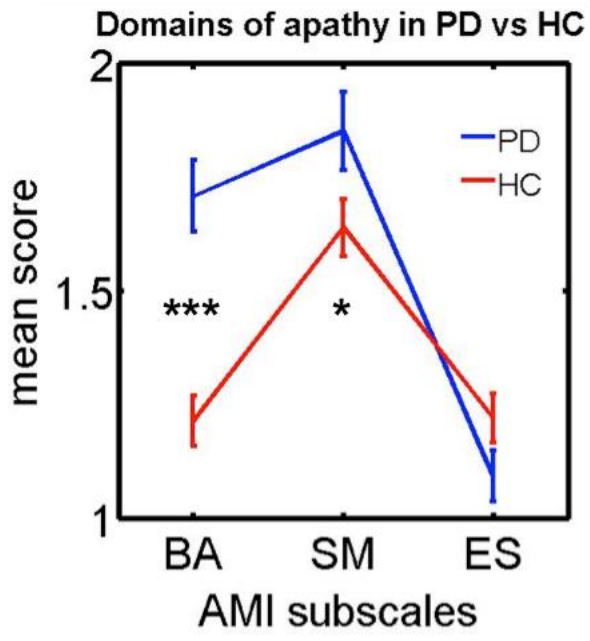


Figure 2.6 Comparison of apathy domains in PD against controls. PD patients exhibited significantly greater levels of behavioural and social apathy compared to age-matched healthy controls, but there was no significant difference in emotional apathy between the two groups. *** $p<0.001$, * $p<0.05$

2.3.2.3 Association of apathy domains with depression and anhedonia

Individuals who were more behaviourally and socially apathetic were more likely to be depressed. However, the emotional apathy subscale did *not* associate with depression in patients, although it was negatively correlated in controls (**Figure 2.7A**; **PD:** r_{BA}=0.51, p<0.001, r_{SM}=0.40, p<0.001, r_{ES}=0.18, p>0.05; **Controls:** r_{BA}=0.34, p=0.001, r_{SM}=0.40, p<0.001, r_{ES}=-0.24, p<0.05). Comparison of correlation coefficients between patients and controls via Fisher's r-to-z transformation confirmed there was a significant difference in only emotional apathy (z_{BA}=1.3, p>0.05; z_{SM}=0.03, p>0.05; z=2.7, p=0.007). This suggests that emotional apathy in PD was not related to depression, but healthy people who were more emotionally apathetic tended to be less depressed.

Patients who had higher levels of behavioural and social apathy were more anhedonic, but there was no association with emotional apathy. For controls, only the social apathy subscale had a significant negative correlation with SHAPS, indicating that healthy people who were more socially apathetic exhibited greater anhedonia (**Figure 2.7B**; **PD:** r_{BA}=-0.28, p=0.01, r_{SM}=-0.37, p<0.001, r_{ES}=-0.05, p>0.05; **Controls:** r_{BA}=-0.16, p>0.05, r_{SM}=-0.35, p=0.004, r_{ES}=-0.11, p>0.05). Fisher's transformation showed no significant differences in anhedonia between groups (z_{BA}=-0.8, p>0.05; z_{SM}=-0.1, p>0.05; z=0.4, p>0.05).

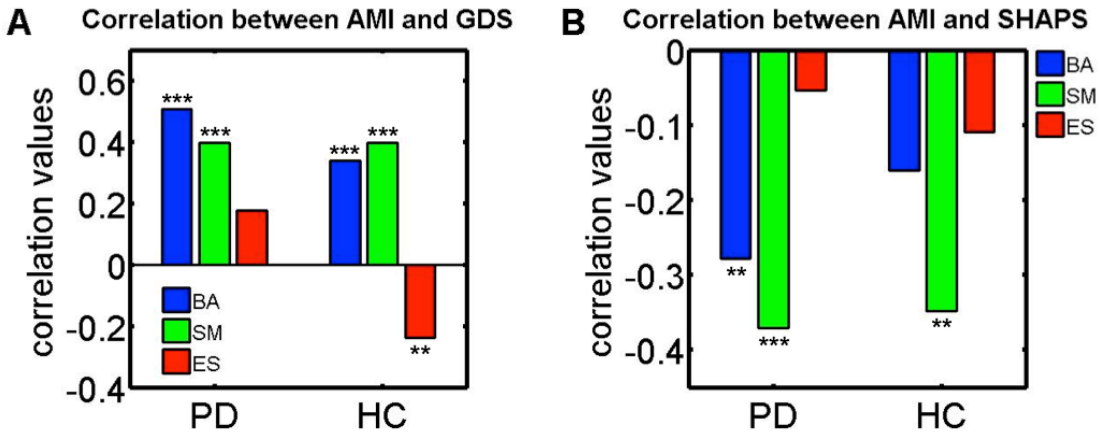


Figure 2.7 Association of apathy domains with depression and anhedonia in PD and controls. (A) **Behavioural Activation (BA)** and **Social Motivation (SM)** correlated positively with Geriatric Depression Scale-15 (GDS) score in both PD and controls, indicating that individuals who were more behaviourally and socially apathetic were more likely to be depressed. **Emotional sensitivity (ES)**, however, did *not* correlate with depression in PD but correlated negatively in controls. (B) **BA** and **SM** correlated negatively with Snaith Hamilton Pleasure Scale (SHAPS) in PD: patients who were behaviourally and socially more apathetic tended to be more anhedonic. However, there was no relationship with **ES**. In controls, only social apathy exhibited a significant correlation with anhedonia.

2.4 Discussion

2.4.1 Healthy population

Here I first developed the Apathy Motivation Index (AMI, **Table 2.2**), a new instrument suitable for assessing levels of apathy and motivation in the healthy population. Results of factor analyses – both exploratory (EFA) and confirmatory (CFA) – in large samples indicated that the AMI has a clear three-factor structure with good psychometric properties. For the first time, it was also shown that different subtypes of apathy are predictive of different associations with depression, anhedonia and fatigue in healthy people (**Figure 2.4**).

Three domains of apathy were identified, namely behavioural activation (BA), emotional sensitivity (ES) and social motivation (SM). The BA subscale focused on the individual's tendency to self-initiate goal-directed behaviour. This appears to relate closely to Stuss's (2011) executive process of 'energization' or the initiating and maintaining of task-relevant responses. By contrast, the ES subscale contained items that probe an individual's feelings of positive and negative affection, which seems similar to the emotional blunting often observed in some patients with apathy (Brown and Pluck, 2000). The two subscales were *not* significantly correlated, suggesting some dissociation between behavioural and emotional aspects of apathy.

Comparing these two subscales to the conceptualisation of apathy by Levy and Dubois (2006) suggests that the BA subscale likely encompasses the 'cognitive' and 'auto-activation' aspects, while the ES domain appears to correspond more to the 'emotional-affective' subtype. This is supported by positive associations found

between the AMI BA subscale with DAS (Dimensional Apathy Scale) executive and behavioural/cognitive initiation but not the emotional subscale. Conversely, the AMI ES subscale was correlated with the DAS emotional subscale but not behavioural/cognitive initiation subscale.

The SM subscale contained items that examine a person's engagement in social interactions. Impaired social life was highlighted in Stuss et al.'s (2000) theoretical account of apathy and by Sockeel and colleagues (2006) as a domain of apathy during the development of the LARS. Factor analyses studies on the AES and GDS have also respectively yielded a distinct subscale of "social indifference" (Ahearn et al., 2012) and "social withdrawal" (Hollocks et al., 2015; Kim et al., 2013), despite it not being specified within other cognitive-behaviour-emotion frameworks of apathy (Levy and Dubois, 2006; Marin, 1991). The AMI SM subscale was correlated with both BA and ES subscales, and with all three subscales of the DAS. This suggests that although separate factors of SM, BA and ES comprise apathy there is also some degree of shared variance between items assessing SM with BA and ES (Figure 2.1).

As expected, the AMI correlated with established assessments of apathy, depression, anhedonia and fatigue, providing evidence of good construct validity (Table 2.6). Rather than discuss every individual association between the scale/subscales, key findings are highlighted here. Distinguishing apathy from depression is challenging due to the overlaps in symptoms e.g. lack of initiation. Nonetheless, it is recognized that apathy may be characterised by emotional blunting whereas depression is an affective disorder featured by extreme emotional fluctuations (Brown and Pluck, 2000). In support of this, I observed that while the AMI

BA and SM subscales correlated positively with the BDI, the ES subscale was negatively associated.

Anhedonia is a mood disorder characterised by an inability to derive pleasure. It has long been established that positive reinforcement is essential to maintain goal-directed behaviour (Everitt and Robbins, 2005). Given this relationship between motivation and reward, it was predicted that anhedonia and apathy would be linked. In support, I found that all subscales of the AMI were related to the SHAPS. This finding suggests that apathy and anhedonia have a close relationship in the general population, with those individuals characterised by higher levels of apathy also more likely to report experiencing anhedonia. However, these measures were not perfectly correlated suggesting that there are also unique aspects of anhedonia not related to apathy.

Fatigue can be a symptom of reduced motivation characterised by the lack of energy to perform actions. Although similar in symptomology to apathy, few studies have investigated their relationship (Cochrane et al., 2015; Skorvanek et al., 2015). It was observed that the AMI BA and SM subscales associated positively with all subscales of the MFIS (namely physical, cognitive and psychosocial). Conversely, the ES subscale correlated negatively with these MFIS domains. These observations suggest that there is a partial overlap between apathy and fatigue. Specifically, while individuals who were behaviourally and/or socially more apathetic were likely to be more fatigued, people who were emotionally apathetic experienced less fatigue in general. Thus, there is also dissociation between fatigue and subtypes of apathy.

By using latent profile analysis (LPA) to group individuals with similar AMI profiles, four subtypes of apathy-motivation in the sample of healthy people were identified (Table 2.8, Figure 2.3). Most people (60.8%) were identified as 'generally motivated' with their group average on each AMI subscale being lower than the overall mean. A small number (2.1%), on the other hand, scored higher than the global mean on all AMI subscales. Thus, these individuals were classified as 'generally apathetic'. The other subtypes were labelled 'emotionally apathetic' (11.9%) and 'behaviourally/socially apathetic' (25.3%) as they had a lower average score than overall only on that/those particular AMI subscale(s).

Intriguingly, these different apathy subtypes were predictive of different associations with depression, anhedonia and fatigue. People identified as 'behaviourally/socially apathetic' were significantly more depressed and fatigued than people who were 'emotionally apathetic' or 'generally motivated'. In addition, individuals who were 'emotionally apathetic', 'behaviourally/socially apathetic' or 'generally apathetic' were significantly more anhedonic than those who were 'generally motivated'. These results indicated that the four apathy subtypes were distinct and overlapped differently with the closely related outcomes of depression, anhedonia and fatigue. Moreover, having high levels of behavioural and social apathy are more associated with other negative states, whereas experiencing emotional apathy on its own may not be associated with higher levels of depression and fatigue.

2.4.2 Parkinson's disease (PD)

Having validated the AMI in the healthy population, I then demonstrated that it is also reliable, valid and has good diagnostic accuracy in PD (**Figure 2.5**). This allows the AMI to be used to investigate two critical issues in the assessment of PD. First, are all domains of apathy equally affected in PD? And second, how are different domains of apathy associated with depression and anhedonia?

PD patients exhibited greater behavioural and social apathy compared to healthy controls. However, there was no difference in levels of emotional apathy, suggesting preserved emotional motivation in PD (**Figure 2.6**). Moreover, the different domains of apathy exhibited differential associations with depression and anhedonia. In particular, whilst behavioural and social apathy were related to both depression and anhedonia, emotional apathy was not (**Figure 2.7**).

The current literature on emotional apathy in PD is mixed (Del-Monte et al., 2017). Some researchers have reported that emotional facial recognition, which correlates with emotional apathy (Lockwood et al., 2017), is impaired in PD (Gray and Tickle-Degnen, 2010) whereas others have found no impairments (Albuquerque et al., 2014). Moreover, both intact emotional motivation (Santangelo et al., 2017) and impaired emotional motivation have been reported (Radakovic et al., 2017). In our study, patients were significantly more apathetic behaviourally and socially but did not differ emotionally compared to healthy controls. This finding is also consistent with clinical observations of reduced goal-directed behaviour being most frequently reported in apathetic PD patients and reduced emotion being least commonly found (Drijgers et al., 2010). Thus it may be important to focus on behavioural and social,

rather than emotional, aspects when developing treatments – including psychological ones – for apathy in PD.

Why might emotional motivation be preserved? One potential explanation relates to a recent neuroimaging study in PD that reported increased medial prefrontal cortex activity might compensate for subcortical limbic circuitry dysfunction leading to intact emotional processing (Moonen et al., 2017). It is possible that such a mechanism might also underlie intact emotional motivation in PD, which could be tested in future studies.

In this study, PD patients who were behaviourally and socially apathetic were also more depressed, but there was no association between emotional apathy and depression. However, in healthy controls, those who were more emotionally apathetic actually tended to be less depressed. This finding dovetails with other reports which show that apathy can be dissociated from depression in PD. Apathy frequently occurs in the absence of depression (Kirsch-Darrow et al., 2011, 2006; Oguru et al., 2010; Pluck and Brown, 2002; Ziropadja et al., 2012) and factor analyses have revealed that the two represent discrete constructs (Kirsch-Darrow et al., 2011). The findings presented herego further by highlighting the importance of considering the multidimensional nature of apathy when assessing relationships with depression.

Studies of anhedonia and apathy in PD are scarce and have also produced mixed results of both greater anhedonia in patients with apathy (Pluck and Brown, 2002), and no association (Isella et al., 2003). We examined this relationship in a large sample and found that behavioural and social, but crucially not emotional, apathy correlated with anhedonia in PD. For controls, only social apathy exhibited a

significant correlation with anhedonia even though a comparison of the correlations between groups showed no difference. This suggests that apathy and anhedonia are separable in the emotional domain, but have a close relationship in behavioural and social aspects.

2.5 Conclusion

The AMI is a reliable instrument suitable for assessing apathy and motivation in the healthy population and in clinical disorders such as Parkinson's disease. The findings presented here show for the first time that apathy in the healthy population can be dissected into four subtypes: 'emotionally apathetic', 'behaviourally/socially apathetic', 'generally motivated' and 'generally apathetic'. These classes showed different propensities for depression, anhedonia and fatigue. The data suggest that there may be particular subtypes of apathy that are more likely to co-occur with these symptoms. Future longitudinal studies would benefit from investigating how particular profiles of apathy are risk factors for the development of depression, anhedonia and fatigue.

It was also demonstrated that not all aspects of motivation are impaired in PD. Specifically, even though behavioural and social apathy are elevated, emotional motivation appears to be preserved. Furthermore, in patients with PD, behavioural and social apathy symptoms are related to depression and anhedonia – whereas emotional apathy is not. Together, these findings may help in guiding the development of more effective, selective treatments for apathy in PD – including non-

pharmacological ones aimed at behavioural and social motivation – as well as assisting in our understanding of how apathy, anhedonia and depression are related.

3 Option Generation and Apathy in Healthy Population

3.1 Introduction

The study of decision-making has become an important focus of neuroscience research (Glimcher and Fehr, 2014). Intriguingly, investigations of how people make decisions typically rely on asking them to select from two or more options provided by the experimenter. Participants are not required to generate options by themselves even though the generation of voluntary actions, which are *self-initiated* by choice, is considered to be a crucial aspect of human behaviour (Kalis et al., 2013).

Several lines of research suggest that brain mechanisms underlying *self-initiated* actions differ from those involved in externally-triggered ones. Experimentally, studies of self-initiated action are typically under-constrained in design, allowing volition on either "what" movement to perform, "when' to perform a

movement or "whether" or not to execute an action (Brass and Haggard, 2008). Lesion and electrophysiological studies in monkeys have implicated dorsal medial frontal regions, including the supplementary motor area (SMA) and anterior cingulate cortex (ACC), in self-initiated movements (Chen et al., 1995; Mushiake et al., 1991; Okano and Tanji, 1987; Romo and Schultz, 1987; Shima et al., 1991; Thaler et al., 1995, 1988). In humans, PET and fMRI studies have also reported greater activity in different brain regions including the pre-SMA and ACC when they are free to decide compared to being externally instructed (Brass and Haggard, 2007; Cunnington et al., 2006, 2002; Debaere et al., 2003; Deiber et al., 1999, 1996, 1991; Frith et al., 1991; Jenkins et al., 2000; Lau et al., 2006, 2004; Nachev et al., 2007, 2005; Playford et al., 1992; Rao et al., 1997, 1993; Rowe et al., 2005; Thimm et al., 2012; van Eimeren et al., 2006; Wessel et al., 1997). These data, taken together, suggest an important role for the medial frontal cortex in self-initiated actions.

Clinically, a poverty of self-initiated actions is characteristic of a neuropsychiatric syndrome known as apathy, which significantly reduces the quality of life for patients and caregivers (Marin, 1991). In its extreme form, akinetic mutism occurs where patients almost completely cease any tendency to self-initiate movements and speech despite being able to do so when prompted (Starkstein and Leentjens, 2008). Focal lesions of medial frontal regions or basal ganglia can induce pathological apathy in humans (Adam et al., 2013; Anderson et al., 2003; Bhatia and Marsden, 1994; Engelborghs et al., 2000; Gerace et al., 2013; Ghika-Schmid and Bogousslavsky, 2000; Krolak-Salmon et al., 2000; Maeda et al., 2012; Mega and Cohenour, 1997; Nishio et al., 2011; Perren et al., 2005; Phillips et al., 1987; Tengvar

et al., 2004). Although pathological apathy in such patients can be striking, it also occurs to varying degrees in the healthy population (Ang et al., 2017) and may negatively impact upon aspects of everyday life such as education and employment opportunities (Vansteenkiste et al., 2004, 2005). Intriguingly in the context of what is known from lesion studies, Bonnelle et al. (2016) recently reported an association between decreased functional connectivity between the ACC and SMA with increased behavioural apathy in healthy people.

Notwithstanding these findings, the cognitive and behavioural mechanisms underlying apathy remain unclear. Sinha and coworkers (2013) proposed a framework based on the processes involved in making decisions to initiate actions. According to their perspective, initiating actions involves first generating possible courses of action (*option generation*); then evaluating and selecting from self-generated options and/or those prompted by external events, cues or rewards in the environment (*option selection*); developing motor plans to execute the chosen option (*motor planning*) and finally initiating behaviour (*action initiation*). For simplicity, this has been conceptualised as a serial process (Figure 3.1), although it should be noted that in reality the various stages might actually occur in parallel in the brain. Previous investigations have focused on how deficits in option selection and learning from feedback after action initiation may lead to apathy, but no work has examined the role of impairments in option generation.

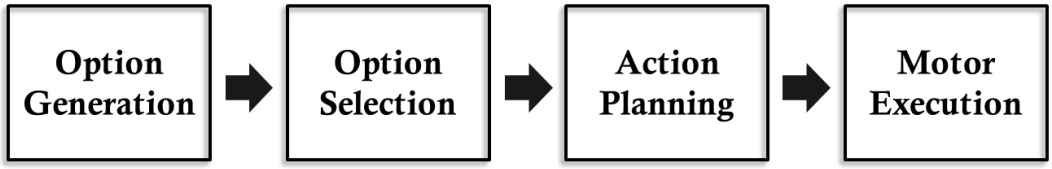


Figure 3.1 Conceptual framework for making decisions to initiate actions. Several processes might underlie decision-making to generate self-initiated actions. First, it might be important to be able to generate possible behavioural options (*option generation*), before selecting from between these internally generated and any externally available options (*option selection*). Once an option is selected, an action plan has to be formulated for the chosen option (*action planning*). Finally, the action is initiated and executed (*motor execution*).

Here, my aim was to examine whether deficits in *option generation* might also contribute to apathy in the healthy population. Some previous studies of option generation have focused on decision-making settings that are very specific e.g. chess problems (Klein et al., 1995) and sports (Johnson and Raab, 2003; Raab et al., 2009; Raab and Johnson, 2007). These complex scenarios have the advantage of affording a wider range of possible options and are consequently more relevant to real life option generation, where the option space is wide. However, in these domains, individuals may still be limited by their understanding of and familiarity with the activity being tested.

Therefore, a novel measure of option generation that is simple and quantitative yet relatively unconstrained and culture-free was developed here. This ensures that educational and cultural background had minimal impact on performing the task. Participants were given a time limit of four minutes to draw on a touchscreen computer as many different paths as they could between two fixed points (**Figure 3.2**). This task is similar in spirit to design fluency tests, which require participants to produce on paper as many different abstract pictures (Jones-Gotman and Milner, 1977) or patterns of lines joining dots (Regard et al., 1982; Ruff et al., 1994) as they can within a fixed duration. However, this paradigm allows the extraction of movement and timing parameters and crucially, also provides an opportunity to evaluate the novelty and diversity of options generated using objective metrics.

This is important because, besides the ability to generate a greater number of options, creativity is considered to be an important aspect of option generation for behaviour (Schweizer et al., 2016). Previous researchers have attempted to explore

aspects of creativity in this context using the Alternative Uses Test, which is a fluency-based creativity measure that requires participants to generate as many unusual uses as possible for a common object e.g. a brick or shoe (Guilford, 1967; Torrance, 1991). Understandably, however, measuring creativity in this way is limited and might depend upon educational and cultural backgrounds. Moreover, as with all fluency tasks, interpretation is made difficult by the strategy used by participants: individuals may choose to produce many simple items, or a few complex items. The novelty and uniqueness of a generated item can be quantified by its uncommonness in a standard corpus, or its distance from other items (Jones and Mewhort, 2007). Search strategies in verbal fluency tasks have indeed been modeled using similarity metrics (Hills et al., 2015), but the space of options is again constrained by individuals' vocabularies. Moreover, verbal output is by nature discrete and the space of words is highly non-homogeneous. Here, objective metrics of individual originality and divergence were developed by mathematically analyzing the trajectories of all generated path options.

In addition, participants were tested on three additional control tasks. Because speed of acting can affect performance on fluency tests (Suchy et al., 2010), they were asked to draw ten straight lines, each as quickly as they could, between the two fixed points (**Figure 3.3**). The mean time served as a baseline index of drawing speed. To control for motor planning ability, a second matched control task was used where options that each require a different action plan were *externally-cued* in turn, so that participants were prompted to respond to a new target location rather than have to self-initiate actions (**Figure 3.4**). To distinguish between option generation and selection, a third matched control task was administered whereby all the potential

options were already provided from the beginning so that options did not need to be self-generated (Figure 3.5).

In sum, these new tasks seek to separate option generation from option selection, motor planning and action initiation (Figure 3.1). Using this battery, I investigated the hypothesis that apathy involves a relatively specific deficit in *generating* options. The results reveal that apathetic individuals generate fewer, yet more novel, options than motivated individuals. In other words, they show greater creativity at the expense of generating fewer options. Crucially, findings from the control tasks suggest that the paucity of option generation cannot be attributed to a difficulty simply in option selection, planning or executing actions.

3.2 Procedure

3.2.1 Participants

96 healthy people were participated in this study. The sample comprised 60 young participants recruited from the Oxford Psychology Research participant recruitment scheme (31 males, 29 females; mean age=24.8 years old, SD=4.7) and 36 older people (22 males, 14 females; mean age=70.3 year old, SD=6.8) from the Oxford Dementia and Ageing Research database. All participants had corrected-to-normal vision, no history of psychiatric or neurological conditions and were paid a fixed rate for participating. They gave written informed consent and the study was approved by the University of Oxford ethics committee.

3.2.2 External measures

Apathy and motivation levels were assessed with the preliminary 51-item version of the Apathy Motivation Index (Table 2.1). Participants had to self-rate on a 5-point Likert scale how true each item was based on the past two weeks of his/her life (e.g. "I got things done when they need to be done, without being reminded by others."). An "N/A" option was also available for items that were not applicable. Each item was scored so that a higher rating indicated more motivation (i.e. less apathy). The higher the mean score of the preliminary AMI, the higher is the level of motivation.

General intelligence was also measured with the Ravens 12-item Advanced Progressive Matrices (Carpenter et al., 1990). Each item was presented as a pattern in the form of a 3-by-3 matrix, but with one missing element that had to be identified from eight given choices. Participants had a time limit of 10 minutes to complete the test and a higher score was taken to indicate higher IQ.

Half of the participants completed the preliminary AMI and Ravens matrices at the start of the study, while the other half performed it at the end after the experimental tasks. Behavioural data was analysed using MATLAB and IBM SPSS Statistics 22.0. All data were normally distributed and homoscedastic, and a p-value <0.05 was taken to be statistically significant unless otherwise stated.

3.2.3 Experimental setup

The experiment was carried out in a dimly-lit quiet room. All tasks were programmed with PsychToolBox on MATLAB (MathWorks) and implemented on a 23"

touchscreen computer (model: Dell P2314T), at screen resolution 1920 x 1080 at 60Hz frame rate, width 509 mm and height 286 mm. The touchscreen was placed vertically upright at a viewing distance of ~50 cm, and the monitor's height and angle of tilt was adjusted to each participant's comfort. Importantly, participants were left alone in the testing room for the option generation task to prevent performance anxiety (Kehrer et al., 2000).

3.3 Option Generation Task

3.3.1 Description

In this task, two red circles were displayed vertically at the centre of a touchscreen computer, separated by a distance of 204mm (Figure 3.2). Each circle had a radius of 13mm. Participants were instructed to "Draw as many different paths as you can from the bottom red circle to the top red circle in 4 minutes." Real-time visual feedback was provided such that paths appeared as participants drew them, regardless of the starting point of the movement. Drawn paths were allowed to intersect, and remained on the screen during the whole task so load on working memory was minimised. Paths were counted as valid as long as they started and ended within 21mm of the centers of the bottom and top circles respectively. This allowed for an error margin in finger movements.

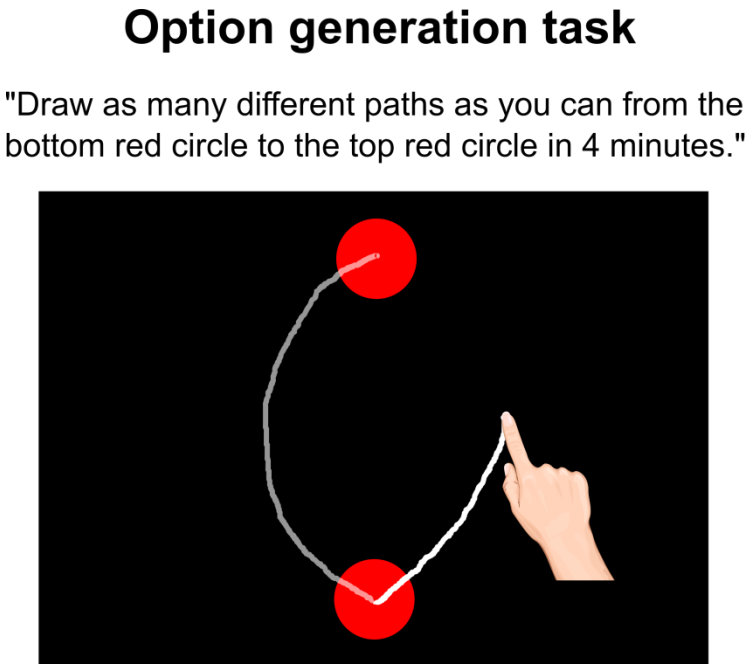


Figure 3.2 Illustration of the option generation task. The option generation task required participants to draw, in 4 minutes, as many different paths as possible from the start-point (bottom circle) to the end-goal (top circle). Paths appeared as participants drew them, and remained displayed on the touchscreen during the task so that participants did not have to remember them.

3.3.2 Quantifying creativity

To quantify uniqueness, an index of similarity between pairs of paths was created (**Figure 3.3**). Each path *i* was represented as a set of coordinates $x_i(t), y_i(t)$, for each time step of the path. First, the coordinates along each path were re-sampled at 200 points along the path, as a function of distance along the path. To do this, distance along the path was calculated as $s_i(t) = \sum_{\tau=1}^{t} \left\| \begin{bmatrix} x_i(\tau) - x_i(\tau-1) \\ y_i(\tau) - y_i(\tau-1) \end{bmatrix} \right\|$, and a new vector of coordinates $\mathbf{h}_i(s)$ was calculated using linear interpolation along $s(t)$. The feature vector $\mathbf{h}_i(s)$ thus describes the trajectory of path *i* with 400 numbers, in a uniform way across different paths drawn. This enables different paths to be compared. In order to include other characteristics of the paths, I included extra features in addition to the screen position, to capture other features of the trajectory's shape. The first derivative of the path direction $\dot{\mathbf{h}} = \mathbf{h}(s) - \mathbf{h}(s-1)$ and the second derivative $\ddot{\mathbf{h}}$ were calculated. These values were averaged for bins of 10 distance units, to give vectors 20 values over the path. Thus in total, the feature vector $\mathbf{v}$ for each path contained 480 values, with $\mathbf{v}_i = [\mathbf{h}_x, \mathbf{h}_y\, \dot{\mathbf{h}}_x, \dot{\mathbf{h}}_y, \ddot{\mathbf{h}}_x, \ddot{\mathbf{h}}_y]$.

To estimate how different any pair of paths were from one another, we subtracted the features of one path from the other to give $d_{ij} = |\mathbf{v}_i - \mathbf{v}_j|$. To account for left-right mirror similarity, the difference d'_{ij} was also calculated using the mirror-image path (i.e. with $\mathbf{h}_x \rightarrow -\mathbf{h}_x$, and the related derivatives), and the minimum value of d_{ij} and d'_{ij} was used.

The difference metric between any pair of paths enabled the uniqueness of a path to be calculated, as the smallest difference from any other path that was

generated by any participant, $u_i = \min_j(d_{ij})$ $[\, i \neq j \,]$. If u_i is large, the path is not similar to any other paths.

To quantify diversity, the distances between a participant's paths were projected onto a 2-dimensional subspace (Figure 3.4). Metric multidimensional scaling was performed on the dissimilarity matrix d_{ij} to visualise how they explored the path space. The default fitting algorithm using a metric stress criterion was used from the Statistics Toolbox in MATLAB. This algorithm assigns a two-dimensional "coordinate" to each path, such that the difference metric between each pair of paths matches (as closely as possible) the distance between the corresponding two points in a 2-dimensional plane. An individual was more explorative, i.e. produced greater variation in generated paths, if the paths (each represented by one point in the dissimilarity space) were more dispersed. Diversity was approximated by calculating the area of the convex hull covering each participant's paths projected in the 2-dimensional subspace.

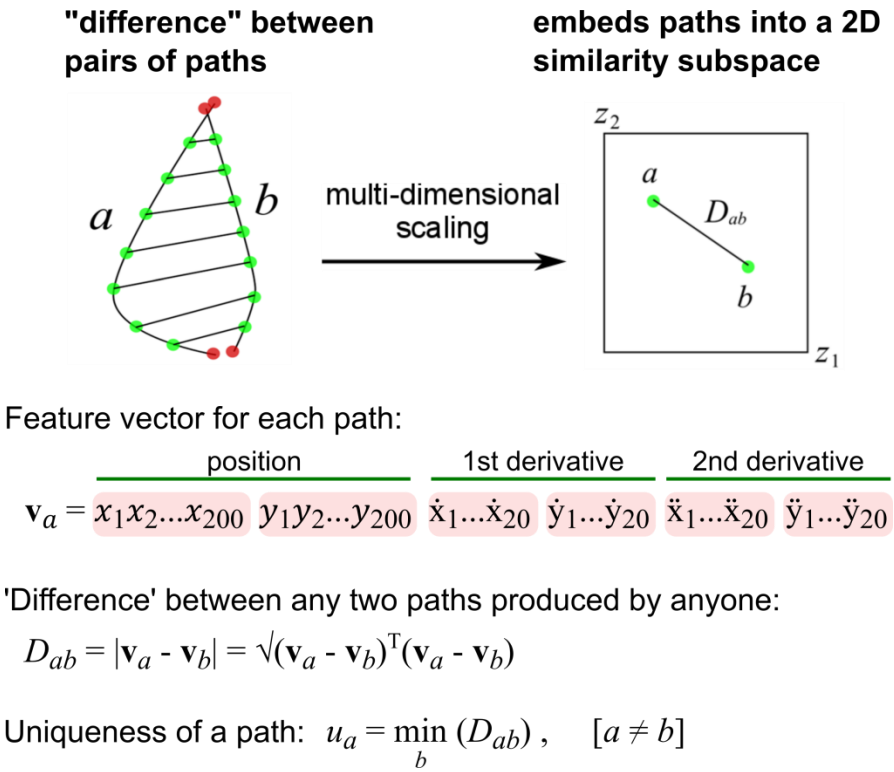


Figure 3.3 Uniqueness metric. To quantify uniqueness, each path was first parameterised by 200 equally spaced points along its length. The "difference" between any two paths is then taken as the sum of the distance between corresponding points. This distance metric also includes the first and second derivatives in order to better account for curvatures in trajectories. Uniqueness of a path is then defined as the "distance" between it and the most similar path generated by any other participant in Chapters 3 – 5 of this thesis. Distances between a participant's paths were also projected into a 2-dimensional subspace using multidimensional scaling, to visualise how individuals explored the space of possible paths by treating each generated path as a point. Points that are closer together indicate more similar paths and *vice versa*.

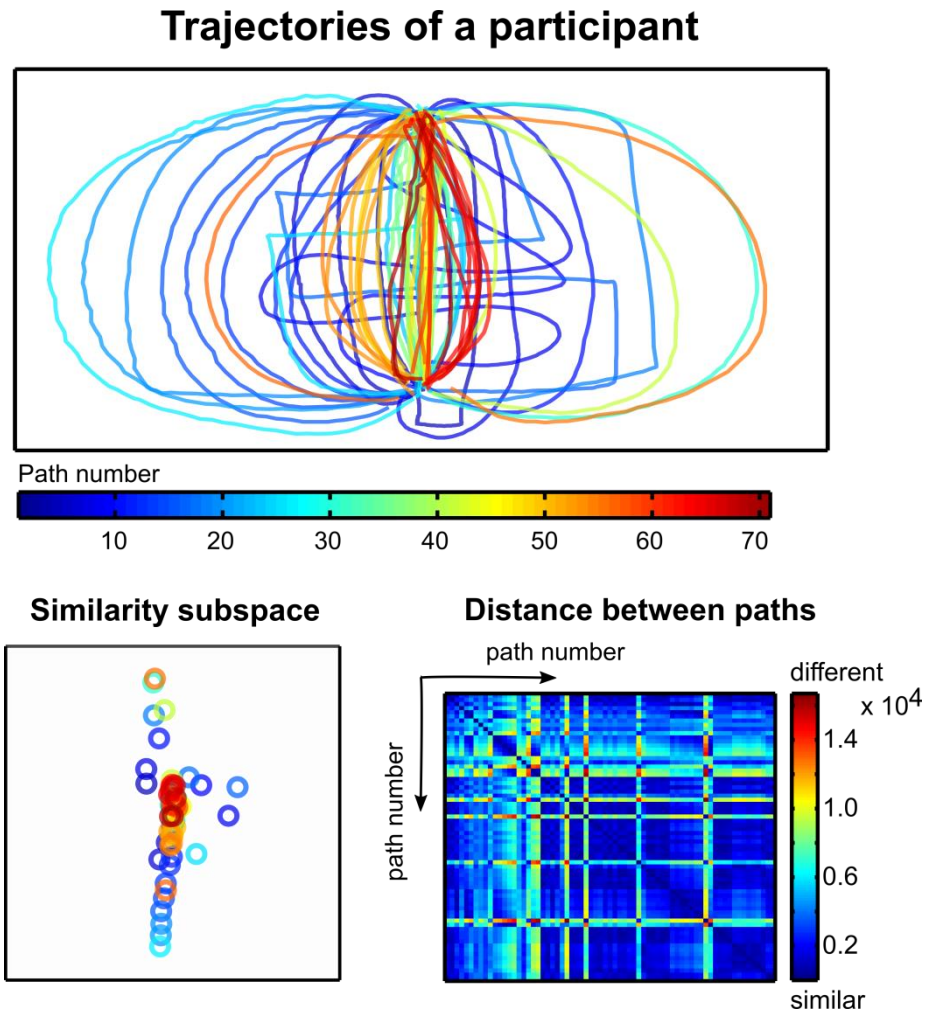


Figure 3.4 Visualisation of similarity subspace and pairwise distance matrix. Illustration of the trajectories of 69 paths generated by one participant (top), his corresponding points in 2-dimensional similarity subspace after multidimensional scaling (bottom left) and the pairwise distance matrix (bottom right).

3.3.3 Results

There was no difference in fluency ($t(94)=0.97$, $p>0.05$), uniqueness ($t(94)=0.19$, $p>0.05$) and diversity ($t(94)=0.57$, $p>0.05$) between the young and elderly groups. Therefore, the data for both cohorts were combined and presented together. Intriguingly, healthy people displayed a *trade-off* between uniqueness and fluency. They tended to either produce many similar paths, or came up with fewer unique paths (r=-0.62, $p<0.001$, **Figure 3.5A**). Nonetheless, generating more paths is not necessarily associated with reduced uniqueness (and vice versa). Some individuals were both fluent and unique, and some non-fluent and non-unique (**Figure 3.6**). The number of options generated did not relate to IQ, indicating that general intelligence did not influence performance (r=-0.03, $p>0.05$).

Individual differences in motivation level as indexed by the preliminary AMI were differentially associated with uniqueness and fluency. Motivation scaled positively with the number of paths generated (r=0.56, $p<0.001$, **Figure 3.5B**), but negatively with overall uniqueness (r=-0.38, $p<0.001$, **Figure 3.5C**). This suggests that motivation level might influence performance along the uniqueness-fluency spectrum. Less motivated – or apathetic – individuals appeared to be biased towards generating fewer paths but crucially with greater uniqueness, while motivated individuals trade uniqueness to produce more paths.

There was also a trend for the area explored in the 2-dimensional path subspace to correlate negatively with an individual's level of motivation, with apathetic people covering a larger area (r=-0.18, $p=0.076$, **Figure 3.5D**). This suggests that

although apathetic individuals generated fewer paths, they tended to be more diverse in terms of the space of possibilities.

Since fluency and uniqueness are correlated, do they independently relate to motivation? A univariate general linear model (GLM) demonstrated that fluency (p=0.01), but not uniqueness (p>0.05) or area of exploration (p>0.05), predicted level of motivation. Fisher-transformed z-tests also showed that the correlation between fluency and motivation is significantly different to that between uniqueness and motivation (z=5.67, p<0.001) and that between area of exploration and motivation (z=4.94, p<0.001).

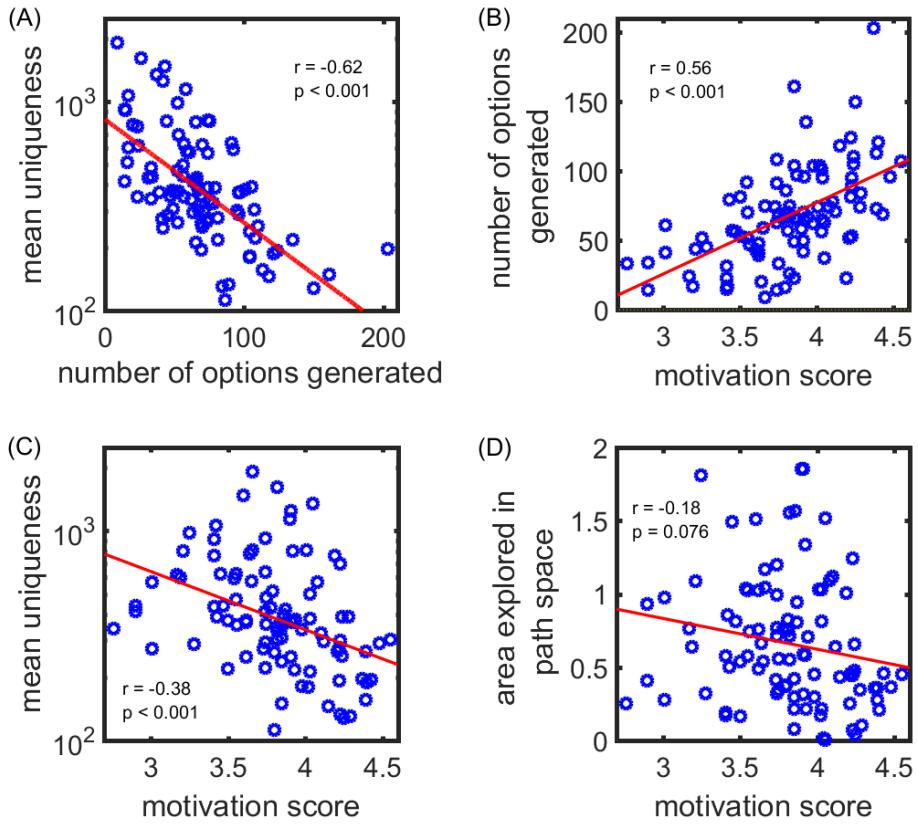


Figure 3.5 Results from the option generation task in healthy people. Each participant is represented by one point. **(A)** A scatterplot of the mean uniqueness against the number of paths generated, or fluency, revealed a uniqueness-fluency trade-off. Participants tended to either generate a few unique paths, or many similar paths. **(B)** The number of paths generated on this task correlated positively with the level of motivation as indexed by a self-report measure. Thus, the more apathetic an individual, the fewer paths they were likely to generate. **(C)** The mean uniqueness of an individual's paths is plotted against their motivation score. Motivated individuals generated less unique paths while apathetic people produced more unique paths. **(D)** Exploration was quantified by treating each generated path as a point in the individual's 2-dimensional uniqueness subspace (see Figure 3.4). The total "area" of different paths explored was defined as the area of a polygon surrounding all the path points (i.e. the convex hull). Explored area correlated negatively with motivation, indicating a greater diversity of paths explored in apathetic individuals, despite the fact that they generated a smaller number of paths.

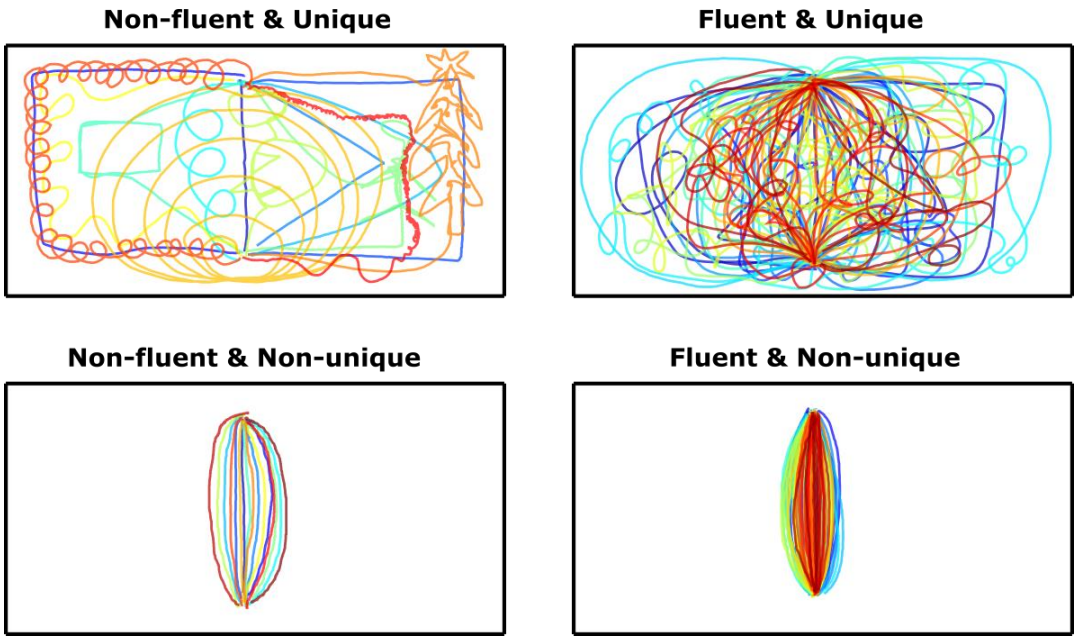


Figure 3.6 Examples of path options produced by individuals. Although participants tended to produce many similar paths (i.e. fluent & non-unique) or came up with fewer unique paths (i.e. non-fluent & unique), generating more paths is not necessarily associated with reduced uniqueness and vice versa. Some individuals were both fluent & unique, and some non-fluent & non-unique. <25th percentile was defined as the cut-off for being non-fluent and non-unique and >75th percentile as that for being fluent and unique.

3.4 Motor Execution Control Task

3.4.1 Description

All participants (*N*=96) completed this task, which was administered *before* the option generation task in order to test baseline drawing speed. They saw two red circles on the touchscreen (as in the option generation task), but were instructed to "Draw ten straight lines, each as quickly as you can, from the bottom red circle to the top red circle" (**Figure 3.7**). Real-time visual feedback was provided such that paths appeared as they were drawn, but lines were erased from the screen between movements. The mean time taken to draw each line (excluding time between lines) served as a baseline index of their motor vigour that was closely matched to the option generation task.

3.4.2 Results

Could participants be generating fewer options on the option generation task because they were slow to execute the drawing of lines? No significant relationship of drawing speed with number of options generated was found (r=-0.13, p>0.05). There was also no correlation between motivation and speed of motor execution (r=-0.08, p>0.05). Thus, motivation correlated with option generation (**Figure 3.5B**) but not with motor execution. These two correlations differed significantly from each other (difference in correlation coefficients, Fisher-transformed Z=4.63, p<0.001). Crucially, a significant correlation between fluency and motivation remained even after controlling for motor execution (r=0.56, p<0.001, **Figure 3.8**).

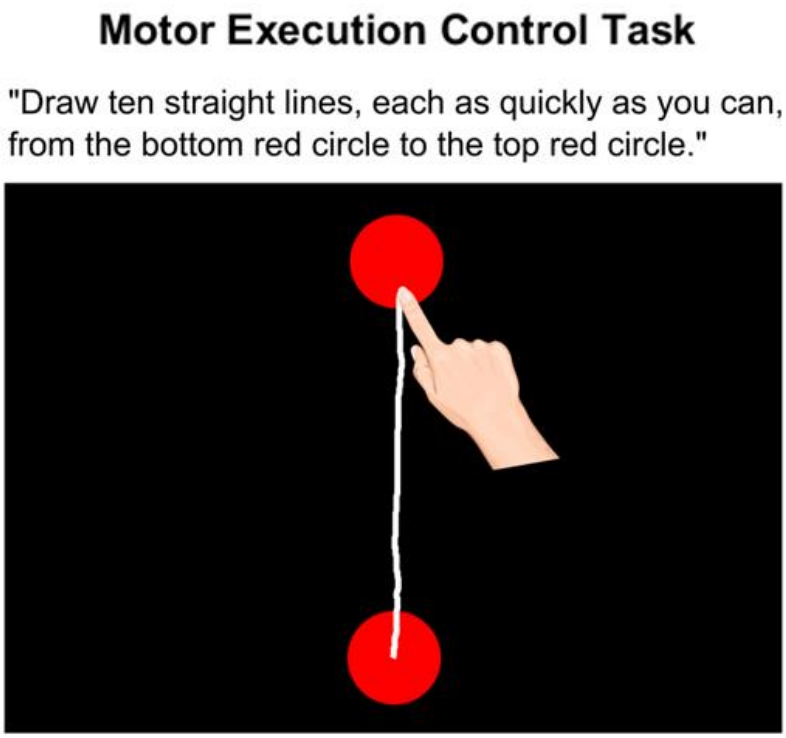


Figure 3.7 Illustration of the motor execution control task. Participants had to draw ten straight lines, each as quickly as they could, from a start-point (bottom circle) to an end-goal (top circle). This serves as a baseline index of their motor vigour.

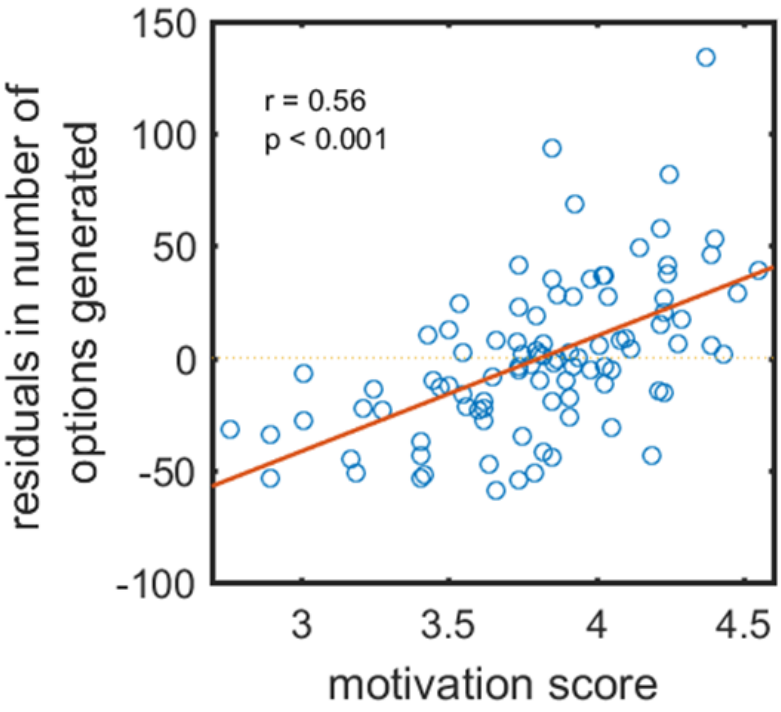


Figure 3.8 Results from motor execution control task. The significant association between fluency in the option generation control task and individual level of motivation remains even after regressing out the mean time taken to draw each line.

3.5 Externally-cued Action Control Task

3.5.1 Description

A subset of participants completed this task (*N*=30). They were required to "Join the bottom red circle to as many target red circles as you can in 90 seconds. Targets appear one at a time, at a random location, and fade to grey after being hit" (Figure 3.9). The starting point (bottom red circle) always remained fixed, at the same position as in the option generation task. Unknown to participants, targets were always equidistant from, but at a random angle to, the starting point. This distance was the same as the two red circles in the option generation task (i.e. 204mm). The range of angles from the starting point to the target was +/- 90 degrees and real-time visual feedback was provided.

Thus in this task, each movement had to be planned to a different target location, but there was no need to generate or select options. Instead the computer generated a new option location, once each path had been completed. This task and the option selection control task (section 3.6) were administered in a counterbalanced order after the option generation task.

3.5.2 Results

Could apathetic individuals be less fluent in generating options because they have difficulty planning different motor actions? The number of targets hit in the externally-cued action control task did not relate to fluency of option generation (r=0.18, p>0.05). There was also no correlation between motivation and performance in this task (r=0.14, p>0.05). Thus, motivation correlated with option generation

(Figure 3.5B) but not with the ability to change action plans. Crucially, a significant correlation between fluency and motivation remained even after controlling for motor planning ability (r=0.45, p=0.01, Figure 3.10).

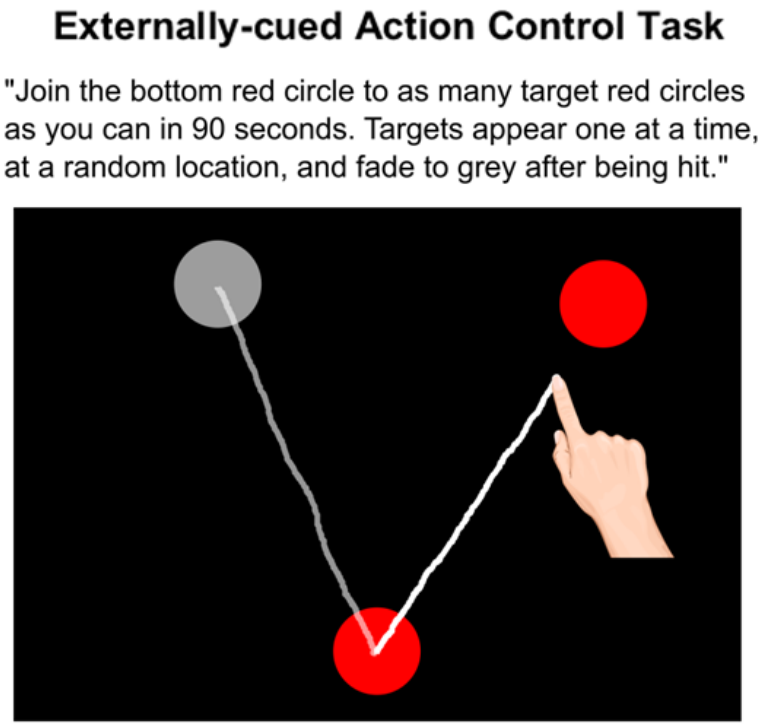


Figure 3.9 Illustration of the externally-cued action control task. Participants were asked to join the bottom circle to as many target circles as possible in 90 seconds. Only one target, which was always red in colour, appeared at a time. It turned grey after being touched, and then a new red target appeared. Thus, this task does not require either option generation or selection, but requires motor planning of a different action each time.

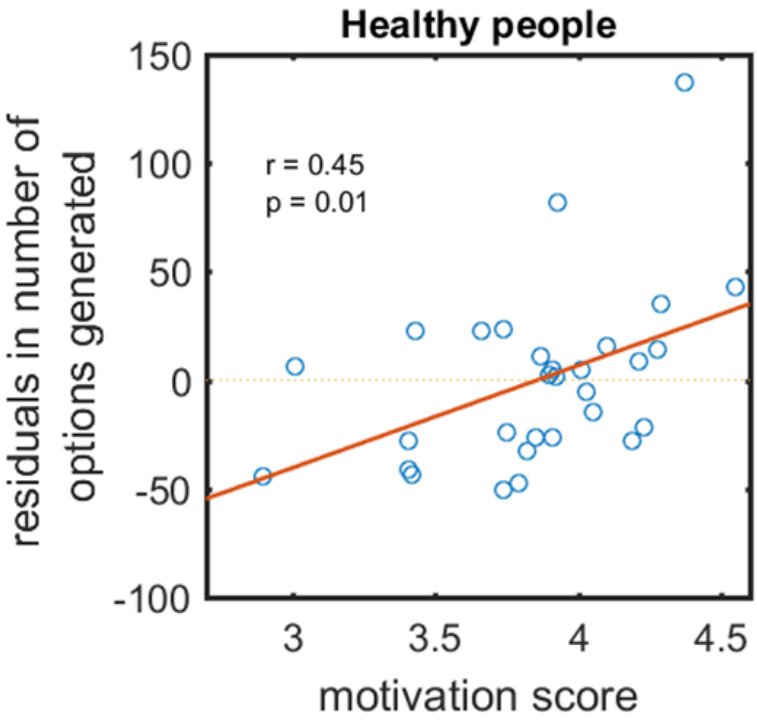


Figure 3.10 Results from the externally-cued action control task. There was a significant correlation between fluency in the option generation task and individual levels of motivation even after regressing out the number of targets hit in the externally-cued action control task.

3.6 Option Selection Control Task

3.6.1 Description

Participants here were the same as the externally-cued action control task (section 3.5). In this task, participants were presented with an array of 24 red targets equally spaced in an arc, each 204mm in distance from the starting point (i.e. red bottom circle). They were required to "Draw as many straight lines as you can from the bottom red circle to any target red circle in 90 seconds. Targets can be revisited." Real-time visual feedback was provided as in the primary option generation task (**Figure 3.11**).

Therefore, this control task was similar to the externally-cued action control task (section 3.5) in that many different paths had to be drawn, but additionally the target had to be selected from a set of 24 targets prior to each movement. Importantly, there was also no need to self-generate novel path options, thereby allowing option generation to be separated from selection. This task and the externally-cued action control task (section 3.5) were administered in a counterbalanced order after the primary option generation task (section 3.3).

3.6.2 Results

Could apathetic individuals have come up with fewer options because they had difficulty selecting amongst various options? There was no significant association between the number of paths drawn in the option selection control task and number of options generated on the option generation task ($r=0.13$, $p>0.05$). Performance on this control task also did not relate to level of motivation ($r=-0.02$, $p>0.05$). Therefore,

motivation correlated with option generation but not with ability to select between options. Importantly, a significant correlation between fluency and motivation remained even after accounting for option selection ability (r=0.47, p=0.01, **Figure 3.12**).

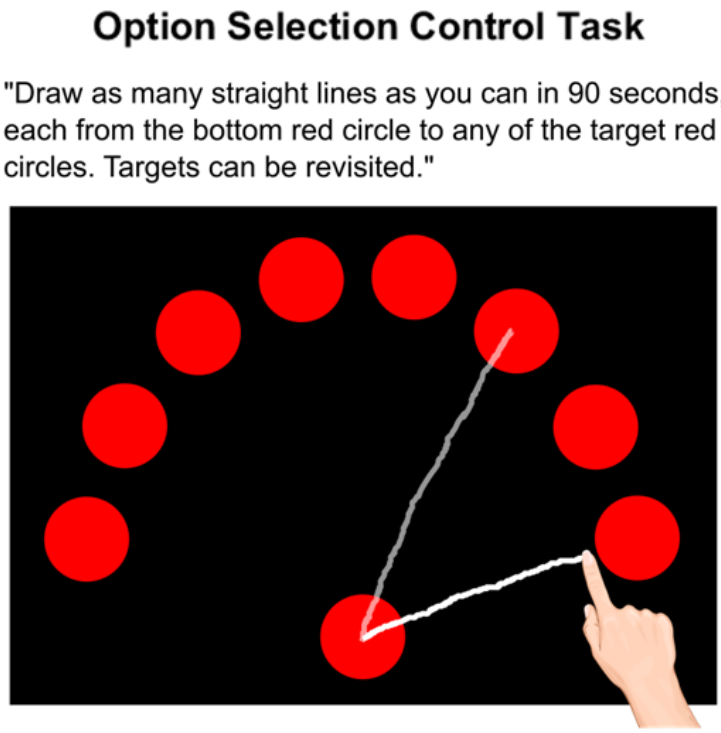


Figure 3.11 Illustration of the option selection control task. Participants had to join the bottom circle to as many target circles as possible in 90 seconds. They saw an array of 24 possible targets on the screen and were free to select any target they wanted for each connection (only 8 targets are illustrated here for simplicity). Thus, this task required selection between options but not the generation of possible options.

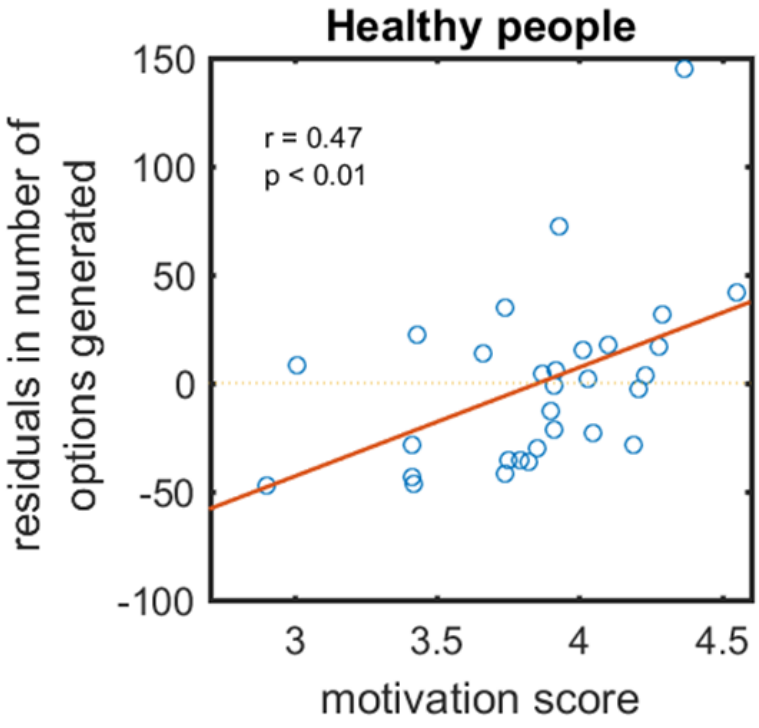


Figure 3.12 Results from the option selection control task. Fluency in the option generation task correlated with individual levels of motivation even after accounting for the ability to select options.

3.7 Option Generation Task with obstacles

3.7.1 Description

Could the presence of constraints such as obstacles to paths act as cues to improve participants' ability to generate options? The option generation task (section 3.3) was modified by adding either 4 or 8 obstacles that had to be avoided between the start and end point (**Figure 3.13**). These were rectangular blue zones where drawn routes were not permitted. In the 4-obstacle condition, each barrier was 27 by 21 mm in dimension while those in the 8-obstacle condition were 19 by 15 mm, such that the total area of the obstacles was equal for both conditions.

The instructions for participants were the same as that for the option generation task except that, additionally, obstacles had to be avoided. This meant that while paths normally appeared as participants drew, points on a path that crossed an obstacle would not be displayed. It was explained that participants could continue drawing after crossing a obstacle, but that path was not counted as valid. 66 participants that completed the option generation and motor execution control tasks, but not the externally-cued action and option selection control tasks, were recruited.

3.7.2 Results

A mixed ANCOVA, with preliminary AMI score (motivation level) as the covariate, was used to investigate the influence of task condition (0, 4 or 8 obstacles) on the number of paths generated. Interestingly, there was no effect of the number of obstacles, nor any interaction with motivation (condition $F(1.39, 88.9)=0.66$, $p>0.05$;

condition*motivation $F(1.39, 88.9)=1.62$, $p>0.05$). Although one might expect obstacles to act as a 'cue' for triggering the generation of options, adding them did not significantly modulate the number of options generated for apathetic people compared to motivated (**Figure 3.14**).

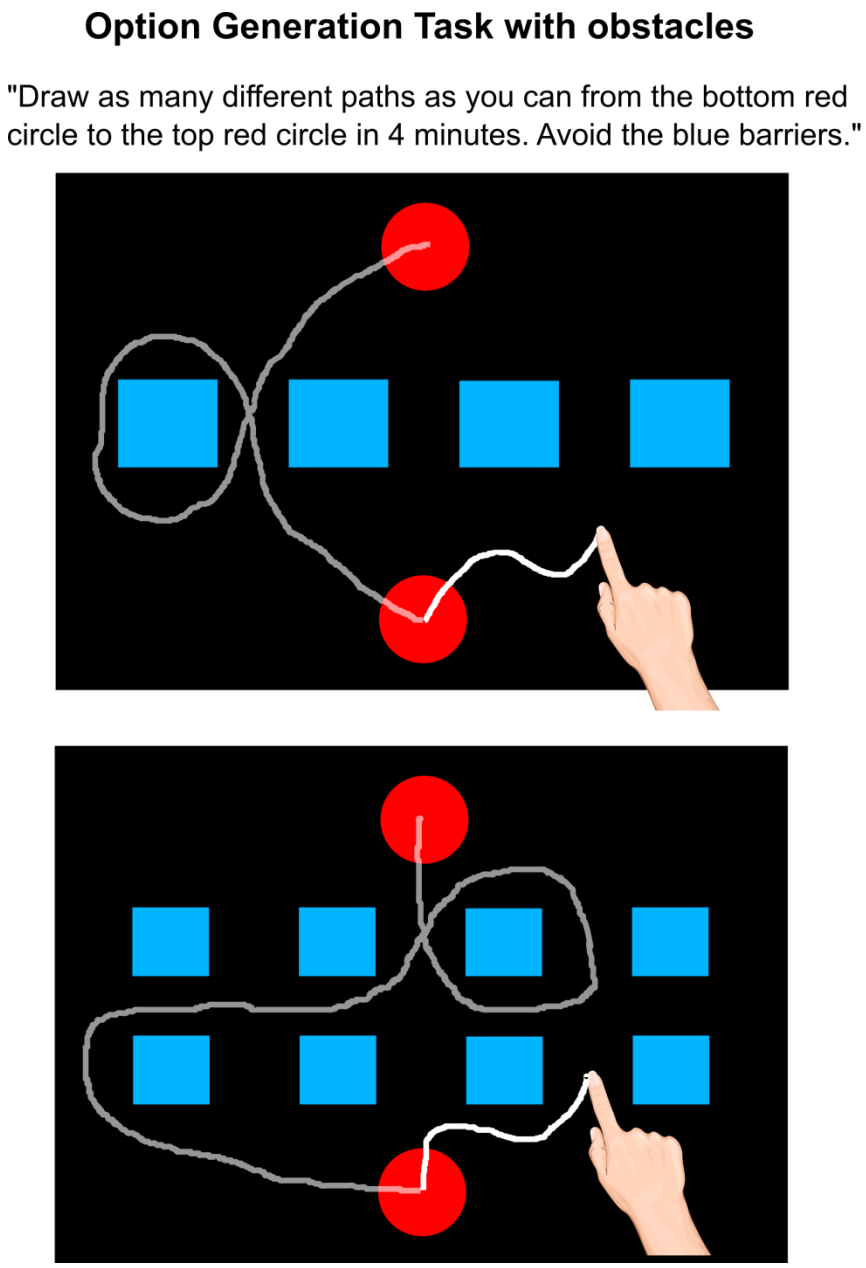


Figure 3.13 Illustration of the option generation task with obstacles to paths. Modified versions of the option generation task contained either 4 or 8 rectangular obstacles. Participants were required to draw, in 4 minutes, as many different paths as possible from the start-point (bottom circle) to the end-goal (top circle). Importantly, they had to avoid the obstacles. This was to assess whether the presence of constraints or cues could improve participants' ability to generate options.

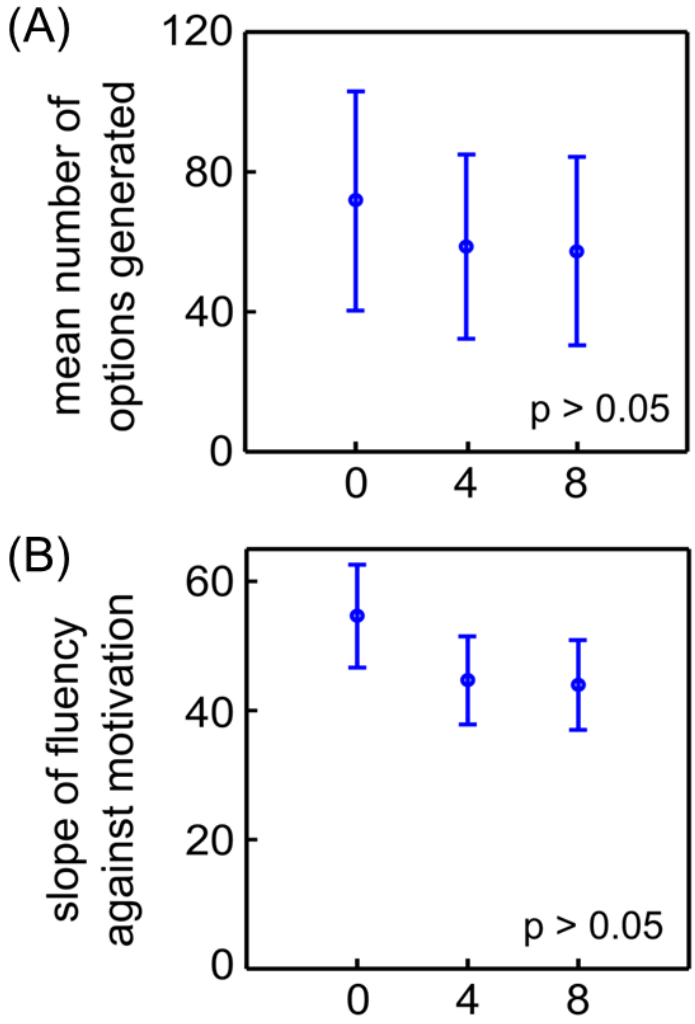


Figure 3.14 Results from the option generation task with obstacles to paths. (A) Modifying the option generation task by adding either 4 or 8 barriers did not significantly change the mean number of options generated. **(B)** The relationship between option generation fluency and motivation level was also not significantly changed. This indicates that the introduction of obstacle "cues" did not modulate the number of options generated for apathetic people compared to motivated.

3.8 Discussion

It was hypothesized that apathy might be an underlying problem in self-initiated behaviour, and one contributing factor might be a specific deficit in generating options for behaviour (Sinha et al., 2013). To examine this, I devised a novel measure of option generation that is quantitative yet relatively unconstrained. Participants were required to connect two points on a touchscreen computer by generating as many different paths as possible within a fixed time (**Figure 3.2**). Healthy people displayed a *trade-off* between uniqueness and fluency, tending to either produce many similar paths or fewer unique paths (**Figure 3.5A**). This trade-off exhibited opposing relationships with motivation. Fluency scaled positively with their level of motivation, indicating that apathetic people tended to generate fewer options compared to their motivated counterparts (**Figure 3.5B**). On the other hand, the generation of more unique options correlated negatively with motivation level, demonstrating that although apathetic people drew fewer paths they tended to be more creative in the options they generated (**Figure 3.5C**).

3.8.1 Apathy is associated with reduced option generation

Previous research in design fluency tests have shown that performance might be influenced by motor speed (Suchy et al., 2010). Indeed, one might suggest that apathetic individuals came up with fewer options here because they were slower to execute the drawing during the task. However, the correlation between the number of options generated and motivation still remains even after controlling for performance on a motor execution control task (**Figures 3.7, 3.8**). This suggests that lower fluency

(reduced option generation) was unlikely to be explained simply by slower motor speed.

Another empirical challenge in investigating option generation is separating it from motor planning ability. In the option generation task, it is possible that reduced number of options were generated because of difficulty in planning the motor action required to execute the option in mind. This was controlled for by employing an externally-cued action control task where participants had to draw straight paths to externally cued location (Figure 3.9). Thus, they did not have to generate novel path options, or select from them after generation. Also, unlike the motor execution control task, each action requires a different motor plan. Fluency on the option generation task remained correlated with motivation even after accounting for performance on this task, which tests motor planning ability (Figure 3.10). Therefore, it is unlikely that apathetic people were producing fewer options because of a deficit in motor planning ability.

One more possibility is that the apathetic individuals might have generated many options but had difficulty selecting one from amongst them to execute. In other words, a deficit in option selection might be mistaken as a deficit in option generation. To examine this, an option selection control task was administered. Participants had to first select an option from a given set of possible target options and then draw a straight path to it (Figure 3.11). Hence, no generation of novel path options was required. A significant relationship between the fluency of option generation and motivation remained despite regressing out performance on this control task (Figure

3.12). This suggests that an inability to select between options is unlikely to account for apathetic people generating fewer options.

Finally, might the addition of 'cues' on screen help apathetic participants generate more options? The option generation task was modified by adding barriers that had to be avoided when participants generated a path between the start and end points on screen (Figure 3.13). Performance of apathetic compared to motivated people did not improve in the presence of cues (Figure 3.14), suggesting that externally-provided barrier cues did not have any particular influence on healthy people.

Together, these results suggest that apathy is associated with a specific impairment in option generation fluency.

3.8.2 Only fluency contributed to the prediction of motivation level

An important component of option generation is the ability to produce novel, creative options. Surprisingly, despite generating fewer paths on the option generation task, apathetic individuals came up with paths of greater mean uniqueness and exhibited greater variation in their generated path options (Figure 3.5B, C). At first sight, one might be tempted to conclude that they have placed greater emphasis on generating *different* compared to *many* paths when instructed to draw as many different paths as possible.

However, a strong negative correlation between the number of paths generated and uniqueness was found (Figure 3.5A). As such, it is not surprising to find significant opposite relationships between motivation and these two variables. To

dissociate these two correlations, fluency and uniqueness were included in a univariate GLM that assesses how much they independently related to motivation. Only fluency predicted level of motivation. Therefore, the association between uniqueness and motivation was simply an artefact of the fluency-uniqueness tradeoff.

This tradeoff is present in all other types of fluency tasks such as the verbal and design fluency tests (Regard et al., 1982; Ruff et al., 1994; Thurstone, 1938) and Alternative Uses Test (Guilford, 1967). However, the option generation task has the advantage over these standard tasks in that this tradeoff between fluency and uniqueness are explicit and measurable. Furthermore, the domain does not rely on prior knowledge and provides a natural continuous, rather than discrete, measure. Also, the process is automated, thereby reducing inter-tester variability and overcoming problems of performance anxiety that may mar performance in some individuals.

3.9 Conclusion

The study of decision-making has become an important focus of neuroscience research. However, investigations of how people make decisions have mostly relied on asking them to select from two or more options provided by the experimenter, rather than requiring participants to generate options by themselves. A novel paradigm that was devised to assess an individual's ability to generate options demonstrated that apathy, or lack of motivation, specifically alters option generation. In healthy people with a range of motivation levels, apathy was found to be associated

with significantly reduced self-initiated option generation. Crucially, this apathy-related paucity of generation was not due to a difficulty in switching between actions, selecting between options or executing actions. It was also not ameliorated by introducing visual cues that might afford novel actions.

4 Influence of Dopamine on Option Generation and Apathy in Parkinson's Disease

4.1 Introduction

In the previous chapter, I have established a novel paradigm of option generation (**Figure 3.2**) and used it to show that reduced ability to generate options associates with individual levels of motivation in the healthy population. This suggests that deficits in option generation may contribute to apathy in healthy people and raises the question: Might apathy in clinical populations be related to impairments in option generation too?

Apathy occurs frequently in patients with neurodegenerative conditions such as Parkinson's Disease (PD) and can severely reduce the quality of life for them and their caregivers (den Brok et al., 2015; Pagonabarraga et al., 2015). Studies across

various neurological disorders have uncovered a fairly consistent picture of the neural correlates by regularly implicating disruptions of the medial frontal cortex and subcortical basal ganglia structures, particularly the anterior cingulate cortex and ventral striatum (see Le Heron et al., 2017 for review). Based on the functional properties of these brain regions, the prevailing theory is that apathy arises from an inability to weigh the effort costs and reward benefits of options for behaviour. In other words, apathy is commonly framed as a disorder of evaluating options during decision-making (Le Heron et al., 2017; Sinha et al., 2013). Apathy has also been thought to stem from deficits in learning the rewarding values of action during outcome processing (Cohen and Ranganath, 2007; Le Heron et al., 2017). Direct support for both proposals may be found in recent investigations targeting PD (Adam et al., 2013; Lawrence et al., 2011; Le Heron et al., 2018; Martinez-Horta et al., 2014; Muhammed et al., 2016). However, these hypotheses bear the inherent assumption that the potential options for action are already available in the environment, which may not always be the case in the real world (Kaiser et al., 2013; Kalis et al., 2008).

The possibility that apathy may also occur in these patients due to a failure to generate options in the first place has never been examined (Sinha et al., 2013). Here, I was interested in exploring whether an impaired ability to generate options contributes to clinical apathy – specifically PD, as this population has been the target of previous works focusing on deficits in selecting between options and learning outcomes during feedback. Furthermore, the investigation of PD affords an opportunity to understand the neurochemical modulation of option generation.

Two different domains of research, executive control and creative cognition, suggest a key role for the prefrontal cortex in generating numerous options for behaviour (*fluency*) and in the *uniqueness* of those options. Prefrontal cortex has long been identified to play an important role in executive functions crucial for the initiation and sustaining of responses (MacPherson et al., 2015; Stuss, 2011; Stuss and Alexander, 2007). Neuroimaging and lesion studies have implicated the frontal lobe in verbal and nonverbal tests of fluency that require the production of as many responses as possible in a fixed time limit (see MacPherson et al., 2015 for review). The frontal cortex is also considered to play a key role in creativity, with evidence from neuroimaging (Dietrich and Kanso, 2010; Gonen-Yaacovi et al., 2013), electrophysiological (Fink and Benedek, 2014) and patient studies (de Souza et al., 2010; Rankin et al., 2007) lending support to this view. Furthermore, focal lesions of the frontal lobe impair performance across various measures of creativity (Abraham et al., 2012; Shamay-Tsoory et al., 2011).

However, the neurochemical modulation of these two aspects of option generation (fluency and uniqueness) remains unknown. Substantial evidences have now implicated the neurotransmitter dopamine in various cognitive functions such as working memory, behavioural flexibility and decision-making (for review, see e.g. Frank and O'Reilly, 2006; Cools and D'Esposito, 2011). Dopamine most likely exerts these modulatory effects via extensive diffuse projections from midbrain dopaminergic nuclei to the basal ganglia and frontal cortex (Arnsten, 1998; Fallon and Moore, 1978; Floresco and Magyar, 2006; Gerfen, 1992). High concentrations of dopamine D1 receptors are also found in the prefrontal cortex (Goldman-Rakic, 1995; Lidow et al.,

1991; Smiley et al., 1994). Furthermore, several neurological disorders involving dysfunctions of the dopaminergic systems (e.g. PD, schizophrenia and attention deficit/ hyperactivity disorder) are often associated with cognitive impairments such as working memory, apathy, impulsivity and cognitive inflexibility (Dujardin et al., 1999; Le Heron et al., 2017; Owen et al., 1992; Roth et al., 2004; Sinha et al., 2013; Verbaan et al., 2007).

Given dopamine's established role in cognition, it has been previously speculated that dopamine might mediate option generation during decision-making (Sinha et al., 2013). A recent theoretical model of creative cognition also proposed that prefrontal dopamine and the mesocortical dopaminergic pathway facilitates persistence and fluency in generating many responses, while striatal dopamine and the nigrostriatal pathway enhances flexibility in thinking of original and novel products (Boot et al., 2017). There is currently no direct evidence for this proposal, but the theory offers a useful starting point for investigating dopamine as the key neurotransmitter of option generation.

To pursue this premise, I have chosen to focus on PD, a neurodegenerative disorder characterised by loss of dopaminergic neurons in the substantia nigra and with evidence of prefrontal cortical dysfunction. This permits an examination of how dopamine might influence uniqueness and fluency on the option generation task (Figure 3.2). Patients with PD were tested twice – once ON dopaminergic medication and once after overnight withdrawal ('OFF' state) – and compared to elderly healthy controls. Such a design allowed performance to be compared when dopamine levels differ within-subject, thereby enabling inferences to be made regarding the influence

of dopamine. I also examined whether the effects of dopamine on option generation was influenced by pathological lack of motivation, or apathy, in PD.

4.2 Procedure

4.2.1 Participants

35 patients with PD (23 males, 12 females; mean age=67.7 years old, SD=8.1) and 34 healthy age-matched controls (21 males, 13 females; mean age=69.1 years old, SD=8.3) participated in this study.

All patients were recruited from clinics in the Oxfordshire area, had a clinical diagnosis of idiopathic PD according to Queen Square Brain Bank criteria and no history of other major neurological or psychiatric conditions. They were established on levodopa therapy. 15 patients took this as their sole PD medication, 11 were on a concomitant dopamine agonist, and a minority were on other adjunctive therapies (Monoamine oxidase inhibitor *N*=8; Amantadine *N*=5; anti-cholinergic *N*=1). Demographics and levodopa equivalent dose are presented in **Table 4.1**. They were tested in two counter-balanced sessions, once after having taken their dopaminergic medication as usual ('ON') and once after overnight withdrawal >12h ('OFF').

All healthy controls were recruited from a volunteer database, had corrected-to-normal colour vision and no history of psychiatric or neurological conditions. 18 controls were tested in a single session while 16 were tested twice across two sessions.

4.2.2 External measures

Participants completed the Lille Apathy Rating Scale (LARS, Sockeel et al., 2006), a clinical interview to measure levels of apathy-motivation. The LARS has a total score ranging from -36 to +36, with a higher score indicating greater apathy (or lower motivation). Participants were screened for clinical depression based on the Beck's Depression Inventory (BDI, Beck et al., 1996) and their cognitive ability was assessed with Addenbrooke's Cognitive Examination (ACE-III) (Hsieh et al., 2013). Patients had significantly lower ACE scores and significantly higher BDI scores compared to the healthy controls; however, the average scores in both groups did not meet the cut-off for suspected dementia (ACE-III<82) nor depression (BDI>20). PD patients also completed the Unified Parkinson's Disease Rating Scale (UPDRS) to assess disease severity. Details of all demographics can be found in the Table 4.1.

Table 4.1 Demographics and measures for PD patients and controls.

Variable	Healthy elderly controls	Parkinson's disease patients	Controls versus Patients *p*-value
N	34	35	n/a
Age (years)	69.1 (±8.3)	67.7 (±8.1)	0.49
Apathy-Motivation (LARS)	26.1 (±4.5)	21.1 (±7.4)	0.001*
Depression score (BDI)	3.5 (±3.0)	14.0 (±7.8)	<0.001*
ACE	95.5 (±4.5)	91.8 (±5.9)	<0.01*
UPDRS III ON	n/a	28.3 (±11.6)	n/a
UPDRS III OFF	n/a	36.3 (±12.5)	n/a
Levodopa equivalent dose (mg/24h)	n/a	623.0 (±359.2)	n/a

*: significant result

4.2.3 Experimental tasks

All participants completed the following tasks:

- Option generation task

Participants were given a time limit of four minutes to draw on a touchscreen computer as many different paths as they could between two vertically aligned, fixed points (Figure 3.2). This allowed movement and timing parameters to be extracted, thereby providing an opportunity to evaluate both the *uniqueness* and *diversity* of paths generated using objective metrics.

To quantify uniqueness, an index of similarity between pairs of paths was created (Figure 3.3). Each path was parameterised by 200 points equally spaced along its length, and the "distance" between a pair of lines drawn on the touchscreen was computed as the sum of distances between pairs of corresponding points. Lines were reflected about the midline such that mirror image paths were considered as similar to each other, and the first and second derivatives were included in the distance metric to better account for differences in the shapes of the curves. This allowed a measurement of "effective distance" between each pair of paths drawn. For every path produced by each participant, uniqueness was defined as the distance between it and the most similar path produced by all other participants.

To quantify diversity, the distances between a participant's paths were projected onto a 2-dimensional subspace using multidimensional scaling to visualise how they explored the path space (Figure 3.3, 3.4). An individual was more explorative, i.e. produced greater variation in generated paths, if the paths (each

represented by one point in the dissimilarity space) were more dispersed. This was approximated by calculating the area of the convex hull covering each participant's paths projected in the 2-dimensional subspace.

This task quantifies option generation using behavioural output. However, as with traditional timed tests of fluency, several other factors may confound this interpretation e.g. ability to execute movements, plan motor actions and select from amongst various competing options. To account for these, three closely-matched control tasks were also administered.

- Motor execution control task

To test baseline drawing speed, participants had to draw ten straight lines, each as quickly as they could, between the two fixed points of the option generation task (Figure 3.7). The mean time taken to draw each line (excluding time between lines) served as a baseline index of their motor vigour that was closely matched to the main task.

- Externally-cued action control task

To examine ability to plan motor actions, an externally-cued action control task was employed in which each movement required a different motor plan, but there was no need to generate unique paths. Instead, participants simply had to draw a straight line to a target location that was randomly generated by the computer. A new target location was generated once the path had been completed, and the goal was to connect to as many target locations as possible in 90 seconds (Figure 3.9). Thus,

motor planning ability could be assessed, in isolation from the ability to generate the option for the next action since this was now provided by the computer.

- Option selection control task

To assess ability to select from amongst options, an option selection control task was administered where participants had to first select an option from a given set of possible target locations, and then draw a straight path to it. The goal was to draw as many individual paths as possible from a central start location in 90 seconds to the displayed possible target locations (Figure 3.11). No unique generation of paths was required as the target options were always displayed.

4.2.4 Statistical analysis

The behavioural data was analysed using MATLAB and IBM SPSS Statistics 22.0. I tested the assumption of normality in all data, and those that were not normally distributed were log-transformed before further analyses. Dependent variables were compared within-subjects using a paired two-tailed *t*-test and between-subjects using an independent-samples two-tailed *t*-test. For all analyses, a *p*-value<0.05 was taken to be statistically significant unless otherwise stated.

4.3 Results from option generation task

4.3.1 No effect of repeated testing was found

There was no significant effect of testing on repeated sessions in PD patients. A repeated measures ANOVA analysis found only a significant main effect of drug state (ON vs. OFF), but not session nor drug*session on the number of paths generated [drug: $F(1,66)=22.6$, $p<0.001$; session: $F(1,66)=1.45$, $p>0.05$; drug*session: $F(1,66)=0.07$, $p>0.05$], mean uniqueness of generated options [drug: $F(1,66)=15.8$, $p<0.001$; session: $F(1,66)=1.29$, $p>0.05$; drug*session: $F(1,66)=0.16$, $p>0.05$], and area of exploration in the 2-dimensional path subspace [drug: $F(1,66)=4.71$, $p<0.05$; session: $F(1,66)=0.03$, $p>0.05$; drug*session: $F(1,66)=0.08$, $p>0.05$].

For the subset of healthy age-matched controls, there was also no significant difference across sessions in number of paths generated ($t(15)=-1.68$, $p>0.05$), or mean uniqueness ($t(15)=2.06$, $p>0.05$), or area of exploration in the 2-dimensional path subspace ($t(15)=1.95$, $p>0.05$).

4.3.2 Apathy in PD did not relate to fluency or creativity

The total score on the LARS clinical interview (measure of apathy-motivation) did not correlate with the number of paths generated, or mean uniqueness, or area explored in path subspace in the ON and OFF states nor with the difference between the two states (all $p>0.05$, see **Table 4.2**).

Table 4.2 Correlations between LARS and task variables in PD patients.

		LARS
Number of paths generated	ON	-0.11
	OFF	-0.09
	ON – OFF	-0.07
Mean uniqueness	ON	-0.33
	OFF	-0.25
	ON – OFF	-0.02
Diversity in 2D subspace	ON	-0.11
	OFF	-0.27
	ON – OFF	-0.30

Note: all $p>0.05$

These patients were then divided into two groups – apathetic (N=18) and motivated (N=17) – based on the LARS apathy cut-off score of >-22. A two-way mixed ANOVA analysis revealed a significant effect of drug (ON, OFF), but not apathy, nor drug*apathy on (i) the number of paths generated [drug: $F(1,33)=20.4$, $p<0.001$; apathy: $F(1,33)=0.65$, $p>0.05$; drug*apathy: $F(1,33)=0.70$, $p>0.05$], (ii) mean uniqueness [drug: $F(1,33)=13.8$, $p<0.01$; apathy: $F(1,33)=1.91$, $p>0.05$; drug*apathy: $F(1,33)=0.09$, $p>0.05$], and (iii) variation in paths [drug: $F(1,33)=5.08$, $p<0.05$; apathy: $F(1,33)=0.24$, $p>0.05$; drug*apathy: $F(1,33)=1.45$, $p>0.05$].

These findings suggest that unlike the healthy population, apathy in PD was not related to fluency of generation or creativity.

4.3.3 Dopamine modulates the balance between fluency and uniqueness

Paired-samples t-test revealed a significant effect of drug state (ON vs. OFF) on performance in the option generation task. PD patients generated fewer paths when OFF compared to ON dopamine ($t(34)=4.51$, $p<0.001$, **Figure 4.1A**). But when OFF medication, they exhibited greater mean uniqueness in their generated paths ($t(34)=-3.76$, $p<0.001$, **Figure 4.1B**) and were more explorative in the 2-dimensional path subspace ($t(34)=-2.16$, $p<0.05$, **Figure 4.1C**). Thus, dopamine modulated the balance between uniqueness of paths and the fluency of path generation (**Figure 4.1D**).

Age-matched controls were both fluent and unique, generating a comparable number of paths to PD patients ON dopamine [ON: $t(67)=-0.51$, $p>0.05$; OFF: $t(67)=-3.55$, $p<0.001$, **Figure 4.1A**] and exhibiting comparable uniqueness to patients when OFF dopamine [ON: $t(67)=-2.03$, $p<0.05$; OFF: $t(67)=-0.03$, $p>0.05$, **Figure 4.1B**]. Note

that data from only the first session of controls was used here as no significant difference across sessions was found.

By comparing the average uniqueness and fluency between the three groups – PD ON, PD OFF and healthy control – it is evident that the PD state lowers the fluency of generation without affecting uniqueness. Treatment with dopamine helps to restore the number of paths generated, but at the expense of uniqueness (Figure 4.2). This suggests that dopamine may play an important role in modulating the balance between generating more options against producing more unique options.

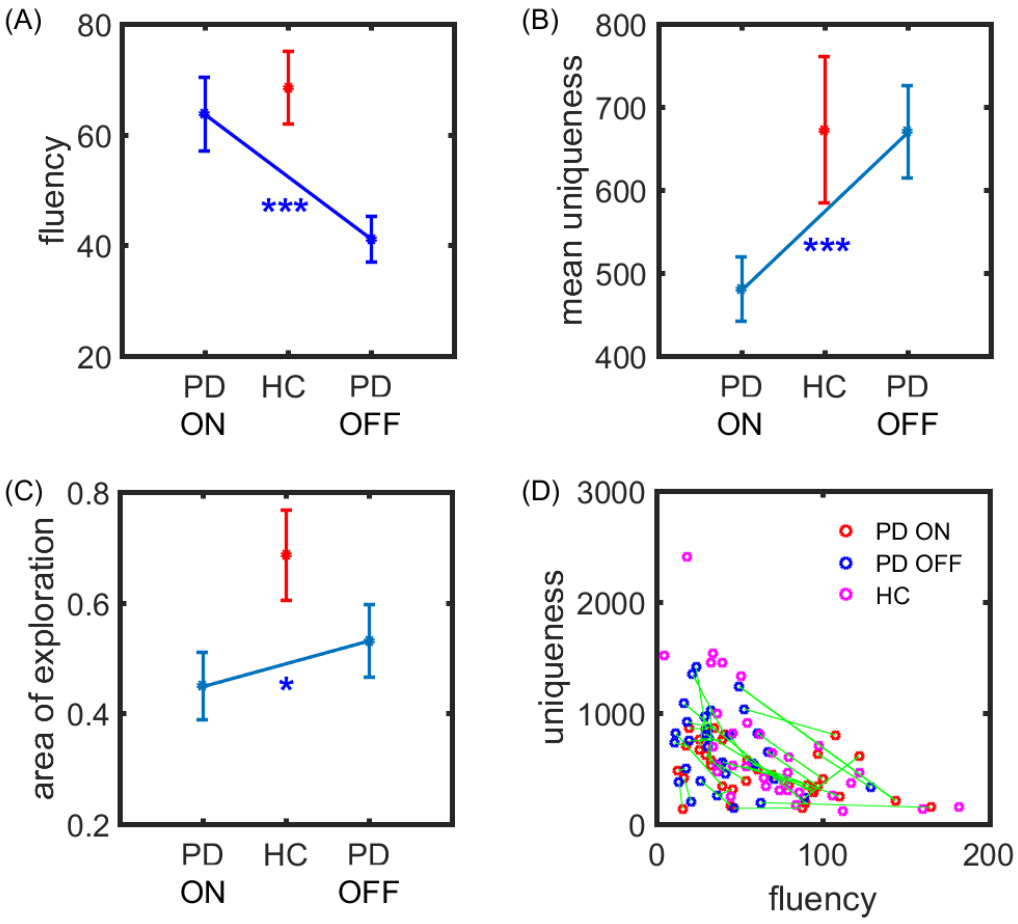


Figure 4.1 Results from option generation task. (A–C) PD patients generated significantly more paths when ON compared to OFF dopamine (p<0.001). Yet, they were more unique (p<0.001) and explored a larger area in the 2-dimensional path subspace (p<0.05) when OFF their medication. Healthy age-matched controls were both fluent and creative, generating a similar number of paths to patients ON dopamine and displaying comparable uniqueness and area of exploration to patients OFF dopamine. **(D)** A scatterplot of each individual's mean uniqueness of paths against their number of paths generated. The same PD patients ON and OFF dopamine are connected by green lines. There appears to be a uniqueness-fluency trade-off between generating more paths and the uniqueness of these paths.

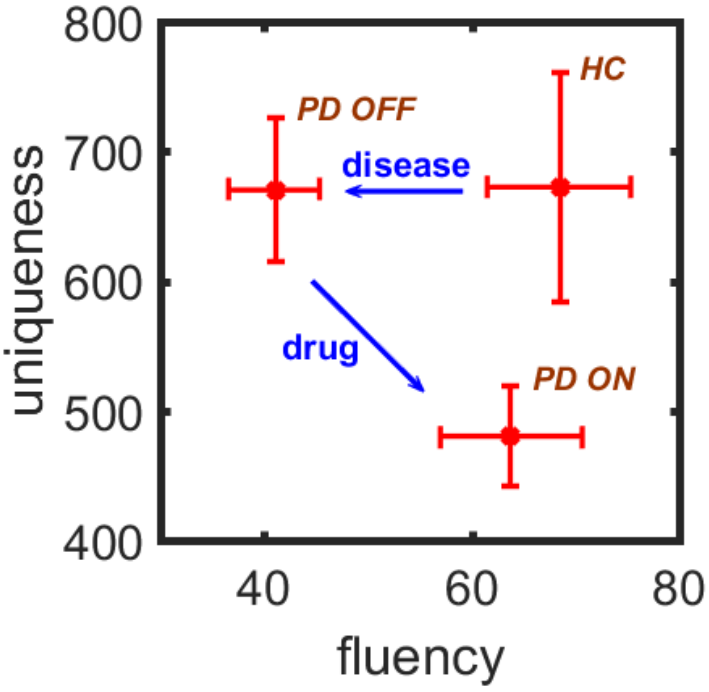


Figure 4.2 Effect of dopamine on fluency and uniqueness of option generation. A comparison of the group averages in uniqueness and fluency shows that PD reduces fluency of generation, although uniqueness is preserved. Administration of dopamine restores the number of paths generated, but at the expense of reduced uniqueness. This suggests that dopamine may play an important role in modulating the balance between generating more options against producing more unique outputs.

4.3.4 Dopamine increases uniqueness for a given fluency

Because fluency correlates with uniqueness (r=-0.46, p<0.001), a linear mixed effects model for the uniqueness of each path produced by the PD patients was fitted by maximal likelihood using the *fitlme* function from the Statistics Toolbox in MATLAB 2017a. I used fixed effects of each path's duration, dopamine drug state, apathy level and their interactions, and random effects of subject.

*Uniqueness ~ Duration + Drug + Apathy + Duration*Drug + Duration*Apathy + Drug*Apathy + Duration*Drug*Apathy + (1|Subject)*

One might notice that path duration, instead of total number of paths, was used as the metric for fluency here. Path duration may be seen as the inverse of fluency, with faster paths (and thus smaller duration) indicating greater fluency and slower paths (or larger duration) indicating lower fluency. In this linear mixed effects model, it was necessary to use path duration as it gives a value for each individual path and the aim was to correct for the effect of each path's 'fluency' on its uniqueness.

In PD, the fixed effect terms of Duration and Drug were significant, indicating that dopamine increases uniqueness when controlling for duration. In other words, given the same duration of drawing time, PD patients when ON dopamine were more likely to generate a path of greater uniqueness than when OFF dopamine. There were also weaker but significant interaction effects of Duration*Drug and Duration*Apathy, indicating that drug and apathy changes the slope of the fluency-uniqueness tradeoff (results in Table 4.3).

This analysis revealed that dopamine crucially increased the uniqueness of paths after correcting for the fact they were faster, but apathy had no main effect or Drug*Apathy interaction effect (**Figure 4.3**). Thus although the major drug effect was to produce a trade-off, with faster and less-unique paths, it also independently improved uniqueness for a given fluency (**Figure 4.4**).

4.3.5 Results were similar even when not correcting for mirror paths

The analyses thus far have taken into account reflections of paths about the midline such that mirror image paths were considered as similar to each other in external space. However, it may be argued that this is arbitrary as mirror image paths require a considerably different motor program and thus, may be dissimilar in joint/muscle space.

The analyses were re-ran using a distance metric that was not corrected for mirroring. Very little changes were found in the uniqueness scores, indicating that mirror images contributed only a small amount of uniqueness (correlation between individual path uniqueness with and without reflection about midline r=0.98, p<0.001). In line with this, the p-values were very similar and do not affect interpretation of the results. The results of the linear mixed effects model analysis without accounting for mirror image paths are in **Table 4.3**.

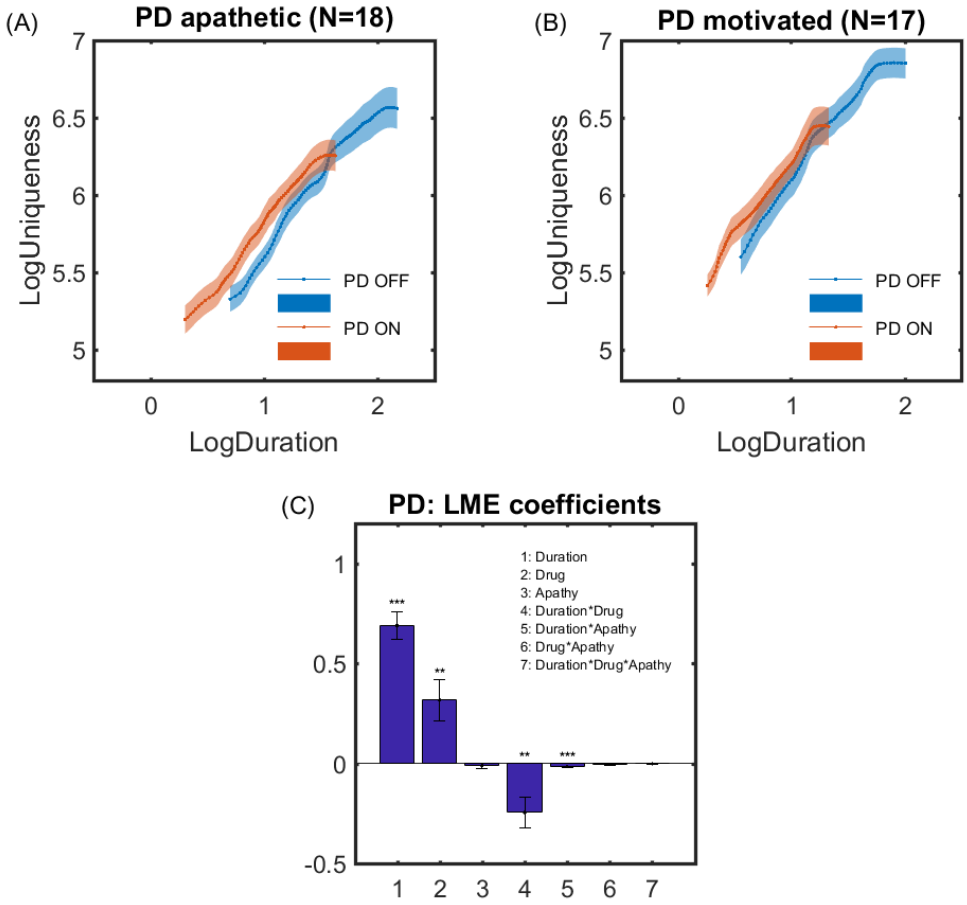


Figure 4.3 Results from the linear mixed effects (LME) model analysis in PD patients. Because fluency correlates with uniqueness, a mixed model was used to examine how each path's duration (or inverse of fluency) influences uniqueness. **(A, B)** Dopamine was found to increase the uniqueness of paths after correcting for the fact that they were faster (red line significantly higher than blue line, p=0.005). However, there was no significant difference in this increase between apathetic and motivated patients (p>0.05). To plot the graphs, for each subject the uniqueness of their generated routes was taken in a sliding window calculated on the route durations. The mean log uniqueness in each of 80 overlapping windows (0.2 quantile width) was averaged across subjects, and plotted against the mean log duration for that window. This was performed for each drug condition separately. Shaded area represents standard error of the mean across subjects. **(C)** Coefficients of the effects from the LME analysis (*** p<0.001, ** p<0.01).

Table 4.3 Results from linear mixed model analysis in PD patients.

	mirroring		not mirroring	
	t	*p*	*t*	*p*
Duration	9.42	<0.001	9.72	<0.001
Drug	2.81	0.005	3.09	0.002
Apathy	-0.77	>0.05	-0.99	>0.05
Duration*Drug	-2.91	0.004	-3.15	0.002
Duration*Apathy	-5.67	<0.001	-5.13	<0.001
Drug*Apathy	-1.26	>0.05	-0.91	>0.05
Duration*Drug*Apathy	-0.29	>0.05	-0.55	>0.05

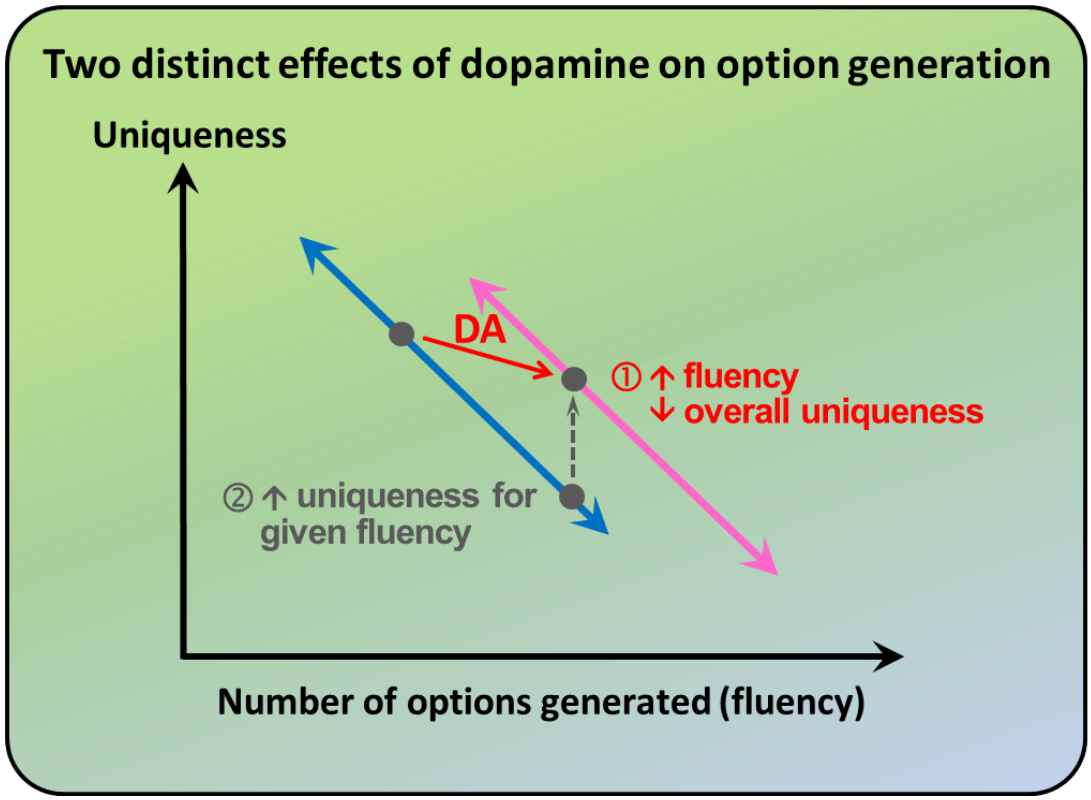


Figure 4.4 Dual effects of dopamine on option generation. Although the major effect of dopamine was to improve the fluency of producing options (1), it also independently improved uniqueness for a given fluency (2).

4.3.6 Increased fluency ON dopamine is not due to improved motor deficits

One might argue that the effect of dopamine on increasing fluency is simply due to improvements in the motor deficits that are characteristic of PD. Further analysis of the data suggests this is unlikely.

The severity of motor deficits for each patient in both the ON and OFF states was examined using the Unified Parkinson's Disease Rating Scale (UPDRS). The difference in UPDRS motor scores between the ON and OFF states correlated strongly with that in the OFF state (r=0.54, p=0.001, **Figure 4.5D**), indicating that patients with worse PD severity also showed greater improvement in motor symptoms when treated with dopamine.

The UPDRS motor scores in the OFF state also correlated with the number of paths generated both when ON and OFF dopamine, but importantly *not* to the difference in fluency between the two states, i.e. ON – OFF [ON: r=-0.36, p<0.05; OFF: r=-0.48, p<0.01; ON – OFF: r=0.08, p>0.05; **Figure 4.5A–C**].

Thus, disease severity (indexed by UPDRS score) modulated the baseline number of paths generated. However, it had no effect on dopaminergic improvement in fluency, despite strongly predicting improvement in motor UPDRS scores when ON dopaminergic drugs (difference in correlation coefficients, Fisher-transformed Z=2.24, p<0.05). The improvement in fluency on dopamine was also not correlated with dopaminergic improvement in motor symptoms based on UPDRS, indicating that the increase in number of options generated was not due to better motor abilities (r=0.14, p>0.05).

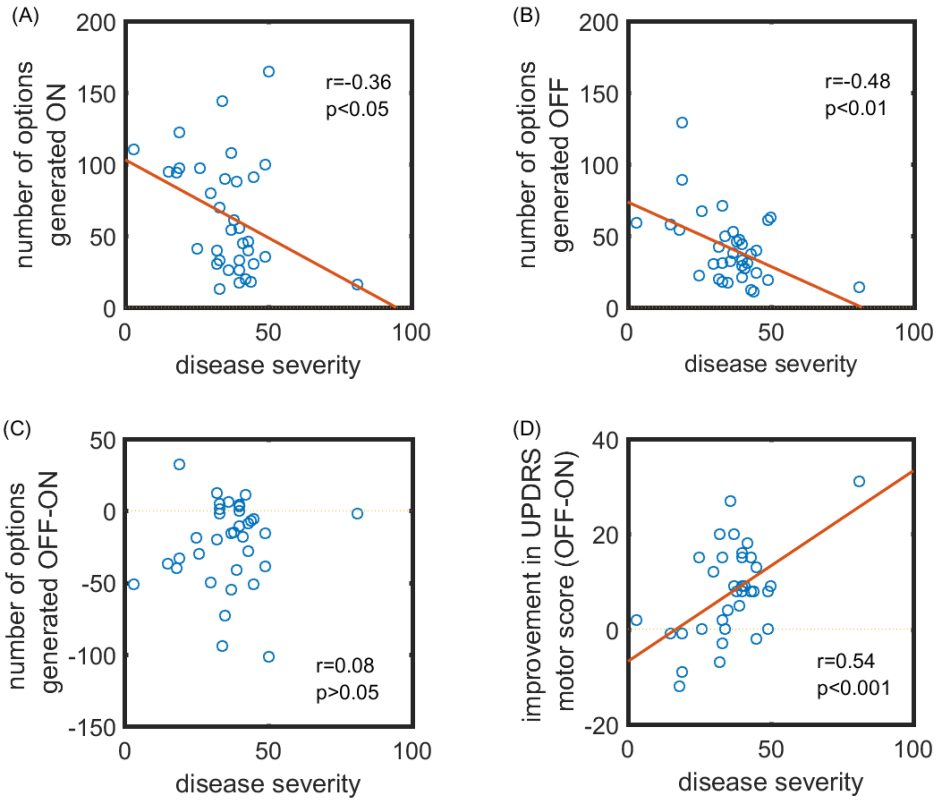


Figure 4.5 Correlation plots for disease severity on option generation. Could the effect of dopamine on increasing fluency be simply due to improvement in the motor deficits that are characteristic of PD? This is unlikely. **(A, B)** Disease severity was assessed using section III of the Unified Parkinson's Disease Rating Scale (UPDRS) when the patient was OFF dopamine. The fluency of generation correlated negatively with disease severity both ON and OFF dopamine, suggesting that the severity of disease modulated baseline number of paths generated. **(C)** Importantly, disease severity did *not* correlate with the difference in fluency between the ON and OFF states. **(D)** The *difference* in UPDRS motor scores between the ON and OFF states correlated strongly with that in the OFF state. This indicates that patients with worse PD severity also showed greater improvement in motor symptoms when treated with dopamine. These results show that disease severity modulates the baseline number of paths generated but has no effect on the dopaminergic improvement in fluency, despite strongly predicting improvement in motor UPDRS scores when on dopaminergic drugs.

4.3.7 Increased uniqueness OFF dopamine is not due to greater tremors

Could the increased uniqueness displayed by PD patients when OFF dopamine be due to increased tremor? This is unlikely. An index of tremor was derived by combining the UPDRS resting and kinetic tremor severity scores. There was no significant relationship between amount of tremor and uniqueness (spearman ρ=0.05, p>0.05). Furthermore in a separate analysis, the raw movement data was first smoothed using a moving average window size of 250 milliseconds (*smoothdata* function in MATLAB R2017a) to remove energy around 4 Hz from tremors, before computing uniqueness. The results revealed that PD patients still displayed greater uniqueness when OFF compared to ON dopamine (t(34)=3.76, p<0.001), suggesting that tremor during the OFF state did not contribute to increased uniqueness.

4.4 Results from control tasks

4.4.1 Motor execution control task

One possible confound in interpreting these findings is that participants might have generated options but not produced them because of deficits in motor execution, such as if the individual was slow to draw on the touchscreen. The difference in number of path options generated by PD patients between ON and OFF states did not correlate with the difference in baseline drawing speed on the motor execution control task (r=0.07, p>0.05, **Figure 4.6**). This suggests that reduced fluency in the OFF state cannot be explained simply by deficits in movement speed or executing actions.

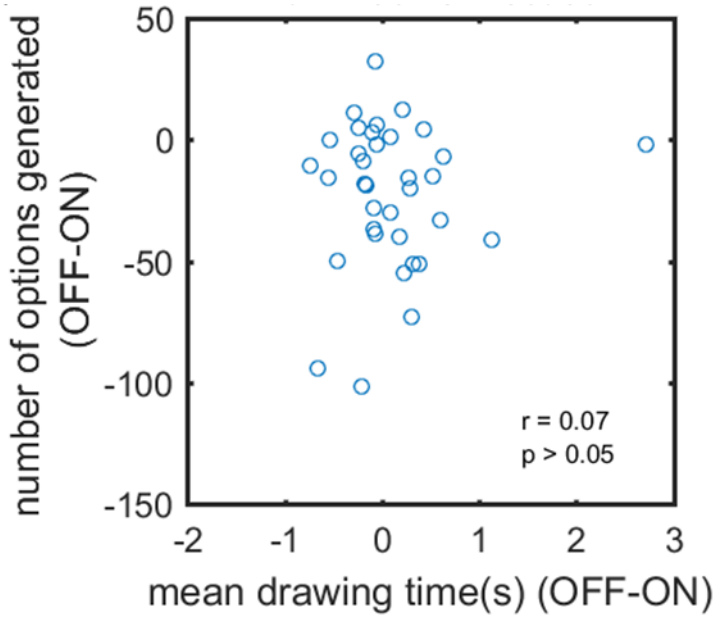


Figure 4.6 Result from motor execution control task. In PD (*N*=35), the difference in the number of paths generated for the option generation task between the ON and OFF states did not correlate with their difference in mean drawing speed on the motor execution control task, suggesting that the reduced fluency in option generation observed when OFF dopamine is not attributable to impairments in movement speed or executing actions.

4.4.2 Externally-cued action control task

Another challenge might be that while participants might have generated options, they encountered difficulty planning the motor actions required to execute them. The difference in fluency of PD patients on the option generation task between ON and OFF states did not correlate with the difference in performance on the externally-cued action control task (r=-0.03, p>0.05, **Figure 4.7**), suggesting that reductions in fluency in the OFF state cannot be attributed to deficits in planning or initiating actions.

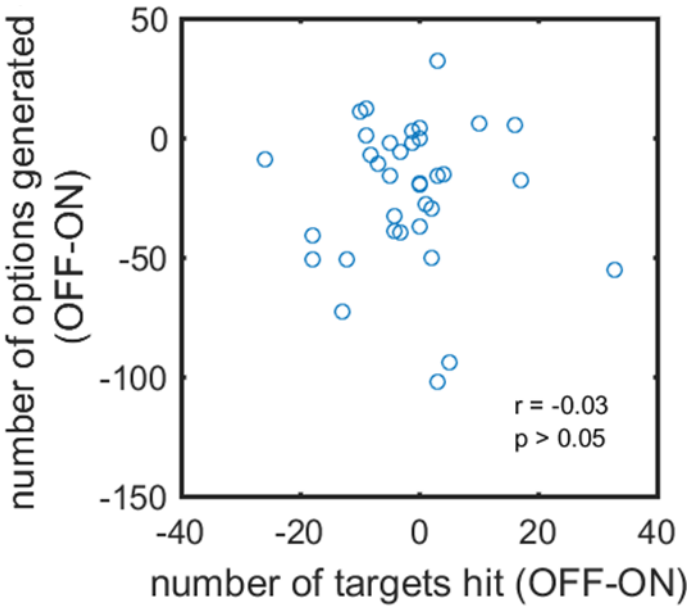


Figure 4.7 Result from externally-cued action control task. In PD (*N*=35), the change in fluency in the option generation task between the ON and OFF states did not relate to the change in the number of targets hit on the externally-cued action control task, indicating that reductions in fluency of option generation when OFF dopamine is not explained simply by deficits in planning or initiating actions.

4.4.3 Option selection control task

Finally, it is possible that while an individual might have generated many path options, they might have encountered difficulty in selecting from amongst them – a deficit in option selection during decision-making. In PD, the difference in performance on the option generation task between ON and OFF states did not associate with that in the option selection control task (r=0.20, p>0.05, **Figure 4.8**). This suggests that reductions in number of options generated in the OFF state are not due to deficits in selecting amongst generated options.

Because only straight lines (direct connections) were required for the option selection control task, this affords an opportunity to further examine whether tremor in the OFF state might have contributed to the greater uniqueness observed on the option generation task. Tremor was assumed to induce periodic patterns in the straight paths, thereby making it oscillate and be detected as being very 'different' to a straight line when subjected to the same method of quantifying uniqueness as on the option generation task. There was no significant difference in uniqueness of lines drawn on the option selection control task between ON and OFF states (t(34)=1.58, p>0.05), suggesting that tremor when OFF dopamine was indeed an unlikely cause of the increased uniqueness on the option generation task.

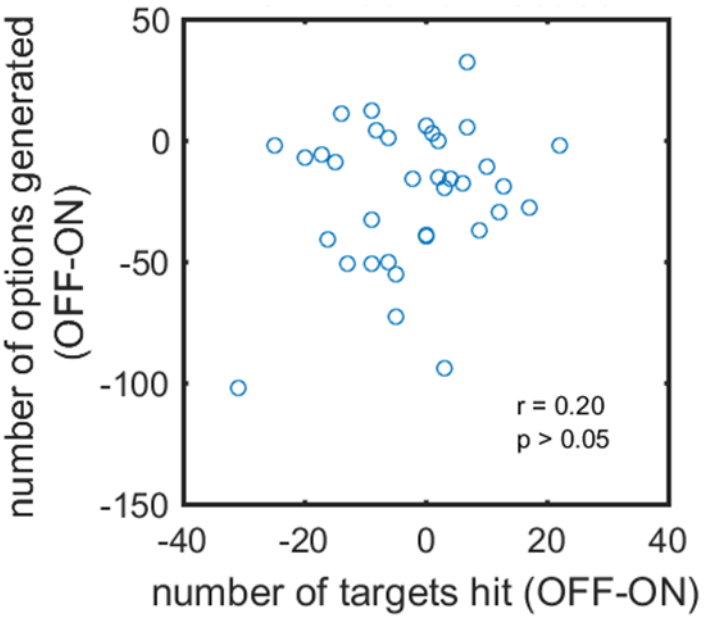


Figure 4.8 Result from option selection control task. In PD (*N*=35), the difference in number of paths generated on the option generation task between the ON and OFF states does not associate with the difference in number of paths drawn on the option selection control task, suggesting that reductions in fluency when OFF dopamine is not simply due to impairments in selecting amongst generated options.

4.4.4 Dopamine's improvement in fluency was specific to option generation

To examine whether the improvement in fluency on dopamine was specific to the option generation task, a repeated measures ANOVA was conducted using fluency per minute as the dependent variable and within-subject factors of drug (ON vs. OFF) and task type (option generation task, externally-cued action control task, option selection control task). There was a significant interaction effect ($F(2, 68)=4.66$, $p=0.01$), indicating that the difference in fluency between the ON and OFF states was different across the three tasks (**Figure 4.9**). Post-hoc comparison tests revealed that dopamine significantly improved fluency on the option generation task ($p<0.001$), but drug status did not have any effect on the externally-cued action ($p=0.37$) or option selection ($p=0.20$) control tasks. This strongly suggests that the improvement in fluency from dopamine is specific to option generation.

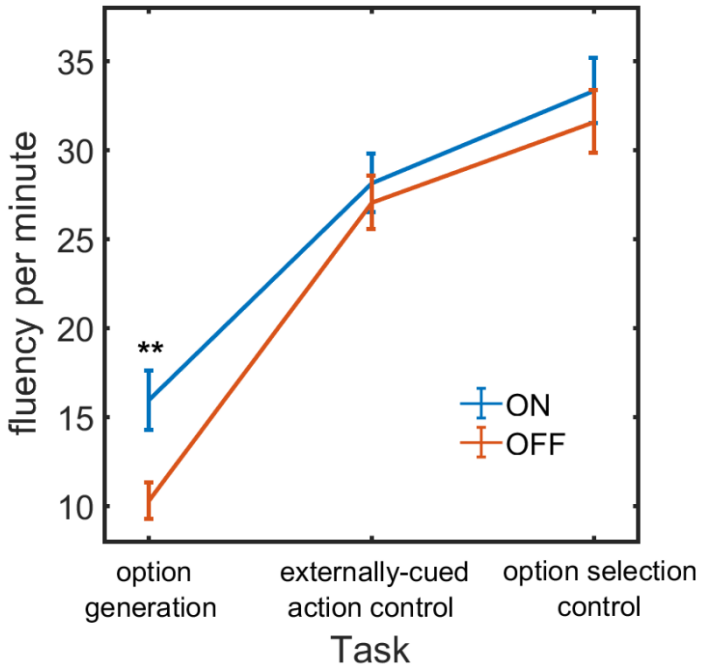


Figure 4.9 Comparison of fluency per minute for different tasks in PD patients. Repeated measures ANOVA found that dopamine's improvement in fluency was specific to the option generation task. There was no effect of dopamine on fluency in the externally-cued action and option selection control tasks.

4.5 Discussion

4.5.1 Dual effects of dopamine on fluency and uniqueness

To the best of my knowledge, this is the first study causally implicating dopamine as a key neuromodulator of self-generated options for behaviour. The prefrontal cortex has long been identified as playing a role in executive functions that may be crucial for the initiation and sustaining of responses (MacPherson et al., 2015; Stuss, 2011; Stuss and Alexander, 2007). Evidence from neuroimaging (Dietrich and Kanso, 2010; Gonen-Yaacovi et al., 2013), electrophysiological (Fink and Benedek, 2014), patient (de Souza et al., 2010; Rankin et al., 2007) and lesion (Abraham et al., 2012; Shamay-Tsoory et al., 2011) studies have also implicated a key role for the frontal lobe in creative thinking. Together, these suggest that the prefrontal cortex plays an important role in producing options that are both numerous (fluent) and unique. The neurochemical basis of these two putative frontal lobe processes, however, was unknown.

The findings presented here using a within-subject manipulation design demonstrated that PD patients performing the option generation task behave differently depending on the level of dopamine present. PD patients ON dopamine generated a larger number of path options, but at the expense of reduced creativity. They produced behavioural options of lower mean uniqueness and exhibited lesser variation in their generated options.

Further analyses uncovered two distinct effects of dopamine: it increased the fluency of generating options, but diminished overall uniqueness due to a natural

trade-off between fluency and uniqueness (**Figure 4.1**). Crucially after correcting for this tradeoff, dopamine was found to in fact increase uniqueness for a given fluency of option generation (**Figure 4.3**, **Table 4.3**). Therefore, although the major effect of dopamine was to improve the fluency of producing options, it also independently improved uniqueness for a given fluency (**Figure 4.4)**.

Nevertheless, because the task employed here seeks to understand option generation based on behavioural output observed on a touchscreen computer, various processes that may confound interpretation might occur (**Figure 3.1**). In particular, path options might have been generated but not produced due to deficits in executing the motor action (*motor execution*), difficulty in planning the motor actions required to execute them (*motor planning*), or impairments in selecting from amongst various generated path options (*option selection*). To account for these, three control tasks that were closely matched to the option generation task and designed to probe each process separately were administered. The results revealed that reductions in the number of options generated in the dopamine OFF state are not due to deficits in movement speed or executing actions, in planning or initiating actions, or in selecting amongst generated options (**Figures 4.6–4.9**).

How might dopamine modulate fluency and uniqueness during option generation? A recent theory by Boot and colleagues (2017) proposed that the balance of fronto-striatal dopamine levels might mediate the trade-off between the processes of flexibility and persistence. Striatal dopamine via the nigrostriatal pathway promotes flexible processing and facilitates original ideation (i.e. uniqueness), while prefrontal dopamine via the mesocortical pathway modulates persistence leading to focused,

systematic thinking within the same conceptual category (i.e. fluency). Although our findings are insufficient to verify the mechanisms proposed by this model, they do provide strong support for the premise that the balance between flexibility and persistence is indeed influenced by dopamine.

Several lines of research, e.g. genetic (Mayseless et al., 2013; Reuter et al., 2006), neuroimaging (de Manzano et al., 2010; Takeuchi et al., 2010) and patient (Faust-Socher et al., 2014; Polner et al., 2015) studies have suggest that dopamine improves creativity. On the option generation task, dopamine decreases overall uniqueness due to its effects on fluency. However, after accounting for the fluency-uniqueness tradeoff, there was a true increase in uniqueness – dopamine shifts the tradeoff line so that participants are more unique for a given fluency. These two distinct effects of dopamine, on fluency and on uniqueness, were separable in the option generation paradigm here as it employs a fine-grained quantification of option uniqueness compared to many other tests.

4.5.2 Deficits in option generation did not contribute to apathy in PD

While understanding the role of dopamine in option generation, I also investigated whether motivation (or apathy) might be related to fluency and uniqueness. In the previous chapter, it was found that motivated healthy individuals generated more options that were less unique compared to their apathetic counterparts (**Figure 3.5**). Intriguingly here in PD, neither apathy nor its interactions with dopamine levels influenced the fluency or uniqueness of options generated (**Table 4.2**, **Table 4.3, Figure 4.3**). This indicates that while difficulty generating options

might contribute to apathy in the healthy population, pathological apathy is likely to be influenced by other factors.

This is interesting because recent findings suggest that dopamine may play a key role in modulating apathy (Sinha et al., 2013). Although apathy is also commonly framed as a disorder of evaluating options, it seems to selectively impair internally-generated action, and thus impairments in the ability to self-generate possible options for action had been predicted to contribute to a lack of motivation to act (Sinha et al., 2013). Nevertheless, the findings here do not support this hypothesis for apathy in PD.

A recent study reported that apathy in PD correlates with sensitivity to the value of rewards being presented (Muhammed et al., 2016). This appears to be consistent with results that demonstrate greater impairments in incentive processing in apathetic PD patients compared to non-apathetic patients and healthy controls (Martinez-Horta et al., 2014). Furthermore, Le Heron et al. (2018) found using a cost-benefit decision-making task that apathy in PD occurs due to reduced incentivisation by reward. Thus, the evaluation and selection of options during decision-making based on their potential rewarding outcomes or the effort required to obtain them might be more important contributory factors to apathy in PD than inability to generate options for behaviour (Muhammed et al., 2016; Sinha et al., 2013).

4.6 Conclusion

The neuroscience of self-generated behavioural choices is an exciting field that is still in its infancy. Uncovering key neurobiological components of option generation

is crucial to advancing our understanding of decision-making. Here, I have shown using PD as a model that dopamine is a key neurotransmitter involved in this process, modulating option generation along a uniqueness-fluency spectrum.

5 Effect of Dopamine Agonist and Antagonist on Option Generation

5.1 Introduction

In the previous chapter, I demonstrated using Parkinson's disease (PD) that dopamine has two distinct effects on option generation. Specifically, the major effect of dopamine was to improve the fluency of producing options, which in turn reduces the overall uniqueness of those options due to the natural tradeoff between fluency and uniqueness. After correcting for this tradeoff, however, dopamine also independently improved uniqueness for a given fluency (Figure 4.4). Might dopamine have similar effects on option generation in healthy people? Here, I investigated this question in two separate within-subject, double-blind and placebo-controlled psychopharmacological studies that transiently manipulate the dopaminergic system.

In a seminal study, Brozoski and coworkers (1979) reported that depletion of dopamine in the dorsolateral prefrontal cortex of rhesus monkeys impaired their performance in a spatial delayed alternation task that assesses spatial working memory. Importantly, administration of dopamine agonists such as apomorphine reversed this deficit and restored normal performance. This was the first study to demonstrate a direct role for dopamine in working memory using psychopharmacological treatments. Following that, many studies have also shown that the administration of dopamine agonists and antagonists to animals and humans can influence a variety of cognitive functions including working memory, attentional selection and inhibitory response control (see review by Frank and O'Reilly, 2006; Robbins and Arnsten, 2009; Cools and D'Esposito, 2011; Husain and Mehta, 2011). For example, the dopamine agonist, bromocriptine, has been found to improve working memory function but impair reversal learning in healthy individuals (Kimberg et al., 1997; Luciana et al., 1992; Mehta et al., 2001). Sulpiride, a dopamine antagonist, also affected planning, attentional set-shifting and spatial working memory (Mehta et al., 1999).

However, the effects of dopaminergic drugs on cognition are complex and may vary depending on factors such as dosage, populations (e.g. young or elderly, healthy or clinical) and specific task used (see e.g. Frank and O'Reilly, 2006 for review). For example, Peretti and colleagues (1997) reported that 1mg of haloperidol, a dopamine antagonist, did not affect executive functioning in healthy young volunteers, but increasing it to 2mg led to impairments being observed. The modulation of working memory has also been revealed to vary in an inverted-U

shaped manner depending on baseline levels of dopamine within the individual (Cools and D'Esposito, 2011). Similarly, recent findings suggest that the effect of dopamine agonists on reversal learning depends on individual differences in trait impulsivity (Clatworthy et al., 2009).

Moreover, neurotransmitters exert their influence via a host of different receptor systems. Early studies have divided dopamine receptors based on their effect on the enzyme adenylyl cyclase (AC). D_1 receptor subtypes typically activate AC, thereby increasing the intracellular concentration of cyclic adenosine monophosphate (cAMP). On the other hand, the D_2 subtypes inhibit AC and synthesis of cAMP (Kebabian and Calne, 1979). More recently, findings utilizing molecular cloning techniques have revealed the existence of at least five dopamine receptor subtypes (D_1, D_2, D_3, D_4 and D_5) in the central nervous system, although the significance of D_3, D_4 and D_5 are unclear due to the lack of specific agonists or antagonists for these subtypes. On the basis on similarities in genetic sequence homology and pharmacology, these five receptors are generally classified into two major subclasses: D1-like (D_1, D_5) and D2-like (D_2, D_3, D_4) receptors (Jaber et al., 1996). Therefore, the action of dopamine on D1 receptors could lead to vastly different influences compared to that on D2 receptors, and dopamine also has varying effects at different regions of the brain (Floresco and Magyar, 2006; Frank and O'Reilly, 2006; Husain and Mehta, 2011; Müller et al., 1998; Robbins and Arnsten, 2009).

To facilitate consistent interpretation with findings from Parkinson's disease (Chapter 4), drugs targeting the D_2 receptor were used here. This allows specific contributions of the basal ganglia to be determined as dopamine D_2 receptors are

predominantly expressed in the basal ganglia compared to the prefrontal cortex (Camps et al., 1989). Further support for the specificity comes from previous studies showing that the administration of dopaminergic D_2 drugs modulated striatal, but not prefrontal, blood flow in humans (Honey et al., 2003; Mehta et al., 2003).

The first study examines the influence of a single dose of dopamine D_2 receptor agonist – cabergoline – on option generation. Dopamine agonists mimic the endogenous neurotransmitter by exerting a direct stimulation on the receptor. Cabergoline was chosen as it has one of the highest affinity for D_2 receptors compared to other drugs such as bromocriptine and pergolide, while having low affinity for D1 receptors (Gerlach et al., 2003). Furthermore, it is long lasting with a plasma half-life of 65 hours (Rinne et al., 1997) and has relatively fewer negative side effects (Biller et al., 1996; Colao et al., 2000; Corsello et al., 2003; Stocchi et al., 2003).

The second study investigates whether a single dose of dopamine D_2 receptor antagonist – haloperidol – has effects on option generation. Dopamine antagonists serve to disturb the activity of dopamine by binding to and blocking the receptor without activating them. Haloperidol was chosen over other drugs because of its good in vivo D_2 binding (Kapur et al., 1996; Seeman and Kapur, 2000). Furthermore, it is highly selective with 25 times greater affinity for D_2 compared to D_1 receptors (Bymaster et al., 1999).

I hypothesized that cabergoline and haloperidol will exert opposing effects on option generation across both studies. Specifically, cabergoline is predicted to increase both fluency and uniqueness in the option generation task. In contrast,

haloperidol is expected to lead to a reduction in the fluency and uniqueness of generating options.

5.2 Study 1: Cabergoline

5.2.1 Methods

5.2.1.1 Participants

29 healthy elderly people (18 males, 11 females; mean age=68.4 years old, SD=4.2) recruited from the Oxford Dementia and Ageing Research database took part in this study. They had corrected-to-normal vision, no history of psychiatric or neurological conditions and were paid a fixed rate for participating. All participants gave written informed consent and the study was approved by the University of Oxford ethics committee. They were tested twice in two counterbalanced sessions, taking a 1mg cabergoline tablet on one session and an indistinguishable placebo tablet on the other.

5.2.1.2 External measures

Participants completed the Lille Apathy Rating Scale (LARS, Sockeel et al., 2006), a clinical interview to measure levels of apathy-motivation. The LARS has a total score ranging from -36 to +36, with a higher score indicating greater apathy (or lower motivation). A cut-off score of >-22 shows the presence of clinical apathy. Considerable variability was found in the sample (mean=21.0, SD=5.2).

Cognitive ability was assessed with Addenbrooke's Cognitive Examination (ACE-III, Hsieh et al., 2013). No participant met the cut-off for suspected dementia (ACE-III<82, mean=97.4, SD=2.8).

5.2.1.3 Experimental tasks

All participants completed the following tasks:

- Option generation task

Participants were given a time limit of four minutes to draw on a touchscreen computer as many different paths as they could between two vertically aligned, fixed points (Figure 3.2). This allowed movement and timing parameters to be extracted, thereby providing an opportunity to evaluate both the *uniqueness* and *diversity* of paths generated using objective metrics.

To quantify uniqueness, an index of similarity between pairs of paths was created (Figure 3.3). Each path was parameterised by 200 points equally spaced along its length, and the "distance" between a pair of lines drawn on the touchscreen was computed as the sum of distances between pairs of corresponding points. Lines were reflected about the midline such that mirror image paths were considered as similar to each other, and the first and second derivatives were included in the distance metric to better account for differences in the shapes of the curves. This allowed the measurement of "effective distance" between each pair of paths drawn. For every path produced by each participant, uniqueness was defined as the distance between it and the most similar path produced by all other participants.

To quantify diversity, the distances between a participant's paths were projected onto a 2-dimensional subspace using multidimensional scaling to visualise how they explored the path space (**Figure 3.3, 3.4**). An individual was more explorative, i.e. produced greater variation in generated paths, if the paths (each represented by one point in the dissimilarity space) were more dispersed. This was approximated by calculating the area of the convex hull covering each participant's paths projected in the 2-dimensional subspace.

This task quantifies option generation using behavioural output. However, as with traditional timed tests of fluency, several other factors may confound this interpretation e.g. ability to execute movements, plan motor actions and select from amongst various competing options. To account for these, three closely-matched control tasks were also administered.

- Motor execution control task

To test baseline drawing speed, participants had to draw ten straight lines, each as quickly as they could, between the two fixed points of the option generation task (**Figure 3.7**). The mean time taken to draw each line (excluding time between lines) served as a baseline index of their motor vigour that was closely matched to the main task.

- Externally-cued action control task

To examine ability to plan motor actions, an externally-cued action control task was employed in which each movement required a different motor plan, but there was no need to generate unique paths. Instead, participants simply had to draw a straight

line to a target location that was randomly generated by the computer. A new target location was generated once the path had been completed, and the goal was to connect to as many target locations as possible in 90 seconds (Figure 3.9). Thus, motor planning ability could be assessed, in isolation from the ability to generate the option for the next action since this was now provided by the computer.

- Option selection control task

To assess ability to select from amongst options, an option selection control task was administered where participants had to first select an option from a given set of possible target locations, and then draw a straight path to it. The goal was to draw as many individual paths as possible from a central start location in 90 seconds to the displayed possible target locations (Figure 3.11). No unique generation of paths was required as the target options were always displayed.

5.2.1.4 Statistical analysis

The behavioural data was analysed using MATLAB and IBM SPSS Statistics 22.0. I tested the assumption of normality in all data. Dependent variables were compared within-subjects using a paired two-tailed *t*-test and between-subjects using an independent-samples two-tailed *t*-test. For all analyses, a *p*-value<0.05 was taken to be statistically significant unless otherwise stated.

5.2.2 Results from option generation task

5.2.2.1 No effect of repeated testing was found

There was no significant effect of testing on repeated sessions. A repeated measures ANOVA analysis found only a significant main effect of drug (cabergoline vs. placebo), but not session nor drug*session interaction on the number of paths generated [drug: $F(1,54)=12.6$, $p<0.001$; session: $F(1,54)=0.26$, $p>0.05$; drug*session: $F(1,54)=0.009$, $p>0.05$], and mean uniqueness of generated options [drug: $F(1,54)=4.89$, $p<0.05$; session: $F(1,54)=0.04$, $p>0.05$; drug*session: $F(1,66)=3.44$, $p>0.05$]. However for area of exploration in the 2-dimensional path subspace, the interaction effect was also significant, suggesting that this variable was influenced by the order in which the drugs were administered [drug: $F(1,54)=5.48$, $p<0.05$; session: $F(1,54)=0.06$, $p>0.05$; drug*session: $F(1,54)=5.75$, $p<0.05$].

5.2.2.2 Dopamine modulates the balance between fluency and uniqueness

Consistent with findings in PD (**Figure 4.1**), healthy elderly individuals were more fluent at generating path options after taking cabergoline compared to placebo ($t(28)=3.49$, $p=0.002$, **Figure 5.1A**). Yet, they exhibited lower mean uniqueness in their paths ($t(28)=-2.17$, $p<0.05$, **Figure 5.1B**) and were less explorative in the 2-dimensional path subspace ($t(28)=-2.31$, $p<0.05$, **Figure 5.1C**). Thus increased levels of dopamine shifted behaviour towards producing more options, at the expense of reduced uniqueness (**Figure 5.1D**).

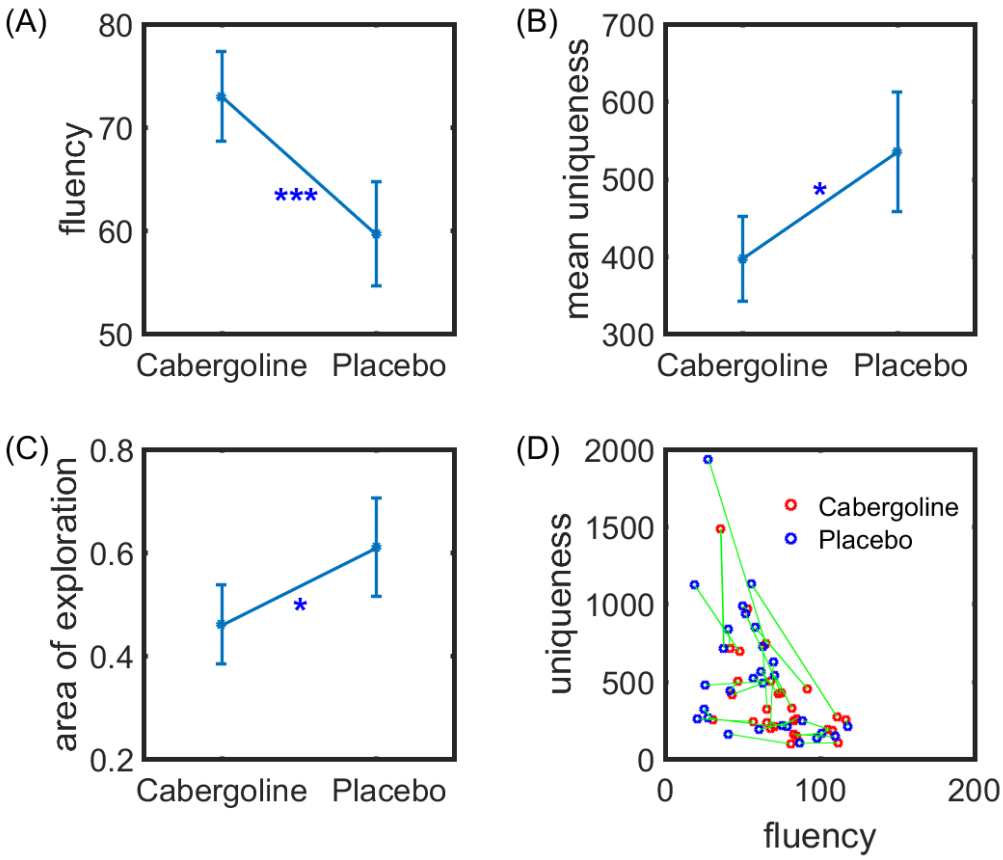


Figure 5.1 Option generation task performance in healthy elderly people on cabergoline and placebo. (A–C) Healthy people generated significantly more path options when they have taken cabergoline (dopamine D_2 agonist) compared to placebo (p<0.001). Yet, they were more unique (p<0.05) and explored a larger area in the 2-dimensional path subspace (p<0.05) when they were on placebo. **(D)** A scatterplot of each individual's mean uniqueness of paths against their number of paths generated. The same individual when on cabergoline and placebo are connected by green lines.

5.2.2.3 Cabergoline increases uniqueness for a given fluency

As for the PD analysis, the correlation between fluency and uniqueness (r=-0.59, $p<0.001$) was corrected for using a mixed model. A linear mixed effects model for the uniqueness of each path produced by the PD patients was fitted by maximal likelihood using the *fitlme* function from the Statistics Toolbox in MATLAB 2017a. I used fixed effects of each path's duration, dopamine drug state, apathy level and their interactions, and random effects of subject.

*Uniqueness ~ Duration + Drug + Apathy + Duration*Drug + Duration*Apathy + Drug*Apathy + Duration*Drug*Apathy + (1|Subject)*

There were significant fixed effects of Duration and Drug, showing that healthy elderly people were likely to generate a more unique path when on cabergoline compared to placebo. The interaction term of Drug*Apathy was also significant, indicating that the effect of cabergoline in increasing uniqueness for a given fluency was stronger in apathetic individuals. Finally, there were also significant interaction terms of Duration*Drug and Duration*Drug*Apathy, indicating that drug and its interaction with apathy changes the slope of the fluency-uniqueness tradeoff (results in Table 5.1).

These results demonstrated that similar to the effect of dopaminergic treatment in PD, the D_2 agonist was found to increase the uniqueness of paths for a given fluency. Furthermore in this study, it was revealed that this increase is stronger in apathetic individuals (Figure 5.2).

5.2.2.4 Results were similar even when not correcting for mirror paths

As for the PD analysis, the analyses thus far have taken into account reflections of paths about the midline such that mirror image paths were considered as similar to each other in external space. However, it may be argued that this is arbitrary as mirror image paths require a considerably different motor program and thus, may be dissimilar in joint/muscle space.

The analyses were re-ran using a distance metric that was not corrected for mirroring. Very little changes were found in the uniqueness scores, indicating that mirror images contributed only a small amount of uniqueness (correlation between individual path uniqueness with and without reflection about midline r=0.98, p<0.001). In line with this, the p-values were very similar and do not affect interpretation of the results. The results of the linear mixed effects model analysis without accounting for mirror image paths are in Table 5.1.

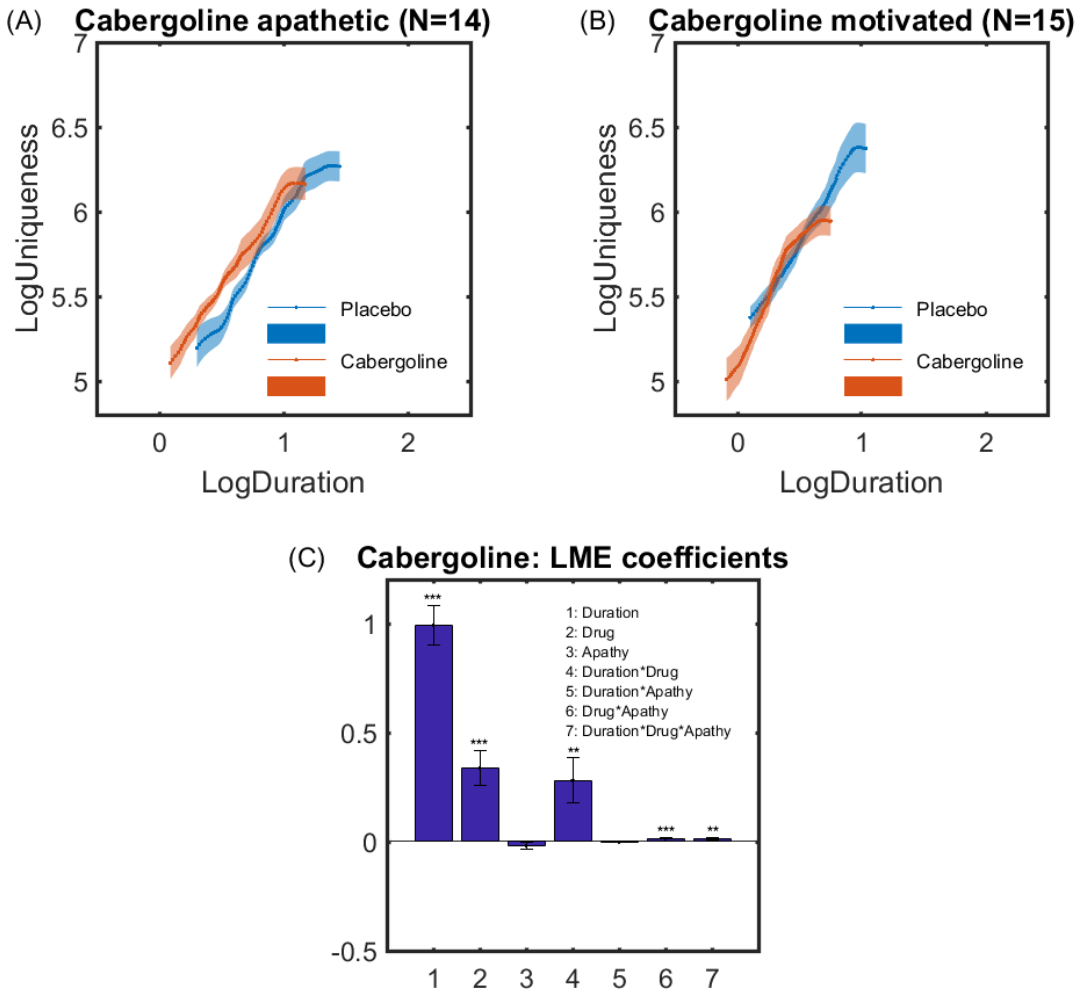


Figure 5.2 Results from the linear mixed effects (LME) model analysis in cabergoline study. Because fluency correlates with uniqueness, a mixed model was used to examine how each path's duration (or inverse of fluency) influences uniqueness. **(A, B)** Dopamine was found to increase the uniqueness of paths after correcting for the fact that they were faster (red line significantly higher than blue line, p=0.005). Furthermore, this increase was significantly greater in apathetic compared to motivated healthy elderly people (p<0.001). To plot the graphs, for each subject the uniqueness of their generated routes was taken in a sliding window calculated on the route durations. The mean log uniqueness in each of 80 overlapping windows (0.2 quantile width) was averaged across subjects, and plotted against the mean log duration for that window. This was performed for each drug condition separately. Shaded area represents standard error of the mean across subjects. **(C)** Coefficients of the effects from the LME analysis (*** p<0.001, ** p<0.01).

Table 5.1 Results from linear mixed model analysis in cabergoline.

	mirroring		not mirroring	
	t	*p*	*t*	*p*
Duration	14.1	<0.001	11.0	<0.001
Drug	3.88	<0.001	4.27	<0.001
Apathy	-0.66	>0.05	-1.10	>0.05
Duration*Drug	3.27	0.001	2.72	0.007
Duration*Apathy	1.44	>0.05	-0.34	>0.05
Drug*Apathy	3.81	<0.001	4.05	<0.001
Duration*Drug*Apathy	3.23	0.001	2.85	0.004

5.2.3 Results from control tasks

5.2.3.1 Motor execution control task

One possible confound in interpreting these findings is that participants might have generated options but not produced them because of deficits in motor execution, such as if the individual was slow to draw on the touchscreen. The difference in number of path options generated by healthy elderly individuals between cabergoline and placebo states did not correlate with the difference in baseline drawing speed on the motor execution control task (r=-0.02, p>0.05, **Figure 5.3**). This suggests that reduced fluency in the placebo state cannot be explained simply by deficits in movement speed or executing actions.

5.2.3.2 Externally-cued action control task

Another challenge might be that while participants might have generated options, they encountered difficulty planning the motor actions required to execute them. The difference in fluency of healthy elderly people on the option generation task between cabergoline and placebo states did not correlate with the difference in performance on the externally-cued action control task (r=0.25, p>0.05, **Figure 5.4**), suggesting that reductions in fluency in the placebo state cannot be attributed to deficits in planning or initiating actions.

5.2.3.3 Option selection control task

Finally, it is possible that while an individual might have generated many path options, they might have encountered difficulty in selecting from amongst them – a deficit in option selection during decision-making. In the healthy elderly sample, the difference in performance on the option generation task between cabergoline and placebo states did not associate with that in the option selection control task (r=0.12, p>0.05, **Figure 5.5**). This suggests that reductions in number of options generated in the placebo state are not due to deficits in selecting amongst generated options.

5.2.3.4 Cabergoline's improvement in fluency was specific to option generation

To examine whether the improvement in fluency on dopamine was specific to the option generation task, a repeated measures ANOVA was conducted using fluency per minute as the dependent variable and within-subject factors of drug (ON vs. OFF) and task type (option generation task, externally-cued action control task, option selection control task). There was a significant interaction effect (F(2, 54)=4.74, p=0.01), indicating that the difference in fluency between the cabergoline and placebo states was different across the three tasks (**Figure 5.6**). Post-hoc comparison tests revealed that dopamine significantly improved fluency on the option generation task (p<0.001), but drug status did not have any effect on the externally-cued action (p=0.89) or option selection (p=0.97) control tasks. This strongly suggests that the improvement in fluency from dopamine is specific to option generation.

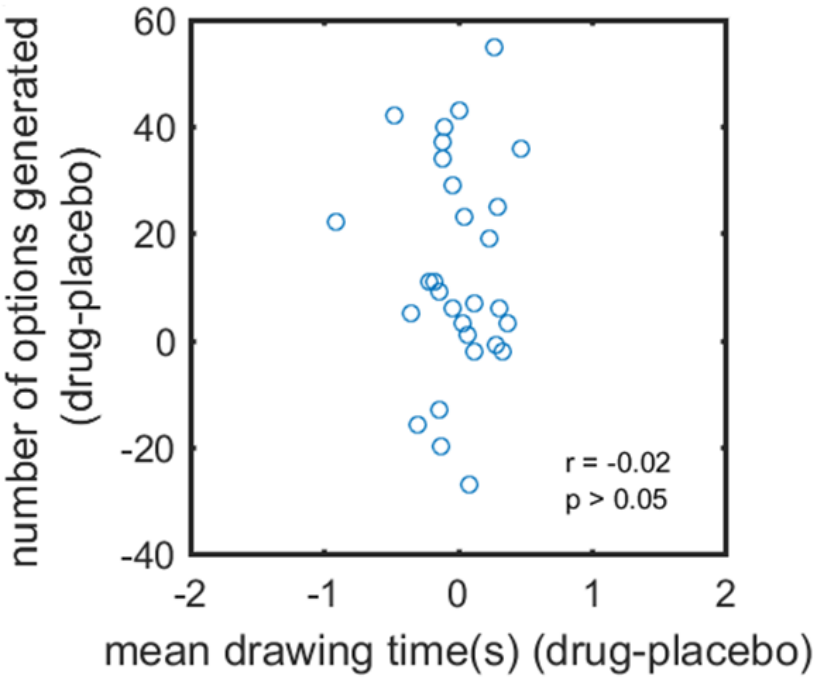


Figure 5.3 Result from motor execution control task. In healthy elderly people (*N*=29), the difference in option generation fluency when on cabergoline and placebo also did not relate that in motor execution ability. These suggest that the reduced fluency in option generation when healthy people are on placebo is not attributable to impairments in movement speed or executing actions.

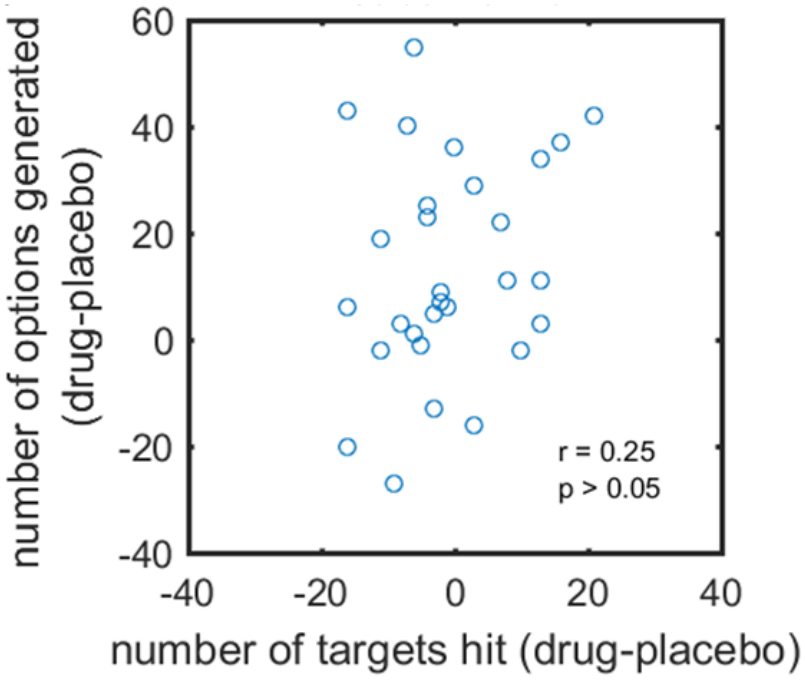


Figure 5.4 Result from externally-cued action control task. In healthy elderly people (*N*=29), the difference in option generation fluency when on cabergoline and placebo also did not relate that in motor planning ability. These indicate that reductions in fluency of option generation when healthy people are on placebo are not explained simply by deficits in planning or initiating actions.

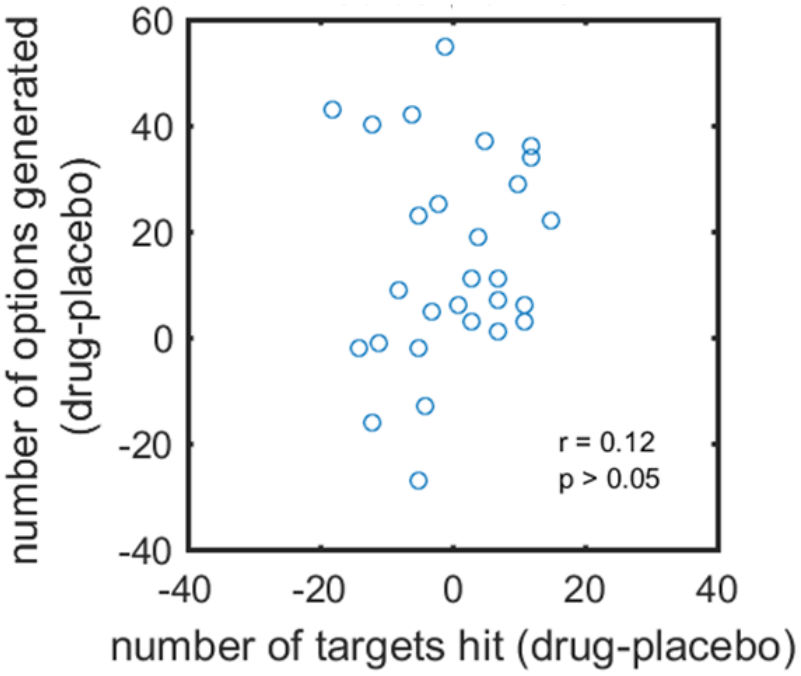


Figure 5.5 Result from option selection control task. In healthy elderly people (*N*=28), the difference in option generation fluency when on cabergoline and placebo also did not relate that in option selection ability. These suggest that reductions in fluency of option generation healthy people are on placebo are not simply due to impairments in selecting amongst generated options.

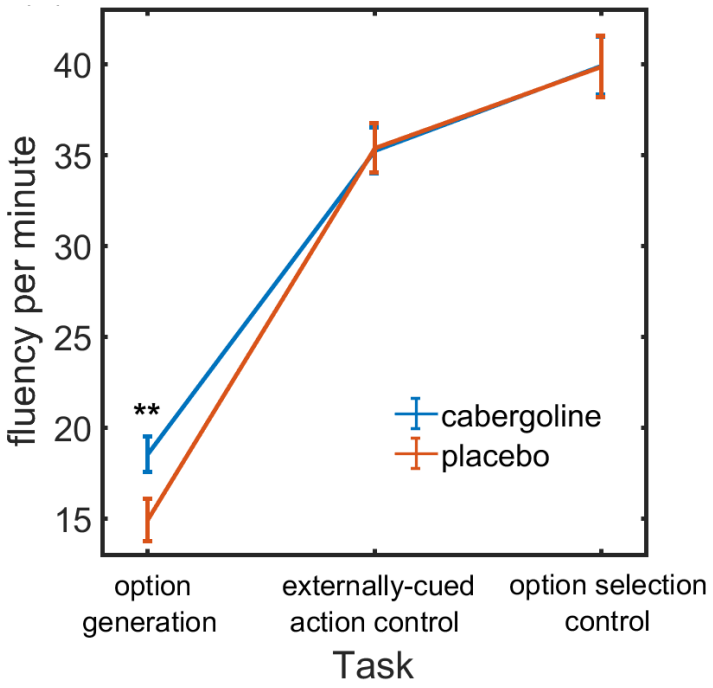


Figure 5.6 Comparison of fluency per minute for different tasks in cabergoline. Repeated measures ANOVA found that dopamine's improvement in fluency was specific to the option generation task. There was no effect of dopamine on fluency in the externally-cued action and option selection control tasks.

5.3 Study 2: Haloperidol

5.3.1 Methods

5.3.1.1 Participants

30 healthy young people were recruited from the Oxford Psychology Research participant recruitment scheme (16 males, 14 females; mean age=25.1 years old, SD=4.4). All participants had corrected-to-normal vision, no history of psychiatric or neurological conditions and were paid a fixed rate for participating. They gave written informed consent and the study was approved by the University of Oxford ethics committee. They were tested twice in two counterbalanced sessions, taking a 2.5mg haloperidol tablet on one session and an indistinguishable placebo tablet on the other.

5.3.1.2 Experimental Tasks

All participants completed the option generation task (**Figure 3.2**) and motor execution control task (**Figure 3.7**). They also performed the option generation task with obstacles, which contained 4 barriers that had to be avoided between the start and end point (**Figure 3.13**). This was designed to assess whether the presence of constraints could modulate participants' ability to generate options.

5.3.1.3 Statistical analysis

The behavioural data was analysed using MATLAB and IBM SPSS Statistics 22.0. I tested the assumption of normality in all data. Dependent variables were compared within-subjects using a paired two-tailed *t*-test and between-subjects using

an independent-samples two-tailed *t*-test. For all analyses, a *p*-value<0.05 was taken to be statistically significant unless otherwise stated.

5.3.2 Results from option generation task

5.3.2.1 No effect of haloperidol on option generation

Paired-samples t-test found that there was no significant difference between drugs (haloperidol vs. placebo) on fluency or the number of options generated ($t(29)=1.17$, $p>0.05$, **Figure 5.7A**), mean uniqueness of generated options ($t(29)=1.80$, $p=0.08$, **Figure 5.7B**) and area of exploration in the 2-dimensional path subspace ($t(29)=0.16$, $p>0.05$, **Figure 5.7C**).

Instead, there was a significant effect of testing on repeated sessions on fluency. A repeated measures ANOVA analysis found only a significant main effect of session, but not drug (haloperidol vs. placebo) nor drug*session interaction on fluency of generation [drug: $F(1,56)=2.33$, $p>0.05$; session: $F(1,56)=19.6$, $p<0.001$; drug*session: $F(1,56)=0.09$, $p>0.05$]. For mean uniqueness of generated options, only the interaction term was significant, suggesting that this variable was influenced by the order in which the drugs were administered [drug: $F(1,56)=3.49$, $p=0.07$; session: $F(1,56)=1.19$, $p>0.05$; drug*session: $F(1,56)=4.62$, $p<0.05$]. On the other hand, none of the effects were significant for area of exploration in the 2-dimensional path subspace [drug: $F(1,56)=0.03$, $p>0.05$; session: $F(1,54)<0.001$, $p>0.05$; drug*session: $F(1,54)=0.02$, $p>0.05$].

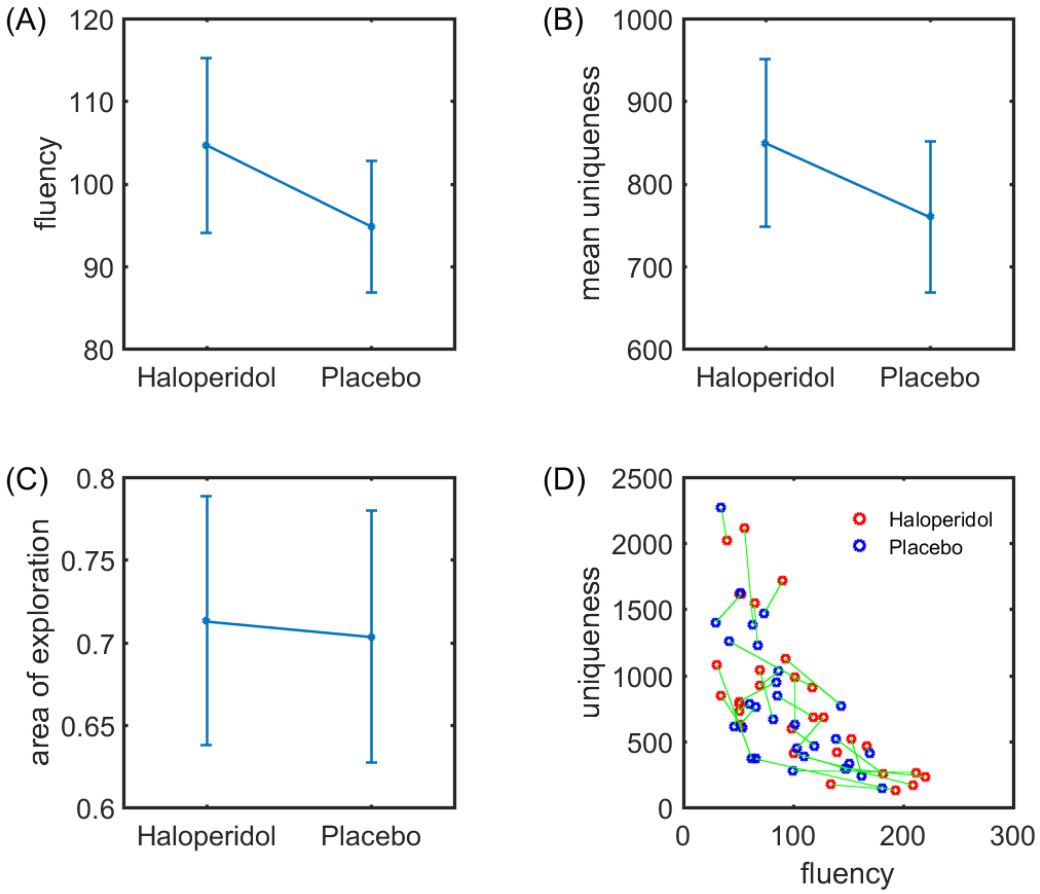


Figure 5.7 Option generation task performance in healthy young people on haloperidol and placebo. (A–C) Healthy people did not exhibit significant differences in number of path options generated, uniqueness and area explored in the 2-dimensional subspace when they have taken haloperidol (dopamine D_2 antagonist) compared to placebo (all $p<0.05$). **(D)** A scatterplot of each individual's mean uniqueness of paths against their number of paths generated. The same individual when on haloperidol and placebo are connected by green lines.

5.3.2.2 Haloperidol increased uniqueness for a given fluency

The previous analyses, however, revealed a trending drug effect on uniqueness. To correct for the correlation between fluency and uniqueness (r=-0.77, p<0.001), a linear mixed effects model for the uniqueness of each path produced by the participants was fitted by maximal likelihood using the *fitlme* function from the Statistics Toolbox in MATLAB 2017a. I used fixed effects of each path's duration, dopamine drug state and their interaction, and random effects of subject.

*Uniqueness ~ Duration + Drug + Duration*Drug + (1|Subject)*

There were significant fixed effects of Duration and Drug but not the interaction term of Duration*Drug, showing that healthy young people were likely to generate a more unique path when on haloperidol compared to placebo (results in **Table 5.2**). These results demonstrated, surprisingly, that the D_2 antagonist increased the uniqueness of paths for a given fluency (**Figure 5.8**).

5.3.2.3 Results were similar even when not correcting for mirror paths

The analyses were also re-ran using a distance metric that was not corrected for mirroring. Very little changes were found in the uniqueness scores, indicating that mirror images contributed only a small amount of uniqueness (correlation between individual path uniqueness with and without reflection about midline r=0.97, p<0.001). In line with this, the p-values were very similar and do not affect interpretation of the results. The results of the linear mixed effects model analysis without accounting for mirror image paths are in **Table 5.2**.

Table 5.2 Results from linear mixed model analysis in haloperidol.

	mirroring		not mirroring	
	t	*p*	*t*	*p*
Duration	62.4	<0.001	61.7	<0.001
Drug	11.3	<0.001	11.2	<0.001
Duration*Drug	1.16	>0.05	1.07	>0.05

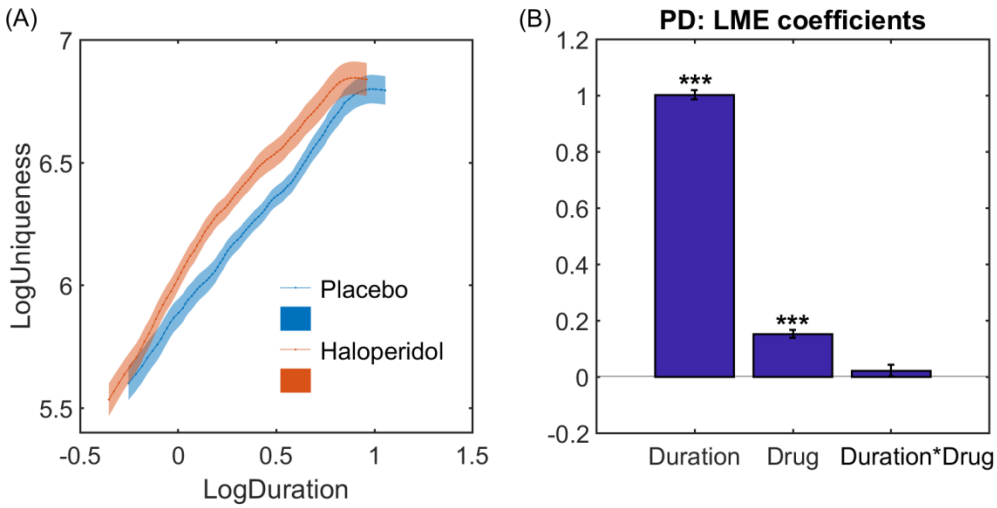


Figure 5.8 Results from the linear mixed effects (LME) model analysis in haloperidol study. Because fluency correlates with uniqueness, a mixed model was used to examine how each path's duration (or inverse of fluency) influences uniqueness. **(A)** Haloperidol was found to increase the uniqueness of paths after correcting for the fact that they were faster (red line significantly higher than blue line, $p<0.001$). To plot the graphs, for each subject the uniqueness of their generated routes was taken in a sliding window calculated on the route durations. The mean log uniqueness in each of 80 overlapping windows (0.2 quantile width) was averaged across subjects, and plotted against the mean log duration for that window. This was performed for each drug condition separately. Shaded area represents standard error of the mean across subjects. **(B)** Coefficients of the effects from the LME analysis (*** $p<0.001$).

5.3.3 Results from motor execution control task

A paired-sample t-test found that there was no significant difference in baseline drawing speed between participants on haloperidol and placebo ($t(29)=-1.71$, $p>0.05$). This suggests that haloperidol did not have any influence on their ability to execute motor actions on the touchscreen (**Figure 5.9**).

5.3.4 Results from option generation task with obstacles

A repeated measures ANOVA was used to analyse how within-subject factors of drug (haloperidol vs. placebo) and number of obstacles (0 vs. 4) influenced the number of options of generated. There was a significant effect of the number of obstacles ($F(1,29)=20.1$, $p<0.001$), but not drug ($F(1,29)=1.74$, $p>0.05$) or their interaction ($F(1,29)=0.05$, $p>0.05$). Posthoc comparison found that more options were generated when there was 0 compared to 4 obstacles ($p<0.001$), indicating that participants were more fluent when obstacles were not present. However, there was no influence of haloperidol on their ability to generate options (**Figure 5.10**).

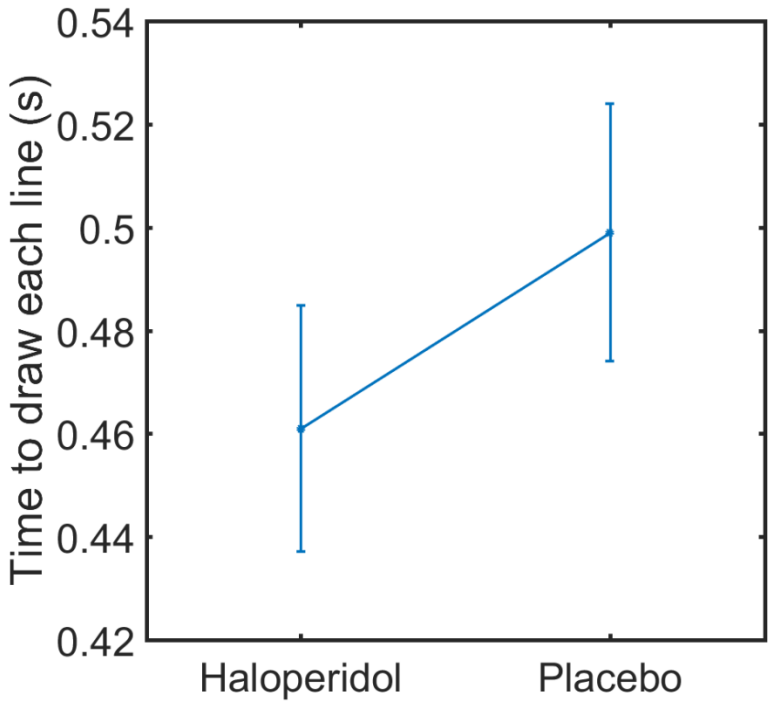


Figure 5.9 Results from the motor execution control task in haloperidol study. There was no difference in baseline drawing speed between participants on haloperidol and placebo, indicating that the dopamine antagonist did not modulate their ability to execute motor actions.

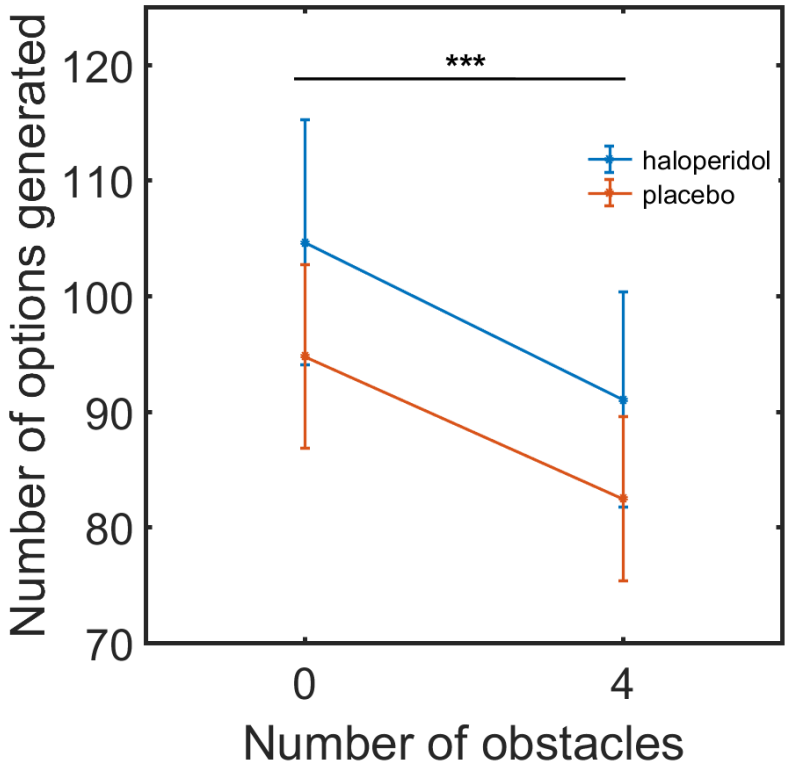


Figure 5.10 Results from the option generation task with 0 and 4 barriers in haloperidol study. Participants generated significantly more options when there were 0 obstacles compared to 4 obstacles. However, haloperidol did not modulate the ability to generate options.

5.4 Discussion

Here, I have used two within-subject, double-blind pharmacological manipulation studies to investigate whether dopamine influences option generation. In the first study, cabergoline (D_2 receptor agonist) improved the fluency of generating options and increased the uniqueness of options at a given fluency in healthy elderly people. Importantly, results from three closely-matched control tasks revealed that these findings cannot be attributed to potential confounds such as changes in motor execution or drawing speed, ability to plan the motor action, and ability to select from amongst generated options. In the second study, haloperidol (D_2 receptor antagonist) surprisingly did not have any effect on the number of options generated in healthy young individuals. Furthermore, contrary to what was predicted, it increased the uniqueness of options for a particular fluency.

5.4.1 Pharmacological mechanisms for findings in cabergoline are unclear

The findings from cabergoline are consistent with results from the previous chapter in Parkinson's disease (PD) patients. How might this drug exert its effects on the brain and influence performance on the option generation task? Several groups have investigated the potential of D_2 agonists on enhancing cognitive performance. However, the results are highly mixed. While some studies reported improvements in domains of working memory and/or executive functions such as planning and task switching (Arnsten et al., 1995; Luciana et al., 1992; Luciana and Collins, 1997; McDowell et al., 1998; Mehta et al., 2001), others have found either no effect (Bartholomeusz et al., 2003; Kimberg et al., 1997; McDowell et al., 1998; Mehta et al.,

2001; Müller et al., 1998) or impairments (Gibbs and D'Esposito, 2005; Mehta et al., 2001) in these areas.

The cause of these mixed findings is not known, not least because the exact mechanism by which these agents act is unclear. Dopamine D_2 receptors exist in two different isoforms (D_2S and D_2L) that are respectively expressed in pre- and postsynaptic neurons (Usiello et al., 2000). Postsynaptic stimulation or blockade modulates background tonic dopamine signaling, whereas pre-synaptic action affects transient phasic release of dopamine during dopaminergic neuron firing (Grace, 1991). D_2 agonists such as bromocriptine and cabergoline are not taken up into presynaptic dopaminergic vesicles. Instead, they bind competitively to and act directly on postsynaptic dopamine receptors, thereby leading to tonically increased dopamine levels (Jaber et al., 1996; Koller and Rueda, 1998; Schreckenberger et al., 2004).

However, studies in the animal literature have also suggested that low doses of D_2 agents may preferentially exert its effects via presynaptic mechanisms (Richfield et al., 1989; Schoemaker et al., 1997; Tissari et al., 1983). Presynaptic D_2 receptors can act as autoreceptors that regulate the level of phasic dopamine release through inhibitory feedback (Schmitz et al., 2003; Starke et al., 1989; Xu et al., 1999). Furthermore, they have a higher affinity for dopamine compared to their postsynaptic D_2 counterpart and thus, are more sensitive to acute drug doses (Cooper et al., 2003). This means that low doses of D_2 agonists may induce tonic activations of presynaptic D_2 autoreceptors and reduce phasic dopamine release (Mercier et al., 2001). In line with this account, administration of low doses of D_2 agonists were found to reduce the release of phasic dopamine (Baudry et al., 1977; Fuller et al., 1982; Schmitz et al.,

2003; Sumners et al., 1981; Tissari et al., 1983) and lower the firing rates of dopamine neurons in the substantia nigra and ventral tegmental area (Piercey et al., 1996).

In this study, cabergoline was shown to facilitate the ability to self-generate options for behaviour. Similar improvements were previously observed in PD patients established on levodopa therapy (Chapter 4). Levodopa, the precursor of dopamine, is taken up by dopamine neurons for conversion into dopamine. Therefore, it increases both tonic and phasic dopaminergic neurotransmission (Robinson et al., 2005). This suggests that tonic increases in dopamine, rather than reduced phasic dopamine signaling, may be responsible for the facilitatory effects of cabergoline on option generation. Nevertheless, interpretations about the potential pharmacological mechanisms underlying the current findings remain tentative. Further investigations using a titration approach are required to determine the effects of gradually changing doses of cabergoline on option generation.

5.4.2 Limitations may explain unexpected pattern of results in haloperidol

The administration of haloperidol, a dopamine D_2 antagonist, was predicted to impair option generation in healthy population. However, no effect on the number of options was found. Furthermore, the uniqueness *increased*, rather than decrease, for a given fluency of generation.

This surprise in findings could have arisen due to the differences in ages of participants. While PD patients and healthy participants on cabergoline were *elderly* individuals above 60 years of age, this study was conducted on young healthy people between 18–35 years old. Thus, the effects of dopaminergic D_2 drugs may not be

comparable between the two age groups. Support for this possibility comes from studies demonstrating that older adults were more sensitive to dopaminergic perturbation via an acute dose of drug than young people (Abdulrahman et al., 2017; Morcom et al., 2010).

The dosage of 2.5mg haloperidol used may also contribute to the deviation of results from predicted. Previous studies of dopamine agonists/antagonists in young people have produced contradictory results from different doses. For example, Luciana et al. (1992) showed that 2.5mg of D_2 agonist bromocriptine improves working memory. However, the same authors could not replicate the results using the same dose and task in a further study. Instead, they (and other investigators later) found facilitatory effects of memory when the dosage of bromocriptine was smaller at 1.25mg (Luciana and Collins, 1997; Mehta et al., 2001). Peretti and colleagues (1997) also reported that 1mg of haloperidol did not have any effect on executive functioning in healthy young people, but increasing it to 2mg led to impairments being observed. These findings suggest that the dosage of dopaminergic agents used may affect performance differently. Future experiments could investigate how variations in the amount of haloperidol would influence fluency and uniqueness during option generation.

Another possibility might be that the effect of haloperidol on option generation varies according to baseline levels of dopamine. Indeed, recent progress have revealed that the influence of dopaminergic agents on cognitive functions may vary in an inverted-U manner depending on baseline levels of dopamine within the individual as indexed by working memory span tasks (Clatworthy et al., 2009; Cools

and D'Esposito, 2011). Specifically, dopamine enhances the performance of volunteers with low baseline dopamine levels but impairs performance of those with high baseline dopamine. Future investigations could examine if this is the case for haloperidol on option generation, by additionally administering a working memory span task as a proxy for baseline dopamine levels.

5.5 Conclusion

Uncovering the neurobiological components of option generation is important for advancing our understanding of decision-making. Here, I have shown that a single dose of dopamine agonist (cabergoline) improves the ability of healthy elderly individuals to self-generate behavioural choices. These findings, together with those from PD, strongly implicate dopamine as a key neuromodulator of option generation. Data from a single dose of dopamine antagonist (haloperidol), however, was not as expected and may require further investigation to understand why that might be so.

6 NEURAL MECHANISMS UNDERLYING PLANNING OF VOLUNTARY ACTION

6.1 Introduction

The generation of voluntary action is a vital feature of human behaviour (Brass and Haggard, 2008; Kalis et al., 2008). From a conceptual point of view, voluntary actions are generated endogenously without the aid of any external agent. This makes them different from externally guided actions that are generated in response to stimuli or events in the surrounding environment. Understanding the neural basis of voluntary actions has become the focus of intensive scientific interest (see reviews by Passingham, 1997; Passingham et al., 2010) and may also be important clinically because the lack of self-generated behaviour is characteristic of apathy, a debilitating disorder of motivation that frequently occurs in and lowers the quality of life of patients with neurodegenerative diseases (Levy and Dubois, 2006; Marin, 1991).

Apathy can also occur to varying degrees in the healthy population and negatively impact their everyday life (Ang et al., 2017).

It has now been established that voluntary action is a non-unitary concept and may be dissociable along three axes of volition (Brass and Haggard, 2008). First, there may be freedom in deciding *when* to execute a particular action. This aspect of voluntary action has been most extensively studied due to the seminal work by Kornhuber and Deecke (1965), who used EEG to record scalp-potentials of humans making self-initiated taps of the right index finger. These investigators discovered the presence of a slow negative increasing cortical wave up to 2 seconds before movement (also known as *Bereitschaftpotential* or readiness potential) and suggested that it was related to the preparation of voluntary movement.

This pre-movement neural activity is now thought to represent the planning of factors relevant to movement, e.g., speed, force, direction and location (Becker et al., 1976; Becker and Kristeva, 1980; Boschert and Deecke, 1986; Cui and Deecke, 1999; Kitamura et al., 1993). It is also considered to mainly reflect activity in the pre-SMA, SMA and ACC (Haggard, 2008; Shibasaki and Hallett, 2006). Findings from functional neuroimaging in humans (Brass and Haggard, 2007; Debaere et al., 2003; Deiber et al., 1999; Jenkins et al., 2000; Rao et al., 1997, 1993; Wessel et al., 1997) and electrophysiological recordings in primates (Mushiake et al., 1991; Okano and Tanji, 1987; Romo and Schultz, 1987; Shima et al., 1991; Thaler et al., 1995, 1988) are generally consistent with this notion, implicating the same regions in the decision of *when* to execute an action. However, some recent evidence also suggests that the posterior parietal cortex is responsible for generating conscious intention to move.

Direct electrical stimulation of this area, particularly the inferior parietal lobule, in patients undergoing brain surgery led to them reporting the experience of 'wanting to move' their body (Desmurget et al., 2009).

A second aspect of voluntary action involves freedom in deciding *what* movement to execute. Typically, the time of action execution is constant and signaled by an external cue, but the participant has free choice between responses. Various studies have again uncovered a preferential involvement for the medial frontal wall in this domain, particularly the pre-SMA and ACC (Cunnington et al., 2006; Deiber et al., 1996, 1991; Frith et al., 1991; Lau et al., 2004; Mueller et al., 2007; Playford et al., 1992; Rowe et al., 2005; Thimm et al., 2012; van Eimeren et al., 2006). Some investigations also reported that the DLPFC was more active when participants freely selected between responses compared to being externally instructed (Frith et al., 1991; Lau et al., 2004; Playford et al., 1992; van Eimeren et al., 2006), although that might occur due to the greater attentional demand required when the response is not fully specified by external parameters (Lau et al., 2004).

The final domain of voluntary action relates to *whether* or not to execute an action. This has been largely neglected by researchers due to the inherent challenge in accurately detecting covert intentions. Nonetheless, two previous studies investigating the neural correlates of intentional action inhibition have both implicated a specific region in the medial frontal cortex that is located anterior to the pre-SMA and dorsal to the rostral cingulate zone (Brass and Haggard, 2007; Kühn et al., 2009).

Taken together, the general consensus currently is that the generation of voluntary actions involves the medial frontal wall, particularly the pre-SMA and ACC.

Nonetheless, some studies have also reported contradictory results, finding no preferential role for these areas in self-generated compared to externally-triggered movements (Cunnington et al., 2002; Jahanshahi et al., 1995; Remy et al., 1994; Van Oostende et al., 1997). One limitation of all previous paradigms is that the planning and execution of movements were not examined separately. This means that signals from planning were contaminated with those due to the execution of movement, and thus it is not possible to determine whether task-related activations were solely due to the planning of movement, execution of actions, or a combination of both.

The present study sought to investigate the neural correlates of the *planning* of voluntary actions. Specifically, I was interested in examining whether the pre-SMA and ACC (**Figure 6.1**) were required for the *planning* of *freely selected* movements (i.e. deciding *what* action to execute). 38 healthy young individuals were scanned using fMRI while performing a simple button pressing task. On each trial, they had to select their first button press followed by their second button press, before executing those selections successively on a button response box. This ensures that the planning and execution phases were explicitly separated in time, so that brain activity related to *planning* could be isolated without contamination from the motor act of pressing.

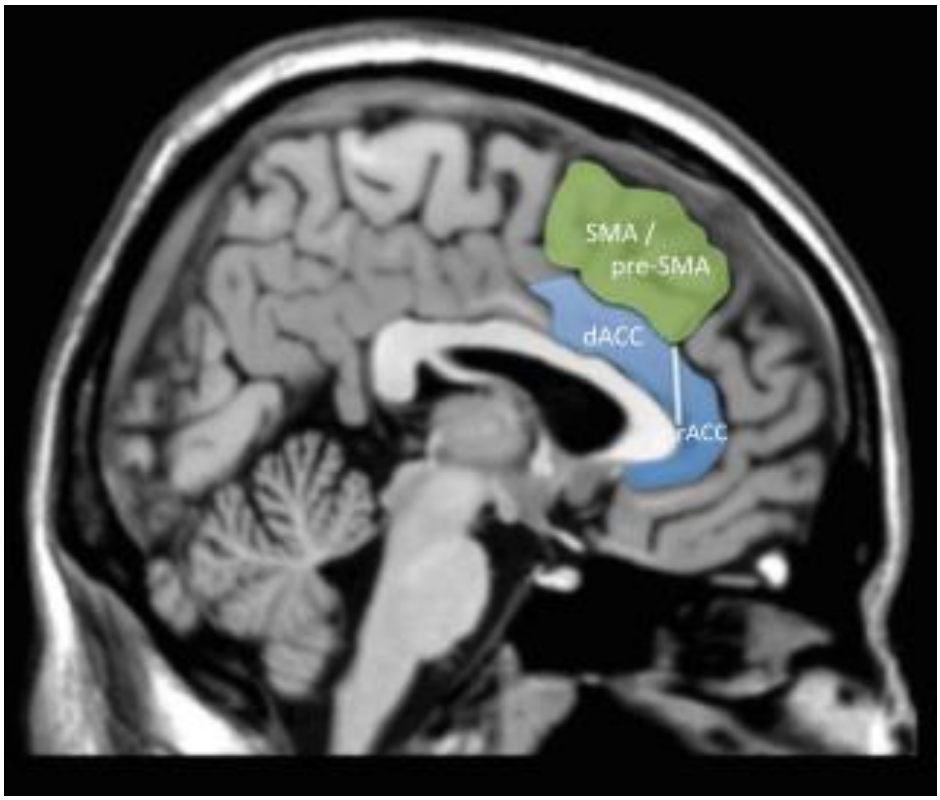


Figure 6.1 Regions of interest in this study. Based on previous literature, it was hypothesized that the pre-SMA (pre-supplementary motor area) and dorsal ACC (anterior cingulate cortex) would be involved in the planning of voluntary actions. Figure adapted from Lieberman and Eisenberger (2015).

Three conditions were imposed. Both buttons could be freely selected (TWO FREE), or one button could be freely selected while the other was externally instructed (ONE FREE), or both buttons could be externally instructed (NO FREE). It was first hypothesized that the pre-SMA and ACC were involved in the *planning* of freely selected actions and thus, activity in these regions were predicted to increase when free selections were required. It has also been found recently that activity in the medial frontal cortex during an effort-based decision-making task correlates with behavioural apathy in the healthy population (Bonnelle et al., 2016). Might similar relations be observed during volitional choice of actions? Based on this possibility, my second hypothesis was that the increase in pre-SMA and ACC activity would correlate with the level of motivation of healthy young individuals.

6.2 Methods

6.2.1 Participants

39 healthy people were recruited from the Oxford Psychology Research participant recruitment scheme to participate in this study (15 males, 24 females; mean age=25.5 years old, SD=5.0). All participants were right-handed, had corrected-to-normal vision, no history of psychiatric or neurological conditions and were paid a fixed rate for participating. They gave written informed consent and the study was approved by the University of Oxford ethics committee. One participant was excluded from the analyses due to excessive head motion in the MRI scanner, leaving a final sample size of N=38.

6.2.2 External measures

Apathy levels were assessed with the Apathy Motivation Index (AMI, **Table 2.2**; Ang et al., 2017). The AMI is an 18-item self-report scale that assesses apathy on three different subscales, namely behavioural activation (BA, e.g. "I get things done when they need to be done, without requiring reminders from others."), social motivation (SM, "I start conversations without being prompted."), and emotional sensitivity (ES, e.g. "I feel awful if I say something insensitive."). Participants had to self-rate each item on a 5-point Likert scale, with a higher score indicating greater apathy (0–4: 0='completely true', 4='completely untrue'). Degree of apathy was determined by taking the mean rating of the items within the subscale.

6.2.3 Task design

All participants completed a practice session of the task before proceeding to the scanning session, where they laid supine inside a 3T MRI scanner with fingers of their right hand (except thumb) positioned on an MRI-compatible four-button response box. Presentation software (Neurobehavioral Systems) was used to present stimulus and collect responses. Stimuli were projected onto a monitor behind the MRI scanner and viewed in a mirror placed above the participant's face.

During scanning, participants performed 384 trials in which they had to first select and then execute two button presses (**Figure 6.2**). Three different conditions were presented in a pseudo-randomised order in the experiment. Participants could be asked to freely select both button presses (i.e. TWO FREE selections, 128 trials), or be asked to freely select one button press and be instructed on the other selection

(i.e. ONE FREE selection, 128 trials), or be instructed fully on which two buttons to select (i.e. NO FREE selection, 128 trials). They were told to be as random as possible whenever free selection was allowed (i.e., do not follow any rules or patterns).

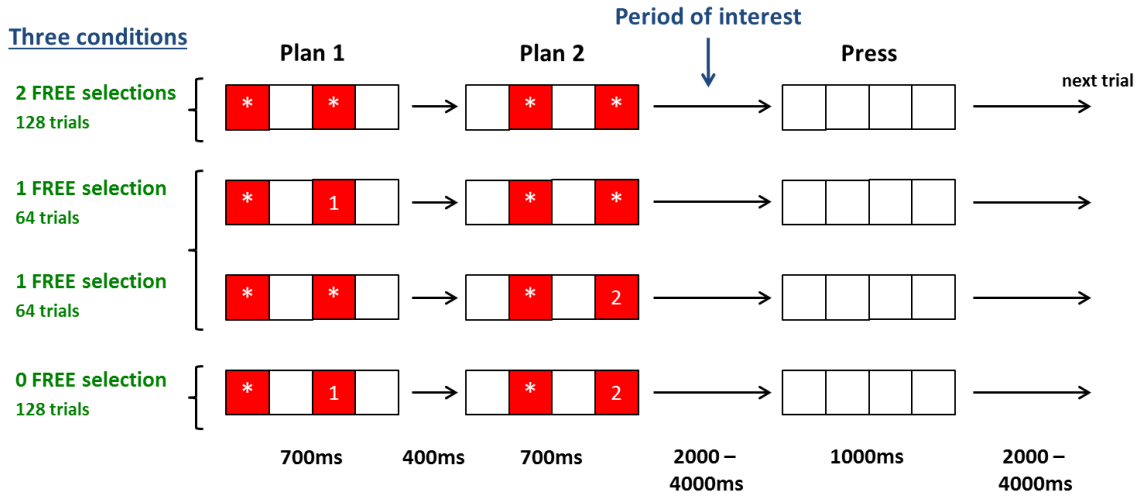


Figure 6.2 Illustration of the fMRI task.

Participants saw four square boxes that each represented a finger on their right hand (except thumb). On each trial, they had to select one of two red boxes during "Plan 1" and "Plan 2", and then execute them in succession during the "Press" phase. Following this, they were shown what their first and second button press was in the form of arrows presented below the boxes (not shown). Three different trial types that varied in the number of free selections to be made were presented. Asterisks in boxes denoted free choice of selection between one of these boxes; whereas a number in a box instructed the participant to select that box for the first or second press, depending upon whether the number was 1 or 2 respectively. Thus, if two asterisks appeared in the red boxes during "Plan 1" or "Plan 2", that meant the participant was free to select between them. However, if they saw the arabic numeral for One and an asterisk in "Plan 1", then they had to select the red box in which the digit 1 appeared for this phase. Similarly, when they saw 2 and an asterisk in "Plan 2", that indicated they must select the red box in which the digit 2 appeared during "Plan 2". This design explicitly separates selection from execution, so that activations time-locked to the planning phase could be examined without contamination from motor act of pressing.

In the TWO FREE condition, participants were first presented with a row of four square boxes and the words "Plan 1" at the center of the screen. Each box represented one finger on their right hand. Two of the boxes were highlighted in red while the other two were white. The two red boxes also each contained an asterisk (*). The presence of these two asterisks indicated to the participants that this was a free selection, and they had 700ms to select and remember one of the two red boxes. After a short delay of 400ms in which a blank screen was shown, participants were presented with a similar setup. However, the words "Plan 2" appeared instead. Again, they saw two red boxes containing asterisks (that may be the same or different from the boxes that were shown in the "Plan 1" phase) and had 700ms to select and remember one of these. This was followed by a variable delay period of 2000ms – 4000ms, where a blank screen was presented.

After that, they saw the four boxes again, but they were all now white in colour. The word "Press" also appeared, and participants had 1000ms to execute, as quickly as they could, their first and second button selection in succession. If two button presses were made, they were then told what their first and second button press was in the form of arrows presented below the boxes. This served as a visual aid to inform the participants of their choices. However, if less than two buttons were pressed, the word "Missed" appeared instead to indicate to the participant that the trial was unsuccessful. This lasted 200ms, and was followed by another long variable delay period of 2000ms – 4000ms before the next trial began.

The structure for the ONE FREE condition was largely similar to TWO FREE, except participants now did *not* always see two asterisks within the red boxes in "Plan

1" and "Plan 2". Instead, they might see the Arabic numeral for One (1) and an asterisk (*) in "Plan 1" followed by two asterisks in "Plan 2". In this case, participants had to select the red box in which the digit 1 appears during "Plan 1", but freely select between the two red boxes in "Plan 2". Alternatively, they might see two asterisks in "Plan 1" followed by the Arabic numeral for Two (2) and an asterisk (*) in "Plan 2". In this scenario, participants were free to select between the two red boxes in "Plan 1", but had to select the red box in which the digit 2 appeared during "Plan 2". In other words, participants had to freely select one button press but were instructed on the other selection for this condition.

Finally, for the NO FREE condition, participants would see the Arabic numeral for One (1) and an asterisk (*) in "Plan 1", followed by the Arabic numeral for Two (2) and an asterisk (*) in "Plan 2". This indicated that they must select the red box in which the digit 1 appeared during "Plan 1" and the red box in which the digit 2 appeared during "Plan 2". Put simply, they were required to make two instructed button selections in this condition, with no free choice.

This design ensured that working memory across the three conditions was equal as participants always had to remember two buttons presses before executing them. Visual stimuli were also closely matched across the three different trial types. Importantly, the selection of buttons was explicitly separated from their execution, which meant that activations time-locked to the planning phase could be examined without contamination from the motor act of pressing. It was predicted that regions of the brain involved in free selection would exhibit greater mean activity when making TWO FREE and ONE FREE selection(s) compared to NO FREE.

6.2.4 Behavioural analysis

A trial was deemed to be incorrect if the participant made less than two button presses during execution. It was also considered erroneous if two button presses were made, but at least one of them was 'illegal' (e.g., selecting a white instead of red box, or not selecting an instructed box). Behavioural analyses were performed in IBM SPSS Statistics version 22.0. A repeated measures ANOVA was conducted to determine the effect of task condition (TWO FREE vs. ONE FREE vs. NO FREE) on task accuracy and median reaction time on correct trials.

6.2.5 Functional imaging and analysis

6.2.5.1 Data Acquisition

A Siemens Magnetom Prisma 3T MRI scanner was used to acquire a three-dimensional T1-weighted structural scan and T2*-weighted echo planar images (EPI). The structural scan was acquired using a magnetization prepared rapid gradient echo (MPRAGE) sequence with 192 slices, slice thickness = 1mm, gap between slices = 0.5mm, TR = 1900ms, TE = 3.97ms, field of view = 192mm × 192mm, voxel size = 1×1×1 mm resolution. The functional imaging sequence was acquired in an ascending manner at an oblique angle (~30^{o}) to the AC-PC line, and had the following acquisition parameters: 2194 volumes, TE = 30ms, TR = 1570ms, flip angle = 70^{o}, field of view = 216mm × 216mm, voxel size = 2×2×2 mm resolution. Immediately following the functional sequence, a GRE field map sequence was used to collect phase and magnitude maps (TE_1 = 4.92ms, TE_2 = 7.36ms).

6.2.5.2 Image preprocessing

Imaging data were preprocessed using SPM12 (www.fil.ion.ucl.ac.uk/spm). To correct for head movements within subject so that the same portion of brain can be compared across time, each EPI in the time-series was first realigned to the first image of the functional sequence. This was achieved by estimating six parameters (translation along x, y, z in mm; rotation by pitch, roll, yaw in degrees) describing the rigid-body transformation between each image and the reference image. Following that, each EPI was re-sampled according to the estimated transformation parameters so that it matches the first image (*realignment step*).

Nonetheless, even after realignment, a large amount of variance may still be explained by effects of movement due to non-linear distortion from magnetic field inhomogeneities. In other words, the brain does not completely satisfy the rigid-body assumption of realignment. This is because different materials such as air, gray matter and white matter possess different magnetic susceptibilities, which refers to the extent of magnetization of a material in response to an applied magnetic field. As a result, field inhomogeneities appear, leading to different deformations occurring at different points in the field over different scans. To overcome this issue of non-rigid deformation, field maps that measure the deformation field were acquired immediately after the functional sequence. They were then used to estimate the derivatives of the deformation with respect to the movement parameters, i.e. the amount of distortion for each scan. Finally, the time-variant deformation field was applied to correct for the movement-by-distortion interaction in the EPIs (*unwarping step*, Andersson et al., 2001; Hutton et al., 2002).

Following this, the mean of the realigned and unwarped functional images was coregistered to the subject's own structural image to ensure superior anatomical localization and greater precision in spatial normalisation. This was done by first realigning the functional image with the structural image. The mutual information cost function between intensities in the functional and structural images was then calculated and maximised (*coregistration step*).

Next, the structural image was subjected to a unified segmentation procedure performing tissue segmentation, intensity non-uniformity (bias) correction and spatial normalisation to the MNI template within the cost function in a generative model (Ashburner and Friston, 2005). This method models intensities of the image with a Gaussian Mixture Model containing a specified number of components. Each Gaussian component was parameterized by its mean, variance and a mixing proportion. Tissue probability maps (TPMs) obtained from the segmented images of multiple subjects in the ICBM (International Consortium for Brain Mapping) project were utilised to provide a spatially varying prior distribution in MNI space. Bayes rule was then used to compute the posterior probability of each tissue class. Because of imperfections in the magnetic field and subject-field interactions, the distribution of intensity in the image is spatially variable. Thus, a smooth intensity correction was also modeled using a linear combination of discrete cosine transform basis functions. Finally, the TPMs were allowed to be deformed and warped to match the subject. Combining deformable TPMs with Gaussian mixture model segmentation means that the inverse of the transformation aligning the TPMs can be utilised to normalize the original image. By performing these steps in an iterative manner until minimization of

the cost function, the structural image gets segmented, bias-corrected and normalised to the MNI template (*segmentation step*).

The same normalisation parameters were then applied to normalise the EPIs (*normalisation step*). The images were resampled to a voxel size of 3×3×3 mm. Finally, the EPIs were spatially smoothed in order to improve the signal-to-noise ratio. This was done by applying a Gaussian smoothing kernel of 8mm FWHM (Full Width at Half Maximum) to each voxel in turn so that the intensity value in that voxel is replaced with a weighted average of values in the surrounding voxels (*smoothing step*).

6.2.5.3 First-level statistical analyses

First-level GLMs were created for factorial analyses. There were six event types of interest, namely correct trials for (i) Plan TWO FREE, (ii) Plan ONE FREE, (iii) Plan NO FREE, (iv) Press TWO FREE, (v) Press ONE FREE, and (vi) Press NO FREE. A regressor was constructed for each event type by convolving the event onsets with the canonical hemodynamic response function (HRF). Note that the onset timings of "Plan 2" and "Press" were used respectively for the planning and pressing events. Contrast images for each of these six event types was computed and brought forward to a flexible factorial model in the second-level analysis. In addition, two separate regressors of no interest were used to model the planning and pressing of all incorrect trials. Six head motion parameters derived during realignment were also included, so as to allow residual effects of head motion to be modeled as covariates of no interest.

6.2.5.4 Second-level statistical analyses

To make inferences and generalise them to the wider population, a random effects analysis has to be conducted. Usually, a hierarchical GLM model should be set up so that parameters for the effects and variances at both the subject and groups levels can be estimated together via iterative looping. However, this method is computationally intensive and difficult to conduct practically. Therefore, SPM uses a summary statistics approach instead where contrast images from each subject at the first-level are brought together into basic statistical tests at the second-level. This method is a good approximation to the hierarchical model as long as the design at the first-level is same for all participants and there are no extreme outliers.

Here, first-level contrast images for each subject were inputted into a second-level 2×3 flexible factorial design matrix with factors Phase (Plan vs. Press) and Condition (TWO vs. ONE vs. NO FREE). To correct for multiple comparisons, a $p<0.05$ family-wise error (FWE) threshold was used. All results reported are significant at $p<0.05$ FWE whole brain correction for multiple comparisons at the voxel level.

6.3 Results

6.3.1 Behavioural data

Participants performed the experiment with high accuracies of >90% in all conditions (TWO FREE: mean=94.2%, SD=3.7; ONE FREE: mean=93.9%, SD=3.3; NO FREE: mean=93.8%, SD=3.5). Repeated measures ANOVA found no significant difference in accuracy across the three conditions ($F(2,74)=0.27$, $p>0.05$), indicating

that they performed equally well regardless of the number of free selections (Figure 6.3A).

Both button presses in each trial were also performed well within the time limit of 1000ms (TWO FREE: mean=589.0ms, SD=98.3; ONE FREE: mean=587.8ms, SD=96.0; NO FREE: mean=602.7ms, SD=85.9). However, there was a significant statistical difference in their reaction times across the three conditions ($F(1.5,55.1)=9.7$, $p<0.001$; Figure 6.3B). Post-hoc comparisons revealed that participants were slower on the NO FREE compared to TWO FREE ($p<0.01$) and ONE FREE ($p<0.001$), but there was no difference between TWO FREE and ONE FREE ($p>0.05$).

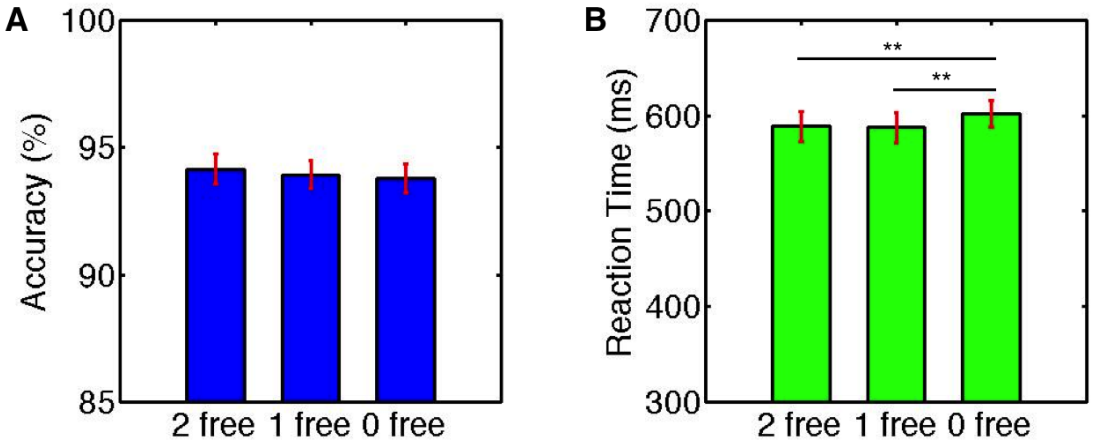


Figure 6.3 Behavioural results. (A) Participants performed well in the task (>90% accuracy). There was no difference in accuracy across the three conditions. **(B)** However, they were significantly slower to execute the button presses when there was NO FREE selection compared to TWO FREE and ONE FREE.

6.3.2 Functional imaging data

6.3.2.1 Main effect of PLAN > PRESS

Areas of significant activation when contrasting the main effect of planning to pressing are presented in **Table 6.1**. The strongest activations were found in the dorsal premotor cortex (**Figure 6.4**). There were also significant clusters in the pre-SMA, visual cortex, intraparietal sulcus and superior parietal lobule.

Table 6.1: Main effect of Plan > Press

Cluster size *k*	T	Z	MNI coordinates	Region	p FWE
112	8.52	>8	24, -1, 53	dorsal premotor	<0.001
159	8.15	7.61	-21, -1, 53	dorsal premotor	<0.001
12	5.56	5.37	-9, 11, 50	pre-SMA	0.001
60	7.37	6.96	21, -100, -1	visual V1	<0.001
21	6.18	5.93	-30, -88, -19	visual V4	<0.001
45	5.75	5.55	-18, -97, -7	visual V3	<0.001
236	6.93	6.59	-39, -40, 41	intraparietal sulcus	<0.001
	6.85	6.52	-27, -52, 47	intraparietal sulcus	<0.001
	6.81	6.48	-18, -64, 56	superior parietal	<0.001
40	5.85	5.64	27, -58, 50	intraparietal sulcus	<0.001
28	5.51	5.33	18, -67, 65	superior parietal	0.001

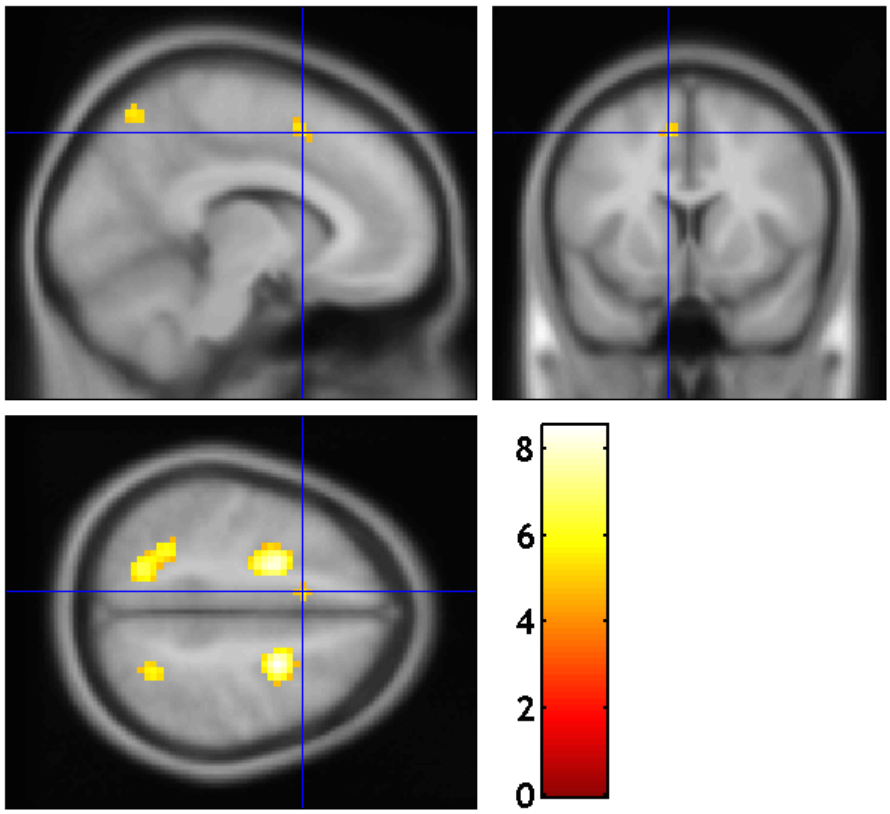


Figure 6.4 Results of main effect PLAN > PRESS. There was a significant cluster in the pre-SMA (crosshair at MNI [x=-9, y=11, z=50]). Significant activations were also present in the dorsal premotor cortex, visual cortex, intraparietal sulcus and superior parietal lobule. Image displayed at $p<0.05$ FWE whole brain corrected level. Colorbar shows T values.

6.3.2.2 Activations for PLAN TWO FREE > PLAN NO FREE

The pre-SMA was most strongly activated when comparing the planning of TWO FREE > NO FREE (**Figure 6.5**). Other significant areas of activation include the dorsal and lateral premotor cortices, insula, middle frontal gyrus, intraparietal sulcus, superior and inferior parietal lobule, and cerebellum. Details of these are presented in **Table 6.2**.

Table 6.2: Activations for PLAN TWO FREE > PLAN NO FREE

Cluster size k	T	Z	MNI coordinates	Region	p(FWE)
1565	10.81	>8	-6, 20, 41	pre-SMA	<0.001
	8.40	7.81	-24, 2 53	dorsal premotor	<0.001
	8.11	7.58	-42, 2, 35	lateral premotor	<0.001
185	8.60	>8	-33, 17, 2	insula	<0.001
286	7.80	7.32	33, 23, 5	insula	<0.001
	6.81	6.48	48, 8, 32	lateral premotor	<0.001
	6.54	6.25	51, 11, 14	lateral premotor	<0.001
172	7.54	7.10	42, 38, 23	middle frontal gyrus	<0.001
365	7.43	7.02	39, -40, 44	intraparietal sulcus	<0.001
	7.27	6.87	48, -37, 47	inferior parietal	<0.001
336	7.34	6.94	-45, -40, 41	intraparietal sulcus	<0.001
	7.23	6.84	-33, -52, 44	intraparietal sulcus	<0.001
128	6.46	6.18	-12, -61, 53	superior parietal	<0.001
78	6.35	6.08	15, -64, 53	superior parietal	<0.001
42	6.07	5.83	-36, -67, -31	cerebellum	<0.001

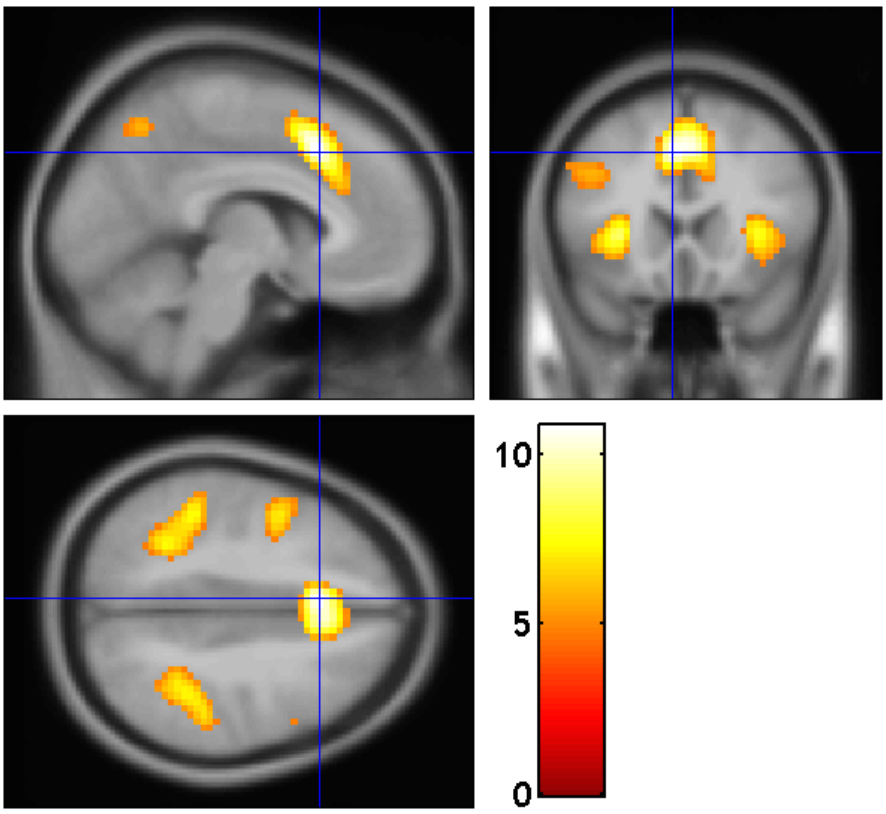


Figure 6.5 Results of contrast PLAN TWO FREE > PLAN NO FREE. The strongest activation was found in the pre-SMA (crosshair at MNI [x=-6, y=20, z=41]). There were also significant activations in the dorsal and lateral premotor cortices, insula, middle frontal gyrus, intraparietal sulcus, superior and inferior parietal lobule, and cerebellum. Image displayed at $p<0.05$ FWE whole brain corrected level. Colorbar shows T values.

6.3.2.3 Activations for PLAN ONE FREE > PLAN NO FREE

The strongest activations were found in the pre-SMA when comparing the planning of ONE FREE > NO FREE (**Figure 6.6**). Besides this, the lateral premotor cortex, intraparietal sulcus, insula, inferior temporal gyrus and cerebellum were also activated. Details of these are presented in **Table 6.3**.

Table 6.3: Activations for PLAN ONE FREE > PLAN NO FREE

Cluster size k	T	Z	MNI coordinates	Region	p(FWE)
3460	11.15	>8	6, 14, 47	pre-SMA	<0.001
	10.85	>8	-3, 14, 47	pre-SMA	<0.001
	10.66	>8	-42, 2, 32	lateral premotor cortex	<0.001
2557	11.08	>8	-30, -52, 41	intraparietal sulcus	<0.001
	10.50	>8	-42, -40, -41	cerebellum	<0.001
	10.44	>8	45, -37, 47	intraparietal sulcus	<0.001
207	9.80	>8	-30, 20, 2	insula	<0.001
41	6.71	6.39	30, -64, -31	cerebellum	<0.001
55	6.57	6.27	-30, -67, -28	cerebellum	<0.001
47	6.16	5.91	54, -52, -13	inferior temporal gyrus	<0.001
36	5.69	5.49	-48, -61, -7	inferior temporal gyrus	0.001
18	5.47	5.30	30, -73, -52	cerebellum	0.002
11	5.01	4.87	-30, -73, -55	cerebellum	0.011

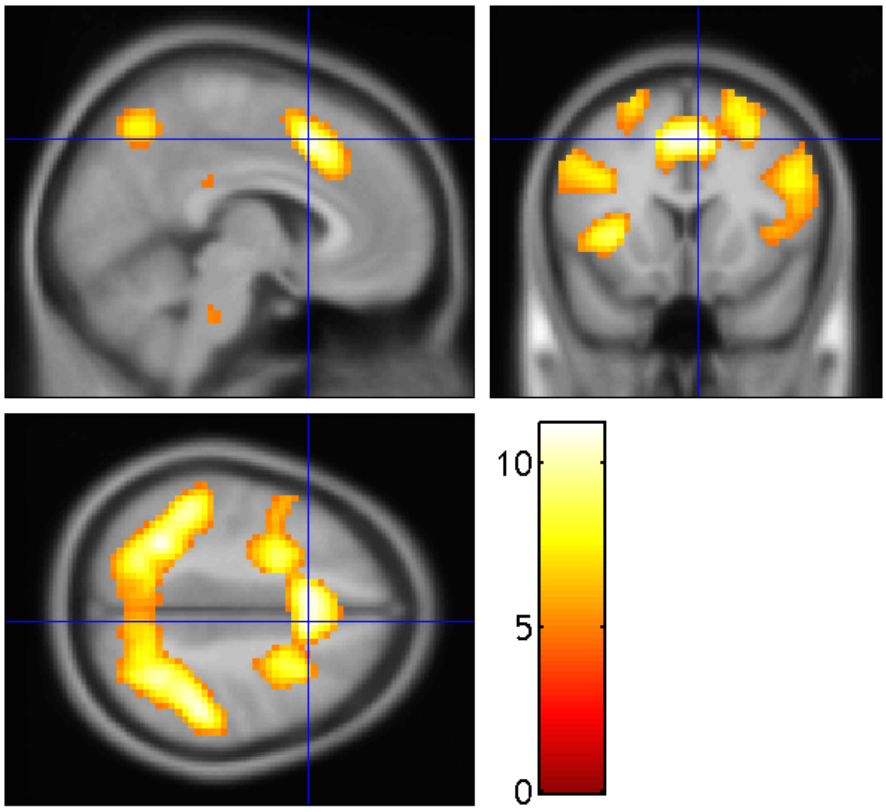


Figure 6.6 Results of contrast PLAN ONE FREE > PLAN NO FREE. The strongest activations were found in the pre-SMA (crosshair at MNI [x=6, y=14, z=47] and [x=-3, y=14, z=47]). There were also significant activations in the lateral premotor cortex, intraparietal sulcus, insula, inferior temporal gyrus and cerebellum. Image displayed at $p<0.05$ FWE whole brain corrected level. Colorbar shows T values.

6.3.2.4 Activations for PLAN TWO FREE vs. PLAN ONE FREE

When comparing the planning of TWO FREE against ONE FREE, there was no difference in activations within the medial frontal cortex. This was the same even after applying small volume correction with a mask comprising of pre-SMA and ACC, which improves sensitivity by restrict the search area for significant voxels to this specific region of interest. However, significantly lower activations were found in the superior parietal lobule (**Figure 6.7**), middle occipital gyrus, middle temporal gyrus, and fusiform gyrus (**Table 6.4**).

Table 6.4: Activations for PLAN TWO FREE < PLAN ONE FREE

Cluster size k	T	Z	MNI coordinates	Region	p(FWE)
96	6.12	5.88	30, -61, 50	superior parietal	<0.001
19	5.64	5.45	36, -46, -22	fusiform gyrus	0.001
84	5.36	5.19	-27, -55, 53	superior parietal	0.003
	5.12	4.97	-27, -67, 38	middle occipital gyrus	0.007
36	5.08	4.93	-45, -64, -13	superior parietal	0.009
	4.80	4.68	-45, -52, -4	middle temporal gyrus	0.026

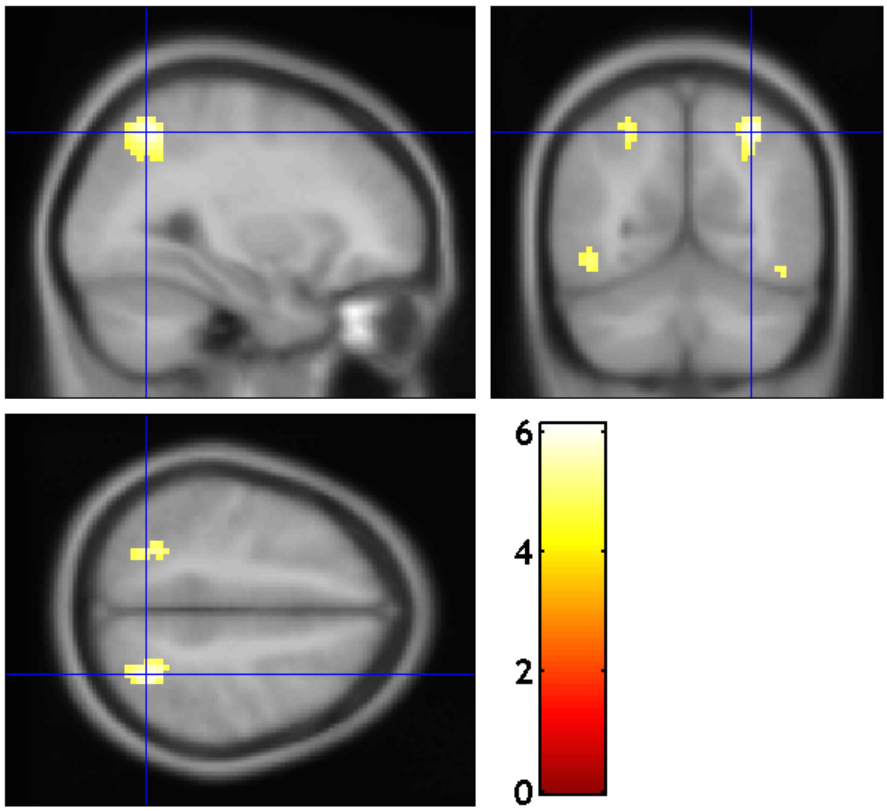


Figure 6.7 Results of contrast PLAN TWO FREE < PLAN ONE FREE. Significant clusters were present in the superior parietal lobule (crosshair at MNI [x=30, y=-61, z=50]), fusiform gyrus, middle occipital gyrus and middle temporal gyrus. Image displayed at $p<0.05$ FWE whole brain corrected level. Colorbar shows T values.

6.3.2.5 Activations for PRESS TWO FREE vs. PRESS NO FREE

Significant activations were found in the superior parietal lobule, intraparietal sulcus, primary motor cortex, middle frontal gyrus, inferior frontal gyrus, inferior temporal gyrus and cerebellum (**Figure 6.8** and **Table 6.5**). Notably, regions in the medial frontal cortex were not found here.

Table 6.5: Activations for PRESS TWO FREE > PRESS NO FREE

Cluster size k	T	Z	MNI coordinates	Region	p(FWE)
817	7.05	6.69	-27, -64, 53	superior parietal	<0.001
	6.67	6.36	-30, -58, 38	intraparietal sulcus	<0.001
713	7.09	6.73	30, -67, 50	superior parietal	<0.001
	6.89	6.55	45, -40, 59	motor M1	<0.001
73	6.44	6.16	-45, 38, 26	middle frontal gyrus	<0.001
	4.77	4.65	-36, 32, 17	inferior frontal gyrus	0.029
39	5.82	5.61	30, -79, -52	cerebellum	<0.001
18	5.47	5.29	57, -52, -16	inferior temporal gyrus	0.002
44	5.23	5.07	39, 32, 20	middle frontal gyrus	0.005
12	5.06	4.92	-30, -73, -52	cerebellum	0.009

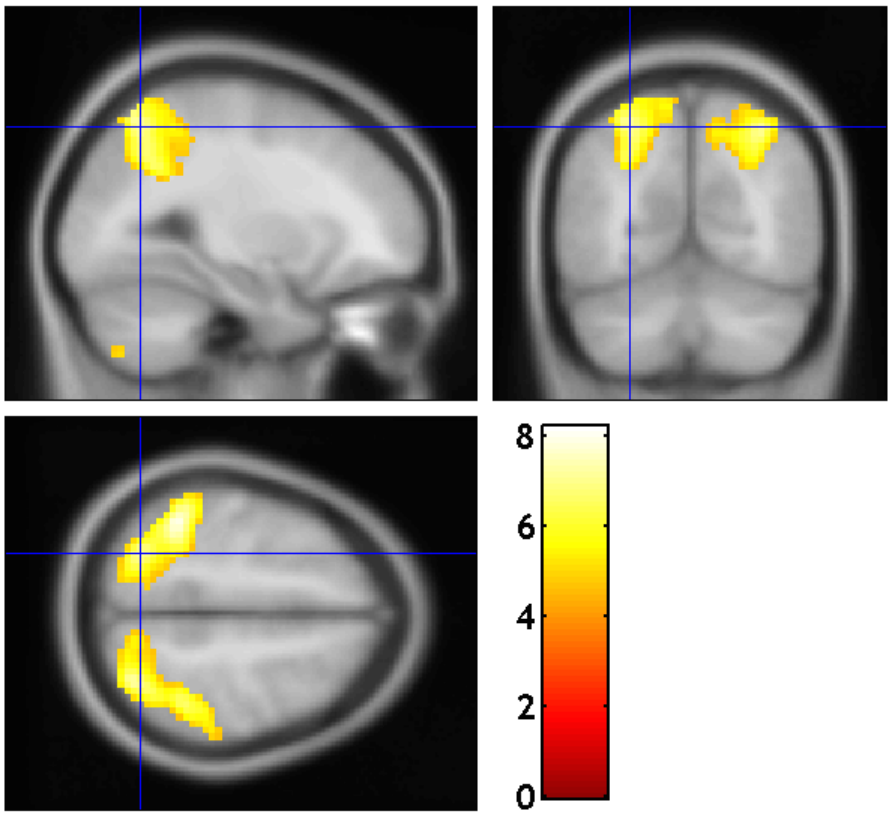


Figure 6.8 Results of contrast PRESS TWO FREE > PRESS NO FREE. Significant activations were found in the superior parietal lobule (crosshair at MNI [x=-27, y=-64, z=53]), intraparietal sulcus, primary motor cortex, middle frontal gyrus, inferior frontal gyrus, inferior temporal gyrus and cerebellum. Image displayed at $p<0.05$ FWE whole brain corrected level. Colorbar shows T values.

6.3.2.6 Activations for PRESS ONE FREE vs. PRESS NO FREE

When comparing the pressing of ONE FREE against NO FREE, there were significant activations of the intraparietal sulcus and superior parietal lobule (**Figure 6.9** and **Table 6.6**).

Table 6.6: Activations for PRESS ONE FREE > PRESS NO FREE

Cluster size k	T	Z	MNI coordinates	Region	p(FWE)
778	7.12	6.75	-42, -49, 59	intraparietal sulcus	<0.001
	6.63	6.33	30, -67, 53	superior parietal lobule	<0.001
	6.54	6.25	-6, -55, 71	superior parietal lobule	<0.001

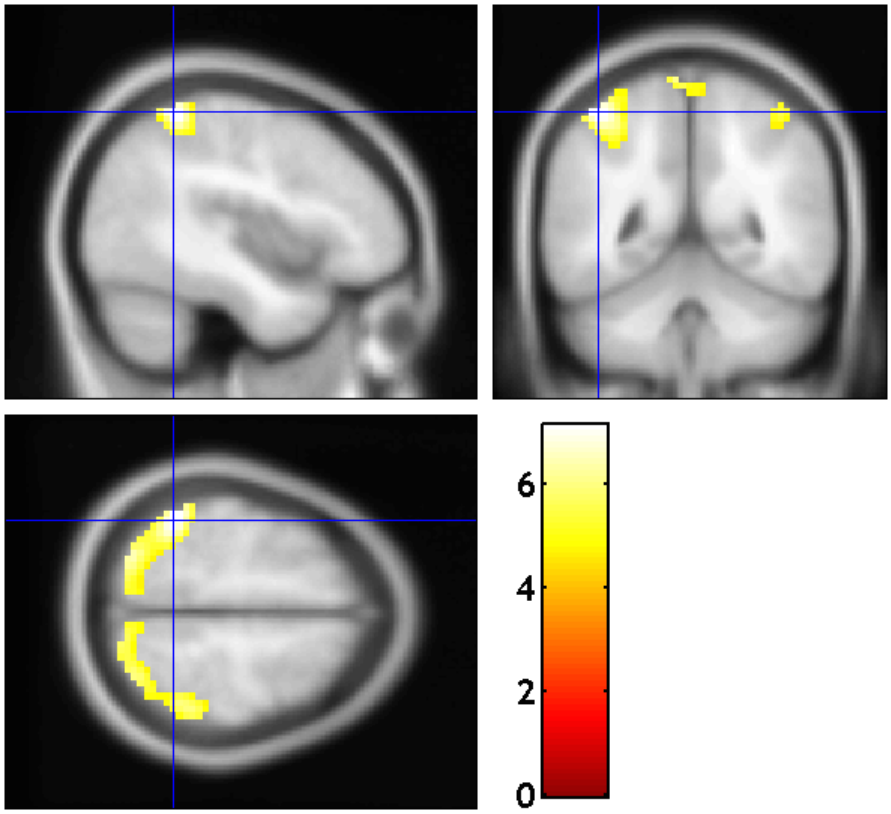


Figure 6.9 Results of contrast PRESS ONE FREE > PRESS NO FREE. Significant activations were found in the intraparietal sulcus (crosshair at MNI [x=-42, y=-49, z=59]) and superior parietal lobule. Image displayed at $p<0.05$ FWE whole brain corrected level. Colorbar shows T values.

6.3.2.7 Activations for PRESS TWO FREE vs. PRESS ONE FREE

There was no significant difference in activations when comparing the pressing of TWO FREE against ONE FREE. This was the same even after relaxing the cluster defining threshold to $p<0.001$ uncorrected.

6.3.2.8 Degree of increase in activation does not correlate with motivation

Might motivated individuals exhibit greater increase in pre-SMA activity when planning FREE selections? MarsBaR (Marseille ROI toolbox) was used to extract parameter estimates for individual regressors at the pre-SMA clusters identified above and correlated with participants' self-reported level of motivation on the AMI. There was no significant correlation between motivation and pre-SMA response to PLAN TWO FREE > PLAN NO FREE and PLAN ONE FREE > PLAN NO FREE, suggesting that the magnitude of increase was not related to individual differences in motivation level (**Table 6.7**).

Table 6.7: Correlations between difference in activation and AMI

		TWO FREE > NO FREE	ONE FREE > NO FREE
Apathy Motivation Index	Behavioural Activation	-0.03	-0.09
	Social Motivation	0.05	-0.07
	Emotional Sensitivity	-0.12	-0.15
	Total	-0.04	-0.15

Note: all $p>0.05$ after correction for multiple comparisons

6.4 Discussion

The goal of this study was to examine hemodynamic responses in the human brain during the *planning* of freely selected button presses. On every trial of the task, participants could be asked to plan TWO FREE, ONE FREE or NO FREE selection(s) of buttons, and then execute them with fingers of their right hand (Figure 6.2). It was chiefly found that activity in the pre-SMA increased during planning, but not execution, of TWO or ONE free selection(s) within a trial. This supports my hypothesis that the medial frontal cortex would be engaged during volitional decisions of *what* action to execute. The second hypothesis that individual differences in levels of motivation would correlate with these increases in activity was not supported. A network of brain regions including the premotor cortex, intraparietal sulcus and superior parietal lobule was also activated in the contrast between number of free selections in the planning and pressing phases.

6.4.1 Pre-SMA plays a role in freely selecting actions

The finding of preferential involvement of the pre-SMA in volitional choices of responses is generally in line with existing literature on voluntary actions. Previous fMRI studies have typically highlighted a crucial role for medial frontal regions, particularly the pre-SMA and ACC (Cunnington et al., 2006; Deiber et al., 1996, 1991; Frith et al., 1991; Lau et al., 2004; Mueller et al., 2007; Playford et al., 1992; Rowe et al., 2005; Thimm et al., 2012; van Eimeren et al., 2006). However, Van Oostende et al. (1997) conducted a button pressing task where participants were required to either execute a self-generated or sensory-guided sequence of finger movements. These

investigators did not find any difference in brain activation areas between the freely selected and externally guided conditions.

Conflicting results have also been found between similar studies. For example, Playford and coworkers (1992) compared participants moving a joystick either freely in any direction or in a single predetermined direction and found greater activation of the DLPFC during the unrestricted condition. Using a similar task, Deiber and colleagues (1991) demonstrated that free selection was associated with pre-SMA activity instead. One limitation of previous studies is that planning and execution of actions were examined together. This means that the activations observed may not only be attributed to the free selection process, but also to the motor act itself.

To overcome this limitation, the paradigm employed here explicitly separated these two stages in time, thereby allowing signals related to selection to be isolated without contamination from signals relevant to execution. It was observed that increases in pre-SMA activity on free selection occurred only during planning but not execution. Indeed, the pre-SMA is thought to be involved in preparing commands for internally generated "intentional" actions that get subsequently executed by the primary motor cortex (Haggard, 2009).

Significant voxels were also found in the premotor cortex (within same cluster as pre-SMA activation) when free selection is required during the planning phase. Previous investigations have implicated the premotor cortex in the sensory guidance of movement and motor preparation (Churchland, 2006; Cisek and Kalaska, 2005; Gentilucci et al., 1988; Graziano et al., 1994, 1999; Graziano and Gross, 1993; Rizzolatti et al., 1981; Wise, 1985). However, some investigations have reported

activations of this region during voluntary action too (Larsson et al., 1996; Van Oostende et al., 1997; Wessel et al., 1997; Jahanshahi et al., 2000; Weeks et al., 2001; van Eimeren et al., 2006). In addition, there is evidence demonstrating that neurons in the lateral premotor cortex strongly encode abstract rules in which the response is not definitively specified, such as that during free selection (Muhammad et al., 2006; Wallis and Miller, 2003). These findings and the ones reported here suggest that the premotor cortex may also contribute towards at a higher-order and more abstract level to intentional selection.

On the other hand, no significant activations of the ACC during free selection were found at the voxel level (although there are indications of pre-SMA clusters extending slightly into that region). One possibility might be that while the pre-SMA plays a role in intentional selection, the ACC is involved in conflict resolution instead (see Rushworth et al., 2004 for review). According to this perspective, selecting in favour of a particular action requires the inhibition of competing alternatives. This competition is elevated in a free choice scenario because unlike externally-guided trials, there is no bias towards any one action thereby leading to presumably similar activation levels in the available choices. In support of this hypothesis, Lau et al. (2006) modified the Erikson Flanker task (Eriksen, 1995) to include a free condition displaying 'OOOOO' that required participants to decide by themselves whether to press a '<' or '>' arrow. They found activations of the ACC when contrasting the incongruent and congruent modes, indicating that this region was involved in response conflict. On the other hand, the pre-SMA distinguished between the free and congruent conditions, suggesting that this area was associated with intentional selection.

In the current study, one might expect the amount of conflict to be greater during free selections and thus, predict activations of ACC when compared to no free selections. However, given that participants only had to choose from a set of binary options, it is possible that the difference in conflict levels do not differ significantly, thereby leading to no difference in ACC activity between conditions.

6.4.2 Activation of posterior parietal cortex

Activations of the posterior parietal cortex, particularly the intraparietal sulcus and superior parietal lobule, were found between conditions in both the planning and pressing phase. This is not surprising as a wealth of literature has established an important role for this region in general visuospatial and attentional processing (see e.g. Nachev and Husain (2006); Sack (2009); Vandenberghe and Gillebert (2009) for reviews). Indeed, many studies have consistently reported posterior parietal activation despite using a diverse range of stimuli and tasks (see Culham and Kanwisher (2001) for review).

More recently, Duncan (2010) identified a network of frontal and parietal regions whose activity increases with cognitive demand, regardless of the particular cognitive manipulation within the task. Also known as the multiple demand system, it comprises the medial frontal cortex, particularly the pre-SMA and ACC; part of the dorsolateral prefrontal cortex, specifically the inferior frontal sulcus; posterior parietal region, in and around the intraparietal sulcus; as well as the anterior insula and frontal operculum. Here, similar regions were activated for free selection compared to externally instructed selection. Thus, an alternative interpretation might be that these

activations reflect greater cognitive demand associated with free choice rather than volitional selection. However, even though planning two free selections is presumably more cognitively demanding than one free selection, no significant activations were found in this task when contrasting PLAN TWO FREE > PLAN ONE FREE. This suggests that the activations found were unlikely to arise due to differences in cognitive load across conditions.

Recently, one theory also postulated that the posterior parietal cortex, particularly the inferior parietal lobule, is responsible for generating the subjective experience of 'wanting to move' (Desmurget and Sirigu, 2009). Evidence for this comes from a direct electrical stimulation experiment on patients undergoing brain surgery (Desmurget et al., 2009). Intriguingly, stimulation of the inferior portion of the posterior parietal cortex resulted in patients reporting an intention to move certain parts of the body, e.g. lips, hands and chest. Crucially, desire to move was not reported when no current was applied, suggesting that conscious intention was a direct consequence of the electrical stimulation. Furthermore, the investigators argued that this reported desire to move was not due to sensory feedback from contractions of muscles, as parietal stimulation did not result in any muscle activity. The findings in the current study agree with the broad suggestion that the posterior parietal cortex, albeit in more superior portions, is involved in voluntary action. However, it is not possible to infer whether the exact role of this region is to generate conscious intention. Further investigations will be needed to examine this.

6.4.3 Motivation is not related to difference in pre-SMA activations

Apathy is a disorder of motivation characterised by reductions in self-generated voluntary actions. A prominent theory posits that impaired motivation arises from deficits in analyzing the effort costs and reward benefits of performing actions (Le Heron et al., 2017; Sinha et al., 2013). In support of this, it had been found that apathy was related to a greater subjective estimate of effort costs (Bonnelle et al., 2015), reduced incentivisation by reward (Le Heron et al., 2018), or an integration of both (Hartmann et al., 2015). Recently, it was found that activity in the medial frontal cortex during an effort-based decision-making task correlated with behavioural apathy (Bonnelle et al., 2016). Based on this observation, I hypothesized that signal changes in the pre-SMA during free selection might relate to apathy too. However, this was not the case as no correlation between motivation level and differences in pre-SMA activity across conditions was found. The effects of apathy might not be present in the current task as no explicit costs and rewards were attributed to the two options.

6.5 Conclusion

The results of the study conducted here revealed that the pre-SMA plays a key role in the *planning*, but not execution, of intentional action selection. These findings may represent an important contribution to the field of voluntary actions by overcoming a major limitation present in the existing literature. Unlike previous studies, the key distinction is that activations in the current paradigm are purely related to the planning process without contamination from motor execution.

7 General Discussion

7.1 Summary

7.1.1 Premise for thesis

In this thesis, I began with a general introduction linking research across the fields of voluntary action, apathy and option generation. Voluntary action is a non-unitary concept that may be empirically investigated along at least three different dimensions, namely decisions of when to initiate a particular movement, what action to execute at a cued timing and whether or not to perform a particular movement (Brass and Haggard, 2008). Substantial evidence from electrophysiological and functional neuroimaging experiments in animals and humans have implicated the medial frontal wall in voluntary action, with particular focuses on the pre-supplementary motor area (pre-SMA) and anterior cingulate cortex (ACC) (see review by e.g. Haggard, 2008). However, the exact roles of these regions remain unclear. In

Chapter 6, I investigated the hypothesis that they are involved in *planning* during volitional decisions of *what* to do.

Seeking clarity on the neural basis of voluntary actions is important because the lack of self-generated actions is characteristic of apathy, a debilitating disorder of motivation prevalent in neurodegenerative diseases and occurring to varying degrees in the healthy population (Marin, 1991). Unfortunately, research on apathy is still in its infancy. The conceptualization of this construct is currently under debate, even though investigators generally agree it is complex and multidimensional in nature. More surprisingly, the construct of apathy has never been thoroughly examined in healthy individuals using experimental tasks. This question was examined in Chapter 2. From a mechanistic perspective, disruptions of the medial frontal cortex and subcortical basal ganglia structures, particularly the ACC and ventral striatum, have been regularly implicated in apathy across neurological conditions such as Parkinson's and Alzheimer's disease (see review by e.g. Le Heron et al., 2017). Consideration of the functional properties of these regions led to proposals of underlying cognitive mechanisms centered on deficits in selecting between options and learning outcomes during feedback (Le Heron et al., 2017). Intriguingly, the possibility that an inability to self-generate action options may also contribute to apathy has barely been considered, and never been examined (Sinha et al., 2013).

This is because neuroscientific researches on decision-making have typically focused on forced choice scenarios where a fixed set of options is already provided (Kalis et al., 2013). Little progress has been made regarding how humans generate possible options for behaviour by themselves. This chiefly stems from challenges in

developing an objective way to specifically measure option generation. I introduced a simple, new experimental paradigm that assesses ability to self-generate behavioural options – albeit within a limited context – in Chapter 3 and utilised it in Chapters 4 and 5 to examine the neurochemical modulation of this process.

7.1.2 Apathy in health and disease

In Chapter 2, I first validated a new questionnaire to detect apathy which is suitable for use in both the healthy population and patients with neurodegenerative diseases. A 51-item self-rated scale (Table 2.1), which was developed with experienced neurologists and researchers, was first administered to 505 individuals from the healthy population. An exploratory factor analysis then reduced it to form the 18-item Apathy Motivation Index (AMI, Table 2.2), which consisted of three subscales: *behavioural activation* (tendency to self-initiate goal-directed behaviour), *social motivation* (level of engagement in social interactions) and *emotional sensitivity* (feelings of positive and negative affection). This three-factor structure was confirmed via a confirmatory factor analysis in another independent sample of 479 healthy people. The AMI also had good internal reliability, test-retest reliability and construct validity.

A latent profile analysis revealed the four subtypes of motivation in the healthy population using the AMI (Figure 2.3). While most people were *generally motivated*, a small number of individuals were *generally apathetic* across all three domains. Two other groups had apathy only on specific subscale(s), and were classified as being either *behaviourally/socially apathetic* or *emotionally apathetic*. These four subtypes

were distinct and overlapped differently with closely related outcomes of depression, anhedonia and fatigue. Having high levels of behavioural and social apathy are associated with other negative states, whereas experiencing emotional apathy on its own may not be associated with higher levels of depression and fatigue (**Figure 2.4**). These findings show for the first time that apathy in the healthy population can be dissected into four classes and suggest that particular subtypes are more likely to co-occur with depression, anhedonia and fatigue. Future longitudinal studies would benefit from investigating how particular profiles of apathy are risk factors for the development of these symptoms.

The AMI proved also to be a quick, simple and useful alternative for assessing apathy in Parkinson's disease (PD). Scores correlated strongly with and had good diagnostic accuracy against the Lille Apathy Rating Scale, an established, semi-structured interview for clinical apathy (**Figure 2.5**). The AMI revealed that while behavioural and social apathy were elevated in 102 patients with PD compared to 147 healthy age-matched controls, emotional motivation was actually preserved (**Figure 2.6**). Patients who were behaviourally and socially apathetic were also more likely to be depressed and anhedonic. However, there was no association between emotional apathy, depression and anhedonia (**Figure 2.7**). These results suggest that not all aspects of motivation are impaired in PD and may have important implications for guiding development of selective treatments.

7.1.3 Dopamine modulates option generation for behaviour

In Chapter 3, I developed an objective, quantitative and culture-free measure of option generation. This was administered to 96 individuals from the healthy population. Participants were required to draw, on a touchscreen computer, as many different paths as they could between two fixed points within a time limit of four minutes (**Figure 3.2**). By applying similarity-based mathematical principles on the movement parameters, I derived a metric of uniqueness that defines how different each path was from all other paths generated by all other participants (**Figure 3.3**). There was a trade-off between fluency (number of path options generated) and uniqueness, with participants tending to generate either many similar paths or a few different ones. Fluency was also found to correlate strongly with motivation level, indicating that apathetic individuals in the healthy population generated significantly fewer options compared to their motivated counterparts (**Figure 3.5**). This suggests that impairments in the ability to generate options contribute to apathy in the healthy population.

Having established this new paradigm, I proceeded to investigate the neurochemical modulation of option generation in Chapter 4. Specifically, it was hypothesized that dopamine would play a key role in this process. 35 patients with PD were tested twice, once when they were taking their normal dopaminergic medication (ON) and once after an overnight withdrawal from these drugs (OFF). 34 age-matched healthy controls also participated. Dopamine improved the fluency of generating options, but diminished the overall uniqueness due to the fluency-uniqueness trade-off (**Figure 4.5**). However, after correcting for this trade-off with a linear mixed effects

model analysis, it was revealed that uniqueness actually increases for any given fluency (Figure 4.7). In other words, there were dual effects of dopamine on option generation. While its major effect was to shift the fluency-uniqueness trade-off such that there were more but less unique paths, dopamine also independently improved uniqueness for any particular level of fluency (Figure 4.8).

In Chapter 5, I enquired whether similar effects of dopamine may be observed in the healthy population (N=29). This was achieved using a double-blind, placebo-controlled crossover study of cabergoline, a dopamine D2 receptor agonist. Consistent with findings in PD, it was observed that healthy elderly individuals produced more options but with reduced uniqueness overall when on cabergoline (Figure 5.5). Nonetheless, correcting for the trade-off between fluency and uniqueness revealed that dopamine also independently increased uniqueness for any given fluency. Interestingly, I also found that this modulatory effect of dopamine depends on individual levels of motivation (Figure 5.6). Specifically, the improvement in uniqueness was greater on apathetic compared to motivated people. This was not observed for patients with PD. These findings in Chapters 4 and 5 provide the first direct evidence for an involvement of dopamine in the process of generating options for behaviour.

A second study using haloperidol, a D_2 receptor antagonist, however did not have any effect on the number of options generated in healthy young individuals (Figure 5.14). Furthermore, contrary to what was predicted, it increased the uniqueness of options for a particular fluency (Figure 5.15). This might be for several reasons, including the use of a much younger age group compared to patients with

PD and the healthy group on cabergoline and the dose administered. Further work will be required to investigate this.

Importantly, various processes that might have confounded interpretation of the findings in Chapters 3 – 5 were investigated by using three additional control tasks. According to Sinha et al. (2013), initiating actions might first involve generating possible courses of action (*option generation*); then evaluating and selecting from self-generated options and/or those prompted by external events, cues or rewards in the environment (*option selection*); developing motor plans to execute the chosen option (*motor planning*) and finally initiating behaviour (*action execution*) (Figure 3.1).

Thus, it might be that fewer paths were produced on the touchscreen not because of difficulty in generating options, but because of deficits in executing an action. To control for this, participants were asked to draw ten straight lines, each as quickly as they could, between the two fixed points. The mean drawing time for each line served as a baseline index of drawing speed (Figure 3.3). Besides that, reduced fluency might also have occurred due to difficulties in planning the motor actions required to execute them. Therefore, a second matched control task was used where options that each require a different action plan were *externally-cued* in turn, so that participants were prompted to respond to a new target location rather than have to self-initiate actions (Figure 3.4). Finally, options might have been generated but not selected. To account for that, a third matched control task was administered whereby all the potential options were already provided from the beginning so that options did not need to be self-generated (Figure 3.5). Findings from these three control tasks suggest that paucities of option generation cannot be attributed to a difficulty simply

in option selection, planning or executing actions (**Figures 3.8, 3.10, 3.12, 4.10 – 4.13, 5.7 – 5.10**).

7.1.4 Pre-SMA plays a key role in planning freely selected actions

In Chapter 6, I conducted an fMRI study to investigate the hypothesis that the medial frontal cortex is involved in planning during volition decisions of *what* action to execute. A key distinguishing feature of the task was the explicit temporal separation of action planning from execution. Participants were first required to plan either two freely selected buttons, one freely selected button and one externally-cued button, or two externally-guided buttons. The two planned buttons then had to be executed after a long variable delay of 2 – 4 seconds (**Figure 6.2**). This design ensured that signals relevant to planning were not contaminated by those due to the motor action itself. In line with my hypothesis, the pre-SMA was found to be most strongly activated when planning freely selected actions (**Figures 6.5**, **6.6**). Importantly, this area was not activated in the corresponding contrasts during the execution phase, thereby suggesting a particular role for the pre-SMA in volitional choice responses (Haggard, 2008; Lau et al., 2004; Nachev et al., 2005; Passingham et al., 2010). Other regions of activation included the dorsal and lateral premotor cortex, superior parietal lobule and intraparietal sulcus.

Results from the fMRI paradigm revealed that while there was no difference in pre-SMA activations, the superior parietal lobule exhibited *reduced* activity when planning TWO FREE selections within a trial compared to ONE FREE. Might this reflect a form of repetition suppression within the superior parietal?

Repetition suppression, also known as neural adaptation, refers to the observation in which neurons reduce their firing upon repeated exposure to stimuli or properties that they are sensitive to (Barron et al., 2016). It has been extensively demonstrated at the single-cell level across a variety of stimuli and brain regions e.g. inferior temporal cortex (Baylis and Rolls, 1987; Gross et al., 1969, 1967; Miller et al., 1996, 1991), visual cortex (Albrecht et al., 1984; Blakemore and Campbell, 1969; Maddess et al., 1988; Maffei et al., 1973; Movshon and Lennie, 1979), prefrontal cortex (Miller et al., 1996; Rainer et al., 1999) and somatosensory cortex (Cohen-Kashi Malina et al., 2013). The effect may be seen across a large range of timescales for repetition times as short as 200ms to as long as 24h (Barron et al., 2016).

This technique has also been utilized in fMRI to examine sensory processing in the human brain (Buckner et al., 1998; Chong et al., 2008; Doeller et al., 2010; Grill-Spector et al., 1999; Kilner et al., 2009; Kourtzi and Kanwisher, 2001; Sawamura et al., 2005; Tootell et al., 1998, 1995), although more recently, it helped to reveal more abstract processes such as number representation (Cohen Kadosh et al., 2007; Piazza et al., 2007) and social computations (Garvert et al., 2015; Jenkins et al., 2008). Given these findings, the prospect of repetition suppression occurring for an abstract process like the *planning* of freely selected actions appears promising.

Unfortunately, the design of the fMRI paradigm in this thesis makes it difficult to determine whether neuronal adaptation actually occurred for planning of free selections. In the task, 'Plan 1' and 'Plan 2' are very closely spaced in time (gap of only 400ms) and thus, only the mean activation from both phases can be derived. It cannot be determined how activity for the second plan actually compares to the first. As such,

it is not possible to conclude whether repetition suppression had occurred or not. Future work could modify the task by adding a long variable delay between the two planning phases so that the activity for the first and second planning phases can be separated.

Together, the findings in this thesis have helped to advance our understanding of option generation, apathy and voluntary actions. They might also point to new directions for future work, which I will discuss in the following sections.

7.2 Greater perspicuity on the relationship between apathy and depression is required

Although the work presented here has shed some light on aspects of motivation and apathy, several important issues were not directly addressed and might be useful to purse in future research endeavours. One key problem is the relationship between apathy and depression.

Some theoretical accounts have asserted that although apathy overlaps with depression in behavioural aspects (e.g. the lack of action initiation), the two are distinguishable in affective aspects (Kirsch-Darrow et al., 2011, 2006). Specifically, emotional apathy is thought to involve the blunting of affect or reduced sensitivity to positive and negative feelings. On the other hand, depression is traditionally associated with extreme fluctuations in emotions (Brown and Pluck, 2000). In this thesis, the AMI revealed that behavioural and social apathy correlated positively with depression as measured by Beck Depression Inventory (BDI), whereas emotional apathy exhibited a negative association. This supports the notion that the two

syndromes are partially overlapping. However, one major caveat is consisderation of depression as a unidimensional construct.

According to the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders 5th Edition), the diagnostic criteria for major depressive disorder require the presence of five symptoms that include at least one out of two key symptoms: (i) depressed mood, and (ii) loss of interest or pleasure. Additionally, a subset of these other symptoms needs to be presented: (iii) significant weight loss, (iv) insomnia or hypersomnia, (v) psychomotor agitation or retardation, (vi) fatigue or loss of energy, (vii) feelings of worthlessness, (viii) diminished ability to think or concentrate, and (ix) suicidal thoughts. Therefore, depression comprises disparate symptoms that occur to varying degrees in different affected individuals (Korszun et al., 2004; van Loo et al., 2012). Indeed, depression has been increasingly recognised to be multidimensional in nature (Korszun et al., 2004; Li et al., 2014; Uher et al., 2012; Vrieze et al., 2014). This means that any investigation into the association between apathy and depression should ideally take into account the multidimensionality of both constructs. In other words, the actual relationship is likely to be more complex than is currently known.

Unfortunately, currently available rating scales of depression have been developed based on theoretical accounts for specific aims such as the evaluation of treatment response (van Loo et al., 2012; Vares et al., 2015). There is also insufficient item content to provide a proper multidimensional assessment (Vares et al., 2015). For example, several groups of investigators have found that all the items in the BDI have a large amount of common variance and thus, clustering into separate dimensions for subscale scoring cannot be justified (Al-Turkait and Ohaeri, 2010; Brouwer et al., 2013;

Osman et al., 2008; Quilty et al., 2010; Ward, 2006). The Hamilton Depression Rating Scale (HDRS), another gold standard for assessing depression, has also been found to have poor content validity and an unstable factor structure (Bagby et al., 2004; Salum et al., 2011).

Thus, the construct for depression will need to be clarified before any attempt can be made to eludicate the full multidimensional relationship between apathy and depression. Nevertheless, this could be a worthwhile undertaking for the future as there might be major implications in terms of more effective diagnosis and treatment of these commonly co-occurring and often-confused syndromes.

7.3 Should the option generation task be framed in terms of creative cognition instead?

A second important issue is how to measure generation of options for behaviour. In this thesis I introduced a very simple paradigm that turned out to be useful in probing aspects of behavioural motivation but it is a task that probes option generation in a very limited context. Ineed, one might argue that interpreting paths between two fixed points to be options for behaviour is perhaps a little far-fetched, and instead suggest that the option generation task developed in this thesis is more similar to standard fluency-based creative cognition measures – which require participants to think of as many different uses as possible for common household objects such as a brick or shoe (Guilford, 1967).

Indeed, there remains an important rift between conceiving a new possibility and the status of that possibility as an option for action. While there is a lack of an

operational definition of an option, at least three different notions with varying levels of abstractness have been proposed or assumed by theoretical and empirical studies. At the lowest level of abstraction, variations in kinematic parameters of the same primitive action had been assumed to result in distinguishable options. For example, Raab and colleagues studied handball and basketball players and considered passes to the same player or shots at the opposing goal as distinct options, as long as they varied in trajectories (Johnson and Raab, 2003; Raab et al., 2009; Raab and Johnson, 2007).

A mid-level abstract use of options may be seen in problem-solving tasks that typically allow a range of actions to be performed, such as the various moves deliberated by a player in a particular chess setting (Klein et al., 1995). Although executing the variety of chess moves could be argued simply as a variation in kinematics of the same primitive action, the mental representations in both scenarios are different. To the chess player, the nuances in angle or direction of movement are not what qualify the action as an option.

At the highest level of abstraction, options are construed as a series of temporally extended primitive actions. This commonly occurs in work on hierarchical reinforcement learning (Matthew M. Botvinick et al., 2009; Holroyd and Yeung, 2012). For example, driving a car might involve shifting the gear, stepping on the gas pedal and then turning the steering wheel etc. It is this sequence of primitive actions that would define the option of 'driving' when faced with a problem of how to get to work.

Integrating these different units of representation, options could be construed as elements of action within a hierarchical decision-making structure (Kalis et al.,

2013). In an unconstrained situation such as deciding what to do on a weekend, one might start with highly abstract options such as sightseeing or exercising. Once it has been decided on what to do, say exercising, more concrete options can be developed for which exercises to perform, e.g., running, swimming or boxing. Down at the finest level, the kinematics of the primitive movement may be considered, e.g., how big a stride to make during a run.

Conceptualizing options in this way also means that the process of option generation could also occur at the various corresponding levels. I have chosen to design the option generation task in accordance with generally agreed notions of what an option is by focusing on the *middle level of abstraction* – to generate as many different options as one can to solve a simple problem of connecting two fixed points.

The basic generative processes involved in this task might potentially be the same as those involved in real-life option generation for more complicated problem solving and decision making. Furthermore, the simplicity of this task offers the advantage of being able to control for potential confounds (e.g., working memory load and option selection) – which are rife in verbal and creative fluency tests, or simply asking one to "think about what you can do on a weekend". Moreover, I have assumed that for a newly conceived action to be executed, it must at some point have been a candidate action, competing with other candidates for execution.

On the other hand, it would be stretching the data to make claims of creativity given the narrow domain of creativity examined, and significant differences in the option generation task compared to traditional creativity tasks such as the Alternative Uses Test (Guilford, 1967) and Remote Associations Test (Mednick, 1968).

Furthermore, I did not include any specific, established creativity tasks in the study. As such, the ecological validity of this paradigm as a measure of creativity was not determined here but might be a potentially interesting avenue for future research.

7.4 Role of serotonin in option generation?

A major finding of this thesis was that dopamine modulates how humans generate options for behaviour. While this represents an important advance in understanding the neurochemical basis of option generation, the potential roles of other neurotransmitters, particularly serotonin (5-hydroxytryptamine, 5-HT), remain to be established. Like dopamine, serotonin has been strongly implicated in many aspects of adaptive behaviour including decision-making and reinforcement learning (see review by e.g. Cools et al., 2011).

Serotonergic neurons are mainly found in the raphe nuclei in the brainstem, with the dorsal and median raphe nucleus projecting to widespread areas in the forebrain, notably the cortex, striatum, ventral tegmental area, nucleus accumbens, hypothalamus, hippocampus and septic nuclei (Azmitia and Segal, 1978; Vertes, 1991; Vertes et al., 1999). Activity in these cells have been associated with a variety of functions such as arousal (Sakai and Crochet, 2001), sensorimotor information (Ranade and Mainen, 2009; Waterhouse et al., 2004), reward magnitude (Bromberg-Martin et al., 2010; Nakamura et al., 2008), delay (Miyazaki et al., 2011) and aversive stimuli (Cohen et al., 2015; Hayashi et al., 2015; Schweimer and Ungless, 2010).

There are at least 13 different receptor subtypes for 5-HT (Barnes and Sharp, 1999; Hoyer et al., 2002). Amongst these, the apparent opponency between 5-HT_{2A}

and 5-HT_{2C} had been particularly highlighted. The 5-HT_{2A} receptor was observed to stimulate the release of dopamine within the nucleus accumbens, striatum and prefrontal cortex, while 5-HT_{2C} seems to exert an inhibitory modulation instead (Alex et al., 2005; De Deurwaerdère and Spampinato, 1999; Di Giovanni et al., 1999; Gobert et al., 2000; Millan et al., 1998; Pehek et al., 2006; Porras et al., 2002). This has been suggested to contribute to the contrasting behavioural observation of 5-HT_{2A} activity being associated with greater impulsivity and 5-HT_{2C} being correlated with reduced impulsivity (Fletcher et al., 2007; Robinson et al., 2008; Winstanley et al., 2004).

Indeed, substantial empirical evidence now indicates that 5-HT can modulate the release of dopamine (see reviews by e.g. Kapur et al., 1996; Daw et al., 2002; Boureau and Dayan, 2011). Unfortunately, this relationship is not simple and may vary according to receptor subtypes. Many studies have implicated 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_3 and 5-HT_4 receptors in facilitating the release of dopamine, and 5-HT_{2C} in inhibiting dopamine release (see e.g. Alex and Pehek, 2007; Di Matteo et al., 2008 for reviews). Yet, 5-HT_{2C} may not always decrease dopamine. Constitutive activity of 5-HT_{2C} receptors in the medial prefrontal cortex have been associated with elevated levels of dopamine within the nucleus accumbens following administrations of cocaine, morphine and haloperidol (Leggio et al., 2009a, 2009b). Administration of 5-HT_{1A} agonists have also been found to decrease dopamine release in the nucleus accumbens and striatum (Ichikawa and Meltzer, 2000; Nomikos et al., 1996; Rasmusson et al., 1994). Moreover, it has been demonstrated that activating 5-HT_{1B} receptors in the nucleus accumbens reduced the potentiating influence of d-

amphetamine on responding for conditioned rewards (Fletcher and Korth, 1999). These examples illustrate the complexities of serotonergic regulation of dopamine.

On the other hand, data showing dopaminergic modulation of serotonin release is sparse and unclear (Ferré et al., 1994; Ferré and Artigas, 1993; Matsumoto et al., 1996; Thorré et al., 1998), which might reflect a hierarchical arrangement whereby 5-HT exerts its effects via manipulations of dopamine (Boureau and Dayan, 2011).

This brief literature review reveals that serotonin is intimately related to dopamine and has a similar degree of functional importance. Thus, I predict that serotonin might also influence how humans generate options for behaviour. Understanding this might be important because many disorders linked to dysfunctions of the serotoninergic system, such as depression and schizophrenia, are also associated with a lack of self-generated behaviour (Cowen and Browning, 2015; Eggers, 2013), which may arise from impairments in option generation during decision-making.

7.5 Conclusion

The major contribution of this thesis was the development of a new paradigm of option generation and the demonstration that dopamine plays a key role in influencing how humans generate options for behaviour. The pre-SMA was also found to be involved in planning during volitional action selection and clarifications were provided for the multidimensional structure of apathy in the healthy population and Parkinson's disease. Together, these findings have provided greater insights on the

interlinking fields of voluntary action, apathy and option generation. They also point to new directions for future work in this field.

8 References

Abdulrahman, H., Fletcher, P.C., Bullmore, E., Morcom, A.M., 2017. Dopamine and memory dedifferentiation in aging. NeuroImage 153, 211–220. https://doi.org/10.1016/j.neuroimage.2015.03.031

Abraham, A., Beudt, S., Ott, D.V.M., Yves von Cramon, D., 2012. Creative cognition and the brain: Dissociations between frontal, parietal–temporal and basal ganglia groups. Brain Research 1482, 55–70. https://doi.org/10.1016/j.brainres.2012.09.007

Adam, R., Leff, A., Sinha, N., Turner, C., Bays, P., Draganski, B., Husain, M., 2013. Dopamine reverses reward insensitivity in apathy following globus pallidus lesions. Cortex 49, 1292–1303. https://doi.org/10.1016/j.cortex.2012.04.013

Adelman, L., Gualtieri, J., Stanford, S., 1995. Examining the Effect of Causal Focus on the Option Generation Process: An Experiment Using Protocol Analysis. Organizational Behavior and Human Decision Processes 61, 54–66. https://doi.org/10.1006/obhd.1995.1005

Ahearn, D.J., McDonald, K., Barraclough, M., Leroi, I., 2012. An Exploration of Apathy and Impulsivity in Parkinson Disease. Current Gerontology and Geriatrics Research 2012, 1–10. https://doi.org/10.1155/2012/390701

Aitkin, M., Rubin, D.B., 1985. Estimation and Hypothesis Testing in Finite Mixture Models. Journal of the Royal Statistical Society. Series B (Methodological) 47, 67–75.

Albrecht, D.G., Farrar, S.B., Hamilton, D.B., 1984. Spatial contrast adaptation characteristics of neurones recorded in the cat's visual cortex. J. Physiol. (Lond.) 347, 713–739.

Albuquerque, L., Coelho, M., Martins, M., Guedes, L.C., Rosa, M.M., Ferreira, J.J., Cattoni, M.B., Carvalho, H., Ferreira, A.G., Martins, I.P., 2014. STN-DBS does not change emotion recognition in advanced Parkinson's disease. Parkinsonism Relat. Disord. 20, 166–169. https://doi.org/10.1016/j.parkreldis.2013.10.010

Alex, K.D., Pehek, E.A., 2007. Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. Pharmacol. Ther. 113, 296–320. https://doi.org/10.1016/j.pharmthera.2006.08.004

Alex, K.D., Yavanian, G.J., McFarlane, H.G., Pluto, C.P., Pehek, E.A., 2005. Modulation of dopamine release by striatal 5-HT2C receptors. Synapse 55, 242–251. https://doi.org/10.1002/syn.20109

Al-Turkait, F.A., Ohaeri, J.U., 2010. Dimensional and hierarchical models of depression using the Beck Depression Inventory-II in an Arab college student sample. BMC Psychiatry 10, 60. https://doi.org/10.1186/1471-244X-10-60

Alvarez, J.A., Emory, E., 2006. Executive function and the frontal lobes: a meta-analytic review. Neuropsychol Rev 16, 17–42. https://doi.org/10.1007/s11065-006-9002-x

Anderson, C.A., Arciniegas, D.B., Huddle, D.C., Leehey, M.A., 2003. Akinetic mutism following unilateral anterior cerebral artery occlusion. J Neuropsychiatry Clin Neurosci 15, 385–386. https://doi.org/10.1176/jnp.15.3.385

Andersson, J.L.R., Hutton, C., Ashburner, J., Turner, R., Friston, K., 2001. Modeling Geometric Deformations in EPI Time Series. NeuroImage 13, 903–919. https://doi.org/10.1006/nimg.2001.0746

Ang, Y.-S., Lockwood, P., Apps, M.A.J., Muhammed, K., Husain, M., 2017. Distinct Subtypes of Apathy Revealed by the Apathy Motivation Index. PLOS ONE 12, e0169938. https://doi.org/10.1371/journal.pone.0169938

Apps, M.A.J., Ramnani, N., 2014. The Anterior Cingulate Gyrus Signals the Net Value of Others' Rewards. Journal of Neuroscience 34, 6190–6200. https://doi.org/10.1523/JNEUROSCI.2701-13.2014

Arnsten, A.F., 1998. Catecholamine modulation of prefrontal cortical cognitive function. Trends Cogn. Sci. (Regul. Ed.) 2, 436–447.

Arnsten, A.F., Cai, J.X., Steere, J.C., Goldman-Rakic, P.S., 1995. Dopamine D2 receptor mechanisms contribute to age-related cognitive decline: the effects of quinpirole on memory and motor performance in monkeys. J. Neurosci. 15, 3429–3439.

Ashburner, J., Friston, K.J., 2005. Unified segmentation. Neuroimage 26, 839–851. https://doi.org/10.1016/j.neuroimage.2005.02.018

Azmitia, E.C., Segal, M., 1978. An autoradiographic analysis of the differential ascending projections of the dorsal and median raphe nuclei in the rat. J. Comp. Neurol. 179, 641–667. https://doi.org/10.1002/cne.901790311

Bagby, R.M., Ryder, A.G., Schuller, D.R., Marshall, M.B., 2004. The Hamilton Depression Rating Scale: has the gold standard become a lead weight? Am J Psychiatry 161, 2163–2177. https://doi.org/10.1176/appi.ajp.161.12.2163

Baggio, H.C., Segura, B., Garrido-Millan, J.L., Marti, M.-J., Compta, Y., Valldeoriola, F., Tolosa, E., Junque, C., 2015. Resting-state frontostriatal functional connectivity in Parkinson's disease-related apathy: FRONTOSTRIATAL CONNECTIVITY AND APATHY IN PD. Movement Disorders 30, 671–679. https://doi.org/10.1002/mds.26137

Baldo, J.V., Shimamura, A.P., 1998. Letter and category fluency in patients with frontal lobe lesions. Neuropsychology 12, 259–267.

Baldo, J.V., Shimamura, A.P., Delis, D.C., Kramer, J., Kaplan, E., 2001. Verbal and design fluency in patients with frontal lobe lesions. J Int Neuropsychol Soc 7, 586–596.

Ball, T., Schreiber, A., Feige, B., Wagner, M., Lücking, C.H., Kristeva-Feige, R., 1999. The role of higher-order motor areas in voluntary movement as revealed by high-resolution EEG and fMRI. Neuroimage 10, 682–694. https://doi.org/10.1006/nimg.1999.0507

Barnes, N.M., Sharp, T., 1999. A review of central 5-HT receptors and their function. Neuropharmacology 38, 1083–1152. https://doi.org/10.1016/S0028-3908(99)00010-6

Barnhart, W.J., Makela, E.H., Latocha, M.J., 2004. SSRI-induced apathy syndrome: a clinical review. J Psychiatr Pract 10, 196–199.

Barone, P., Antonini, A., Colosimo, C., Marconi, R., Morgante, L., Avarello, T.P., Bottacchi, E., Cannas, A., Ceravolo, G., Ceravolo, R., Cicarelli, G., Gaglio, R.M., Giglia, R.M., Iemolo, F., Manfredi, M., Meco, G., Nicoletti, A., Pederzoli, M., Petrone, A., Pisani, A., Pontieri, F.E., Quatrale, R., Ramat, S., Scala, R., Volpe, G., Zappulla, S., Bentivoglio, A.R., Stocchi, F., Trianni, G., Dotto, P.D., PRIAMO study group, 2009. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov. Disord. 24, 1641–1649.

Barrett, G., Shibasaki, H., Neshige, R., 1986. Cortical potentials preceding voluntary movement: evidence for three periods of preparation in man. Electroencephalogr Clin Neurophysiol 63, 327–339.

Barron, H.C., Garvert, M.M., Behrens, T.E.J., 2016. Repetition suppression: a means to index neural representations using BOLD? Philosophical Transactions of the Royal Society B: Biological Sciences 371, 20150355. https://doi.org/10.1098/rstb.2015.0355

Bartholomeusz, C.F., Box, G., Van Rooy, C., Nathan, P.J., 2003. The modulatory effects of dopamine D1 and D2 receptor function on object working memory in humans. Journal of Psychopharmacology 17, 9–15. https://doi.org/10.1177/0269881103017001688

Baudry, M., Martres, M.P., Schwartz, J.C., 1977. In vivo binding of 3H-pimozide in mouse striatum: effects of dopamine agonists and antagonists. Life Sci. 21, 1163–1170.

Baylis, G.C., Rolls, E.T., 1987. Responses of neurons in the inferior temporal cortex in short term and serial recognition memory tasks. Exp Brain Res 65, 614–622.

Beck, A.T., Steer, R.A., Ball, R., Ranieri, W.F., 1996. Comparison of Beck Depression Inventories-IA and-II in Psychiatric Outpatients. Journal of Personality Assessment 67, 588–597.

Becker, W., Iwase, K., JüRgens, R., Kornhuber, H.H., 1976. Bereitschaftspotential Preceding Voluntary Slow and Rapid Hand Movements, in: The Responsive Brain. Elsevier, pp. 99–102. https://doi.org/10.1016/B978-0-7236-0443-3.50032-5

Becker, W., Kristeva, R., 1980. Cerebral potentials prior to various force deployments. Prog. Brain Res. 54, 189–194. https://doi.org/10.1016/S0079-6123(08)61624-6

Benjamini, Y., Hochberg, Y., 1995. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society. Series B (Methodological) 57, 289–300.
Benoit, M., Clairet, S., Koulibaly, P.M., Darcourt, J., Robert, P.H., 2004. Brain perfusion correlates of the apathy inventory dimensions of Alzheimer's disease. International Journal of Geriatric Psychiatry 19, 864–869. https://doi.org/10.1002/gps.1163
Benton, A.L., 1968. Differential behavioral effects in frontal lobe disease. Neuropsychologia 6, 53–60. https://doi.org/10.1016/0028-3932(68)90038-9
Bhatia, K.P., Marsden, C.D., 1994. The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain 117, 859–876. https://doi.org/10.1093/brain/117.4.859
Biller, B.M., Molitch, M.E., Vance, M.L., Cannistraro, K.B., Davis, K.R., Simons, J.A., Schoenfelder, J.R., Klibanski, A., 1996. Treatment of prolactin-secreting macroadenomas with the once-weekly dopamine agonist cabergoline. J. Clin. Endocrinol. Metab. 81, 2338–2343. https://doi.org/10.1210/jcem.81.6.8964874
Blakemore, C., Campbell, F.W., 1969. Adaptation to spatial stimuli. J. Physiol. (Lond.) 200, 11P-13P.
Böcker, K.B.E., Brunia, C.H.M., Cluitmans, P.J.M., 1994. A spatio-temporal dipole model of the readiness potential in humans. I. Finger movement. Electroencephalography and Clinical Neurophysiology 91, 275–285. https://doi.org/10.1016/0013-4694(94)90191-0
Bonnelle, V., Manohar, S., Behrens, T., Husain, M., 2016. Individual Differences in Premotor Brain Systems Underlie Behavioral Apathy. Cerebral Cortex 26, bhv247. https://doi.org/10.1093/cercor/bhv247
Bonnelle, V., Veromann, K.-R., Burnett Heyes, S., Lo Sterzo, E., Manohar, S., Husain, M., 2015. Characterization of reward and effort mechanisms in apathy. Journal of Physiology-Paris 109, 16–26.
Boot, N., Baas, M., van Gaal, S., Cools, R., De Dreu, C.K.W., 2017. Creative cognition and dopaminergic modulation of fronto-striatal networks: Integrative review and research agenda. Neuroscience & Biobehavioral Reviews 78, 13–23. https://doi.org/10.1016/j.neubiorev.2017.04.007
Boschert, J., Deecke, L., 1986. Cerebral potentials preceding voluntary toe, knee and hip movements and their vectors in human precentral gyrus. Brain Res. 376, 175–179.
Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S., Cohen, J.D., 2001. Conflict monitoring and cognitive control. Psychol Rev 108, 624–652.
Botvinick, M. M., Huffstetler, S., McGuire, J.T., 2009. Effort discounting in human nucleus accumbens. Cognitive, Affective, & Behavioral Neuroscience 9, 16–27. https://doi.org/10.3758/CABN.9.1.16
Botvinick, Matthew M., Niv, Y., Barto, A.C., 2009. Hierarchically organized behavior and its neural foundations: A reinforcement learning perspective. Cognition 113, 262–280. https://doi.org/10.1016/j.cognition.2008.08.011

Bötzel, K., Plendl, H., Paulus, W., Scherg, M., 1993. Bereitschaftspotential: is there a contribution of the supplementary motor area? Electroencephalogr Clin Neurophysiol 89, 187–196.
Boureau, Y.-L., Dayan, P., 2011. Opponency Revisited: Competition and Cooperation Between Dopamine and Serotonin. Neuropsychopharmacology 36, 74–97. https://doi.org/10.1038/npp.2010.151
Brass, M., Haggard, P., 2008. The What, When, Whether Model of Intentional Action. The Neuroscientist 14, 319–325. https://doi.org/10.1177/1073858408317417
Brass, M., Haggard, P., 2007. To do or not to do: the neural signature of self-control. J. Neurosci. 27, 9141–9145. https://doi.org/10.1523/JNEUROSCI.0924-07.2007
Breitmeyer, B.G., 1985. Problems with the psychophysics of intention. Behavioral and Brain Sciences 8, 539. https://doi.org/10.1017/S0140525X00044915
Bromberg-Martin, E.S., Hikosaka, O., Nakamura, K., 2010. Coding of task reward value in the dorsal raphe nucleus. J. Neurosci. 30, 6262–6272. https://doi.org/10.1523/JNEUROSCI.0015-10.2010
Brouwer, D., Meijer, R.R., Zevalkink, J., 2013. On the factor structure of the Beck Depression Inventory-II: G is the key. Psychol Assess 25, 136–145. https://doi.org/10.1037/a0029228
Brown, R.G., Pluck, G., 2000. Negative symptoms: the 'pathology' of motivation and goal-directed behaviour. Trends in Neurosciences 23, 412–417.
Brozoski, T.J., Brown, R.M., Rosvold, H.E., Goldman, P.S., 1979. Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. Science 205, 929–932.
Bruen, P.D., McGeown, W.J., Shanks, M.F., Venneri, A., 2008. Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimer's disease. Brain 131, 2455–2463. https://doi.org/10.1093/brain/awn151
Buckner, R.L., Goodman, J., Burock, M., Rotte, M., Koutstaal, W., Schacter, D., Rosen, B., Dale, A.M., 1998. Functional-Anatomic Correlates of Object Priming in Humans Revealed by Rapid Presentation Event-Related fMRI. Neuron 20, 285–296. https://doi.org/10.1016/S0896-6273(00)80456-0
Burgess, P.W., 2000. Strategy application disorder: the role of the frontal lobes in human multitasking. Psychol Res 63, 279–288.
Burke, C.J., Brünger, C., Kahnt, T., Park, S.Q., Tobler, P.N., 2013. Neural integration of risk and effort costs by the frontal pole: only upon request. J. Neurosci. 33, 1706-1713a. https://doi.org/10.1523/JNEUROSCI.3662-12.2013
Bymaster, F., Perry, K.W., Nelson, D.L., Wong, D.T., Rasmussen, K., Moore, N.A., Calligaro, D.O., 1999. Olanzapine: a basic science update. Br J Psychiatry Suppl 36–40.
Camps, M., Cortés, R., Gueye, B., Probst, A., Palacios, J.M., 1989. Dopamine receptors in human brain: Autoradiographic distribution of D2 sites. Neuroscience 28, 275–290. https://doi.org/10.1016/0306-4522(89)90179-6
Carlsson, I., Wendt, P.E., Risberg, J., 2000. On the neurobiology of creativity. Differences in frontal activity between high and low creative subjects. Neuropsychologia 38, 873–885.

Carpenter, P.A., Just, M.A., Shell, P., 1990. What one intelligence test measures: a theoretical account of the processing in the Raven Progressive Matrices Test. Psychol Rev 97, 404–431.

Carriere, N., Besson, P., Dujardin, K., Duhamel, A., Defebvre, L., Delmaire, C., Devos, D., 2014. Apathy in Parkinson's disease is associated with nucleus accumbens atrophy: A magnetic resonance imaging shape analysis: An Mri Shape Analysis. Movement Disorders 29, 897–903. https://doi.org/10.1002/mds.25904

Carter, C.S., Braver, T.S., Barch, D.M., Botvinick, M.M., Noll, D., Cohen, J.D., 1998. Anterior cingulate cortex, error detection, and the online monitoring of performance. Science 280, 747–749.

Cattell, R.B., 1966. The Scree Test For The Number Of Factors. Multivariate Behavioral Research 1, 245–276.

Channon, S., Crawford, S., 1999. Problem-solving in real-life-type situations: the effects of anterior and posterior lesions on performance. Neuropsychologia 37, 757–770.

Chávez-Eakle, R.A., Graff-Guerrero, A., García-Reyna, J.-C., Vaugier, V., Cruz-Fuentes, C., 2007. Cerebral blood flow associated with creative performance: a comparative study. Neuroimage 38, 519–528. https://doi.org/10.1016/j.neuroimage.2007.07.059

Chen, Y.-C., Thaler, D., Nixon, P.D., Stern, C.E., Passingham, R.E., 1995. The functions of the medial premotor cortex: II. The timing and selection of learned movements. Experimental Brain Research 102. https://doi.org/10.1007/BF00230650

Chong, T.T.-J., Apps, M., Giehl, K., Sillence, A., Grima, L.L., Husain, M., 2017. Neurocomputational mechanisms underlying subjective valuation of effort costs. PLOS Biology 15, e1002598. https://doi.org/10.1371/journal.pbio.1002598

Chong, T.T.-J., Bonnelle, V., Husain, M., 2016. Quantifying motivation with effort-based decision-making paradigms in health and disease., in: Progress in Brain Research. Elsevier, Amsterdam, pp. 71–100.

Chong, T.T.-J., Cunnington, R., Williams, M.A., Kanwisher, N., Mattingley, J.B., 2008. fMRI Adaptation Reveals Mirror Neurons in Human Inferior Parietal Cortex. Current Biology 18, 1576–1580. https://doi.org/10.1016/j.cub.2008.08.068

Churchland, M.M., 2006. Neural Variability in Premotor Cortex Provides a Signature of Motor Preparation. Journal of Neuroscience 26, 3697–3712. https://doi.org/10.1523/JNEUROSCI.3762-05.2006

Cisek, P., Kalaska, J.F., 2005. Neural Correlates of Reaching Decisions in Dorsal Premotor Cortex: Specification of Multiple Direction Choices and Final Selection of Action. Neuron 45, 801–814. https://doi.org/10.1016/j.neuron.2005.01.027

Clatworthy, P.L., Lewis, S.J.G., Brichard, L., Hong, Y.T., Izquierdo, D., Clark, L., Cools, R., Aigbirhio, F.I., Baron, J.-C., Fryer, T.D., Robbins, T.W., 2009. Dopamine release in dissociable striatal subregions predicts the different effects of oral methylphenidate on reversal learning and spatial working memory. J. Neurosci. 29, 4690–4696. https://doi.org/10.1523/JNEUROSCI.3266-08.2009

Cochrane, G.D., Rizvi, S., Abrantes, A.M., Crabtree, B., Cahill, J., Friedman, J.H., 2015. The association between fatigue and apathy in patients with either Parkinson's disease or multiple sclerosis. Parkinsonism & Related Disorders 21, 1093–1095.
Cohen, J.D., Perlstein, W.M., Braver, T.S., Nystrom, L.E., Noll, D.C., Jonides, J., Smith, E.E., 1997. Temporal dynamics of brain activation during a working memory task. Nature 386, 604–608. https://doi.org/10.1038/386604a0
Cohen, J.Y., Amoroso, M.W., Uchida, N., 2015. Serotonergic neurons signal reward and punishment on multiple timescales. eLife 4. https://doi.org/10.7554/eLife.06346
Cohen Kadosh, R., Cohen Kadosh, K., Kaas, A., Henik, A., Goebel, R., 2007. Notation-Dependent and -Independent Representations of Numbers in the Parietal Lobes. Neuron 53, 307–314. https://doi.org/10.1016/j.neuron.2006.12.025
Cohen, M.X., Ranganath, C., 2007. Reinforcement learning signals predict future decisions. J. Neurosci. 27, 371–378. https://doi.org/10.1523/JNEUROSCI.4421-06.2007
Cohen-Kashi Malina, K., Jubran, M., Katz, Y., Lampl, I., 2013. Imbalance between excitation and inhibition in the somatosensory cortex produces postadaptation facilitation. J. Neurosci. 33, 8463–8471. https://doi.org/10.1523/JNEUROSCI.4845-12.2013
Colao, A., Lombardi, G., Annunziato, L., 2000. Cabergoline. Expert Opinion on Pharmacotherapy 1, 555–574. https://doi.org/10.1517/14656566.1.3.555
Cools, R., D'Esposito, M., 2011. Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol. Psychiatry 69, e113-125. https://doi.org/10.1016/j.biopsych.2011.03.028
Cools, R., Nakamura, K., Daw, N.D., 2011. Serotonin and dopamine: unifying affective, activational, and decision functions. Neuropsychopharmacology 36, 98–113. https://doi.org/10.1038/npp.2010.121
Cooper, J.R., Bloom, F.E., Roth, R.H., 2003. The biochemical basis of neuropharmacology, 8th ed. ed. Oxford University Press, Oxford ; New York.
Corsello, S.M., Ubertini, G., Altomare, M., Lovicu, R.M., Migneco, M.G., Rota, C.A., Colosimo, C., 2003. Giant prolactinomas in men: efficacy of cabergoline treatment. Clin. Endocrinol. (Oxf) 58, 662–670.
Coslett, H.B., Bowers, D., Verfaellie, M., Heilman, K.M., 1991. Frontal verbal amnesia. Phonological amnesia. Arch. Neurol. 48, 949–955.
Cousins, M.S., Atherton, A., Turner, L., Salamone, J.D., 1996. Nucleus accumbens dopamine depletions alter relative response allocation in a T-maze cost/benefit task. Behav. Brain Res. 74, 189–197.
Cousins, M.S., Sokolowski, J.D., Salamone, J.D., 1993. Different effects of nucleus accumbens and ventrolateral striatal dopamine depletions on instrumental response selection in the rat. Pharmacol. Biochem. Behav. 46, 943–951.
Cousins, M.S., Wei, W., Salamone, J.D., 1994. Pharmacological characterization of performance on a concurrent lever pressing/feeding choice procedure: effects of dopamine antagonist, cholinomimetic, sedative and stimulant drugs. Psychopharmacology (Berl.) 116, 529–537.
Cowen, P.J., Browning, M., 2015. What has serotonin to do with depression? World Psychiatry 14, 158–160. https://doi.org/10.1002/wps.20229

Croxson, P.L., Walton, M.E., O'Reilly, J.X., Behrens, T.E.J., Rushworth, M.F.S., 2009. Effort-Based Cost-Benefit Valuation and the Human Brain. Journal of Neuroscience 29, 4531–4541. https://doi.org/10.1523/JNEUROSCI.4515-08.2009

Cui, R.Q., Deecke, L., 1999. High resolution DC-EEG of the Bereitschaftspotential preceding anatomically congruent versus spatially congruent bimanual finger movements. Brain Topogr 12, 117–127.

Cui, R.Q., Huter, D., Lang, W., Deecke, L., 1999. Neuroimage of Voluntary Movement: Topography of the Bereitschaftspotential, a 64-Channel DC Current Source Density Study. NeuroImage 9, 124–134. https://doi.org/10.1006/nimg.1998.0388

Culham, J.C., Kanwisher, N.G., 2001. Neuroimaging of cognitive functions in human parietal cortex. Current Opinion in Neurobiology 11, 157–163. https://doi.org/10.1016/S0959-4388(00)00191-4

Cummings, J.L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D.A., Gornbein, J., 1994. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 44, 2308–2314.

Cunnington, R., Iansek, R., Bradshaw, J.L., Phillips, J.G., 1995. Movement-related potentials in Parkinson's disease. Presence and predictability of temporal and spatial cues. Brain 118 (Pt 4), 935–950.

Cunnington, R., Windischberger, C., Deecke, L., Moser, E., 2003. The preparation and readiness for voluntary movement: a high-field event-related fMRI study of the Bereitschafts-BOLD response. Neuroimage 20, 404–412.

Cunnington, R., Windischberger, C., Deecke, L., Moser, E., 2002. The Preparation and Execution of Self-Initiated and Externally-Triggered Movement: A Study of Event-Related fMRI. NeuroImage 15, 373–385. https://doi.org/10.1006/nimg.2001.0976

Cunnington, R., Windischberger, C., Robinson, S., Moser, E., 2006. The selection of intended actions and the observation of others' actions: A time-resolved fMRI study. NeuroImage 29, 1294–1302. https://doi.org/10.1016/j.neuroimage.2005.09.028

Dan, R., Růžička, F., Bezdicek, O., Růžička, E., Roth, J., Vymazal, J., Goelman, G., Jech, R., 2017. Separate neural representations of depression, anxiety and apathy in Parkinson's disease. Scientific Reports 7. https://doi.org/10.1038/s41598-017-12457-6

Daw, N.D., Kakade, S., Dayan, P., 2002. Opponent interactions between serotonin and dopamine. Neural Netw 15, 603–616.

De Deurwaerdère, P., Spampinato, U., 1999. Role of serotonin(2A) and serotonin(2B/2C) receptor subtypes in the control of accumbal and striatal dopamine release elicited in vivo by dorsal raphe nucleus electrical stimulation. J. Neurochem. 73, 1033–1042.

de Manzano, Ö., Cervenka, S., Karabanov, A., Farde, L., Ullén, F., 2010. Thinking Outside a Less Intact Box: Thalamic Dopamine D2 Receptor Densities Are Negatively Related to Psychometric Creativity in Healthy Individuals. PLoS ONE 5, e10670. https://doi.org/10.1371/journal.pone.0010670

de Souza, L.C., Volle, E., Bertoux, M., Czernecki, V., Funkiewiez, A., Allali, G., Leroy, B., Sarazin, M., Habert, M.-O., Dubois, B., Kas, A., Levy, R., 2010. Poor creativity in frontotemporal dementia: A window into the neural bases of the creative mind. Neuropsychologia 48, 3733–3742. https://doi.org/10.1016/j.neuropsychologia.2010.09.010

Debaere, F., Wenderoth, N., Sunaert, S., Van Hecke, P., Swinnen, S.P., 2003. Internal vs external generation of movements: differential neural pathways involved in bimanual coordination performed in the presence or absence of augmented visual feedback. NeuroImage 19, 764–776. https://doi.org/10.1016/S1053-8119(03)00148-4

Deiber, M.-P., Honda, M., Ibañez, V., Sadato, N., Hallett, M., 1999. Mesial Motor Areas in Self-Initiated Versus Externally Triggered Movements Examined With fMRI: Effect of Movement Type and Rate. Journal of Neurophysiology 81, 3065–3077. https://doi.org/10.1152/jn.1999.81.6.3065

Deiber, M.P., Ibanez, V., Sadato, N., Hallett, M., 1996. Cerebral structures participating in motor preparation in humans: a positron emission tomography study. Journal of Neurophysiology 75, 233–247. https://doi.org/10.1152/jn.1996.75.1.233

Deiber, M.P., Passingham, R.E., Colebatch, J.G., Friston, K.J., Nixon, P.D., Frackowiak, R.S., 1991. Cortical areas and the selection of movement: a study with positron emission tomography. Exp Brain Res 84, 393–402.

Del Missier, F., Visentini, M., MÃ¤ntylÃ¤, T., 2015. Option generation in decision making: ideation beyond memory retrieval. Frontiers in Psychology 5. https://doi.org/10.3389/fpsyg.2014.01584

Del-Monte, J., Bayard, S., Graziani, P., Gély-Nargeot, M.C., 2017. Cognitive, Emotional, and Auto-Activation Dimensions of Apathy in Parkinson's Disease. Frontiers in Behavioral Neuroscience 11. https://doi.org/10.3389/fnbeh.2017.00230

den Brok, M.G.H.E., van Dalen, J.W., van Gool, W.A., Moll van Charante, E.P., de Bie, R.M.A., Richard, E., 2015. Apathy in Parkinson's disease: A systematic review and meta-analysis. Mov. Disord. 30, 759–769. https://doi.org/10.1002/mds.26208

Denk, F., Walton, M.E., Jennings, K.A., Sharp, T., Rushworth, M.F.S., Bannerman, D.M., 2005. Differential involvement of serotonin and dopamine systems in cost-benefit decisions about delay or effort. Psychopharmacology (Berl.) 179, 587–596. https://doi.org/10.1007/s00213-004-2059-4

Desmurget, M., Reilly, K.T., Richard, N., Szathmari, A., Mottolese, C., Sirigu, A., 2009. Movement intention after parietal cortex stimulation in humans. Science 324, 811–813. https://doi.org/10.1126/science.1169896

Desmurget, M., Sirigu, A., 2009. A parietal-premotor network for movement intention and motor awareness. Trends in Cognitive Sciences 13, 411–419. https://doi.org/10.1016/j.tics.2009.08.001

D'Esposito, M., Aguirre, G.K., Zarahn, E., Ballard, D., Shin, R.K., Lease, J., 1998. Functional MRI studies of spatial and nonspatial working memory. Brain Res Cogn Brain Res 7, 1–13.

D'Esposito, M., Postle, B.R., Rypma, B., 2000. Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. Exp Brain Res 133, 3–11. https://doi.org/10.1007/s002210000395

Di Giovanni, G., De Deurwaerdére, P., Di Mascio, M., Di Matteo, V., Esposito, E., Spampinato, U., 1999. Selective blockade of serotonin-2C/2B receptors enhances mesolimbic and mesostriatal dopaminergic function: a combined in vivo electrophysiological and microdialysis study. Neuroscience 91, 587–597.

Di Matteo, V., Di Giovanni, G., Pierucci, M., Esposito, E., 2008. Serotonin control of central dopaminergic function: focus on in vivo microdialysis studies. Prog. Brain Res. 172, 7–44. https://doi.org/10.1016/S0079-6123(08)00902-3

Dietrich, A., Kanso, R., 2010. A review of EEG, ERP, and neuroimaging studies of creativity and insight. Psychological Bulletin 136, 822–848. https://doi.org/10.1037/a0019749

Doeller, C.F., Barry, C., Burgess, N., 2010. Evidence for grid cells in a human memory network. Nature 463, 657–661. https://doi.org/10.1038/nature08704

Drijgers, R.L., Dujardin, K., Reijnders, J.S.A.M., Defebvre, L., Leentjens, A.F.G., 2010. Validation of diagnostic criteria for apathy in Parkinson's disease. Parkinsonism & Related Disorders 16, 656–660. https://doi.org/10.1016/j.parkreldis.2010.08.015

Dujardin, K., Degreef, J.F., Rogelet, P., Defebvre, L., Destee, A., 1999. Impairment of the supervisory attentional system in early untreated patients with Parkinson's disease. J. Neurol. 246, 783–788.

Duncan, J., 2010. The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. Trends Cogn. Sci. (Regul. Ed.) 14, 172–179. https://doi.org/10.1016/j.tics.2010.01.004

Eccles, J.C., 1982. The initiation of voluntary movements by the supplementary motor area. Arch Psychiatr Nervenkr (1970) 231, 423–441.

Eggers, A.E., 2013. A serotonin hypothesis of schizophrenia. Med. Hypotheses 80, 791–794. https://doi.org/10.1016/j.mehy.2013.03.013

Engelborghs, S., Marien, P., Pickut, B.A., Verstraeten, S., De Deyn, P.P., 2000. Loss of Psychic Self-Activation After Paramedian Bithalamic Infarction. Stroke 31, 1762–1765. https://doi.org/10.1161/01.STR.31.7.1762

Eriksen, C.W., 1995. The flankers task and response competition: A useful tool for investigating a variety of cognitive problems. Visual Cognition 2, 101–118. https://doi.org/10.1080/13506289508401726

Eslinger, P., Peachie, M., Shweta, A., Chivon, A., Murray, G., 2012. Apathy in frontotemporal dementia: Behavioral and neuroimaging correlates. Behavioural Neurology 127–136. https://doi.org/10.3233/BEN-2011-0351

Eslinger, P.J., Damasio, A.R., 1985. Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. Neurology 35, 1731–1741.

Evensen, J., Røssberg, J.I., Barder, H., Haahr, U., Hegelstad, W. ten V., Joa, I., Johannessen, J.O., Larsen, T.K., Melle, I., Opjordsmoen, S., Rund, B.R., Simonsen, E., Sundet, K., Vaglum, P., Friis, S., McGlashan, T., 2012. Apathy in first episode psychosis patients: A ten year longitudinal follow-up study. Schizophrenia Research 136, 19–24. https://doi.org/10.1016/j.schres.2011.12.019

Everitt, B.J., Robbins, T.W., 2005. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nature Neuroscience 8, 1481–1489.
Fallon, J.H., Moore, R.Y., 1978. Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. J. Comp. Neurol. 180, 545–580. https://doi.org/10.1002/cne.901800310
Farrar, A.M., Font, L., Pereira, M., Mingote, S., Bunce, J.G., Chrobak, J.J., Salamone, J.D., 2008. Forebrain circuitry involved in effort-related choice: Injections of the GABAA agonist muscimol into ventral pallidum alter response allocation in food-seeking behavior. Neuroscience 152, 321–330. https://doi.org/10.1016/j.neuroscience.2007.12.034
Farrar, A.M., Pereira, M., Velasco, F., Hockemeyer, J., Müller, C.E., Salamone, J.D., 2007. Adenosine A(2A) receptor antagonism reverses the effects of dopamine receptor antagonism on instrumental output and effort-related choice in the rat: implications for studies of psychomotor slowing. Psychopharmacology (Berl.) 191, 579–586. https://doi.org/10.1007/s00213-006-0554-5
Farrar, A.M., Segovia, K.N., Randall, P.A., Nunes, E.J., Collins, L.E., Stopper, C.M., Port, R.G., Hockemeyer, J., Müller, C.E., Correa, M., Salamone, J.D., 2010. Nucleus accumbens and effort-related functions: behavioral and neural markers of the interactions between adenosine A2A and dopamine D2 receptors. Neuroscience 166, 1056–1067. https://doi.org/10.1016/j.neuroscience.2009.12.056
Faust-Socher, A., Kenett, Y.N., Cohen, O.S., Hassin-Baer, S., Inzelberg, R., 2014. Enhanced creative thinking under dopaminergic therapy in Parkinson disease: Creative Thinking in PD. Annals of Neurology 75, 935–942. https://doi.org/10.1002/ana.24181
Ferré, S., Artigas, F., 1993. Dopamine D2 receptor-mediated regulation of serotonin extracellular concentration in the dorsal raphe nucleus of freely moving rats. J. Neurochem. 61, 772–775.
Ferré, S., Cortés, R., Artigas, F., 1994. Dopaminergic regulation of the serotonergic raphe-striatal pathway: microdialysis studies in freely moving rats. J. Neurosci. 14, 4839–4846.
Fink, A., Benedek, M., 2014. EEG alpha power and creative ideation. Neuroscience & Biobehavioral Reviews 44, 111–123. https://doi.org/10.1016/j.neubiorev.2012.12.002
Fink, A., Grabner, R.H., Benedek, M., Reishofer, G., Hauswirth, V., Fally, M., Neuper, C., Ebner, F., Neubauer, A.C., 2009. The creative brain: investigation of brain activity during creative problem solving by means of EEG and FMRI. Hum Brain Mapp 30, 734–748. https://doi.org/10.1002/hbm.20538
Finke, R.A., Ward, T.B., Smith, S.M., 1992. Creative cognition: theory, research, and applications. MIT Press, Cambridge, Mass.
Fletcher, P.J., Korth, K.M., 1999. Activation of 5-HT1B receptors in the nucleus accumbens reduces amphetamine-induced enhancement of responding for conditioned reward. Psychopharmacology (Berl.) 142, 165–174.
Fletcher, P.J., Tampakeras, M., Sinyard, J., Higgins, G.A., 2007. Opposing effects of 5-HT(2A) and 5-HT(2C) receptor antagonists in the rat and mouse on premature

responding in the five-choice serial reaction time test. Psychopharmacology (Berl.) 195, 223–234. https://doi.org/10.1007/s00213-007-0891-z
Floresco, S.B., Ghods-Sharifi, S., 2007. Amygdala-Prefrontal Cortical Circuitry Regulates Effort-Based Decision Making. Cerebral Cortex 17, 251–260. https://doi.org/10.1093/cercor/bhj143
Floresco, S.B., Magyar, O., 2006. Mesocortical dopamine modulation of executive functions: beyond working memory. Psychopharmacology (Berl.) 188, 567–585. https://doi.org/10.1007/s00213-006-0404-5
Font, L., Mingote, S., Farrar, A.M., Pereira, M., Worden, L., Stopper, C., Port, R.G., Salamone, J.D., 2008. Intra-accumbens injections of the adenosine A2A agonist CGS 21680 affect effort-related choice behavior in rats. Psychopharmacology (Berl.) 199, 515–526. https://doi.org/10.1007/s00213-008-1174-z
Frank, M.J., O'Reilly, R.C., 2006. A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. Behav. Neurosci. 120, 497–517. https://doi.org/10.1037/0735-7044.120.3.497
Franken, I.H.A., Rassin, E., Muris, P., 2007. The assessment of anhedonia in clinical and non-clinical populations: Further validation of the Snaith–Hamilton Pleasure Scale (SHAPS). Journal of Affective Disorders 99, 83–89.
Frith, C.D., Friston, K., Liddle, P.F., Frackowiak, R.S.J., 1991. Willed Action and the Prefrontal Cortex in Man: A Study with PET. Proceedings of the Royal Society B: Biological Sciences 244, 241–246. https://doi.org/10.1098/rspb.1991.0077
Fuller, R.W., Clemens, J.A., Hynes, M.D., 1982. Degree of selectivity of pergolide as an agonist at presynaptic versus postsynaptic dopamine receptors: implications for prevention or treatment of tardive dyskinesia. J Clin Psychopharmacol 2, 371–375.
Gard, D.E., Gard, M.G., Kring, A.M., John, O.P., 2006. Anticipatory and consummatory components of the experience of pleasure: A scale development study. Journal of Research in Personality 40, 1086–1102. https://doi.org/10.1016/j.jrp.2005.11.001
Garvert, M.M., Moutoussis, M., Kurth-Nelson, Z., Behrens, T.E.J., Dolan, R.J., 2015. Learning-Induced Plasticity in Medial Prefrontal Cortex Predicts Preference Malleability. Neuron 85, 418–428. https://doi.org/10.1016/j.neuron.2014.12.033
Gentilucci, M., Fogassi, L., Luppino, G., Matelli, M., Camarda, R., Rizzolatti, G., 1988. Functional organization of inferior area 6 in the macaque monkey. I. Somatotopy and the control of proximal movements. Exp Brain Res 71, 475–490.
Gerace, C., Corsi, F.M., Comanducci, G., 2013. Apathetic syndrome from carotid dissection: a dangerous condition. Case Reports 2013, bcr2013009686–bcr2013009686. https://doi.org/10.1136/bcr-2013-009686
Gerfen, C.R., 1992. The neostriatal mosaic: multiple levels of compartmental organization. Trends Neurosci. 15, 133–139.
Gerlach, M., Double, K., Arzberger, T., Leblhuber, F., Tatschner, T., Riederer, P., 2003. Dopamine receptor agonists in current clinical use: comparative dopamine

receptor binding profiles defined in the human striatum. Journal of Neural Transmission 110, 1119–1127. https://doi.org/10.1007/s00702-003-0027-5
Gettys, C.F., Pliske, R.M., Manning, C., Casey, J.T., 1987. An evaluation of human act generation performance. Organizational Behavior and Human Decision Processes 39, 23–51. https://doi.org/10.1016/0749-5978(87)90044-6
Ghika-Schmid, F., Bogousslavsky, J., 2000. The acute behavioral syndrome of anterior thalamic infarction: a prospective study of 12 cases. Ann. Neurol. 48, 220–227.
Gibbs, S.E.B., D'Esposito, M., 2005. A functional MRI study of the effects of bromocriptine, a dopamine receptor agonist, on component processes of working memory. Psychopharmacology 180, 1–10. https://doi.org/10.1007/s00213-005-0077-5
Gibson, C., Folley, B.S., Park, S., 2009. Enhanced divergent thinking and creativity in musicians: a behavioral and near-infrared spectroscopy study. Brain Cogn 69, 162–169. https://doi.org/10.1016/j.bandc.2008.07.009
Glimcher, P.W., Fehr, E. (Eds.), 2014. Neuroeconomics: decision making and the brain, Second edition. ed. Elsevier/AP, Academic Press is an imprint of Elsevier, Amsterdam : Boston.
Gobert, A., Rivet, J.M., Lejeune, F., Newman-Tancredi, A., Adhumeau-Auclair, A., Nicolas, J.P., Cistarelli, L., Melon, C., Millan, M.J., 2000. Serotonin(2C) receptors tonically suppress the activity of mesocortical dopaminergic and adrenergic, but not serotonergic, pathways: a combined dialysis and electrophysiological analysis in the rat. Synapse 36, 205–221. https://doi.org/10.1002/(SICI)1098-2396(20000601)36:3<205::AID-SYN5>3.0.CO;2-D
Goel, V., 2010. Neural basis of thinking: laboratory problems versus real-world problems: Neural basis of thinking. Wiley Interdisciplinary Reviews: Cognitive Science 1, 613–621. https://doi.org/10.1002/wcs.71
Goel, V., Grafman, J., Tajik, J., Gana, S., Danto, D., 1997. A study of the performance of patients with frontal lobe lesions in a financial planning task. Brain 120 (Pt 10), 1805–1822.
Goldberg, G., 1985. Supplementary motor area structure and function: Review and hypotheses. Behavioral and Brain Sciences 8, 567. https://doi.org/10.1017/S0140525X00045167
Goldman-Rakic, P.S., 1995. Architecture of the prefrontal cortex and the central executive. Ann. N. Y. Acad. Sci. 769, 71–83.
Goldman-Rakic, P.S., 1992. Working memory and the mind. Sci. Am. 267, 110–117.
Gomes, G., 2002. The Interpretation of Libet's Results on the Timing of Conscious Events: A Commentary. Consciousness and Cognition 11, 221–230. https://doi.org/10.1006/ccog.2002.0556
Gomes, G., 1998. The Timing of Conscious Experience: A Critical Review and Reinterpretation of Libet's Research. Consciousness and Cognition 7, 559–595. https://doi.org/10.1006/ccog.1998.0332
Gonen-Yaacovi, G., de Souza, L.C., Levy, R., Urbanski, M., Josse, G., Volle, E., 2013. Rostral and caudal prefrontal contribution to creativity: a meta-analysis of functional imaging data. Frontiers in Human Neuroscience 7. https://doi.org/10.3389/fnhum.2013.00465

Grace, A.A., 1991. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience 41, 1–24.
Gray, H.M., Tickle-Degnen, L., 2010. A meta-analysis of performance on emotion recognition tasks in Parkinson's disease. Neuropsychology 24, 176–191. https://doi.org/10.1037/a0018104
Graziano, M., Yap, G., Gross, C., 1994. Coding of visual space by premotor neurons. Science 266, 1054–1057. https://doi.org/10.1126/science.7973661
Graziano, M.S., Gross, C.G., 1993. A bimodal map of space: somatosensory receptive fields in the macaque putamen with corresponding visual receptive fields. Exp Brain Res 97, 96–109.
Graziano, M.S.A., Reiss, L.A.J., Gross, C.G., 1999. A neuronal representation of the location of nearby sounds. Nature 397, 428–430. https://doi.org/10.1038/17115
Grill-Spector, K., Kushnir, T., Edelman, S., Avidan, G., Itzchak, Y., Malach, R., 1999. Differential Processing of Objects under Various Viewing Conditions in the Human Lateral Occipital Complex. Neuron 24, 187–203. https://doi.org/10.1016/S0896-6273(00)80832-6
Gross, C.G., Bender, D.B., Rocha-Miranda, C.E., 1969. Visual receptive fields of neurons in inferotemporal cortex of the monkey. Science 166, 1303–1306.
Gross, C.G., Schiller, P.H., Wells, C., Gerstein, G.L., 1967. Single-unit activity in temporal association cortex of the monkey. Journal of Neurophysiology 30, 833–843. https://doi.org/10.1152/jn.1967.30.4.833
Guilford, J.P., 1967. The Nature of Human Intelligence. McGraw-Hill, New York.
Haggard, P., 2009. The Sources of Human Volition. Science 324, 731–733. https://doi.org/10.1126/science.1173827
Haggard, P., 2008. Human volition: towards a neuroscience of will. Nature Reviews Neuroscience 9, 934–946. https://doi.org/10.1038/nrn2497
Haggard, P., Eimer, M., 1999. On the relation between brain potentials and the awareness of voluntary movements. Exp Brain Res 126, 128–133.
Hahn, C., Lim, H.-K., Won, W.Y., Ahn, K.J., Jung, W.-S., Lee, C.U., 2013. Apathy and White Matter Integrity in Alzheimer's Disease: A Whole Brain Analysis with Tract-Based Spatial Statistics. PLoS ONE 8, e53493. https://doi.org/10.1371/journal.pone.0053493
Hartmann, M.N., Hager, O.M., Reimann, A.V., Chumbley, J.R., Kirschner, M., Seifritz, E., Tobler, P.N., Kaiser, S., 2015. Apathy But Not Diminished Expression in Schizophrenia Is Associated With Discounting of Monetary Rewards by Physical Effort. Schizophrenia Bulletin 41, 503–512. https://doi.org/10.1093/schbul/sbu102
Hayashi, K., Nakao, K., Nakamura, K., 2015. Appetitive and aversive information coding in the primate dorsal raphé nucleus. J. Neurosci. 35, 6195–6208. https://doi.org/10.1523/JNEUROSCI.2860-14.2015
Hayden, B.Y., Heilbronner, S.R., Pearson, J.M., Platt, M.L., 2011. Surprise Signals in Anterior Cingulate Cortex: Neuronal Encoding of Unsigned Reward Prediction Errors Driving Adjustment in Behavior. Journal of Neuroscience 31, 4178–4187. https://doi.org/10.1523/JNEUROSCI.4652-10.2011

Henry, J.D., Crawford, J.R., 2004. A meta-analytic review of verbal fluency performance following focal cortical lesions. Neuropsychology 18, 284–295. https://doi.org/10.1037/0894-4105.18.2.284

Hills, T.T., Todd, P.M., Jones, M.N., 2015. Foraging in Semantic Fields: How We Search Through Memory. Topics in Cognitive Science 7, 513–534. https://doi.org/10.1111/tops.12151

Hollocks, M.J., Lawrence, A.J., Brookes, R.L., Barrick, T.R., Morris, R.G., Husain, M., Markus, H.S., 2015. Differential relationships between apathy and depression with white matter microstructural changes and functional outcomes. Brain 138, 3803–3815. https://doi.org/10.1093/brain/awv304

Holroyd, C.B., Coles, M.G.H., 2008. Dorsal anterior cingulate cortex integrates reinforcement history to guide voluntary behavior. Cortex 44, 548–559. https://doi.org/10.1016/j.cortex.2007.08.013

Holroyd, C.B., Yeung, N., 2012. Motivation of extended behaviors by anterior cingulate cortex. Trends in Cognitive Sciences 16, 122–128. https://doi.org/10.1016/j.tics.2011.12.008

Holthoff, V.A., Beuthien-Baumann, B., Kalbe, E., Lüdecke, S., Lenz, O., Zündorf, G., Spirling, S., Schierz, K., Winiecki, P., Sorbi, S., Herholz, K., 2005. Regional cerebral metabolism in early Alzheimer's disease with clinically significant apathy or depression. Biological Psychiatry 57, 412–421. https://doi.org/10.1016/j.biopsych.2004.11.035

Honey, G.D., Suckling, J., Zelaya, F., Long, C., Routledge, C., Jackson, S., Ng, V., Fletcher, P.C., Williams, S.C.R., Brown, J., Bullmore, E.T., 2003. Dopaminergic drug effects on physiological connectivity in a human cortico-striato-thalamic system. Brain 126, 1767–1781. https://doi.org/10.1093/brain/awg184

Hoyer, D., Hannon, J.P., Martin, G.R., 2002. Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol. Biochem. Behav. 71, 533–554.

Hsieh, S., Schubert, S., Hoon, C., Mioshi, E., Hodges, J.R., 2013. Validation of the Addenbrooke's Cognitive Examination III in Frontotemporal Dementia and Alzheimer's Disease. Dementia and Geriatric Cognitive Disorders 36, 242–250. https://doi.org/10.1159/000351671

Hu, L., Bentler, P.M., 1999. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Structural Equation Modeling: A Multidisciplinary Journal 6, 1–55.

Huang, C., Ravdin, L.D., Nirenberg, M.J., Piboolnurak, P., Severt, L., Maniscalco, J.S., Solnes, L., Dorfman, B.J., Henchcliffe, C., 2013. Neuroimaging Markers of Motor and Nonmotor Features of Parkinson's Disease: An [^{18} F]Fluorodeoxyglucose Positron Emission Computed Tomography Study. Dementia and Geriatric Cognitive Disorders 35, 183–196. https://doi.org/10.1159/000345987

Husain, M., Mehta, M.A., 2011. Cognitive enhancement by drugs in health and disease. Trends Cogn. Sci. (Regul. Ed.) 15, 28–36. https://doi.org/10.1016/j.tics.2010.11.002

Hutton, C., Bork, A., Josephs, O., Deichmann, R., Ashburner, J., Turner, R., 2002. Image distortion correction in fMRI: A quantitative evaluation. Neuroimage 16, 217–240. https://doi.org/10.1006/nimg.2001.1054

Ichikawa, J., Meltzer, H.Y., 2000. The effect of serotonin1A receptor agonism on antipsychotic drug-induced dopamine release in rat striatum and nucleus accumbens. Brain Research 858, 252–263. https://doi.org/10.1016/S0006-8993(99)02346-X

Isella, V., Iurlaro, S., Piolti, R., Ferrarese, C., Frattola, L., Appollonio, I., Melzi, P., Grimaldi, M., 2003. Physical anhedonia in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 74, 1308–1311.

Jaber, M., Robinson, S.W., Missale, C., Caron, M.G., 1996. Dopamine receptors and brain function. Neuropharmacology 35, 1503–1519.

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. https://doi.org/10.1006/nimg.2000.0647

Jahanshahi, M., Jenkins, I.H., Brown, R.G., Marsden, C.D., Passingham, R.E., Brooks, D.J., 1995. Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. Brain 118 (Pt 4), 913–933.

Jahn, A., Nee, D.E., Alexander, W.H., Brown, J.W., 2016. Distinct Regions within Medial Prefrontal Cortex Process Pain and Cognition. The Journal of Neuroscience 36, 12385–12392. https://doi.org/10.1523/JNEUROSCI.2180-16.2016

Jenkins, A.C., Macrae, C.N., Mitchell, J.P., 2008. Repetition suppression of ventromedial prefrontal activity during judgments of self and others. Proceedings of the National Academy of Sciences 105, 4507–4512. https://doi.org/10.1073/pnas.0708785105

Jenkins, I.H., Jahanshahi, M., Jueptner, M., Passingham, R.E., Brooks, D.J., 2000. Self-initiated versus externally triggered movements. II. The effect of movement predictability on regional cerebral blood flow. Brain 123 (Pt 6), 1216–1228.

Jocham, G., Neumann, J., Klein, T.A., Danielmeier, C., Ullsperger, M., 2009. Adaptive Coding of Action Values in the Human Rostral Cingulate Zone. Journal of Neuroscience 29, 7489–7496. https://doi.org/10.1523/JNEUROSCI.0349-09.2009

Johnson, J.G., Raab, M., 2003. Take The First: Option-generation and resulting choices. Organizational Behavior and Human Decision Processes 91, 215–229. https://doi.org/10.1016/S0749-5978(03)00027-X

Jones, M.N., Mewhort, D.J.K., 2007. Representing word meaning and order information in a composite holographic lexicon. Psychological Review 114, 1–37. https://doi.org/10.1037/0033-295X.114.1.1

Jones-Gotman, M., Milner, B., 1977. Design fluency: the invention of nonsense drawings after focal cortical lesions. Neuropsychologia 15, 653–674.

Jordan, L.L., Zahodne, L.B., Okun, M.S., Bowers, D., 2013. Hedonic and behavioral deficits associated with apathy in Parkinson's disease: potential treatment implications. Mov. Disord. 28, 1301–1304. https://doi.org/10.1002/mds.25496

Jung, R.E., Segall, J.M., Jeremy Bockholt, H., Flores, R.A., Smith, S.M., Chavez, R.S., Haier, R.J., 2010. Neuroanatomy of creativity. Hum Brain Mapp 31, 398–409. https://doi.org/10.1002/hbm.20874

Kaiser, S., Simon, J.J., Kalis, A., Schweizer, S., Tobler, P.N., Mojzisch, A., 2013. The cognitive and neural basis of option generation and subsequent choice. Cognitive, Affective, & Behavioral Neuroscience 13, 814–829. https://doi.org/10.3758/s13415-013-0175-5

Kalis, A., Kaiser, S., Mojzisch, A., 2013. Why we should talk about option generation in decision-making research. Frontiers in Psychology 4. https://doi.org/10.3389/fpsyg.2013.00555

Kalis, A., Mojzisch, A., Schweizer, T.S., Kaiser, S., 2008. Weakness of will, akrasia, and the neuropsychiatry of decision making: An interdisciplinary perspective. Cognitive, Affective, & Behavioral Neuroscience 8, 402–417. https://doi.org/10.3758/CABN.8.4.402

Kang, J.Y., Lee, J.S., Kang, H., Lee, H.-W., Kim, Y.K., Jeon, H.J., Chung, J.-K., Lee, M.C., Cho, M.J., Lee, D.S., 2012. Regional cerebral blood flow abnormalities associated with apathy and depression in Alzheimer disease. Alzheimer Dis Assoc Disord 26, 217–224. https://doi.org/10.1097/WAD.0b013e318231e5fc

Kapur, S., Remington, G., Jones, C., Wilson, A., DaSilva, J., Houle, S., Zipursky, R., 1996. High levels of dopamine D2 receptor occupancy with low-dose haloperidol treatment: a PET study. Am J Psychiatry 153, 948–950. https://doi.org/10.1176/ajp.153.7.948

Kebabian, J.W., Calne, D.B., 1979. Multiple receptors for dopamine. Nature 277, 93–96.

Kehrer, C.A., Sanchez, P.N., Habif, U., Rosenbaum, G.J., Townes, B.D., 2000. Effects of a Significant-Other Observer on Neuropsychological Test Performance. The Clinical Neuropsychologist (Neuropsychology, Development and Cognition: Section D) 14, 67–71. https://doi.org/10.1076/1385-4046(200002)14:1;1-8;FT067

Keller, I., Heckhausen, H., 1990. Readiness potentials preceding spontaneous motor acts: voluntary vs. involuntary control. Electroencephalogr Clin Neurophysiol 76, 351–361.

Keller, L.R., Ho, J.L., 1988. Decision problem structuring: generating options. IEEE Transactions on Systems, Man, and Cybernetics 18, 715–728. https://doi.org/10.1109/21.21599

Kennerley, S.W., Dahmubed, A.F., Lara, A.H., Wallis, J.D., 2009. Neurons in the frontal lobe encode the value of multiple decision variables. J Cogn Neurosci 21, 1162–1178. https://doi.org/10.1162/jocn.2009.21100

Kiang, M., Christensen, B.K., Remington, G., Kapur, S., 2003. Apathy in schizophrenia: clinical correlates and association with functional outcome. Schizophrenia Research 63, 79–88.

Kilner, J.M., Neal, A., Weiskopf, N., Friston, K.J., Frith, C.D., 2009. Evidence of Mirror Neurons in Human Inferior Frontal Gyrus. Journal of Neuroscience 29, 10153–10159. https://doi.org/10.1523/JNEUROSCI.2668-09.2009

Kim, G., DeCoster, J., Huang, C.-H., Bryant, A.N., 2013. A meta-analysis of the factor structure of the Geriatric Depression Scale (GDS): the effects of language. International Psychogeriatrics 25, 71–81. https://doi.org/10.1017/S1041610212001421

Kim, J.W., Lee, D.Y., Choo, I.H., Seo, E.H., Kim, S.G., Park, S.Y., Woo, J.I., 2011. Microstructural Alteration of the Anterior Cingulum is Associated With Apathy in Alzheimer Disease. The American Journal of Geriatric Psychiatry 19, 644–653. https://doi.org/10.1097/JGP.0b013e31820dcc73

Kimberg, D.Y., D'Esposito, M., Farah, M.J., 1997. Effects of bromocriptine on human subjects depend on working memory capacity. Neuroreport 8, 3581–3585.

Kirsch-Darrow, L., Fernandez, H.H., Marsiske, M., Okun, M.S., Bowers, D., 2006. Dissociating apathy and depression in Parkinson disease. Neurology 67, 33–38.

Kirsch-Darrow, L., Marsiske, M., Okun, M.S., Bauer, R., Bowers, D., 2011. Apathy and Depression: Separate Factors in Parkinson's Disease. Journal of the International Neuropsychological Society 17, 1058–1066.

Kitamura, J., Shibasaki, H., Kondo, T., 1993. A cortical slow potential is larger before an isolated movement of a single finger than simultaneous movement of two fingers. Electroencephalogr Clin Neurophysiol 86, 252–258.

Klein, G., Wolf, S., Militello, L., Zsambok, C., 1995. Characteristics of Skilled Option Generation in Chess. Organizational Behavior and Human Decision Processes 62, 63–69. https://doi.org/10.1006/obhd.1995.1031

Klein, S.A., 2002. Libet's Temporal Anomalies: A Reassessment of the Data. Consciousness and Cognition 11, 198–214. https://doi.org/10.1006/ccog.2002.0573

Klein-Flugge, M.C., Kennerley, S.W., Friston, K., Bestmann, S., 2016. Neural Signatures of Value Comparison in Human Cingulate Cortex during Decisions Requiring an Effort-Reward Trade-off. Journal of Neuroscience 36, 10002–10015. https://doi.org/10.1523/JNEUROSCI.0292-16.2016

Knösche, T., Praamstra, P., Stegeman, D., Peters, M., 1996. Linear estimation discriminates midline sources and a motor cortex contribution to the readiness potential. Electroencephalogr Clin Neurophysiol 99, 183–190.

Koch, M., Schmid, A., Schnitzler, H.U., 2000. Role of muscles accumbens dopamine D1 and D2 receptors in instrumental and Pavlovian paradigms of conditioned reward. Psychopharmacology (Berl.) 152, 67–73.

Koller, W.C., Rueda, M.G., 1998. Mechanism of action of dopaminergic agents in Parkinson's disease. Neurology 50, S11-14; discussion S44-48.

Kolling, N., Wittmann, M.K., Behrens, T.E.J., Boorman, E.D., Mars, R.B., Rushworth, M.F.S., 2016. Value, search, persistence and model updating in anterior cingulate cortex. Nature Neuroscience 19, 1280–1285. https://doi.org/10.1038/nn.4382

Kornhuber, H.H., Deecke, L., 1965. [CHANGES IN THE BRAIN POTENTIAL IN VOLUNTARY MOVEMENTS AND PASSIVE MOVEMENTS IN MAN:

READINESS POTENTIAL AND REAFFERENT POTENTIALS]. Pflugers Arch Gesamte Physiol Menschen Tiere 284, 1–17.
Korszun, A., Moskvina, V., Brewster, S., Craddock, N., Ferrero, F., Gill, M., Jones, I.R., Jones, L.A., Maier, W., Mors, O., Owen, M.J., Preisig, M., Reich, T., Rietschel, M., Farmer, A., McGuffin, P., 2004. Familiality of symptom dimensions in depression. Arch. Gen. Psychiatry 61, 468–474. https://doi.org/10.1001/archpsyc.61.5.468
Kourtzi, Z., Kanwisher, N., 2001. Representation of Perceived Object Shape by the Human Lateral Occipital Complex. Science 293, 1506–1509. https://doi.org/10.1126/science.1061133
Krieghoff, V., Brass, M., Prinz, W., Waszak, F., 2009. Dissociating what and when of intentional actions. Frontiers in Human Neuroscience 3. https://doi.org/10.3389/neuro.09.003.2009
Krolak-Salmon, P., Croisile, B., Houzard, C., Setiey, A., Girard-Madoux, P., Vighetto, A., 2000. Total Recovery after Bilateral Paramedian Thalamic Infarct. European Neurology 44, 216–218. https://doi.org/10.1159/000008239
Kühn, S., Haggard, P., Brass, M., 2009. Intentional inhibition: How the "veto-area" exerts control. Human Brain Mapping 30, 2834–2843. https://doi.org/10.1002/hbm.20711
Kurata, K., Hoffman, D.S., 1994. Differential effects of muscimol microinjection into dorsal and ventral aspects of the premotor cortex of monkeys. J Neurophysiol 71, 1151.
Kurniawan, I.T., Seymour, B., Talmi, D., Yoshida, W., Chater, N., Dolan, R.J., 2010. Choosing to Make an Effort: The Role of Striatum in Signaling Physical Effort of a Chosen Action. Journal of Neurophysiology 104, 313–321. https://doi.org/10.1152/jn.00027.2010
Lanctôt, K.L., Moosa, S., Herrmann, N., Leibovitch, F.S., Rothenburg, L., Cotter, A., Black, S.E., 2007. A SPECT Study of Apathy in Alzheimer's Disease. Dementia and Geriatric Cognitive Disorders 24, 65–72. https://doi.org/10.1159/000103633
Landes, A.M., Sperry, S.D., Strauss, M.E., Geldmacher, D.S., 2001. Apathy in Alzheimer's disease. J Am Geriatr Soc 49, 1700–1707.
Lange, N.D., Thomas, R.P., Davelaar, E.J., 2012. Temporal Dynamics of Hypothesis Generation: The Influences of Data Serial Order, Data Consistency, and Elicitation Timing. Frontiers in Psychology 3. https://doi.org/10.3389/fpsyg.2012.00215
Larsson, J., Gulyás, B., Roland, P.E., 1996. Cortical representation of self-paced finger movement. Neuroreport 7, 463–468.
Lau, H.., Rogers, R.., Ramnani, N., Passingham, R.., 2004. Willed action and attention to the selection of action. NeuroImage 21, 1407–1415. https://doi.org/10.1016/j.neuroimage.2003.10.034
Lau, H., Rogers, R.D., Passingham, R.E., 2006. Dissociating response selection and conflict in the medial frontal surface. NeuroImage 29, 446–451. https://doi.org/10.1016/j.neuroimage.2005.07.050

Lawrence, A.D., Goerendt, I.K., Brooks, D.J., 2011. Apathy blunts neural response to money in Parkinson's disease. Soc Neurosci 6, 653–662. https://doi.org/10.1080/17470919.2011.556821

Le Heron, C., Apps., M.A.J., Husain, M., 2017. The anatomy of apathy: A neurocognitive framework for amotivated behaviour. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2017.07.003

Le Heron, C., Plant, O., Manohar, S., Ang, Y.-S., Jackson, M., Lennox, G., Hu, M.T., Husain, M., 2018. Distinct effects of apathy and dopamine on effort-based decision-making in Parkinson's disease. Brain. https://doi.org/10.1093/brain/awy110

Leentjens, A.F.G., Dujardin, K., Marsh, L., Martinez-Martin, P., Richard, I.H., Starkstein, S.E., Weintraub, D., Sampaio, C., Poewe, W., Rascol, O., Stebbins, G.T., Goetz, C.G., 2008. Apathy and anhedonia rating scales in Parkinson's disease: Critique and recommendations. Movement Disorders 23, 2004–2014.

Leggio, G.M., Cathala, A., Moison, D., Cunningham, K.A., Piazza, P.V., Spampinato, U., 2009a. Serotonin2C receptors in the medial prefrontal cortex facilitate cocaine-induced dopamine release in the rat nucleus accumbens. Neuropharmacology 56, 507–513. https://doi.org/10.1016/j.neuropharm.2008.10.005

Leggio, G.M., Cathala, A., Neny, M., Rouge-Pont, F., Drago, F., Piazza, P.V., Spampinato, U., 2009b. In vivo evidence that constitutive activity of serotonin2C receptors in the medial prefrontal cortex participates in the control of dopamine release in the rat nucleus accumbens: differential effects of inverse agonist versus antagonist. J. Neurochem. 111, 614–623. https://doi.org/10.1111/j.1471-4159.2009.06356.x

Levenson, R.W., Sturm, V.E., Haase, C.M., 2014. Emotional and behavioral symptoms in neurodegenerative disease: a model for studying the neural bases of psychopathology. Annu Rev Clin Psychol 10, 581–606. https://doi.org/10.1146/annurev-clinpsy-032813-153653

Levy, R., Dubois, B., 2006. Apathy and the Functional Anatomy of the Prefrontal Cortex-Basal Ganglia Circuits. Cerebral Cortex 16, 916–928.

Li, Y., Aggen, S., Shi, S., Gao, J., Li, Y., Tao, M., Zhang, K., Wang, X., Gao, C., Yang, L., Liu, Y., Li, K., Shi, J., Wang, G., Liu, L., Zhang, J., Du, B., Jiang, G., Shen, J., Zhang, Z., Liang, W., Sun, J., Hu, J., Liu, T., Wang, X., Miao, G., Meng, H., Li, Y., Hu, C., Li, Y., Huang, G., Li, G., Ha, B., Deng, H., Mei, Q., Zhong, H., Gao, S., Sang, H., Zhang, Y., Fang, X., Yu, F., Yang, D., Liu, T., Chen, Y., Hong, X., Wu, W., Chen, G., Cai, M., Song, Y., Pan, J., Dong, J., Pan, R., Zhang, W., Shen, Z., Liu, Z., Gu, D., Wang, X., Liu, X., Zhang, Q., Flint, J., Kendler, K.S., 2014. The structure of the symptoms of major depression: exploratory and confirmatory factor analysis in depressed Han Chinese women. Psychol Med 44, 1391–1401. https://doi.org/10.1017/S003329171300192X

Libet, B., Gleason, C.A., Wright, E.W., Pearl, D.K., 1983. Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential). The unconscious initiation of a freely voluntary act. Brain 106 (Pt 3), 623–642.

Lidow, M.S., Goldman-Rakic, P.S., Gallager, D.W., Rakic, P., 1991. Distribution of dopaminergic receptors in the primate cerebral cortex: quantitative

autoradiographic analysis using [3H]raclopride, [3H]spiperone and [3H]SCH23390. Neuroscience 40, 657–671.
Lieberman, A., 2006. Depression in Parkinson's disease - a review. Acta Neurologica Scandinavica 113, 1–8.
Lieberman, M.D., Eisenberger, N.I., 2015. The dorsal anterior cingulate cortex is selective for pain: Results from large-scale reverse inference. Proc. Natl. Acad. Sci. U.S.A. 112, 15250–15255. https://doi.org/10.1073/pnas.1515083112
Lo, Y., Mendell, N.R., Rubin, D.B., 2001. Testing the number of components in a normal mixture. Biometrika 88, 767–778.
Lockwood, P.L., Ang, Y.-S., Husain, M., Crockett, M.J., 2017. Individual differences in empathy are associated with apathy-motivation. Scientific Reports 7. https://doi.org/10.1038/s41598-017-17415-w
Lockwood, P.L., Apps, M.A.J., Valton, V., Viding, E., Roiser, J.P., 2016. Neurocomputational mechanisms of prosocial learning and links to empathy. Proceedings of the National Academy of Sciences 113, 9763–9768. https://doi.org/10.1073/pnas.1603198113
Luciana, M., Collins, P.F., 1997. Dopaminergic Modulation of Working Memory for Spatial but Not Object Cues in Normal Humans. Journal of Cognitive Neuroscience 9, 330–347. https://doi.org/10.1162/jocn.1997.9.3.330
Luciana, M., Depue, R.A., Arbisi, P., Leon, A., 1992. Facilitation of Working Memory in Humans by a D_2 Dopamine Receptor Agonist. Journal of Cognitive Neuroscience 4, 58–68. https://doi.org/10.1162/jocn.1992.4.1.58
MacPherson, S.E., Della Sala, S., Cox, S.R., Girardi, A., Iveson, M.H., 2015. Handbook of frontal lobe assessment, First edition. ed. Oxford University Press, Oxford, United Kingdom ; New York, NY, United States of America.
Maddess, T., McCourt, M.E., Blakeslee, B., Cunningham, R.B., 1988. Factors governing the adaptation of cells in area-17 of the cat visual cortex. Biological Cybernetics 59, 229–236. https://doi.org/10.1007/BF00332911
Maeda, K., Idehara, R., Shiraishi, T., 2012. Micrographia and Abulia due to Frontal Subcortical Infarction. Internal Medicine 51, 1953–1954. https://doi.org/10.2169/internalmedicine.51.7721
Maffei, L., Fiorentini, A., Bisti, S., 1973. Neural Correlate of Perceptual Adaptation to Gratings. Science 182, 1036–1038. https://doi.org/10.1126/science.182.4116.1036
Marin, R.S., 1991. Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci 3, 243–254.
Marin, R.S., Biedrzycki, R.C., Firinciogullari, S., 1991. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res 38, 143–162.
Markou, A., Salamone, J.D., Bussey, T.J., Mar, A.C., Brunner, D., Gilmour, G., Balsam, P., 2013. Measuring reinforcement learning and motivation constructs in experimental animals: relevance to the negative symptoms of schizophrenia. Neurosci Biobehav Rev 37, 2149–2165. https://doi.org/10.1016/j.neubiorev.2013.08.007
Marshall, G.A., Monserratt, L., Harwood, D., Mandelkern, M., Cummings, J.L., Sultzer, D.L., 2007. Positron Emission Tomography Metabolic Correlates of Apathy in

Alzheimer Disease. Archives of Neurology 64, 1015. https://doi.org/10.1001/archneur.64.7.1015
Martin, R.C., Loring, D.W., Meador, K.J., Lee, G.P., 1990. The effects of lateralized temporal lobe dysfunction on formal and semantic word fluency. Neuropsychologia 28, 823–829.
Martinez-Horta, S., Riba, J., de Bobadilla, R.F., Pagonabarraga, J., Pascual-Sedano, B., Antonijoan, R.M., Romero, S., Mananas, M.A., Garcia-Sanchez, C., Kulisevsky, J., 2014. Apathy in Parkinson's Disease: Neurophysiological Evidence of Impaired Incentive Processing. Journal of Neuroscience 34, 5918–5926. https://doi.org/10.1523/JNEUROSCI.0251-14.2014
Massar, S.A.A., Libedinsky, C., Weiyan, C., Huettel, S.A., Chee, M.W.L., 2015. Separate and overlapping brain areas encode subjective value during delay and effort discounting. NeuroImage 120, 104–113. https://doi.org/10.1016/j.neuroimage.2015.06.080
Matsumoto, M., Matsumoto, K., Abe, H., Tanaka, K., 2007. Medial prefrontal cell activity signaling prediction errors of action values. Nature Neuroscience 10, 647–656. https://doi.org/10.1038/nn1890
Matsumoto, M., Yoshioka, M., Togashi, H., Ikeda, T., Saito, H., 1996. Functional regulation by dopamine receptors of serotonin release from the rat hippocampus: in vivo microdialysis study. Naunyn Schmiedebergs Arch. Pharmacol. 353, 621–629.
Mayseless, N., Uzefovsky, F., Shalev, I., Ebstein, R.P., Shamay-Tsoory, S.G., 2013. The association between creativity and 7R polymorphism in the dopamine receptor D4 gene (DRD4). Frontiers in Human Neuroscience 7. https://doi.org/10.3389/fnhum.2013.00502
McClure, S.M., Berns, G.S., Montague, P.R., 2003. Temporal prediction errors in a passive learning task activate human striatum. Neuron 38, 339–346.
McDowell, S., Whyte, J., D'Esposito, M., 1998. Differential effect of a dopaminergic agonist on prefrontal function in traumatic brain injury patients. Brain 121 (Pt 6), 1155–1164.
McLachlan, G.J., Peel, D., 2000. Finite mixture models, Wiley series in probability and statistics. Applied probability and statistics section. Wiley, New York.
Mednick, S.A., 1968. The Remote Associates Test*. The Journal of Creative Behavior 2, 213–214. https://doi.org/10.1002/j.2162-6057.1968.tb00104.x
Mega, M.S., Cohenour, R.C., 1997. Akinetic mutism: disconnection of frontal-subcortical circuits. Neuropsychiatry Neuropsychol Behav Neurol 10, 254–259.
Mehta, M.A., McGowan, S.W., Lawrence, A.D., Aitken, M.R.F., Montgomery, A.J., Grasby, P.M., 2003. Systemic sulpiride modulates striatal blood flow: relationships to spatial working memory and planning. Neuroimage 20, 1982–1994.
Mehta, M.A., Sahakian, B.J., McKenna, P.J., Robbins, T.W., 1999. Systemic sulpiride in young adult volunteers simulates the profile of cognitive deficits in Parkinson's disease. Psychopharmacology (Berl.) 146, 162–174.
Mehta, M.A., Swainson, R., Ogilvie, A.D., Sahakian, B., Robbins, T.W., 2001. Improved short-term spatial memory but impaired reversal learning following the

dopamine D2 agonist bromocriptine in human volunteers. Psychopharmacology 159, 10–20. https://doi.org/10.1007/s002130100851
Mercier, D., Falardeau, P., Lévesque, D., 2001. Autoreceptor preference of dopamine D2 receptor agonists correlates with preferential coupling to cyclic AMP. Neuroreport 12, 1473–1479.
Meyniel, F., Goodwin, G.M., Deakin, J.W., Klinge, C., MacFadyen, C., Milligan, H., Mullings, E., Pessiglione, M., Gaillard, R., 2016. A specific role for serotonin in overcoming effort cost. Elife 5. https://doi.org/10.7554/eLife.17282
Miceli, G., Caltagirone, C., Gainotti, G., Masullo, C., Silveri, M.C., 1981. Neuropsychological correlates of localized cerebral lesions in non-aphasic brain-damaged patients. J Clin Neuropsychol 3, 53–63.
Migneco, O., Benoit, M., Koulibaly, P.M., Dygai, I., Bertogliati, C., Desvignes, P., Robert, P.H., Malandain, G., Bussiere, F., Darcourt, J., 2001. Perfusion Brain SPECT and Statistical Parametric Mapping Analysis Indicate That Apathy Is a Cingulate Syndrome: A Study in Alzheimer's Disease and Nondemented Patients. NeuroImage 13, 896–902. https://doi.org/10.1006/nimg.2000.0741
Mikami, K., Jorge, R.E., Moser, D.J., Arndt, S., Jang, M., Solodkin, A., Small, S.L., Fonzetti, P., Hegel, M.T., Robinson, R.G., 2013. Prevention of poststroke apathy using escitalopram or problem-solving therapy. Am J Geriatr Psychiatry 21, 855–862. https://doi.org/10.1016/j.jagp.2012.07.003
Millan, M.J., Dekeyne, A., Gobert, A., 1998. Serotonin (5-HT)2C receptors tonically inhibit dopamine (DA) and noradrenaline (NA), but not 5-HT, release in the frontal cortex in vivo. Neuropharmacology 37, 953–955.
Miller, E.K., Erickson, C.A., Desimone, R., 1996. Neural mechanisms of visual working memory in prefrontal cortex of the macaque. J. Neurosci. 16, 5154–5167.
Miller, E.K., Li, L., Desimone, R., 1991. A neural mechanism for working and recognition memory in inferior temporal cortex. Science 254, 1377–1379.
Milner, B., 1964. Some effects of frontal lobectomy in man., in: Warren, J.M., Akert, K. (Eds.), The Frontal Granular Cortex and Behavior. New York: McGraw-Hill, pp. 313–334.
Miyazaki, K., Miyazaki, K.W., Doya, K., 2011. Activation of dorsal raphe serotonin neurons underlies waiting for delayed rewards. J. Neurosci. 31, 469–479. https://doi.org/10.1523/JNEUROSCI.3714-10.2011
Mogenson, G.J., Jones, D.L., Yim, C.Y., 1980. From motivation to action: functional interface between the limbic system and the motor system. Prog. Neurobiol. 14, 69–97.
Moonen, A.J.H., Weiss, P.H., Wiesing, M., Weidner, R., Fink, G.R., Reijnders, J.S.A.M., Weber, W.M., Leentjens, A.F.G., 2017. An fMRI study into emotional processing in Parkinson's disease: Does increased medial prefrontal activation compensate for striatal dysfunction? PLOS ONE 12, e0177085. https://doi.org/10.1371/journal.pone.0177085
Moore, D.W., Bhadelia, R.A., Billings, R.L., Fulwiler, C., Heilman, K.M., Rood, K.M.J., Gansler, D.A., 2009. Hemispheric connectivity and the visual-spatial divergent-thinking component of creativity. Brain Cogn 70, 267–272. https://doi.org/10.1016/j.bandc.2009.02.011

Morcom, A.M., Bullmore, E.T., Huppert, F.A., Lennox, B., Praseedom, A., Linnington, H., Fletcher, P.C., 2010. Memory Encoding and Dopamine in the Aging Brain: A Psychopharmacological Neuroimaging Study. Cerebral Cortex 20, 743–757. https://doi.org/10.1093/cercor/bhp139

Mott, A.M., Nunes, E.J., Collins, L.E., Port, R.G., Sink, K.S., Hockemeyer, J., Müller, C.E., Salamone, J.D., 2009. The adenosine A2A antagonist MSX-3 reverses the effects of the dopamine antagonist haloperidol on effort-related decision making in a T-maze cost/benefit procedure. Psychopharmacology (Berl.) 204, 103–112. https://doi.org/10.1007/s00213-008-1441-z

Mottaghy, F.M., Gangitano, M., Krause, B.J., Pascual-Leone, A., 2003. Chronometry of parietal and prefrontal activations in verbal working memory revealed by transcranial magnetic stimulation. Neuroimage 18, 565–575.

Movshon, J.A., Lennie, P., 1979. Pattern-selective adaptation in visual cortical neurones. Nature 278, 850–852.

Mueller, V.A., Brass, M., Waszak, F., Prinz, W., 2007. The role of the preSMA and the rostral cingulate zone in internally selected actions. NeuroImage 37, 1354–1361. https://doi.org/10.1016/j.neuroimage.2007.06.018

Muhammad, R., Wallis, J.D., Miller, E.K., 2006. A comparison of abstract rules in the prefrontal cortex, premotor cortex, inferior temporal cortex, and striatum. J Cogn Neurosci 18, 974–989. https://doi.org/10.1162/jocn.2006.18.6.974

Muhammed, K., Husain, M., 2016. Clinical significance of apathy in Parkinson's disease. EMJ Neurol. 4, 56–63.

Muhammed, K., Manohar, S., Ben Yehuda, M., Chong, T.T.-J., Tofaris, G., Lennox, G., Bogdanovic, M., Hu, M., Husain, M., 2016. Reward sensitivity deficits modulated by dopamine are associated with apathy in Parkinson's disease. Brain 139, 2706–2721. https://doi.org/10.1093/brain/aww188

Mull, B.R., Seyal, M., 2001. Transcranial magnetic stimulation of left prefrontal cortex impairs working memory. Clin Neurophysiol 112, 1672–1675.

Müller, U., von Cramon, D.Y., Pollmann, S., 1998. D1- versus D2-receptor modulation of visuospatial working memory in humans. J. Neurosci. 18, 2720–2728.

Multiple Sclerosis Council for Clinical Practice Guidelines, 1998. Fatigue and multiple sclerosis: evidence-based management strategies for fatigue in multiple sclerosis. Paralyzed Veterans of America, Washington (DC).

Mushiake, H., Inase, M., Tanji, J., 1991. Neuronal activity in the primate premotor, supplementary, and precentral motor cortex during visually guided and internally determined sequential movements. J. Neurophysiol. 66, 705–718.

Muthen, L.K., Muthen, B.O., 1998. Mplus User's Guide. Seventh Edition. Los Angeles, CA: Muthen & Muthen.

Nachev, P., Husain, M., 2006. Disorders of visual attention and the posterior parietal cortex. Cortex 42, 766–773.

Nachev, P., Rees, G., Parton, A., Kennard, C., Husain, M., 2005. Volition and Conflict in Human Medial Frontal Cortex. Current Biology 15, 122–128. https://doi.org/10.1016/j.cub.2005.01.006

Nachev, P., Wydell, H., O'Neill, K., Husain, M., Kennard, C., 2007. The role of the pre-supplementary motor area in the control of action. NeuroImage 36, T155–T163. https://doi.org/10.1016/j.neuroimage.2007.03.034

Nakamura, K., Matsumoto, M., Hikosaka, O., 2008. Reward-dependent modulation of neuronal activity in the primate dorsal raphe nucleus. J. Neurosci. 28, 5331–5343. https://doi.org/10.1523/JNEUROSCI.0021-08.2008

Neshige, R., Lüders, H., Shibasaki, H., 1988. Recording of movement-related potentials from scalp and cortex in man. Brain 111 (Pt 3), 719–736.

Nishio, Y., Hashimoto, M., Ishii, K., Mori, E., 2011. Neuroanatomy of a neurobehavioral disturbance in the left anterior thalamic infarction. Journal of Neurology, Neurosurgery & Psychiatry 82, 1195–1200. https://doi.org/10.1136/jnnp.2010.236463

Nobis, L., Husain, M., 2018. Apathy in Alzheimer's disease. Current Opinion in Behavioral Sciences 22, 7–13. https://doi.org/10.1016/j.cobeha.2017.12.007

Nomikos, G.G., Arborelius, L., Höök, B.B., Hacksell, U., Svensson, T.H., 1996. The 5-HT1A receptor antagonist (S)-UH-301 decreases dopamine release in the rat nucleus accumbens and striatum. J Neural Transm (Vienna) 103, 541–554. https://doi.org/10.1007/BF01273152

Nowend, K.L., Arizzi, M., Carlson, B.B., Salamone, J.D., 2001. D1 or D2 antagonism in nucleus accumbens core or dorsomedial shell suppresses lever pressing for food but leads to compensatory increases in chow consumption. Pharmacol. Biochem. Behav. 69, 373–382.

O'Doherty, J.P., Dayan, P., Friston, K., Critchley, H., Dolan, R.J., 2003. Temporal difference models and reward-related learning in the human brain. Neuron 38, 329–337.

Oguru, M., Tachibana, H., Toda, K., Okuda, B., Oka, N., 2010. Apathy and Depression in Parkinson Disease. Journal of Geriatric Psychiatry and Neurology 23, 35–41. https://doi.org/10.1177/0891988709351834

Okano, K., Tanji, J., 1987. Neuronal activities in the primate motor fields of the agranular frontal cortex preceding visually triggered and self-paced movement. Experimental Brain Research 66. https://doi.org/10.1007/BF00236211

Osman, A., Barrios, F.X., Gutierrez, P.M., Williams, J.E., Bailey, J., 2008. Psychometric properties of the Beck Depression Inventory-II in nonclinical adolescent samples. J Clin Psychol 64, 83–102. https://doi.org/10.1002/jclp.20433

Owen, A.M., 1997. The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. Eur. J. Neurosci. 9, 1329–1339.

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 (Pt 6), 1727–1751.

Owen, A.M., Stern, C.E., Look, R.B., Tracey, I., Rosen, B.R., Petrides, M., 1998. Functional organization of spatial and nonspatial working memory processing within the human lateral frontal cortex. Proc. Natl. Acad. Sci. U.S.A. 95, 7721–7726.

Padala, P.R., Padala, K.P., Monga, V., Ramirez, D.A., Sullivan, D.H., 2012. Reversal of SSRI-associated apathy syndrome by discontinuation of therapy. Ann Pharmacother 46, e8. https://doi.org/10.1345/aph.1Q656

Pagonabarraga, J., Kulisevsky, J., Strafella, A.P., Krack, P., 2015. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. The

Lancet Neurology 14, 518–531. https://doi.org/10.1016/S1474-4422(15)00019-8
Papa, S.M., Artieda, J., Obeso, J.A., 1991. Cortical activity preceding self-initiated and externally triggered voluntary movement. Mov. Disord. 6, 217–224. https://doi.org/10.1002/mds.870060305
Passingham, R., 1997. The frontal lobes and voluntary action, Reprint. ed, Oxford psychology series. Univ. Press, Oxford.
Passingham, R.E., Bengtsson, S.L., Lau, H.C., 2010. Medial frontal cortex: from self-generated action to reflection on one's own performance. Trends Cogn. Sci. (Regul. Ed.) 14, 16–21. https://doi.org/10.1016/j.tics.2009.11.001
Pehek, E.A., Nocjar, C., Roth, B.L., Byrd, T.A., Mabrouk, O.S., 2006. Evidence for the preferential involvement of 5-HT2A serotonin receptors in stress- and drug-induced dopamine release in the rat medial prefrontal cortex. Neuropsychopharmacology 31, 265–277. https://doi.org/10.1038/sj.npp.1300819
Pendleton, M.G., Heaton, R.K., Lehman, R.A., Hulihan, D., 1982. Diagnostic utility of the Thurstone Word Fluency Test in neuropsychological evaluations. J Clin Neuropsychol 4, 307–317.
Peretti, C.S., Danion, J.M., Kauffmann-Muller, F., Grangé, D., Patat, A., Rosenzweig, P., 1997. Effects of haloperidol and amisulpride on motor and cognitive skill learning in healthy volunteers. Psychopharmacology (Berl.) 131, 329–338.
Perren, F., Clarke, S., Bogousslavsky, J., 2005. The Syndrome of Combined Polar and Paramedian Thalamic Infarction. Archives of Neurology 62, 1212. https://doi.org/10.1001/archneur.62.8.1212
Perret, E., 1974. The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. Neuropsychologia 12, 323–330.
Peters, S.L., Fellows, L.K., Sheldon, S., 2017. The Ventromedial Frontal Lobe Contributes to Forming Effective Solutions to Real-world Problems. Journal of Cognitive Neuroscience 29, 991–1001. https://doi.org/10.1162/jocn_a_01088
Phillips, S., Sangalang, V., Sterns, G., 1987. Basal forebrain infarction. A clinicopathologic correlation. Arch. Neurol. 44, 1134–1138.
Piazza, M., Pinel, P., Le Bihan, D., Dehaene, S., 2007. A Magnitude Code Common to Numerosities and Number Symbols in Human Intraparietal Cortex. Neuron 53, 293–305. https://doi.org/10.1016/j.neuron.2006.11.022
Piercey, M.F., Hoffmann, W.E., Smith, M.W., Hyslop, D.K., 1996. Inhibition of dopamine neuron firing by pramipexole, a dopamine D3 receptor-preferring agonist: comparison to other dopamine receptor agonists. Eur. J. Pharmacol. 312, 35–44.
Playford, E.D., Jenkins, I.H., Passingham, R.E., Nutt, J., Frackowiak, R.S.J., Brooks, D.J., 1992. Impaired mesial frontal and putamen activation in Parkinson's disease: A positron emission tomography study. Annals of Neurology 32, 151–161. https://doi.org/10.1002/ana.410320206
Pluck, G.C., Brown, R.G., 2002. Apathy in Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry 73, 636–642.

Pockett, S., 2002. On Subjective Back-Referral and How Long It Takes to Become Conscious of a Stimulus: A Reinterpretation of Libet's Data. Consciousness and Cognition 11, 144–161. https://doi.org/10.1006/ccog.2002.0549

Poldrack, R.A., Fletcher, P.C., Henson, R.N., Worsley, K.J., Brett, M., Nichols, T.E., 2008. Guidelines for reporting an fMRI study. Neuroimage 40, 409–414. https://doi.org/10.1016/j.neuroimage.2007.11.048

Polner, B., Nagy, H., Takáts, A., Kéri, S., 2015. Kiss of the muse for the chosen ones: De novo schizotypal traits and lifetime creative achievement are related to changes in divergent thinking during dopaminergic therapy in Parkinson's disease. Psychology of Aesthetics, Creativity, and the Arts 9, 328–339. https://doi.org/10.1037/a0039303

Porras, G., Di Matteo, V., Fracasso, C., Lucas, G., De Deurwaerdère, P., Caccia, S., Esposito, E., Spampinato, U., 2002. 5-HT2A and 5-HT2C/2B receptor subtypes modulate dopamine release induced in vivo by amphetamine and morphine in both the rat nucleus accumbens and striatum. Neuropsychopharmacology 26, 311–324. https://doi.org/10.1016/S0893-133X(01)00333-5

Praamstra, P., Stegeman, D.F., Horstink, M.W., Cools, A.R., 1996. Dipole source analysis suggests selective modulation of the supplementary motor area contribution to the readiness potential. Electroencephalogr Clin Neurophysiol 98, 468–477.

Prévost, C., Pessiglione, M., Météreau, E., Cléry-Melin, M.-L., Dreher, J.-C., 2010. Separate valuation subsystems for delay and effort decision costs. J. Neurosci. 30, 14080–14090. https://doi.org/10.1523/JNEUROSCI.2752-10.2010

Quilty, L.C., Zhang, K.A., Bagby, R.M., 2010. The latent symptom structure of the Beck Depression Inventory-II in outpatients with major depression. Psychol Assess 22, 603–608. https://doi.org/10.1037/a0019698

Raab, M., de Oliveira, R.F., Heinen, T., 2009. How do people perceive and generate options? Prog. Brain Res. 174, 49–59. https://doi.org/10.1016/S0079-6123(09)01305-3

Raab, M., Johnson, J.G., 2007. Expertise-based differences in search and option-generation strategies. Journal of Experimental Psychology: Applied 13, 158–170. https://doi.org/10.1037/1076-898X.13.3.158

Radakovic, R., Abrahams, S., 2014. Developing a new apathy measurement scale: Dimensional Apathy Scale. Psychiatry Research 219, 658–663.

Radakovic, R., Davenport, R., Starr, J.M., Abrahams, S., 2017. Apathy dimensions in Parkinson's disease. Int J Geriatr Psychiatry. https://doi.org/10.1002/gps.4697

Rainer, G., Rao, S.C., Miller, E.K., 1999. Prospective coding for objects in primate prefrontal cortex. J. Neurosci. 19, 5493–5505.

Ranade, S.P., Mainen, Z.F., 2009. Transient firing of dorsal raphe neurons encodes diverse and specific sensory, motor, and reward events. J. Neurophysiol. 102, 3026–3037. https://doi.org/10.1152/jn.00507.2009

Randall, P.A., Lee, C.A., Nunes, E.J., Yohn, S.E., Nowak, V., Khan, B., Shah, P., Pandit, S., Vemuri, V.K., Makriyannis, A., Baqi, Y., Müller, C.E., Correa, M., Salamone, J.D., 2014. The VMAT-2 inhibitor tetrabenazine affects effort-related decision making in a progressive ratio/chow feeding choice task: reversal with

antidepressant drugs. PLoS ONE 9, e99320. https://doi.org/10.1371/journal.pone.0099320

Randall, P.A., Pardo, M., Nunes, E.J., López Cruz, L., Vemuri, V.K., Makriyannis, A., Baqi, Y., Müller, C.E., Correa, M., Salamone, J.D., 2012. Dopaminergic modulation of effort-related choice behavior as assessed by a progressive ratio chow feeding choice task: pharmacological studies and the role of individual differences. PLoS ONE 7, e47934. https://doi.org/10.1371/journal.pone.0047934

Rankin, K.P., Liu, A.A., Howard, S., Slama, H., Hou, C.E., Shuster, K., Miller, B.L., 2007. A Case-controlled Study of Altered Visual Art Production in Alzheimer's and FTLD: Cognitive and Behavioral Neurology 20, 48–61. https://doi.org/10.1097/WNN.0b013e31803141dd

Rao, S.M., Binder, J.R., Bandettini, P.A., Hammeke, T.A., Yetkin, F.Z., Jesmanowicz, A., Lisk, L.M., Morris, G.L., Mueller, W.M., Estkowski, L.D., 1993. Functional magnetic resonance imaging of complex human movements. Neurology 43, 2311–2318.

Rao, S.M., Harrington, D.L., Haaland, K.Y., Bobholz, J.A., Cox, R.W., Binder, J.R., 1997. Distributed neural systems underlying the timing of movements. J. Neurosci. 17, 5528–5535.

Rasmusson, A.M., Goldstein, L.E., Deutch, A.Y., Bunney, B.S., Roth, R.H., 1994. 5-HT $_{1a}$ agonist ±- 8-OH-DPAT modulates basal and stress-induced changes in medial prefrontal cortical dopamine: ±8-OH-DPAT EFFECTS ON DOPAMINE NEUROCHEMISTRY. Synapse 18, 218–224. https://doi.org/10.1002/syn.890180307

Regard, M., Strauss, E., Knapp, P., 1982. Children's production on verbal and non-verbal fluency tasks. Percept Mot Skills 55, 839–844. https://doi.org/10.2466/pms.1982.55.3.839

Reijnders, J.S.A.M., Scholtissen, B., Weber, W.E.J., Aalten, P., Verhey, F.R.J., Leentjens, A.F.G., 2010. Neuroanatomical correlates of apathy in Parkinson's disease: A magnetic resonance imaging study using voxel-based morphometry. Movement Disorders 25, 2318–2325. https://doi.org/10.1002/mds.23268

Remy, P., Zilbovicius, M., Leroy-Willig, A., Syrota, A., Samson, Y., 1994. Movement-and task-related activations of motor cortical areas: A positron emission tomographic study. Annals of Neurology 36, 19–26. https://doi.org/10.1002/ana.410360107

Reuter, M., Roth, S., Holve, K., Hennig, J., 2006. Identification of first candidate genes for creativity: A pilot study. Brain Research 1069, 190–197. https://doi.org/10.1016/j.brainres.2005.11.046

Richfield, E.K., Penney, J.B., Young, A.B., 1989. Anatomical and affinity state comparisons between dopamine D1 and D2 receptors in the rat central nervous system. Neuroscience 30, 767–777.

Rinne, U.K., Bracco, F., Chouza, C., Dupont, E., Gershanik, O., Marti Masso, J.F., Montastruc, J.L., Marsden, C.D., Dubini, A., Orlando, N., Grimaldi, R., 1997. Cabergoline in the treatment of early Parkinson's disease: results of the first

year of treatment in a double-blind comparison of cabergoline and levodopa. The PKDS009 Collaborative Study Group. Neurology 48, 363–368.
Rizzolatti, G., Scandolara, C., Matelli, M., Gentilucci, M., 1981. Afferent properties of periarcuate neurons in macaque monkeys. II. Visual responses. Behav. Brain Res. 2, 147–163.
Robbins, T.W., Arnsten, A.F.T., 2009. The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. Annu. Rev. Neurosci. 32, 267–287. https://doi.org/10.1146/annurev.neuro.051508.135535
Robert, G.H., Le Jeune, F., Lozachmeur, C., Drapier, S., Dondaine, T., Peron, J., Houvenaghel, J.-F., Travers, D., Sauleau, P., Millet, B., Verin, M., Drapier, D., 2014. Preoperative factors of apathy in subthalamic stimulated Parkinson disease: A PET study. Neurology 83, 1620–1626. https://doi.org/10.1212/WNL.0000000000000941
Robert, P.H., Clairet, S., Benoit, M., Koutaich, J., Bertogliati, C., Tible, O., Caci, H., Borg, M., Brocker, P., Bedoucha, P., 2002. The apathy inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. Int J Geriatr Psychiatry 17, 1099–1105. https://doi.org/10.1002/gps.755
Robert, P.H., Darcourt, G., Koulibaly, M.P., Clairet, S., Benoit, M., Garcia, R., Dechaux, O., Darcourt, J., 2006. Lack of initiative and interest in Alzheimer's disease: a single photon emission computed tomography study. European Journal of Neurology 13, 729–735. https://doi.org/10.1111/j.1468-1331.2006.01088.x
Robinson, E.S.J., Dalley, J.W., Theobald, D.E.H., Glennon, J.C., Pezze, M.A., Murphy, E.R., Robbins, T.W., 2008. Opposing roles for 5-HT2A and 5-HT2C receptors in the nucleus accumbens on inhibitory response control in the 5-choice serial reaction time task. Neuropsychopharmacology 33, 2398–2406. https://doi.org/10.1038/sj.npp.1301636
Robinson, G., Shallice, T., Bozzali, M., Cipolotti, L., 2012. The differing roles of the frontal cortex in fluency tests. Brain 135, 2202–2214. https://doi.org/10.1093/brain/aws142
Robinson, S., Sandstrom, S.M., Denenberg, V.H., Palmiter, R.D., 2005. Distinguishing whether dopamine regulates liking, wanting, and/or learning about rewards. Behav. Neurosci. 119, 5–15. https://doi.org/10.1037/0735-7044.119.1.5
Romo, R., Schultz, W., 1987. Neuronal activity preceding self-initiated or externally timed arm movements in area 6 of monkey cortex. Exp Brain Res 67, 656–662.
Rosen, H.J., Allison, S.C., Schauer, G.F., Gorno-Tempini, M.L., Weiner, M.W., Miller, B.L., 2005. Neuroanatomical correlates of behavioural disorders in dementia. Brain 128, 2612–2625. https://doi.org/10.1093/brain/awh628
Roth, R.M., Flashman, L.A., Saykin, A.J., McAllister, T.W., Vidaver, R., 2004. Apathy in schizophrenia: reduced frontal lobe volume and neuropsychological deficits. Am J Psychiatry 161, 157–159. https://doi.org/10.1176/appi.ajp.161.1.157
Rowe, J.B., Stephan, K.E., Friston, K., Frackowiak, R.S.J., Passingham, R.E., 2005. The prefrontal cortex shows context-specific changes in effective connectivity to motor or visual cortex during the selection of action or colour. Cereb. Cortex 15, 85–95. https://doi.org/10.1093/cercor/bhh111

Ruff, R.M., Allen, C.C., Farrow, C.E., Niemann, H., Wylie, T., 1994. Figural fluency: differential impairment in patients with left versus right frontal lobe lesions. Arch Clin Neuropsychol 9, 41–55.
Rushworth, M., Walton, M., Kennerley, S., Bannerman, D., 2004. Action sets and decisions in the medial frontal cortex. Trends in Cognitive Sciences 8, 410–417. https://doi.org/10.1016/j.tics.2004.07.009
Rushworth, M.F.S., Behrens, T.E.J., 2008. Choice, uncertainty and value in prefrontal and cingulate cortex. Nature Neuroscience 11, 389–397. https://doi.org/10.1038/nn2066
Sack, A.T., 2009. Parietal cortex and spatial cognition. Behav. Brain Res. 202, 153–161. https://doi.org/10.1016/j.bbr.2009.03.012
Sakai, K., Crochet, S., 2001. Differentiation of presumed serotonergic dorsal raphe neurons in relation to behavior and wake-sleep states. Neuroscience 104, 1141–1155.
Salamone, J.D., Arizzi, M.N., Sandoval, M.D., Cervone, K.M., Aberman, J.E., 2002. Dopamine antagonists alter response allocation but do not suppress appetite for food in rats: contrast between the effects of SKF 83566, raclopride, and fenfluramine on a concurrent choice task. Psychopharmacology (Berl.) 160, 371–380. https://doi.org/10.1007/s00213-001-0994-x
Salamone, J.D., Correa, M., Yang, J.-H., Rotolo, R., Presby, R., 2018. Dopamine, Effort-Based Choice, and Behavioral Economics: Basic and Translational Research. Frontiers in Behavioral Neuroscience 12. https://doi.org/10.3389/fnbeh.2018.00052
Salamone, J.D., Cousins, M.S., Bucher, S., 1994. Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. Behav. Brain Res. 65, 221–229.
Salamone, J.D., Steinpreis, R.E., McCullough, L.D., Smith, P., Grebel, D., Mahan, K., 1991. Haloperidol and nucleus accumbens dopamine depletion suppress lever pressing for food but increase free food consumption in a novel food choice procedure. Psychopharmacology (Berl.) 104, 515–521.
Salamone, J.D., Yohn, S.E., López-Cruz, L., San Miguel, N., Correa, M., 2016. Activational and effort-related aspects of motivation: neural mechanisms and implications for psychopathology. Brain 139, 1325–1347. https://doi.org/10.1093/brain/aww050
Salum, G.A., Manfro, G.G., Fleck, M.P., 2011. What is not "Effective" in Mild to Moderate Depression: Antidepressants or the Hamilton Rating Scale for Depression? CNS Spectr 16, 99. https://doi.org/10.1017/S1092852912000259
Sanders, A.C., Hussain, A.J., Hen, R., Zhuang, X., 2007. Chronic blockade or constitutive deletion of the serotonin transporter reduces operant responding for food reward. Neuropsychopharmacology 32, 2321–2329. https://doi.org/10.1038/sj.npp.1301368
Sansone, R.A., Sansone, L.A., 2010. SSRI-Induced Indifference. Psychiatry (Edgmont) 7, 14–18.
Santangelo, G., D'Iorio, A., Piscopo, F., Cuoco, S., Longo, K., Amboni, M., Baiano, C., Tafuri, D., Pellecchia, M.T., Barone, P., Vitale, C., 2017. Assessment of apathy

minimising the effect of motor dysfunctions in Parkinson's disease: a validation study of the dimensional apathy scale. Qual Life Res. https://doi.org/10.1007/s11136-017-1569-6

Sawamura, H., Georgieva, S., Vogels, R., Vanduffel, W., Orban, G.A., 2005. Using Functional Magnetic Resonance Imaging to Assess Adaptation and Size Invariance of Shape Processing by Humans and Monkeys. Journal of Neuroscience 25, 4294–4306. https://doi.org/10.1523/JNEUROSCI.0377-05.2005

Schmidt, L., Lebreton, M., Cléry-Melin, M.-L., Daunizeau, J., Pessiglione, M., 2012. Neural mechanisms underlying motivation of mental versus physical effort. PLoS Biol. 10, e1001266. https://doi.org/10.1371/journal.pbio.1001266

Schmitz, Y., Benoit-Marand, M., Gonon, F., Sulzer, D., 2003. Presynaptic regulation of dopaminergic neurotransmission. J. Neurochem. 87, 273–289.

Schoemaker, H., Claustre, Y., Fage, D., Rouquier, L., Chergui, K., Curet, O., Oblin, A., Gonon, F., Carter, C., Benavides, J., Scatton, B., 1997. Neurochemical characteristics of amisulpride, an atypical dopamine D2/D3 receptor antagonist with both presynaptic and limbic selectivity. J. Pharmacol. Exp. Ther. 280, 83–97.

Scholl, J., Kolling, N., Nelissen, N., Wittmann, M.K., Harmer, C.J., Rushworth, M.F.S., 2015. The Good, the Bad, and the Irrelevant: Neural Mechanisms of Learning Real and Hypothetical Rewards and Effort. Journal of Neuroscience 35, 11233–11251. https://doi.org/10.1523/JNEUROSCI.0396-15.2015

Schreckenberger, M., Hägele, S., Siessmeier, T., Buchholz, H.-G., Armbrust-Henrich, H., Rösch, F., Gründer, G., Bartenstein, P., Vogt, T., 2004. The dopamine D2 receptor ligand 18F-desmethoxyfallypride: an appropriate fluorinated PET tracer for the differential diagnosis of parkinsonism. Eur. J. Nucl. Med. Mol. Imaging 31, 1128–1135. https://doi.org/10.1007/s00259-004-1465-5

Schroeter, M.L., Vogt, B., Frisch, S., Becker, G., Seese, A., Barthel, H., Mueller, K., Villringer, A., Sabri, O., 2011. Dissociating behavioral disorders in early dementia—An FDG-PET study. Psychiatry Research: Neuroimaging 194, 235–244. https://doi.org/10.1016/j.pscychresns.2011.06.009

Schultz, W., 2013. Updating dopamine reward signals. Current Opinion in Neurobiology 23, 229–238. https://doi.org/10.1016/j.conb.2012.11.012

Schultz, W., Dickinson, A., 2000. Neuronal coding of prediction errors. Annu. Rev. Neurosci. 23, 473–500. https://doi.org/10.1146/annurev.neuro.23.1.473

Schweimer, J., Hauber, W., 2005. Involvement of the rat anterior cingulate cortex in control of instrumental responses guided by reward expectancy. Learn. Mem. 12, 334–342. https://doi.org/10.1101/lm.90605

Schweimer, J., Saft, S., Hauber, W., 2005. Involvement of catecholamine neurotransmission in the rat anterior cingulate in effort-related decision making. Behav. Neurosci. 119, 1687–1692. https://doi.org/10.1037/0735-7044.119.6.1687

Schweimer, J.V., Ungless, M.A., 2010. Phasic responses in dorsal raphe serotonin neurons to noxious stimuli. Neuroscience 171, 1209–1215. https://doi.org/10.1016/j.neuroscience.2010.09.058

Schweizer, T.S., Schmalenberger, K.M., Eisenlohr-Moul, T.A., Mojzisch, A., Kaiser, S., Funke, J., 2016. Cognitive and Affective Aspects of Creative Option Generation in Everyday Life Situations. Frontiers in Psychology 07. https://doi.org/10.3389/fpsyg.2016.01132

Seeman, P., Kapur, S., 2000. Schizophrenia: more dopamine, more D2 receptors. Proc. Natl. Acad. Sci. U.S.A. 97, 7673–7675.

Shamay-Tsoory, S.G., Adler, N., Aharon-Peretz, J., Perry, D., Mayseless, N., 2011. The origins of originality: The neural bases of creative thinking and originality. Neuropsychologia 49, 178–185. https://doi.org/10.1016/j.neuropsychologia.2010.11.020

Shibasaki, H., Barrett, G., Halliday, E., Halliday, A.., 1980. Components of the movement-related cortical potential and their scalp topography. Electroencephalography and Clinical Neurophysiology 49, 213–226. https://doi.org/10.1016/0013-4694(80)90216-3

Shibasaki, H., Hallett, M., 2006. What is the Bereitschaftspotential? Clin Neurophysiol 117, 2341–2356. https://doi.org/10.1016/j.clinph.2006.04.025

Shima, K., Aya, K., Mushiake, H., Inase, M., Aizawa, H., Tanji, J., 1991. Two movement-related foci in the primate cingulate cortex observed in signal-triggered and self-paced forelimb movements. J. Neurophysiol. 65, 188–202.

Sinha, N., Manohar, S., Husain, M., 2013. Impulsivity and apathy in Parkinson's disease. Journal of Neuropsychology 7, 255–283. https://doi.org/10.1111/jnp.12013

Sink, K.S., Vemuri, V.K., Olszewska, T., Makriyannis, A., Salamone, J.D., 2008. Cannabinoid CB1 antagonists and dopamine antagonists produce different effects on a task involving response allocation and effort-related choice in food-seeking behavior. Psychopharmacology (Berl.) 196, 565–574. https://doi.org/10.1007/s00213-007-0988-4

Skidmore, F.M., Yang, M., Baxter, L., von Deneen, K., Collingwood, J., He, G., Tandon, R., Korenkevych, D., Savenkov, A., Heilman, K.M., Gold, M., Liu, Y., 2013. Apathy, depression, and motor symptoms have distinct and separable resting activity patterns in idiopathic Parkinson disease. NeuroImage 81, 484–495. https://doi.org/10.1016/j.neuroimage.2011.07.012

Skorvanek, M., Gdovinova, Z., Rosenberger, J., Ghorbani Saeedian, R., Nagyova, I., Groothoff, J.W., van Dijk, J.P., 2015. The associations between fatigue, apathy, and depression in Parkinson's disease. Acta Neurologica Scandinavica 131, 80–87.

Skvortsova, V., Palminteri, S., Pessiglione, M., 2014. Learning To Minimize Efforts versus Maximizing Rewards: Computational Principles and Neural Correlates. Journal of Neuroscience 34, 15621–15630. https://doi.org/10.1523/JNEUROSCI.1350-14.2014

Smiley, J.F., Levey, A.I., Ciliax, B.J., Goldman-Rakic, P.S., 1994. D1 dopamine receptor immunoreactivity in human and monkey cerebral cortex: predominant and extrasynaptic localization in dendritic spines. Proc. Natl. Acad. Sci. U.S.A. 91, 5720–5724.

Snaith, R.P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., Trigwell, P., 1995. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. The British Journal of Psychiatry 167, 99–103.

Sockeel, P., Dujardin, K., Devos, D., Deneve, C., Destee, A., Defebvre, L., 2006. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry 77, 579–584.

Soon, C.S., Brass, M., Heinze, H.-J., Haynes, J.-D., 2008. Unconscious determinants of free decisions in the human brain. Nature Neuroscience 11, 543–545. https://doi.org/10.1038/nn.2112

Starke, K., Göthert, M., Kilbinger, H., 1989. Modulation of neurotransmitter release by presynaptic autoreceptors. Physiol. Rev. 69, 864–989. https://doi.org/10.1152/physrev.1989.69.3.864

Starkstein, S.E., Ingram, L., Garau, M.L., Mizrahi, R., 2005. On the overlap between apathy and depression in dementia. J. Neurol. Neurosurg. Psychiatry 76, 1070–1074. https://doi.org/10.1136/jnnp.2004.052795

Starkstein, S.E., Leentjens, A.F.G., 2008. The nosological position of apathy in clinical practice. Journal of Neurology, Neurosurgery & Psychiatry 79, 1088–1092. https://doi.org/10.1136/jnnp.2007.136895

Starkstein, S.E., Migliorelli, R., Manes, F., Tesón, A., Petracca, G., Chemerinski, E., Sabe, L., Leiguarda, R., 1995. The prevalence and clinical correlates of apathy and irritability in Alzheimer's disease. European Journal of Neurology 2, 540–546. https://doi.org/10.1111/j.1468-1331.1995.tb00171.x

Stocchi, F., Vacca, L., Berardelli, A., Onofrj, M., Manfredi, M., Ruggieri, S., 2003. Dual dopamine agonist treatment in Parkinson's disease. J. Neurol. 250, 822–826. https://doi.org/10.1007/s00415-003-1086-0

Strauss, M.E., Sperry, S.D., 2002. An informant-based assessment of apathy in Alzheimer disease. Neuropsychiatry Neuropsychol Behav Neurol 15, 176–183.

Stuss, D.T., 2011. Functions of the Frontal Lobes: Relation to Executive Functions. Journal of the International Neuropsychological Society 17, 759–765.

Stuss, D.T., Alexander, M.P., 2007. Is there a dysexecutive syndrome? Philosophical Transactions of the Royal Society B: Biological Sciences 362, 901–915. https://doi.org/10.1098/rstb.2007.2096

Stuss, D.T., Alexander, M.P., Hamer, L., Palumbo, C., Dempster, R., Binns, M., Levine, B., Izukawa, D., 1998. The effects of focal anterior and posterior brain lesions on verbal fluency. J Int Neuropsychol Soc 4, 265–278.

Stuss, D.T., Van Reekum, R., Murphy, K.J., 2000. Differentiation of states and causes of apathy., in: Series in Affective Science. The Neuropsychology of Emotion. Oxford University Press, New York, pp. 340–363.

Suchy, Y., Kraybill, M.L., Gidley Larson, J.C., 2010. Understanding design fluency: Motor and executive contributions. Journal of the International Neuropsychological Society 16, 26. https://doi.org/10.1017/S1355617709990804

Sumners, C., de Vries, J.B., Horn, A.S., 1981. Behavioural and neurochemical studies on apomorphine-induced hypomotility in mice. Neuropharmacology 20, 1203–1208.

Takeuchi, H., Taki, Y., Sassa, Y., Hashizume, H., Sekiguchi, A., Fukushima, A., Kawashima, R., 2010. Regional gray matter volume of dopaminergic system associate with creativity: Evidence from voxel-based morphometry. NeuroImage 51, 578–585. https://doi.org/10.1016/j.neuroimage.2010.02.078

Tengvar, C., Johansson, B., Sorensen, J., 2004. Frontal lobe and cingulate cortical metabolic dysfunction in acquired akinetic mutism: a PET study of the interval form of carbon monoxide poisoning. Brain Injury 18, 615–625. https://doi.org/10.1080/02699050310001622806

Thaler, D., Chen, Y.-C., Nixon, P.D., Stern, C.E., Passingham, R.E., 1995. The functions of the medial premotor cortex: I. Simple learned movements. Experimental Brain Research 102. https://doi.org/10.1007/BF00230649

Thaler, D.E., Rolls, E.T., Passingham, R.E., 1988. Neuronal activity of the supplementary motor area (SMA) during internally and externally triggered wrist movements. Neurosci. Lett. 93, 264–269.

Thimm, M., Weidner, R., Fink, G.R., Sturm, W., 2012. Neural mechanisms underlying freedom to choose an object. Hum Brain Mapp 33, 2686–2693. https://doi.org/10.1002/hbm.21393

Thomas, R.P., Dougherty, M.R., Sprenger, A.M., Harbison, J.I., 2008. Diagnostic hypothesis generation and human judgment. Psychological Review 115, 155–185. https://doi.org/10.1037/0033-295X.115.1.155

Thorré, K., Sarre, S., Smolders, I., Ebinger, G., Michotte, Y., 1998. Dopaminergic regulation of serotonin release in the substantia nigra of the freely moving rat using microdialysis. Brain Res. 796, 107–116.

Thurstone, L.L., 1938. Primary mental abilities. University of Chicago Press, Chicago.

Tissari, A.H., Rossetti, Z.L., Meloni, M., Frau, M.I., Gessa, G.L., 1983. Autoreceptors mediate the inhibition of dopamine synthesis by bromocriptine and lisuride in rats. Eur. J. Pharmacol. 91, 463–468.

Tootell, R.B.H., Hadjikhani, N.K., Vanduffel, W., Liu, A.K., Mendola, J.D., Sereno, M.I., Dale, A.M., 1998. Functional analysis of primary visual cortex (V1) in humans. Proceedings of the National Academy of Sciences 95, 811–817. https://doi.org/10.1073/pnas.95.3.811

Tootell, R.B.H., Reppas, J.B., Dale, A.M., Look, R.B., Sereno, M.I., Malach, R., Brady, T.J., Rosen, B.R., 1995. Visual motion aftereffect in human cortical area MT revealed by functional magnetic resonance imaging. Nature 375, 139–141. https://doi.org/10.1038/375139a0

Torrance, E.P., 1991. The Nature of Creativity as Manifested in its Testing., in: The Nature of Creativity. Cambridge University Press, New York, pp. 76–98.

Trevena, J.A., Miller, J., 2002. Cortical Movement Preparation before and after a Conscious Decision to Move. Consciousness and Cognition 11, 162–190. https://doi.org/10.1006/ccog.2002.0548

Tucha, O.W., Smely, C.W., Lange, K.W., 1999. Verbal and figural fluency in patients with mass lesions of the left or right frontal lobes. J Clin Exp Neuropsychol 21, 229–236. https://doi.org/10.1076/jcen.21.2.229.928

Tunnard, C., Whitehead, D., Hurt, C., Wahlund, L., Mecocci, P., Tsolaki, M., Vellas, B., Spenger, C., Kłoszewska, I., Soininen, H., Lovestone, S., Simmons, A., on behalf of the AddNeuroMed Consortium, 2011. Apathy and cortical atrophy in

Alzheimer's disease. International Journal of Geriatric Psychiatry 26, 741–748. https://doi.org/10.1002/gps.2603
Uher, R., Perlis, R.H., Henigsberg, N., Zobel, A., Rietschel, M., Mors, O., Hauser, J., Dernovsek, M.Z., Souery, D., Bajs, M., Maier, W., Aitchison, K.J., Farmer, A., McGuffin, P., 2012. Depression symptom dimensions as predictors of antidepressant treatment outcome: replicable evidence for interest-activity symptoms. Psychological Medicine 42, 967–980. https://doi.org/10.1017/S0033291711001905
Usiello, A., Baik, J.H., Rougé-Pont, F., Picetti, R., Dierich, A., LeMeur, M., Piazza, P.V., Borrelli, E., 2000. Distinct functions of the two isoforms of dopamine D2 receptors. Nature 408, 199–203. https://doi.org/10.1038/35041572
Uslaner, J.M., Acerbo, M.J., Jones, S.A., Robinson, T.E., 2006. The attribution of incentive salience to a stimulus that signals an intravenous injection of cocaine. Behav. Brain Res. 169, 320–324. https://doi.org/10.1016/j.bbr.2006.02.001
van Eimeren, T., Wolbers, T., Münchau, A., Büchel, C., Weiller, C., Roman Siebner, H., 2006. Implementation of visuospatial cues in response selection. NeuroImage 29, 286–294. https://doi.org/10.1016/j.neuroimage.2005.07.014
van Loo, H.M., de Jonge, P., Romeijn, J.-W., Kessler, R.C., Schoevers, R.A., 2012. Data-driven subtypes of major depressive disorder: a systematic review. BMC Med 10, 156. https://doi.org/10.1186/1741-7015-10-156
Van Oostende, S., Van Hecke, P., Sunaert, S., Nuttin, B., Marchal, G., 1997. FMRI Studies of the Supplementary Motor Area and the Premotor Cortex. NeuroImage 6, 181–190. https://doi.org/10.1006/nimg.1997.0287
Vandenberghe, R., Gillebert, C.R., 2009. Parcellation of parietal cortex: convergence between lesion-symptom mapping and mapping of the intact functioning brain. Behav. Brain Res. 199, 171–182. https://doi.org/10.1016/j.bbr.2008.12.005
Vansteenkiste, M., Lens, W., De Witte, H., Feather, N.T., 2005. Understanding unemployed people's job search behaviour, unemployment experience and well-being: a comparison of expectancy-value theory and self-determination theory. Br J Soc Psychol 44, 268–287.
Vansteenkiste, M., Lens, W., De Witte, S., De Witte, H., Deci, E.L., 2004. The'why' and'why not' of job search behaviour: their relation to searching, unemployment experience, and well-being. European Journal of Social Psychology 34, 345–363.
Vares, E.A., Salum, G.A., Spanemberg, L., Caldieraro, M.A., Fleck, M.P., 2015. Depression Dimensions: Integrating Clinical Signs and Symptoms from the Perspectives of Clinicians and Patients. PLOS ONE 10, e0136037. https://doi.org/10.1371/journal.pone.0136037
Vassena, E., Silvetti, M., Boehler, C.N., Achten, E., Fias, W., Verguts, T., 2014. Overlapping Neural Systems Represent Cognitive Effort and Reward Anticipation. PLoS ONE 9, e91008. https://doi.org/10.1371/journal.pone.0091008
Verbaan, D., Marinus, J., Visser, M., van Rooden, S.M., Stiggelbout, A.M., Middelkoop, H. a. M., van Hilten, J.J., 2007. Cognitive impairment in

Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 78, 1182–1187. https://doi.org/10.1136/jnnp.2006.112367
Verbaarschot, C., Farquhar, J., Haselager, P., 2015. Lost in time... Consciousness and Cognition 33, 300–315. https://doi.org/10.1016/j.concog.2015.01.011
Vertes, R.P., 1991. A PHA-L analysis of ascending projections of the dorsal raphe nucleus in the rat. The Journal of Comparative Neurology 313, 643–668. https://doi.org/10.1002/cne.903130409
Vertes, R.P., Fortin, W.J., Crane, A.M., 1999. Projections of the median raphe nucleus in the rat. The Journal of Comparative Neurology 407, 555–582. https://doi.org/10.1002/(SICI)1096-9861(19990517)407:4<555::AID-CNE7>3.0.CO;2-E
Vrieze, E., Demyttenaere, K., Bruffaerts, R., Hermans, D., Pizzagalli, D.A., Sienaert, P., Hompes, T., de Boer, P., Schmidt, M., Claes, S., 2014. Dimensions in major depressive disorder and their relevance for treatment outcome. Journal of Affective Disorders 155, 35–41. https://doi.org/10.1016/j.jad.2013.10.020
Wallis, J.D., Miller, E.K., 2003. From Rule to Response: Neuronal Processes in the Premotor and Prefrontal Cortex. Journal of Neurophysiology 90, 1790–1806. https://doi.org/10.1152/jn.00086.2003
Walsh, M.M., Anderson, J.R., 2012. Learning from experience: event-related potential correlates of reward processing, neural adaptation, and behavioral choice. Neurosci Biobehav Rev 36, 1870–1884. https://doi.org/10.1016/j.neubiorev.2012.05.008
Walton, M.E., Bannerman, D.M., Alterescu, K., Rushworth, M.F.S., 2003. Functional specialization within medial frontal cortex of the anterior cingulate for evaluating effort-related decisions. J. Neurosci. 23, 6475–6479.
Walton, M.E., Bannerman, D.M., Rushworth, M.F.S., 2002. The role of rat medial frontal cortex in effort-based decision making. J. Neurosci. 22, 10996–11003.
Walton, M.E., Croxson, P.L., Rushworth, M.F.S., Bannerman, D.M., 2005. The mesocortical dopamine projection to anterior cingulate cortex plays no role in guiding effort-related decisions. Behav. Neurosci. 119, 323–328. https://doi.org/10.1037/0735-7044.119.1.323
Ward, L.C., 2006. Comparison of factor structure models for the Beck Depression Inventory--II. Psychol Assess 18, 81–88. https://doi.org/10.1037/1040-3590.18.1.81
Waterhouse, B.D., Devilbiss, D., Seiple, S., Markowitz, R., 2004. Sensorimotor-related discharge of simultaneously recorded, single neurons in the dorsal raphe nucleus of the awake, unrestrained rat. Brain Res. 1000, 183–191. https://doi.org/10.1016/j.brainres.2003.11.030
Weeks, R.A., Honda, M., Catalan, M.-J., Hallett, M., 2001. Comparison of Auditory, Somatosensory, and Visually Instructed and Internally Generated Finger Movements: A PET Study. NeuroImage 14, 219–230. https://doi.org/10.1006/nimg.2001.0780
Wessel, K., Zeffiro, T., Toro, C., Hallett, M., 1997. Self-Paced Versus Metronome-Paced 7 Finger Movements: A Positron Emission Tomography Study. Journal of Neuroimaging 7, 145–151. https://doi.org/10.1111/jon199773145

Winstanley, C.A., Theobald, D.E.H., Dalley, J.W., Glennon, J.C., Robbins, T.W., 2004. 5-HT2A and 5-HT2C receptor antagonists have opposing effects on a measure of impulsivity: interactions with global 5-HT depletion. Psychopharmacology (Berl.) 176, 376–385. https://doi.org/10.1007/s00213-004-1884-9

Wise, S.P., 1985. The primate premotor cortex: past, present, and preparatory. Annu. Rev. Neurosci. 8, 1–19. https://doi.org/10.1146/annurev.ne.08.030185.000245

Wongpakaran, N., van Reekum, R., Wongpakaran, T., Clarke, D., 2007. Selective serotonin reuptake inhibitor use associates with apathy among depressed elderly: a case-control study. Ann Gen Psychiatry 6, 7. https://doi.org/10.1186/1744-859X-6-7

Worden, L.T., Shahriari, M., Farrar, A.M., Sink, K.S., Hockemeyer, J., Müller, C.E., Salamone, J.D., 2009. The adenosine A2A antagonist MSX-3 reverses the effort-related effects of dopamine blockade: differential interaction with D1 and D2 family antagonists. Psychopharmacology (Berl.) 203, 489–499. https://doi.org/10.1007/s00213-008-1396-0

Xu, M., Koeltzow, T.E., Cooper, D.C., Tonegawa, S., White, F.J., 1999. Dopamine D3 receptor mutant and wild-type mice exhibit identical responses to putative D3 receptor-selective agonists and antagonists. Synapse 31, 210–215. https://doi.org/10.1002/(SICI)1098-2396(19990301)31:3<210::AID-SYN6>3.0.CO;2-0

Yesavage, J.A., Sheikh, J.I., 1986. 9/Geriatric Depression Scale (GDS): Recent Evidence and Development of a Shorter Version. Clinical Gerontologist 5, 165–173. https://doi.org/10.1300/J018v05n01_09

Yohn, S.E., Collins, S.L., Contreras-Mora, H.M., Errante, E.L., Rowland, M.A., Correa, M., Salamone, J.D., 2016. Not All Antidepressants Are Created Equal: Differential Effects of Monoamine Uptake Inhibitors on Effort-Related Choice Behavior. Neuropsychopharmacology 41, 686–694. https://doi.org/10.1038/npp.2015.188

Yohn, S.E., Santerre, J.L., Nunes, E.J., Kozak, R., Podurgiel, S.J., Correa, M., Salamone, J.D., 2015. The role of dopamine D1 receptor transmission in effort-related choice behavior: Effects of D1 agonists. Pharmacol. Biochem. Behav. 135, 217–226. https://doi.org/10.1016/j.pbb.2015.05.003

Yuen, G.S., Gunning, F.M., Woods, E., Klimstra, S.A., Hoptman, M.J., Alexopoulos, G.S., 2014. Neuroanatomical correlates of apathy in late-life depression and antidepressant treatment response. J Affect Disord 166, 179–186. https://doi.org/10.1016/j.jad.2014.05.008

Zamboni, G., Huey, E.D., Krueger, F., Nichelli, P.F., Grafman, J., 2008. Apathy and disinhibition in frontotemporal dementia: Insights into their neural correlates. Neurology 71, 736–742. https://doi.org/10.1212/01.wnl.0000324920.96835.95

Ziropadja, L., Stefanova, E., Petrovic, M., Stojkovic, T., Kostic, V.S., 2012. Apathy and depression in Parkinson's disease: The Belgrade PD study report. Parkinsonism & Related Disorders 18, 339–342. https://doi.org/10.1016/j.parkreldis.2011.11.020