DOCTOR OF PHILOSOPHY

Neuropsychology of Motivated Forgetting

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Award date:
2016

Awarding institution:
Bangor University

PRIFYSGOL
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Neuropsychology of Motivated Forgetting

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A thesis submitted for the degree of

Doctor of Philosophy (Neuropsychology)

September 2012 - August 2016

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Funding body (if any):

1. School of Psychology, Bangor University funded my PhD studentship and the tDCS Study (Experiment 2)
2. Medical Research Council Grant awarded to Michael C. Anderson supported the Lesion Study (Experiment 1); and the data for the Diffusion Tensor Imaging Study (Experiment 3)

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DEDICATION PAGE

To people who believed in me…

My mentors Anthony Wagner & Mike Anderson…

My PhD Committee: Oliver Turnbull, Martyn Bracewell, Richard Ramsey & Helen Morgan

Shanker who supported this dream and has loved me throughout this journey. Savithri for her strength and the unending support.

Finally, to all my patients and participants, who always had time for my long studies.

Acknowledgements

A year later since I initially hoped to have submitted, I have enjoyed the process of writing-up this PhD. Last year I crossed two milestones. Firstly, I completed all the studies that were integral to this PhD. Secondly, got appointed to my first full-time academic position, a Lecturer (Cognitive Psychology) at Bournemouth University.

The idea for this PhD was born as a result of an interesting discussion with Mike. His support, advise, conversations and presence have been a crucial to my growth and development. The PhD would not have been such a fun journey without the support and guidance from Oliver, Martyn, Richard, Erin and Helen. This PhD has been all that I wanted, at this point, I realise how important it is to not only have a passion for my work, but also live my life beyond academia.

There are so many people, who have supported this journey in various roles at different levels, it's impossible to list them all. I would sincerely like to thank everyone I can…

Bangor University, North Wales: Oliver Turnbull, Martyn Bracewell, Helen Morgan, Erin Heerey, Richard Ramsay, Robert Rogers, Paloma Mari-Beffa, Marie-Josephe Taintuer, Charles Leek, Paul Mullins, Mihela Erjavec,, Simon Viktor, Stephan Boehm, Bob Rafal, Andrea Reynolds, Charu Dada, Anthony Brooks, Tech-team (IT, Psychology) …

M**RC Cognition and Brain Sciences Unit, Cambridge**

Michael Anderson (Mike), Polly Peers, John Duncan, Taylor Schmitz, Ana Catarino, John Fawcett, Fionnuala Murphy, Susan Gathercole, Anthea, Rosemary,

Sharon, Howard, Russel, Tammy, and the spirit of MRC CBU that can never be explained…

People, colleagues and friends who I would like to acknowledge and cherish: Victoria Lovett, Christian Salas, Steve Johnstone, Joe Bathelt, Chris Rorden, Gary Oppenheim, Kami Koldewyn, Andrew Fischer, Emma Woodberry, Georgina Browne, Dennis Chan, Jon Simons, Rik Henson, Remco Polman, Ellen Sellis, GG, Vijaya Gurumurthi, Nilesh, & Shriya, Georgina (Lumi), Riya (my adorable niece), Sham, Mahesh, Shakti and my in-laws.

Contents

List of Abbreviations **10**

Abstract **11**

1. Introduction **12**

1.1 Introduction to Memory **12**

Memory is desired. 12

Less or more memory. 15

1.2 Memory Retrieval **18**

1.3 Forgetting **20**

Why do we forget? 21

Mechanisms of forgetting. 23

Forgetting due to failed encoding. 23

a) Forgetting due to disrupted consolidation. 25

b) Intentional Forgetting. 27

c) Forgetting due to interference (retrieval competition). 29

d) Forgetting due to resolving competition. 33

1.4 Motivated Forgetting **41**

Think/No-Think (TNT) task. 41

Inhibitory accounts for TNT task. 42

Neural mechanisms of motivated forgetting 44

Cortical regions 44

Hippocampus 47

Pre-frontal hippocampal connections 48

Motivated forgetting in a clinical context 49

Motivated forgetting or repression? 50

1.5 Rationale for this thesis **52**

2. The effect of transcranial Direct Current stimulation (tDCS) on the ability to suppress or facilitate specific memories. 54

2.1 Introduction 54

2.2 Aim and hypothesis 58

2.3 Experiment (2.1) 60

Methods 60

Participants 60

Materials & Procedure 60

The Think/No-Think (TNT) Task 60

Data Analysis 62

Results (Experiment 2.1) 62

2.4 Interim Discussion 63

2.5 Experiment 2.2 (tDCS Study) 64

2.6 Assumptions of tDCS 64

tDCS Methods 66

Participants 66

Methods and Materials 66

tDCS stimulation parameters 66

Questionnaire (tDCS Study). 68

Data Analysis (Exp. 2.2) 69

Results (Experiment 2.2) 69

Questionnaire results 72

2.7 Results (comparing the behavioural results of the experiment without [2.1] and with stimulation [2.2]) 73

2.8 Discussion 75

3. Developing the Patient friendly TNT (*pf*-TNT) 83

3.1 Introduction 83

3.2 Methods 84

Participants 84

3.3 Procedure 85

Pilot Experiment 1 (PE1): TNT Pilot in healthy older adults 86

Pilot Experiment 2 (PE2): TNT Single Case Study (Patient MJ) 88

Pilot Experiment 3 (PE3): TNT in patients (n = 6) with focal lesions. 88

3.4 Results 90

Pilot Experiment 1 (PE1): TNT Pilot in healthy older adults 90

Pilot Experiment 2 (PE2): TNT Single Case Study (Patient MJ) 92

Pilot Experiment 3 (PE3): TNT in patients (n = 5, plus Patient MJ). 93

3.5 Summary of the pilot studies 94

Modifications in the delivery method of the instruction. 96

3.6 Discussion 98

Adaptations to designing a patient friendly TNT task 98

4. Neuropsychology of motivated forgetting: Insights from patients with focal neurological lesions. 101

4.1 Introduction 101

Think/no-think task 104

Mechanisms of motivated forgetting 105

Motivated forgetting: Insights from neuroscience 106

Motivated forgetting in patient populations 106

Laterality in Motivated forgetting 109

4.2 Methods 111

Materials: *Patient friendly*-Think/No-Think (*Pf*-TNT) Task 113

Learning Phase 114

TNT Phase 116

Memory Retrieval Phase 118

Randomization parameters for TNT Task 118

4.3 Demographic and other measures 119

4.4 Results (Behavioural) 120

Question 1: Can patients with left frontal lesions suppress unwanted memories? 121

Performances across the Independent and Same Probe 122

Question 2: Can patients with right frontal lesions suppress unwanted memories? 122

Performances across the Independent and Same Probe 124

124

Question 3a: Is there a significant difference between patients with LFL and RFL in the ability to supress unwanted memories 124

Question 3b: Is there a significant difference between patients with LFL and RFL in the ability to recall memories (facilitation effect)? 126

4.5 Methods (Lesion Analysis) 127

4.6 Results (Lesion Analysis) 128

Question 4: Whether the size of lesion correlates with the ability to suppress. 128

Question 5: Whether all patients with lesions to the right hemisphere have impaired performance on inhibition measured by TNT or is the lesion to specific regions (rDLPF or superior frontal) that affect behaviour? 130

4.7 Discussion 132

Lateral differences in memory inhibition 133

Individual Differences 134

Clinical Implications 135

5. Frontal-hippocampal pathways underlying inhibitory control of unwanted memories. 138

5.1 Introduction 138

Right Lateral prefrontal cortex. 139
Subcortical structures 140
The prefrontal-hippocampal structural connections 141
Cingulum Bundle 142
Entorhinal gating hypothesis 143
The thalamo-hippocampal modulation hypothesis 143
Motivation for the current study 144
5.2 Methods 145
Think/No-Think task 145
Scanning Parameters 146
Anatomical 146
Diffusion Tensor Imaging [DTI] 147
Diffusion MRI pre-processing 147
Probalistic Tractography (analysis undertaken, but not reported in this thesis). 147
Dissection of the frontal-hippocampal connections in human brain (deterministic tractography) 148
Diffusion Tensor Estimation 148
Regions of Interest 149
5.3 Results (Deterministic Tractography) 150
Frontal-hippocampal connectivity 150
Correlation between individual performances and tractography 151
5.4 Discussion 152
6. Discussion 155
6.1 General summary 155
6.2 Direct-suppression is more right lateralised 156
6.3 Can direct-suppression be modulated? 158
6.4 Structural connections underlying motivated forgetting? 159
6.5 Limitations 160

6.6 Future directions 162

6.7 Conclusion 164

7. References 166

8. Appendix A (Chapter 2) 213

9. Appendix B (Chapter 4) 215

10. Appendix C: Ethics Approvals etc. 217

Ethics Approval: BCUHB R&D and NISHR, RES, North Wales 217

11. Appendix D: Publications and Abstracts 221

11.1 First Author Publications (In preparation) 221

11.2 Co-authored Publications (Appendix E) 221

11.3 First author abstracts 221

12. Emotion-based learning: Insights from the IGT (Appendix E) 222

List of Abbreviations

AC	Anodal-Cathodal
BA	Brodmann area
CA	Cathodal-Anodal
ns.	Not significant
CBU	Cognition and Brain Sciences Unit
DLPFC	Dorsolateral pre-frontal cortex
DTI	Diffusion Tensor Imaging
FA	Fractional Anaisotrophy
fMRI	functional Magnetic Resonance Imaging
Hipp.	Hippocampus
IP	Independent Probe
LFL	Left frontal lesions
MFG	Medial frontal gyrus
mins	minutes
MRC	Medical Research Council
ms	Milli seconds
PFC	Prefrontal cortex
Pre-SMA	Pre-supplementary motor area
R	right
RFL	Right frontal lesion
s	seconds
SP	Same Probe
SPIP	Same Probe Independent Probe
tDCS	transcranial Direct Current Stimulation
TNT	Think/No-Think
VLPFC	Ventrolateral pre-frontal cortex

Abstract

When confronted with an unwelcome reminder, people often inhibit the unwanted memory from awareness, a process that causes forgetting. This *suppression-induced forgetting* (SIF), also sometimes known as *motivated forgetting,* can be empirically measured by the Think/No-Think (TNT) task. Chapter 1 reviews the literature on memory inhibition. Imaging work indicates suppressing retrieval engages the right dorsolateral prefrontal cortex (rDLPFC), which in turn may inhibit the retrieval processes within the hippocampus. This thesis, using a range of methods, aims to better understand the neuropsychology of motivated forgetting. Chapter 2 investigates whether the ability to inhibit unwanted memories can be modulated through electrical stimulation. Stimulation methods do not appear to improve inhibition, at least in this cohort, one possible reason for this being the increased perceived thought control ability. Chapter 3 reports the first ever adaptation of the TNT task in patients with unilateral frontal lesions. Pilot testing in Chapter 4 reports the study in patients with unilateral frontal lesions. The results suggested that patients with left frontal lesions showed a robust SIF, compared to those with right-frontal lesions who showed none. Finally, Chapter 5 attempted to identify the structural connectivity underlying inhibitory control of motivated forgetting. The results indicate that the DLPFC is connected to the hippocampus by a subset of the two tracts, namely the anterior thalamic projection connecting the DLPFC to the caudate nucleus, and the fornix. Future directions to expand on the finding of this thesis are discussed in Chapter 6.

1. Introduction

1.1 Introduction to Memory

Memory refers to one's ability to encode, store and reconstruct past experiences, but is also commonly associated with retrieving events from the past. Documented attempts to understand human memory have antecedents back at least to Aristotle (Ross, 1930) and has sparked interest amongst philosophers like Plato (in Theaetetus (191c.d; Pilebus, 39b,), Leibniz and Herbart (Schacter & Tulving, 1994), as well as a wide range of scientists (e.g. Atkinson & Shiffrin, 1968; James, 1890; Nadel & O'Keefe, 1974; Reiff and Scheerer, 1959; Schacter et al., 2012; Tulving, 1962; Tulving, 2002; Waugh & Norman, 1965). Early research on memory was based on every day experiences, and studying patients with memory impairment (e.g. Ribot, 1881; Winslow, 1861; Korsakoff, 1887). Since Ebbinghaus (1885) and Bartlett (1932) introduced the study of memory from an experimental context, there has been over a hundred years of memory research.

Memory is desired.

An overarching theme of memory research has focused on memory being essential to having continuity in everyday life (Baddeley, Anderson & Eysenck, 2012). In recent times, memory research has extended beyond understanding the systems of memory (e.g. Addis et al., 2014; Aleman, Hijman, deHaan & Khan, 1999; Brown & Aggleton, 2001; Doll, Shohamy, & Daw, 2015; Eichenbaum et al., 2007; Foerde, Braun, & Shohamy, 2012; Graham et al., 2006; Maguire et al., 2000; Schacter, 2013; Tulving, 2002; Yonelinas, 2002). Between 1960s and 1980s a number of studies in patients with amnesia informed the progress of memory

research and today there continues to be interest in how different clinical conditions impair memory and learning (Cohen & Squire, 1980; Milner, Corkin, & Teuber, 1968; Poldrack et al., 2001; Squire, 2004; Warrington & Weiskrantz, 1968).

The first experimental study of memory demonstrated the 'rate of decline', using a list of nonsense syllables, (Ebbinghaus, 1885). The documented rapid loss of information over the first few hours or days, with a more gradual and steady decline of information rate of forgetting over time, is the well-known forgetting curve (Ebbinghaus, 1885). A key empirical contribution, and an important landmark, this study shifted the focus of memory studies, from observational studies of everyday events to using empirical and cognitive approaches to understand underlying (cognitive) mechanisms (see Squire, 2004; Tulving, 2002 for a review).

Bartlett argued that learning meaningless words in an experimental setting cannot be applied to understanding memory in everyday life, and favoured more ecologically valid paradigms. An idea empirically laid down by Bartlett (1932) further shifted the process of studying memory, from memory being passive, it was suggested that the memory retrieval is affected during recall, and individuals are agents in this memory process. Bartlett analysed the changes in memory over time, using serial reproduction of a story (War of the Ghosts). He concluded that after the first recall the general form or outline stays constant. Over time, the precise details and construction were not reproduced, but instead the items to be remembered were simplified and transformed into a more familiar context. Bartlett suggested that existing knowledge of the world, or

context (which he termed *Schema),* affects the storage and recall of the newly learnt information (Bartlett, 1932; also see Baddeley, 1976).

Initially, memory was separated into (so-called) primary and secondary memory (James, 1890), a distinction that was later developed into short-term and long-term memory (Hebb, 1949; Atkinson & Shiffrin, 1968). Tulving (1972) introduced the key distinction between episodic and semantic memory, suggesting multiple types of long-term memory (Jacoby, 1991; see Hodges & Patterson, 1997 for review; see also Dew & Cabez 2011).

Today, long-term memory is no longer thought of as a single unit, but it is now well-established that it is composed of several separate systems, that may be sub-served by different brain networks (see Figure 1.1, Henke 2010; Nadel & Hardt, 2011; Schacter & Tulving, 1994; Squire, 2009). This multisystem process must presumably depend on different operating principles (Nelson, 1995;

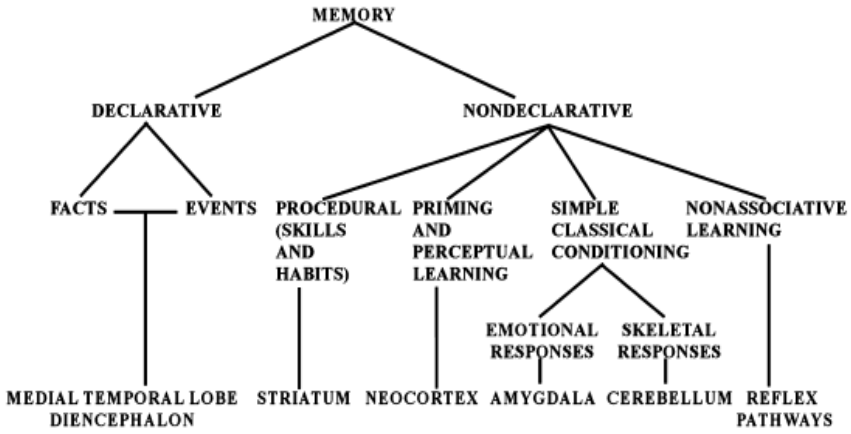


Figure 1.1 A taxonomy of mammalian long-term memory systems. This figure lists the brain region thought to be most important for each form of declarative and non-declarative memory (Squire, 2004).

Schacter and Moscovitch, 1984, 1985; Schacter and Tulving, 1994; Squire, 1987, 1992; Squire, 2004; Squire, 2009; Tulving and Schacter, 1990; Tulving, 1983, 1985; Warrington, 1981).

More than a century of work in memory has focused on the importance of remembering in learning and methods of memory *enhancement* (Karpicke and Roediger, 2008; Glisky & Schacter, 1988; Hersh & Treadgold, 1994; Oudman et al., 2015). Implicitly, literature had retained that remembering is generally *desired*, and better memory is essential for everyday life and continuity of self (Glisky & Schacter, 1986; Meacham, 1972; Patten, 1972; Wilson, Baddeley, & Kapoor, 1995) until recent years.

Less or more memory.

An era of research inquiry into the role of how the brain stores or processes memories (see Yonelinas, 2002). Investigations in patients with memory deficits have repeatedly shown how debilitating memory loss can be. For example, research on retrograde amnesia (Ribot, 1881/1887; Russell and Nathan, 1946) suggests that memory deficits following brain injury could be a result of problems during retrieval or in storage. Neuropsychological studies have substantially advanced the field of memory research (Milner, Corkin & Teuber, 1968; Warrington & Weiskrantz, 1968; Squire, 2004). emphasized on the importance of having a good memory.

Patient H.M. is the best-known, and most extensively reported single patient in neuroscience (Corkin, 2002; Squire, 2009). He was left with severe amnesia after he underwent a bilateral medial temporal resection to control his epileptic seizures (Scoville and Milner, 1957; see also Squire, 2011 for a recent review). Corkin (1968) demonstrated that H.M. was still able to learn procedural skills (e.g. mirror drawing, Milner, Corkin & Teuber, 1968). In the 1980s this idea was expanded by studies in amnesic patients (Cohen & Squire, 1980), supporting the idea that that skill learning was different from a more cognitive form of

memory (Cohen & Squire, 1980; Knowlton, Ramus, & Squire, 1992; Knowlton & Squire, 1993). Patient R.B, who had a lesion confined to the hippocampus (specifically to the CA1 field) developed memory impairments following an ischemic episode (Zola-Morgan et al., 1986). This was the first reported case suggesting specific lesion to the CA1 field could impair memory.

Evidence from the multiple domains, including work in healthy controls, patients and animals (monkeys and rodents) using various techniques have contributed to understanding that the hippocampus is essential to encoding, and spatial memory (Burgess, Maguire, & O'Keefe, 2002; Corkin, 1984; Graham, Barense & Lee, 2010; Hartley et al., 2007; Ranganath, 2010; Ranganath & Hsieh, 2016; Squire, 1992; Squire & Wixted, 2011; Nader et al., 2000; Victor, Victor & Agamanolis, 1990; Zola-Morgan et al., 1986; O'Keefe & Dostrovsky, 1971). Specific lesions to some or most of the hippocampus and related medial temporal structures can cause profound impairments in memory (Banks, Feindel, Milner & Jones-Gotman 2014; Squire, 1992; Squire & Wixted, 2011). Patients with amnesia implicitly suggest to us that memory retention is essential and has positive consequences. However, every coin has two sides, what then are the consequences of having an excellent memory or indeed the ability to *not* forget?

Patients with hyperthymestic syndrome are known to be plagued with experiences of the past, with an inability to forget. Luria's patient Shereshevsky could recall speech word by word, even after decades. A phenomenon usually attributed to his synaesthesia, he appeared able to recall limitless information, which he found at times frustrating and distressing (Luria, 1982). Importantly, Shreshevsky found it extremely difficult to forget, but chanced on the fact that if

he made an attempt to *inhibit* something from awareness, he was able to do so (Luria, 1972). Although, Luria did not empirically test this ability, this provides further support that selective forgetting may indeed be an active process, where one might actively *choose* (or wish) to forget something[1] .

Patient AJ another reported case who had a superior autobiographical memory, but was not a professional memorizer like Patient Shreshevsky. She constantly had uncontrolled remembering, in her words, "a running movie that never stops" (Parker, Cahill, & McGaugh, 2006, p.46). The ability of having exceptional memory for episodic events appears to impairs day-to-day function and is also known to cause distress. They remember not only the good times, but suffer with memories that remind them of unpleasant experiences. Case studies of such patients (e.g. Luria, 1972) have often described that they wish they could learn to forget (see Price, 2008, for a personal account). Therefore, we can conclude that it is not about having too much or too little of memory, but being able to remember or forget experiences *that are no longer needed,* which allows us to re-live moments we cherish, and is equally important for one's wellbeing (Baddeley, Eysenck & Anderson, 2010; Conway, 2005; Tulving, 1972). As suggested by William James (p. 167, 1890) "In the practical use of our intellect, forgetting is as important as remembering..."

Just as the memory system is composed of several components, forgetting is a result of different causes and has only recently gained empirical interest (Anderson, 2003; Anderson & Hanslmayr, 2014; Anderson, Bjork, & Bjork, 1994;

---

[1] Jorge Luis Borges (1962) in his fictional short-story *Funes, the Memorious* – describes a character like Shereshevsky. Funes had a rich representation for each object, but could not see the tree for the leaf.

Bjork, 1989; Kuhl, Dudukovic, Khan & Wagner; 2007; Levy, Kuhl, & Wagner, 2010; Schacter, 1999). The cognitive and neural process underlying memory has been well studied, but there are still many unanswered questions, especially when trying to understand the cognitive and neural mechanisms underlying forgetting (Anderson & Hanslmayr, 2014; Squire, Stark, & Clark, 2004). The next section provides a brief overview on memory retrieval.

1.2 Memory Retrieval

Over 40 years of results from converging studies in cognition, neuropsychology and neuroscience have identified recollection and as processes within memory recognition (Atkinson & Juola, 1973; 1974; Mandler, 1980; Johnson et al., 1993; Yonelinas et al., 2010; Schacter & Tulving, 1994; Henson & Gagnepain, 2010; see Yonelinas, 2002 for review). After encoding, it may be during the retrieval processes that difficulties are encountered, and memories may be malleable, for myriad reasons (Anderson & Spellman, 1995; Loftus, 2005; Mensink & Raajimakers, 1988; Wixted, 2004). The cognitive and neural mechanisms of memory retrieval have been well established over the decades (see Rugg & Vilberg, 2013; Yonelinas, 2002 for a review). Poor retrieval is one of the causes of memory impairment; however, there are several factors that affect retrieval, some of which will be reviewed in the following sections, before discussing the cognitive and neural mechanisms of forgetting.

One important factor affecting retrieval is *attention to the cue.* Empirical evidence comes from studies where participants are engaged in a secondary activity, such as simple visuo-motor task (Craik, Govoni, Naveh-Benjamin, and Anderson, 1996), or other semantic or phonological distractor tasks (Fernandes, & Moscovitch, 2002; 2003) while trying to recall.

A second commonly recognized factor is *encoding specificity* (Tulving & Thompson, 1973). This suggests that the cue presented at encoding, when presented during retrieval, will have increased retrieval accuracy compared to presenting a related cue during retrieval (Morris, Bransford & Franks, 1977). The *cue-target associative strength* proposes that retrieval fails if the cue is relevant but weak (e.g. Badre & Wagner, 2007). The *number of cues* (Rubin & Wallace, 1989) and the *strength of the target memory* (Wagner et al. 1998) also affect successful retrieval. Finally, the *retrieval mode* (i.e. the cognitive frame or set of mind, orienting the person towards retrieval) is of critical importance (e.g. Tulving, 1983; Herron & Wilding, 2006).

Many of these factors may be at play when discussing intentional retrieval. During this process, there is presumably some degree of control that depends on prefrontal cortex (Bunge, Burrows, & Wagner, 2004). When retrieving memories, the frontal lobes (and related cortical networks)[2] play a critical role in memory selection and attention (Hutchinson, et al., 2012; Duncan, 2010; Wagner & Scachter, 1998). The right prefrontal regions that have been correlated with memory retrieval and control process include: the Brodmann's area 10; the frontal operculum (BA47/45) and the lateral dorsal area (BA 8/9) (Badre, Hoffman, Cooney & D'Esposito, 2009; Badre & D'Esposito, 2009). The medial temporal lobe (MTL, including the hippocampus, entorhinal and parahippocampal cortices) has long been known to support episodic memory (Yonelinas, 2002; Montaldi, Spencer, Roberts, & Mayes, 2006; Brown & Aggleton,

[2] Amongst other brain regions, parietal cortex has also been suggested to contribute to memory retrieval (Wagner, Shannon, Khan & Buckner, 2005; Simons et al., 2009).

2001; Brown & Xiang, 1998; Bowles et al., 2007). Empirical evidence from the above mentioned studies suggest that, during retrieval, there is an orchestration between the frontal and the MTL regions (Rugg and Vilberg, 2013; Ranganathan, 2010). Patients with prefrontal lesions (Gershberg & Shimamura, 1995) were less likely to use retrieval strategies compared to controls; however, the patients benefited when a strategy was provided to them (Gershberg & Shimamura,). Forgetting is one of the results of failed retrieval, and can be incidental or motivated.

The next section briefly reviews the literature on forgetting, with an emphasis on forgetting due to retrieval completion.

1.3 Forgetting

Remembering and *forgetting* are two essential components of the larger system of memory (James, 1890). Until the early 1990's forgetting was typically considered to be a passive process, generally considered to disrupt our everyday functioning (Singer & Conway, 2008). Often postulated to be a result of failed encoding, consolidation, or retrieval competition, forgetting was largely ignored in the more cognitive-experimental domain (Levy, Kuhl & Wagner, 2007; Wixted, 2004). Only recent empirical studies have proposed that forgetting can be highly desirable, and an adaptive process, especially when confronted with unpleasant memories or when we *wish* to forget some memories (Anderson & Green, 2001).

A recent PubMed search, using the terms memory produced roughly 240,000 publications; compared to only 3289 publications on forgetting (see Fig. 1.2)[3]. Even though forgetting may not be as well researched as remembering, it is

[3] PubMed search using the terms memory and forgetting done on May, 5th 2016.

clearly an important component of the memory system (James, 1890 Ch. XVI; Freud, 1915; Ebbinghaus, 1885/1913; Niezsche, 1844; Descartes; Anderson & Huddleston, 2011; Anderson & Hanslmayr, 2014; Hardt, Nader, & Nadel, 2013).

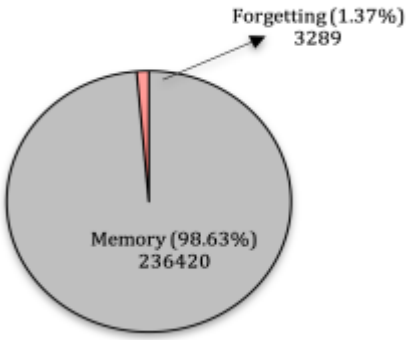


Figure 1.2 PubMed search for 'Memory' & 'Forgetting', May 5, 2016

The next section will review the mechanisms that underlie forgetting, motivated forgetting in everyday life, and the cognitive abilities that influence our ability to forget and/or inhibit unwanted memories.

Why do we forget?

Initially forgetting was thought to be a result of phenomena such as disuse, and regarded as a passive process where unwanted information decayed over time (McGeoch, 1932). Earlier research suggested that forgetting may be a result of overlaying of new memories over the older; known today as the interference theory (Underwood, 1957; Adam, 1961). The multicomponent theory of the memory trace proposed unique memory trace that is neutrally encoded (Ebbinghaus, 1913; c.f. Bower, 1967; also see Baddeley, 1976). Thereby, suggesting that changes in the memories may be due a range of physiological and metabolic process affecting the nature of the memory (e.g. Morris et al., 2003;

Schwabe, Nader, & Prussner, 2014). Some (past) events are more easily forgotten than others (i.e. normal or incidental forgetting), usually explained as a result of decay or stimulus generalization (Tulving & Craik, 2000, pp. 12-13; Baddeley, Eysenck & Anderson, 2010, pp. 198-200; see Storm & Levy 2012 for a review). Many factors determine whether a certain memory will be remembered or forgotten after it has been encoded (Kuhl, Shah, SuBrow & Wagner, 2010; Dudai, 2004; Hupbach, Gomez, Hardt, & Nadel, 2007). More recent empirical evidence suggests that forgetting is not a result of a single cognitive process, but a consequence of a number of causes (for review Levy, Kuhl, & Wagner, 2010; see also Wixted, 2004).

It has long been established that forgetting increases over time (Ebbinghaus, 1913), which describes the logarithmic decline between time and memory (e.g. Chessa & Murre, 2002; Wickens, 1999; for review see Rubin & Wezel, 1996). Nonetheless, many questions regarding retention still remained unresolved. There may be myriad reasons for forgetting, but many studies have focused on the effects of learning and age on retention (Cohen, Stanhope, & Conway, 2000; Loftus, 1985; Wheeler, 2000; see Johnson & Anderson, 2004). Meeter et al. (2006) in a study using an ecologically sound stimuli addressed some of these questions with an extremely large sample size (14,000 participants). The results suggested that within a year there is a steep drop in retention, after which forgetting slowed over time, and performance on recognition was better than recall. Forgetting is suggested to be independent of the degree of learning when information was intentionally learnt (Rubin & Wenzel, 1996), so what of information that is not intentionally learnt?

Bahrick and colleagues (1975) traced American high-school graduates and tested their memory for names and faces of their classmates; the results suggest that recognition memory for names and faces remained high for over thirty years. Research has suggested that retention is affected by age, recall is affected by time compared to recognition especially for material that is not intentionally learnt. While, for well-learnt materials it seems that the forgetting curve flattens initially, and then there is minimal change over long periods of time. Different theories that explain forgetting are discussed in the next section.

Mechanisms of forgetting.

Why might something not come to mind? Is it because at some point we did not *want* it to come into mind, or because of external factors that may interfere with the unwanted memory? Or was it because the information was not needed, and without being rehearsed, it decayed over time? What are mechanisms in the brain that contribute to such forgetting?

The following section will review findings from psychology and neuroscience pulling together evidence from research on five mechanisms that are accepted to account for forgetting (e.g. Levy, Kuhl, & Wagner, 2010; Anderson, 2003; Anderson & Hanslymar, 2014).

Forgetting due to failed encoding.

Forgetting in every-day life often occurs because of failed encoding, classic example would be failed encoding due to distraction. However, this theory has been ignored as it is difficult to assess how they may be forgotten, as they were never stored as memories. The fact that such distraction including any temporary distraction/s, absent-mindedness, or sustained preoccupation with

another thought affects the *encoding* of any event. What is this if not a deficit in attention? One interpretation from neuroimaging studies suggest that the fronto-parietal control mechanisms are engaged during encoding, suggesting that increased engagement of this network supports subsequent remembering (Paller & Wagner, 2002; Davachi, 2006; Unchaper & Wagner, 2009).

Behavioural studies confirm that attention directed to certain stimuli increase the possibility that the stimuli will be remembered (Craik, & Lockhart, 1972; Craick & Tulving, 1975) and stored (e.g. Mitchell, Macrae, & Banaji, 2004; Otten, Henson & Rugg, 2002; Otten & Rugg, 2001a; Tulving & Thomson, 1973). As expected, loading the attentional resources of participants, by asking them to engage in a secondary task during encoding, impairs the later memory recall (e.g. Craik, Govoni, Naveh-Benjamin, & Anderson, 1996).

In an attempt to know why encoding fails on some occasions, neuroimaging studies have tried to understand the mechanisms underpinning successful encoding (e.g. Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Paller, Kutas, & Mayes, 1987; Wagner et al., 1998; Davachi & Wagner, 2002). A large number of functional magnetic resonance imaging (fMRI) studies show a network, including ventrolateral prefrontal cortex (VLPFC), medial temporal lobe (MTL) and dorsal parietal cortex (for reviews see Blumenfeld & Ranganath, 2006; Uncapher & Wagner, 2009). The neural activity during encoding from remembered trials was compared to those subsequently forgotten. The resulting activity was then associated with successful encoding. Introducing secondary tasks during encoding not only affects later memory for those items, but there is a change in the neural pattern, with reduced activation of the fronto-parietal regions (e.g. Fletcher, Frith, Grasby, Shallice, Frackowiak, & Dolan, 1995; Shallice,

Fletcher, Frith, Grasby, Frackowiak, & Dolan, 1994; Uncapher & Rugg, 2005, 2008). This evidence attributes unsuccessful encoding to failure to engage top-down control, and further provides evidence that increase in activation in regions of ventral lateral pre frontal cortex (VLPFC), medial parietal and posterior cingulate gyrus predicts subsequent forgetting (Wagner & Davachi, 2001; for a review see Uncapher & Wagner, 2009).

Although it is clear that the fronto-parietal control mechanisms are essential for the top-down control during event encoding, forgetting occurs when these networks are not engaged, or in cases where the VLPFC regions are engaged in the secondary task-irrelevant information (e.g. Weissman, Roberts, Visscher, & Woldorff, 2006; Kim, 2011). This suggests that these networks interfere with encoding of the new information, and when not recruited, there is no retrieval of this information – resulting in forgetting.

However, this mechanism can only explain a certain kind of forgetting, i.e. information not well encoded. How does one explain forgetting of *once remembered* information which is no longer accessible?

a) Forgetting due to disrupted consolidation.

Studies in the mid-1900s primarily focused on forgetting as a result of interference or decay (McGeoch, 1932). A study using nonsense syllables asked participants to either sleep or remain awake during retention (Jenkins & Dallenbach 1924). Results suggested that participants had better retention when they slept, which led to the conclusion that interference was a reason for forgetting, rather than decay. Over time, decay was no longer accounted to be a reason for forgetting and interference theory became influential (Tomlinson,

Huber, Rieth & Davelaar, 2009; Jenkins & Dallenbach, 1924; see Wixted 2004 for a review; also see McGeoch & Irion, 1952).

Disrupted consolidation has been another known mechanism that causes forgetting (Müller & Pilzecker, 1900; Squire & Alvarez, 1995). The process of consolidation requires time, and may take anywhere from hours to years (Squire, 1992). The consolidated memory is more enduring, and appears to be represented in the cortex (McGaugh, 2000; 2015; Squire & Alvarez, 1995). Occasionally, experiencing new events before the earlier events have been consolidated, can result in forgetting (Wixted, 2004; 2005), presumably because these are more susceptible to disruption (Loftus, 2005; Schacter & Addis, 2007; Wixted, 2004). The observed temporal gradient is similar to that found in the classic forgetting curves (Ebbinghaus, 1885/1913), leading to the postulate that disrupted consolidation may account for much of the forgetting in healthy individuals (Schwabe, Nader, & Prussner, 2014). Most empirical studies have fixed retention times, which fall within the consolidation period (which could be a few days or may be even months). Hence, such paradigms are not capable of detecting if forgetting occurs due to disrupted consolidation. This has been one of the major issues of testing the consolidation hypothesis.

The medial temporal lobe (MTL), specifically the hippocampus (e.g. Eichenbaum, 2004), is a well-known hub for consolidating memory (Debiec, LeDoux, & Nader, 2002; Ranganathan, 2010; Brown, Warburton & Aggleton, 2010). Evidence from patients with damage to the MTL (specifically the hippocampal formation) favours the idea of disrupted consolidation (Squire, Stark & Clark, 2004). These patients have impairments in learning new information, but also show graded forgetting of memories acquired before the

damage occurred, with most recently acquired memories most likely to be forgotten (e.g. Ribot, 1822; Squire, Slater, & Chace, 1975, Squire, Stark & Clark, 2004). Forgetting due to failed encoding and disrupted consolidation happens often, but definitely does not account for all of the forgetting.

In some cases, the memory trace does exist, but is not accessible. Often noted in clinical reports, unwanted memories of unpleasant events can be inhibited (e.g. Koutstaal & Schacter, 1997; Kaszniak, Nussbaum, Berren, & Santiago, 1988; Christianson & Engelberg, 1997). One can debate whether this inhibition is a conscious or unconscious process, and this difference has not been explored in the studies here (Erdelyi, 2001; 2006). How might we explain such memory phenomena?

b) Intentional Forgetting.

Intentional forgetting was often linked to the directed-forgetting paradigm (see MacLeod, 1999). It referred to the process where participants were shown lists of words or syllables and are instructed to forget one of the lists. However, today the concept of intentional forgetting extends beyond the to-be-forgotten lists (Bjork & Bjork, 2003; see also Johnson, 1994). Intentional forgetting differs from motivated forgetting which emphasised on the underlying motivational processes which may be modulated by cognitive control (Anderson & Hanslmayr, 2014).

Directed forgetting (for review, see MacLeod, 1999) is the most commonly used paradigm designed to investigate intentional forgetting, where participants are asked to remember or to forget information presented to them. Many variants of this paradigm have been used – most of which have been categorised as belonging to an item (e.g. Hourihan, Ozubko, & MacLeod, 2009;

Quinlan, Taylor & Fawcett, 2010) or a list (Bjork, LaBerge, & Legrand, 1968; see also Basden, Basden, & Gargano, 1993) method. Participants were presented with items (or a list) one at a time. These are followed by instructions to either remember (R) or to forget (F). The principal finding of directed forgetting studies is that memory performance for R items is better than for the F items. This suggests that there is a cost: i.e. worse memory for F (forget) items and a benefit (better memory) for R (to be remembered) items (e.g. Sahakyan & Foster, 2009).

The list and item method paradigms are not functionally interchangeable, as considered previously (Basden, Basden, & Gargano, 1993). The item method is often used to investigate intentional forgetting at *encoding* – where recognition is robust at retrieval (see Macleod 1998 for a review). In contrast to study intentional forgetting at *retrieval* – generally the list method paradigm is used (e.g. McNally, Clancy, Barrett, & Parker, 2004). In the list method, participants received only one R or F instruction, presented after a discrete list of items. Participants are then asked to remember a second list. Some theorists proposed that this effect was a result of inhibition of the F list at test (e.g. Basden et al., 1993), while others have thought rehearsal strategies might have a critical role (Sheard & MacLeod, 2005). Sahakyan and Kelly (2002) have convincingly put forward the idea that list-method forgetting may be related to a change in mental context between presentation of the R and F list. This is observed when the recall is preceded by a recognition test, when the effect of forgetting observed for recall disappears (e.g. Basden et al., 1993).

The thought suppression task (Wegner, Schneider, Carter, & White, 1987; for review see Wenzlaff & Wegner, 2000) is another paradigm often reported

and compared to directed forgetting. Participants are instructed to avoid thinking about a white bear for a brief period, then they were allowed to think about whatever they chose. Participants responded (e.g. rang a bell) whenever they thought of a white bear. Results suggested that participants were unable to prevent the target thought during the suppression period, and later they had twice the number of intrusions compared to the group that expressed, instead of suppressing. The results from this paradigm suggest that avoiding a thought increases the probability of occurrence later – as intrusions.

However, this alone does not account for the number of clinical cases reporting amnesia for traumatic events (Anderson, 2001; see also Anderson & Huddleston, 2012). As often noted in clinical reports, memories of unpleasant events that are unwanted are often inhibited. How can we explain such memories, or loss of these unwanted memories? How does this explain selective forgetting that occurs in day-to-day life? What happens when the neural mechanisms underlying this ability is impaired? This paradigm, though interesting, does not account for a motivation that underlies our ability to forget; nor does it account for forgetting that occurs as result of resolving competition during retrieval.

c) Forgetting due to interference (retrieval competition).

The other well-known and documented cause of forgetting is that of interference. The first empirical investigation of forgetting was reported in 1900 - a classic study where new experiences interfere with memories that have been previously encoded, an effect named retroactive interference (Müller & Plizecker, 1900). There are various mechanisms in the classic interference theory: including response (McGeoch, 1942; McGeoch & Irion, 1952) or retrieval

competition (e.g. Anderson, 1983; Mensink & Raaijmakers, 1988); unlearning theory (Melton & Irwin, 1940); the reciprocal inhibition approach (Osgood, 1946, 1948); and response-set suppression (Postman, Stark, & Fraser, 1968; see Anderson 2003 for review). However, this review will focus on the account of retrieval completion.

An initial model explaining retrieval was the probabilistic search of associative memory (SAM) theory (Raaijmakers & Shiffrin, 1981a), which predicted some of the memory phenomena, such as list- length effects, serial positioning effects, and response-latency (Gillund & Shiffrin, 1984; Raaijmakers & Shiffrin, 1980; 1981a; 1981b). Extending this model, they propose that interference accounts for forgetting, when irrelevant memories compete with relevant memories (Mensink and Raajimaker, 1988; also see Underwood, 1957). This is significantly affected by the number and strength of the irrelevant memories (for a review see Anderson & Spellman, 1994; Wixted, 2004). Interference is generally understood to occur during retrieval, causing what is known as *retrieval competition.* Several types of interference have been classically studied in behavioural paradigms, including proactive and retroactive interference (McGeoch, 1942; Mensink & Raaijmakers, 1988), and have been empirically tested using the A-B, A-C paradigm (see Figure 1.3).

Proactive interference (PI) occurs when memories of past experiences interfere with our ability to retrieve more recent memories (Badre & Wagner, 2005). For example, if participants learn list A-B, and then are asked to learn a new list A-C. They then are asked to recall new list, A- C. Proactive interference means, that words from list A-B interfere with recall the newly learnt list.

Retroactive interference (RI) affects recent memories while retrieving memories from the past (see Bäuml, 1996 for a review). Here, when trying to recall words from list A-B, there would be interference from the newly learnt list (i.e. A-C). PI is often seen when there is a time lag between the study and recall, especially, when there is a delay between the first learnt list and its recall (Müller & Pilzecker, 1900; Lechner, Squire, & Byrne, 1999). Not surprisingly, more RI is seen when there is a shorter delay between studying the new list (i.e., A-C) and recalling the old list (A-B). Also, RI is greater when the same cue is presented with a new pair (i.e. A-B followed by A-C) compared to introducing a different second list (e.g. A-B followed by C-D; see also McGeoch & McDonald, 1931).

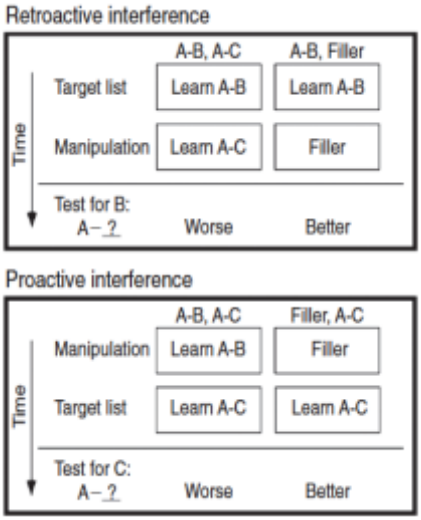


Figure 1.3 Pictorial representation of proactive and retroactive interference (source: Kuhl & Wagner, 2009)

Over the years, interference theories appeared not to be robust enough to account for all aspects of forgetting. The importance of PI in forgetting (Underwood, 1957) was based on the findings of a sleep study by Jenkins and Dallenbach (1924; Wixted, 2004). Ekstrand (1967) reported that sleeping improved retention of both lists (i.e. A-B & A-C) and it has been suggested that RI to be one of causes for forgetting (Postman, 1971, p. 1123). While PI and RI do

contribute to forgetting they may not necessarily account for everyday forgetting (especially for unwanted memories).

The *fan effect* (Anderson, 1974, see Figure 1.4) refers to learning about a fact in general, which affects retrieval because the amount of related information in long-term memory grows, taking longer to verify and recognise the piece of relevant memory (implying that the order of learning may not be relevant). In a fan effect task, participants study a series of propositions (e.g. "The boy is in the park", "The hippie is in the park", "The policeman is in the bank"). In this example park is associated with the boy and the hippie- thus when an element (in this case 'park') is associated with multiple propositions (here 'boy' & 'hippie') it takes longer to recognise such propositions – a "fan effect".

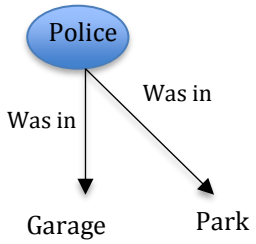


Figure 1.4 Diagrammatic representation of the fan effect (Anderson, 1976).

The fan effect (Anderson, 1974) has been reported in a number of studies and is a robust finding. It has been known to influence models of human memory (Anderson, 1976; 1983a): for example, the Adaptive Control of Thought (Anderson, 1983) and the Adaptive Control of Thought –Rational (ACT-R, see Anderson & Reder, 1999 for more details) models.

More recently, distinct mechanisms have been proposed (Levy, Kuhl, and Wagner 2010; Anderson & Hanslmayr, 2014) to understand forgetting, which includes ineffective retrieval cues (Tulving & Thompson, 1973; Estes, 1955;

Mensink & Raaijmarkers, 1989), and retrieval competition (e.g. McGoech, 1942, Anderson, 1983; Mensink & Raaijmakers, 1988; Anderson & Neely, 1996) that were discussed above. Forgetting could also occur due to failed encoding (e.g. Uncapher &Wagner, 2009; Weissman et al., 2006), disrupted consolidation (e.g. Wixted, 2004), and resolving competition (see Anderson, 2003; Levy & Anderson, 2002 for reviews).

Thus the ACT-R proposed that, as more facts associate with a particular concept, the lower is the probability of any one fact occurring in the presence of that concept: thereby weakening the strength across of that concept. They further suggest that the link between the cue and target is affected by interference (Anderson & Reder, 1999). Conversely, others (Anderson, Bjork, & Bjork, 1994; Anderson & Spellman, 1995; Conway & Engle, 1994) contend that forgetting is the result of suppression or inhibition of memories, rather than weakening in the strength of specific links. Further, Mensink & Raaijmakers (1988) suggest a common competition mechanism that underlies the effects of proactive and retroactive interference. However, none of these individually can account for forgetting. The next section will review behavioural and neuroimaging evidence for forgetting, that occurs as a result of resolving competition during retrieval.

d) Forgetting due to resolving competition.

Remembering a project that you did in high school may trigger other memories, that may be strongly related; for example, another project that won a prize. The memory for the second project may interfere with your ability to remember the goal relevant (or desired) information. Thus, when a cue is related to a number of associated memories, this is likely to trigger other

memories, some of which may be more strongly associated with the cue. This interference prevents the ability to retrieve the desired memory (McGeoch, 1942; Underwood, 1957; see also Anderson, 2003). This is further modelled as one of the primary mechanisms causing forgetting (known as retrieval competition; e.g. Anderson, 1983; Mensink & Raaijmakers, 1988). This interference has been empirically tested using the fan effect studies (Anderson, 1974) and the classic A-B, A-C paradigms (discussed above). Participants (in the fan effect studies) are taught a set of propositions (e.g. "the *plumber* is in the garage", and "the *artist* is at the bank") where some words have multiple propositions (e.g. "the *plumber* is in the park"). The resulting effect is that participants are generally slower, and not very accurate in recognising items with multiple propositions. This suggests that there are finite numbers of activations for each representation, making it difficult to retrieve any one of them. Likewise, strengthening one representation weakens the other associations. Temporal order is quite influential in studies that have used the classic A-B, A-C paradigms to investigate interference (retroactive or proactive) in memory (for review see Wixted, 2004). This attributes the interference (RI & PI) to effects of a common competition mechanism (Mensink & Raaijmakers, 1988).

This competition requires a form of conflict resolution, in order to allow access to the desired memory. One explanation is that this is achieved through inhibitory control mechanisms that weaken traces of prepotent competitors (Anderson, 2003). This reduces their interference, allowing for the goal-directed control of retrieval (for reviews see Anderson, 2003; Levy & Anderson, 2002). This line of research claims that forgetting does not occur at the initial level of

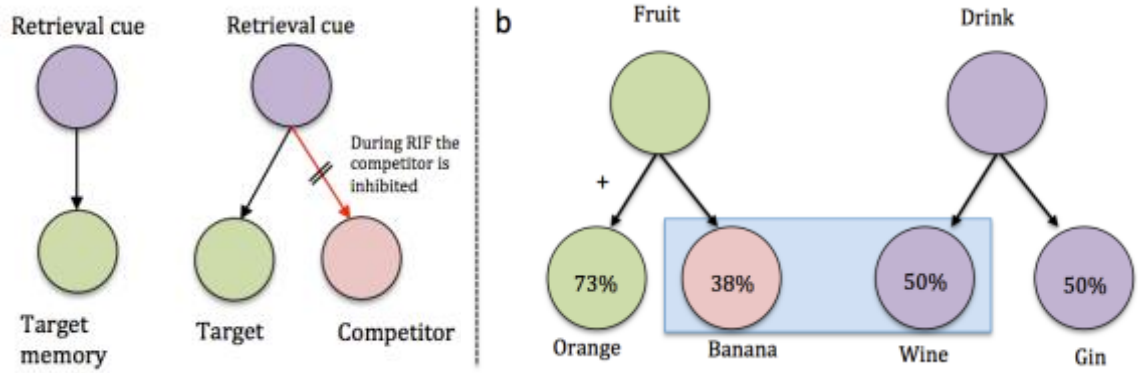
retrieval, but rather that it reduces the retrieval competition, and facilitates effective remembering. Later, when the inhibited memory becomes goal-relevant, it is difficult to recall this memory, producing forgetting. For example, if you are trying to recall the day where you withdrew £50 from a particular ATM, a stronger memory of withdrawing £30 from the café near the petrol station where you had an excellent coffee may come to mind. If the goal was to remember the first memory, one would inhibit the second memory. A few days later, when someone asks the name of a good café, you will have to recall the second memory (that you had suppressed initially). Some of the details now may be forgotten. Thus, forgetting may be a result of having resolved a retrieval competition in the past. From an empirical point of view, this perspective in experimental or cognitive psychology is fairly recent (Anderson, Bjork, & Bjork, 1994; for review see Anderson, 2003).

At least two situations have now been suggested to use such inhibitory processes: a) *Selective retrieval*: when a particular memory is selected amongst other competing alternatives (because we choose this, or it is goal-relevant); and b) *Stopping retrieval*: when there is an explicit attempt to prevent a memory from coming to mind or being retrieved.

1) Selective retrieval.

Choosing to select certain memories over others causes forgetting of the memory that is not selected (inhibited), in order to resolve completion. One view (Conway, et al. 2000) suggests that inhibition is an automatic process, because of making a choice (Engle et al., 1995; see also Tipper, 2001). Such types of inhibition lack the *intention to* forget, and may not necessarily be mediated by executive functions (Aron et al., 2004; 2014). Other authors suggest that

executive functions *are* involved in resolving completion, and forgetting occurs when such competition is resolved (Anderson, Bjork & Bjork, 1994). The latter aspect of inhibition can be empirically studied using the procedure known as a *retrieval practice* paradigm (Anderson et al., 1994). The forgetting that occurs due to inhibition during retrieval competition is known as *retrieval-induced forgetting* (RIF, Anderson et al., 1994 see Figure. 1.5).



A retrieval cue associated to a single target item. Right: The retrieval cue becomes associated to a competitor interfering with recall of the target. (Adapted from: Anderson & Neely, 1996). b. An example of RIF – participants performed retrieval practice on orange but not on banana or any members from the *drink* category (baseline). Final score indicates (in %) that relative to baseline, practice facilitates recall of practiced items, while unpractised items from practiced categories suffer retrieval-induced forgetting. (Adapted from Anderson, 2003).

Figure 1.5 Diagrammatic representation of selective retrieval.

RIF has three phases (Anderson, 2003). In the study phase, participants learn category-exemplar pairs. This is followed by the practice phase, in which they repeatedly retrieve half of the exemplars, from half of the categories (Rp+ items). The remaining exemplars from the practiced categories are excluded from this phase (Rp- items), as are all exemplars from non-practiced categories (Nrp items). During the final test phase, participants' memory is tested for *all* of

the items from the original study phase. Relative to baseline performance (Nrp items), memory is typically better for practiced items (Rp+) and worse for non-practiced items (Rp-) from the practiced categories (Anderson, Bjork & Bjork, 1994; Storm & Levy, 2012). The improvement in performance for the practiced items (Rp+), compared to the baseline, is known as the facilitation effect (FAC). The impairment in performance for non-practiced items, compared to the practiced categories (Rp-) is referred as the retrieval-induced forgetting effect (RIF). The FAC is thought to represent the strengthening of connections, between the cue and the practiced items. In contrast, RIF is thought to represent the suppression of the unpractised items, that interfere with retrieval.

The impact of retrieval practice, on high frequency items, in the retrieval practice paradigm favours the suppression (or inhibition) based account (Anderson, 2003). The argument for suppression/inhibition versus interference/competition in the literature has been a long-standing one (Anderson & Hanslmayr, 2014; Storm & Levy, 2012). The suppression hypothesis proposes that if the unpractised item (e.g. banana) is suppressed when the other items (e.g. orange) are practiced, the suppression will occur not only for the *fruit-banana* association, but actually suppress the representation of *banana*. If this is true, inhibition for banana should be measureable, when cued by other related retrieval cues, for example using *monkey* to cue *banana* instead of fruit. This form of testing retrieval has been known as the *independent probe method.* It is often used as a test of retrieval, along with tests that use the same probe (i.e. the original cue).

In another experiment (Anderson & Spellman, 1995), participants studied the categories of *red* and *food,* a subset of items from the *red* category was

practiced during the retrieval practice phase (Rp+). Unknown to the participants, some of the non-practiced items of the *red* study category were also a *food item*. It was reasoned that if participants suppressed *tomato* (Rp-), as it interfered with another practiced item that was *red,* example *blood* (Rp+), their ability to retrieve *radish* when tested with an independent cue for *food,* would also be suppressed due to the prior semantic association to the *red* category (Anderson & Bell, 2001; Anderson, Green, & McCulloch, 2000; Anderson & Spellman, 1995; MacLeod, & Saunders, 2005; Saunders & MacLeod, 2006; see Anderson & Neely, 1996, for a review). These results supported the hypothesis that inhibition is indeed a primary process underlying retrieval induced forgetting (Storm & Levy, 2012). Conversely, the results did not support the associative learning hypothesis where the ability to retrieve *radish* on an independent cue would have been unaffected (Anderson & Spellman, 1995). Cue-independent forgetting has now been reported consistently (e.g. Anderson & Bell, 2001; Anderson, Green, & McCulloch, 2000; Camp, Pecher, & Schmidt, 2005; Radvansky, 1999), when retrieval is tested on recognition tests (Hicks & Starns, 2004; Starns & Hicks, 2004) and also noticed when using implicit lexical tests (Veling & van Knoppenberg, 2004).

Retrieval Induced Forgetting (RIF) has shown consistent effects, and has been extensively investigated across domains (e.g. Johnson, & Anderson, 2004; Galfano et al., 2011; also see Anderson & Levy, 2007; Penolazzi et al., 2014; Shilling, Storm, & Anderson, 2014; see also Anderson & Hanslmayr, 2014). Research using RIF in bilingual participants suggests that native language phonology of the word is inhibited, when they retrieve the non-native word for that concept (Levy, McVeigh, Marful, & Anderson, 2007). The RIF effect is not

only seen in context of word lists, but can also be noticed for numbers (Phenix & Campbell, 2004) suggesting that this interference is a result of an underlying inhibition process, and not necessarily tied to any particular contextual stimuli (Strom & Levy, 2012). Another study investigated this effect using characteristics from stereotyped groups has suggested, that although participant's stereotype beliefs affected inhibition, practicing individuating information (during RIF), may allow the participant to forget the stereotypical information (Dunn & Spellman, 2003). Finally, results suggest that semantically related items are inhibited, even if they had not been studied during the experiment (Johnson & Anderson, 2004; Starns & Hicks, 2004). These results strongly support the inhibitory (suppression) account of RIF which contributes to some of the forgetting in everyday life.

Recent neuroimaging studies (Waskom, Kumaran, Gordon, Rissman, & Wagner, 2014; also Botvinick, Braver, Barch, Carter, & Cohen, 2001) suggest the role for pre-frontal cortex (PFC) during goal directed cognition or conflict resolution. Certain frontal regions including the right DLPFC are thought to directly mediate the inhibitory process during RIF (e.g. Kuhl, Dudukovic, Kahn, & Wagner, 2007; Penolazzi et al., 2014). Other regions like the left mid-VLPFC are known to be engaged post-retrieval, especially when selecting the specific memory amongst many active representation (Badre & Wagner, 2007; Mecklinger, 2007). The growing neuroimaging evidence suggests the role of regions like dorsolateral pre-frontal cortex (DLPFC~ BA46, 9), anterior VLPFC (~BA 47), and Anterior Cingulate cortex (ACC , ~BA 32, 33) when inhibitory processes are engaged, in order to forget (Storm and Levy, 2012). These results support the idea that the DLPFC and right anterior-VLPFC guide attention to the

relevant representation, and therefore the process of orienting attention, indirectly results in inhibition (Miller & Cohen, 2001). A computational model of RIF proposes that PFC may be involved in selecting representation, and may not be actively inhibiting processes with the medial temporal lobe (MTL) that is associated with weakening of the competing responses (Storm & Levy 2012). A third alternative suggests that lateral PFC implements a form of inhibitory control that directly weakens the competing response (see Levy & Anderson, 2002).

Studies of RIF in patients with frontal lobe damage (Conway & Fthenaki, 2003), suggests that "frontally impaired" groups show normal RIF, suggesting that this form of inhibition may not necessarily depend *primarily* on frontal functions. However, RIF is also impaired in patients diagnosed with Alzheimer's disease (Moulin, Perfect, Conway, North, Jones, & James, 2002). This view contradicts with other studies that suggest the involvement of only the right DLPFC in inhibition during RIF (e.g. Penolazzi et al., 2014), indicating that there are processes underlying forgetting due to retrieval are still not very well-understood. What happens when individuals actively stop retrieval? RIF cannot explain that, while there are other paradigms that have been used to empirically tests the process underling active inhibition, which will be reviewed in the next section.

2) Stopping Retrieval.

Recent empirical evidence suggests that a subset of forgetting in everyday life may not be accidental, but may occur as a result of a desire to forget some unpleasant experience, or because that experience may not necessarily fit into beliefs or schemas about ourselves (Anderson, & Green, 2001; Freud & Breuer,

1895; see Anderson & Huddleston, 2012 for a review). Recent studies (e.g. Anderson & Green, 2001; Storm & Levy, 2012; Anderson et al., 2004; Benoit & Anderson; Catarino et al., 2015) have shown that forgetting is an essential element of memory, and may be an active cognitive process. For the first time, the field of experimental and cognitive psychology viewed forgetting as an active process, with a purposeful and functional role in everyday life (Anderson & Hanslmayr, 2014). The ability to suppress these unwanted memories is known to affect the conscious recall of these memories (Anderson and Green, 2001; Anderson, and Huddleston, 2012; Gagnepain, Henson & Anderson, 2014), empirically tested using the Think/No-Think (TNT) task (Anderson & Green, 2001; Anderson et al., 2004; Benoit & Anderson, 2012; Levy & Anderson, 2008). The ability to stop retrieval might be by inhibiting the unwanted memory (known as direct suppression; Anderson & Green, 2001; Anderson et al., 2004 Benoit & Anderson, 2012) or by redirecting the retrieval process (referred to as thought substitution; Benoit & Anderson, 2012; Bergström et al., 2009; Hertel & Calcaterra, 2005). The next section will briefly review the literature on motivated forgetting.

1.4 Motivated Forgetting

Think/No-Think (TNT) task.

The Think/No-Think task (Figure 1.6A) is an empirical method which tests the active inhibitory process that is suggested to weaken, and over time erase, the to-be-forgotten memory. A typical TNT task (Anderson & Green, 2001) has three phases: first, in the learning phase, participants learn a list of word pairs (e.g. ordeal – roach). In the second TNT Phase, they are presented with the right hand side word (hint word), and are asked to either think of, or not think of, the

associated respond word (the left had side word). Participants see these think and no-think cues multiple times. Finally, in the memory retrieval phase, they are tested on recall for all the word pairs. If participants did indeed recruit the control mechanisms, their performance on the No-Think trials would be worse than their memory for the baseline word pairs. This is known as the *suppression* or *inhibition* effect (see figure 1.6B; Anderson & Green, 2001; Anderson et al., 2004; Catarino et al., 2015; Depue, Banich & Curran, 2006; Depue, Curran & Banich, 2007; Hertel & Calcaterra, 2005; Hulbert, Henson, & Anderson, 2016; Joorman, Hertel, Brozovitch, & Gotlib, 2005; Wessel, Wetzels, Jelicic & Merckelbach, 2005; Wimber, Alink, Charest, Kriegeskorte & Anderson, 2015; although see Bulevich, Roediger, Balota & Butler, 2006).

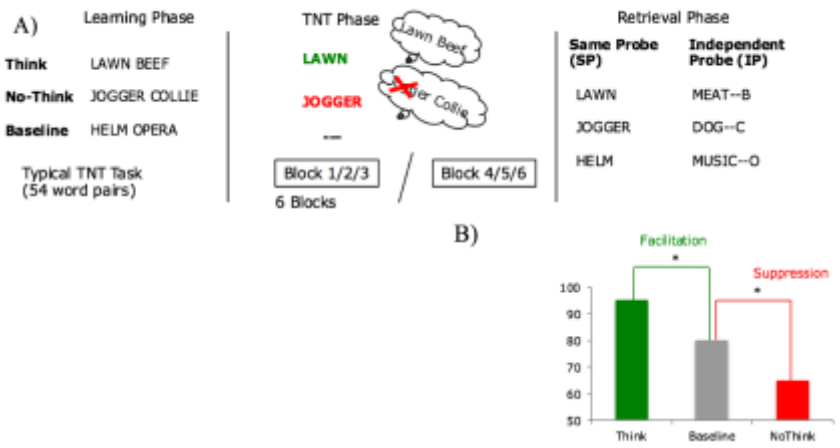


Figure 1.6. A) The design of the TNT paradigm (Benoit & Anderson, 2012). **B)** The suppression and facilitation effect (Benoit & Anderson, 2012; Anderson & Green, 2001; Levy & Anderson, 2008)

Inhibitory accounts for TNT task.

The no-think effect in the Think/No-Think task was initially suggested to be a result of inhibitory processes (Anderson & Green, 2001; Anderson et al.,

2004). However, later researchers have argued that there may be an underlying non-inhibitory process in TNT (Hertel & Calcatera, 2005). The non-inhibitory account refers to instances when participants use an alternative thought, or diversion, as a means of preventing the original word from coming to mind (Hertel & Calcaterra, 2005; Tomlinson, Huber, Rieth & Davelaar, 2009). Rather than push (or inhibit) the unwanted memory away (Anderson & Green, 2001), they redirect the retrieval processes using different memories. The evidence from the final retrieval test, using the independent probe method (e.g. insect –r; Anderson & Green, 2001; Anderson & Spellman, 1995), suggests that retrieval competition from diversionary thoughts cannot account for the memory impairments, thus arguing for an inhibitory account irrespective of the method used (del Prete, Hanczakowski, Bajo, & Mazzoni, 2015; Anderson & Hanslmayr, 2014). Two studies, using the TNT task, have investigated the processes underlying memory control, first pushing the unwanted memory away (referred to as direct suppression method); second, using the alternative thought or word pairs (known as thought-substitution). Empirical evidence thus suggests that there are two opposing mechanisms of mnemonic control, which are supported by different brain regions (Benoit & Anderson, 2012; Wimber et al., 2008, see figure 1.7).

Most of the TNT neuroimaging studies have used the direct suppression approach (Anderson & Huddleston, 2012; Anderson & Hanslmayr, 2014). These studies have found the striking role of DLPFC engagement during the No-Think trials, suggesting the lateral PFC, specifically the DLPFC, plays a key role, and orchestrates the hippocampus, subsequently aiding the forgetting of these to-be avoided memories (Anderson et al., 2004; Depue et al., 2004; Schmitz, Ferreira,

Guo & Anderson, 2015). What then of the neural mechanisms underlying motivated forgetting?

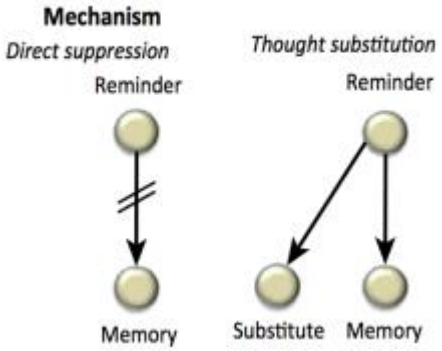


Figure 1.7. Direct suppression and thought substitution involve distinct networks result in forgetting, but have differing effects on the hippocampus (Benoit & Anderson, 2012; Anderson & Haslmayr, 2014)

Neural mechanisms of motivated forgetting

Cortical regions

The frontal/prefrontal cortex (PFC) is well known for its role in inhibition, and often identified as an important centre for cognitive control (Miller, 2000; see Stuss & Alexander, 2000 for a review). Specifically, it is postulated to be essential for attention, the top-down process of managing thought and behaviour, and in maintaining internal goals (Miller, 1999; Miller & Cohen, 2001, Badre & Wagner, 2007, Peers et al., 2005). Amongst other things the PFC is also known to play an important role in inhibiting strong but inappropriate responses. Indeed, there is a growing literature that investigates neural correlates of motor inhibition (Aron, 2007; Aron et al., 2015).

A review of this literature reveals that a range of cortical regions including some outside the frontal lobes are important in the organization and control of

goal-directed behaviour (Fuster, 1989; Mesulam, 1986; Stuss and Knight, 2013; Luria, 1966). These regions include the bilateral dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), the anterior cingulate cortex (ACC), the posterior parietal cortex (PPC) and the anterior insula (Nee, Wager, et al., 2007; Szczeanski & Knight, 2014). Neuroimaging studies suggest the role of the right inferior frontal cortex (IFC), with some engagement of the subthalamic nucleus, during the go/no-go task (STN, Aron et al., 2007). The DLPFC and ACC are also known to be co-activated in *other* cognitive tasks requiring a process of inhibition, for example the Stroop task, the anti-saccade task, working memory and the perception of degraded visual stimuli (Duncan & Owen, 2000; Duncan, 2010).

There is an increasing empirical evidence on inhibition, but almost all of it comes from domains of motor or attention research (Aron et al, 2014). As regards to response inhibition, the right IFG, VLPFC and also the OFC are known to play a crucial role. Patients with damage to right IFG are known to be slower to stop, during the Go/No-Go task (Aron, et al. 2003). The IFG is also known to play a more general role in response inhibition (Cohen et al., 2013). A study by Krämer et al., (2013) suggests that the responses to infrequent stops may be a result of attention capture, but there is a lack of evidence from lesion studies to support this claim. Studies in patients with ventrolateral prefrontal lesions (VLPFC) have shown deficits in inhibitory oculomotor control (Hodgson et al., 2007). In contrast damage to VLPFC and orbitofrontal cortex (OFC) results in increased risk-taking behaviours (Bechara, Tranel and Damasion, 2000; Rogers et al., 1999).

To better understand the cognitive process underlying higher cognitive control, it is important to integrate findings from both animal and human research (Szczepanski & Knight, 2014; Petrides and Pandya, 1999, 2002; Yeterian, Pandya, Tomaiuolo & Petrides, 2012). Especially, as animal work alone does not provide answers to the underlying motivation, or opportunity to account for it retrospectively (Aron et al., 2003; Hampshire et al., 2010).

Lack of initiative, motivation and other "pseudo-depressive" syndromes (Blumer and Benson, 1975) are often associated with damage to the DLPFC. Similarly, patients with damage to DLPFC also often display "goal neglect," a process where they often show disregard for the task requirements even when they understand and remember the rules, but fail to align their actions to achieve the goal (Duncan et al., 2008). Several studies have linked specific functions of control to sub regions within the PFC (e.g. Aron et al., 2014; Hodgson et al., 2007; Floden et al., 2008). This, coupled with the extensive interconnections between PFC sub-regions (Catani et al., 2012) and the cortical/subcortical regions, suggests overlapping functions across these regions (Duncan, 2010).

The pre-frontal cortex is known to have both functional and structural connections with various posterior cortical and subcortical regions (Anderson, Bunce and Barbas, 2015; Aron et al., 2007; Depue et al., 2015; Miller and Cohen, 2001; Miller and D'Esposito, 2005; Stuss & Benson, 1984). In summary, these cortical (especially pre-frontal) regions are known to be involved in tasks that demand interference resolution and response stopping, both in motor inhibition (Aron et al., 2015) and memory inhibition (Anderson & Hanslmayr, 2014). So, what effects does damage to these frontal systems have on memory or memory control?

Damage to the prefrontal cortex may not cause severe amnesia, but damage to the DLPFC is known to affect aspects of encoding and retrieval, especially in relation to episodic memory (Uncapher & Wagner 2009). Patients with lateral frontal damage may also have difficulty in source memory (i.e. where and/or when information is learned, Duarte et al., 2005). In addition, damage to the orbital and ventromedial PFC may lead to confabulatory behaviour (Schneider & Ptak, 1999; Turner et al., 2008; Fotopoulou, Solms, & Turnbull, 2004). These findings are usually interpreted as suggesting that most of the deficits in episodic memory are due to the failure of prefrontal cortex to inhibit an unwanted memory, or to select among competing memories, resulting in interference (Shimamura et al., 1995). Most of these studies discuss the role of PFC in controlling memory during the encoding and/or retrieval phase. Unfortunately, this account has not been deployed to explain how the frontal regions influence our ability to actively forget (or inhibit) unwanted memories (Duncan, 2013).

Hippocampus

Hippocampus has been the second brain region that is activated in imaging studies of TNT. Engaging in suppression is known to reduce the blood-oxygen-level dependent activation in the hippocampus, which also impairs the retention of the memory (Anderson et al., 2004; Depue et al, 2007; Levy & Anderson, 2012; Benoit & Anderson, 2012; Gagnepain, Henson & Anderson, 2014; Anderson & Hanslmayr, 2014; Hulbert, Henson & Anderson, 2016). In contrast, when alternative memories are retrieved, there is *increased* activation in the hippocampus (Eichenbaum, Yonelinas & Ranganathan, 2007; Karpicke & Roediger, 2008).

When certain memories need to be inhibited, especially using a direct suppression method (i.e. pushing away the unwanted memory, Benoit & Anderson,2012), one hypothesis is that the pre-frontal regions orchestrate and inhibit the hippocampus, and thereby facilitate forgetting (by preventing memories from coming to mind; Anderson et al., 2004; Benoit & Anderson, 2012; Gagnepain, Henson & Anderson, 2015; Hulbert, Henson & Anderson, 2016;). Recent work builds on this idea, suggesting that engaging in motivated forgetting targets a broader reduction of the hippocampal activity (known as 'systematic suppression'), rather than supressing selective memories (Hulbert, Henson & Anderson, 2016). So, how are the control mechanisms within the pre-frontal regions connected to the hippocampus?

Pre-frontal hippocampal connections

Neuroimaging studies in the TNT literature have consistently supported a functional connection between the rDLPFC and the hippocampus (Benoit & Anderson, 2012; Gagnepain, Henson & Anderson, 2015; Hulbert, Henson & Anderson, 2016; Wimber et al., 2015). Specifically, there is an increased blood-oxygen-related activity in the dorsolateral prefrontal cortex (DLPFC; Broadmann areas (BAs) 9 and 46), and the anterior cingulate cortex (ACC; BA 24 and BA 32; Anderson et al., 2004; Benoit & Anderson, 2012) coupled with simultaneous down-regulation of the medial-temporal lobe (MTL; Depue, Banich & Curran, 2007; Anderson, Oschner, & Kuhl 2004; Benoit & Anderson, 2012; Schmitz et al., in preparation, Levy & Anderson, 2002). This suggests that the DLPFC appears to play a critical role in successful suppression of unwanted memories, but only in concert with medial temporal structures (Schmitz et al., 2016). This is especially true when using the method of *direct suppression* (Benoit & Anderson,

2012; Anderson et al., 2004; Hulbert, Henson, & Anderson, 2016; Anderson, et al., 2004; Benoit & Anderson, 2012; Wimber et al., 2015; Levy & Anderson, 2013; Depue, Curran & Banich, 2007; Levy & Anderson 2012; Gagnepain, Henson & Anderson, 2014; Bergström, Fokert, & Richardson-Klavehn, 2009; Depue et al., 2013; Waldhouser, Bäuml, & Hanslmayr, 2014).

Motivated forgetting in a clinical context

First observed and reported by clinicians, a classic literature describes 'events that we *wish* we had forgotten' (Breuer & Freud, 1895d; James, 1890). However, these were never investigated using a strict empirical method. Some psychoanalytical literature suggests that the amnesia that occurs during post-traumatic stress disorders (PTSD) may be a result of the inability to lay down the episodic memory (McGaugh, 1998; Yovell, 2003). Extreme stress experienced during trauma may lead to secretion of glucorticoids, which may disrupt hippocampal processes (Frodl & O'Keane 2013; McNally, Lasko, Macklin & Pitman, 1995; Roozendaal, 2002; Solms & Turnbull, 2002; Van der Kolk, 1994; Van der Kolk & Fisler, 1995). Using this argument, one could contend that memories suppressed or inhibited during certain periods may be accessible in some other context, where there may be less threatening or better trusted (for example, a therapeutic setting, Yovell, 2003). Literature from both the clinical and cognitive domain have consensus regarding a (stronger) motivation that underpins this inability to remember, but it has been difficult to test for this motivation in a clinical or empirical context (Anderson & Hansymayr, 2014; Elderly, 2006; Yovell, 2003).

Motivated forgetting or repression?

The ability to actively inhibit or "*purge*" unpleasant memories from consciousness is often first dated to Freud, and usually labelled as repression (Freud, in Breuer & Freud, 1895d, p.10; Freud 1917; see Boag, 2012 for review). However, it may have antecedents as far back as Aristotle (Ross, 1930) and expresses a clear *advantage* of forgetting. As discussed above, patient Shereshevsky (Luria, 1968) had remarkable memory for information, and patient AJ also had superior autobiographical memory (Parker, Cahill and McGaugh, 2006), both patients found it impossible to forget or purge memories that were no longer needed. A more troublesome question that follows this inability to forget, is how do we to *learn* to forget?

The concept of 'repression' (Freud 1925a) is a well-documented process, often reported in a clinical context. Reported in case studies and psychoanalytical papers, testing repression (or suppression coincided) has been difficult to test or replicate (Elderly, 2006). The difficulty of empirically investigating repression, coupled with the increased focus on understanding memory systems, did not really provide much opportunity for experimental paradigms that investigated motivated forgetting (Anderson, 2006). As already discussed, until early twentieth century, causes of forgetting were mostly believed to be due to interference or decay. Forgetting was also not regarded to be beneficial, therefore, there lacked any coherent theory, aimed to understand the process of active or selective forgetting (Jenkins & Dallenbach, 1924; Wixted 2004; Levy, Kuhl, and Wagner, 2010).

The word "repression" (and/or "suppression") has been interpreted in many ways (Erdelyi 2006). The psychoanalytical approach, for example, views

repression to be a defense mechanism that inhibits unwanted memories, feelings, or ideas into (Freud, 1918) the 'unconscious', thereby reducing conflict or pain (see Erdelyi, 2006 for review). Alternatively, it has been interpreted as an intentional goal-directed process to exclude memories from coming into awareness (Anderson & Brojk, 1994; Anderson and Green, 2001). Nevertheless, there is an overall consensus that an underlying *motivation* drives what we *wish* to forget (for example inhibition, avoidance, thought substitution etc., Erdelyi, 2006; McNally, 2005). Regardless of the debates on the nature of conscious vs. unconscious, or that of repression vs. suppression (used as synonyms), there is agreement that this specific kind of forgetting has an underlying *motivation,* so that the central scientific question is *how* and *when* one controls awareness of unwanted memories (Anderson and Green, 2001; see Huddleston & Anderson, 2011 for review).

This form of forgetting, that occurs as a process of inhibiting unwanted memory, is the central theme of this thesis, and is referred to as *motivated forgetting* (Freud, 1894a). Freud believed that "traumatic" memories are difficult to access, due to motivated forgetting. Thus, in his earlier writing Breuer and Freud wrote, "it was a question of things which a person wished to forget, and therefore intentionally repressed from his conscious thought and inhibited and suppressed" (1895d, p.10). A key issue of course, is how much of influence has the Freudian concept of repression have on this kind of forgetting?

Although there are many reasons that can contribute to forgetting, both philosophically and scientifically, forgetting certain experiences or memories is beneficial to us. As very rightly noted by James (1980/1950, p. 680) "…[i]f we remembered everything, we should on most occasions be as ill off as if we

remembered nothing". Freud refers to repression as '…things that the patient wished to forget and therefore intentionally repressed from conscious thought and inhibited and suppressed' (Breuer & Freud, 1985d, p.10; see also Boag, 2012). Freud further states the act of repression is 'introduced by an effort of will, for which motive can be assigned' (Freud, 1894). This suggests that repression is a "motivated response to pain that could occur without knowledge of its occurrence" (Breuer & Freud, 1895d, p. 10n). Therefore, we can conclude that, when participants engage in active forgetting, there is some kind of motivation. When we choose certain unwanted or unpleasant event to not come to mind, this choice triggers the inhibitory mechanisms that prevents the memory from coming to awareness (Anderson et al., 2004; Benoit & Anderson, 2012). The underlying motivation may be an unconscious choice (when memories may be traumatic, Yovell, 2003) or a conscious choice, when we actively inhibit the memory, when faced with the reminder (Anderson et al., 2004). Questions that may come to mind include, whether individuals learn to substitute or suppress information? What happens when the neural mechanisms supporting these inhibitory mechanisms are impaired, possibly due to stroke or tumour excisions? Can we manipulate this ability using electric stimulation? We know that there is a functional coupling between frontal and hippocampal networks (Benoit & Anderson, 2012; Depue et al., 2015; Anderson, Bunce & Barbas, 2015), but how are these fronto-hippocampal regions structurally connected?

1.5 Rationale for this thesis

The original motivation for this thesis was to investigate the processes underlying 'motivated forgetting' in patients with frontal lesions.

A recent study (Benoit & Anderson, 2012) has proposed that the ability to supress unwanted thoughts was a more right lateralised function, while thought substitution was more left lateralised. Therefore, the central hypothesis underlying the thesis was whether patients with right frontal lesions were unable to engage in direct suppression (study reported in Chapter 4). [Investigating patients with left frontal lesions, and their ability to use thought substitution, is clearly an additional and obvious hypothesis, but was beyond the scope of this PhD].

The TNT task had to be adapted for patients, keeping in mind the constraints in their cognitive abilities due to their brain lesion (Murray, Anderson and Kensinger, 2015; Szczepanski & Knight, 2014). The next phase was to test this *patient-friendly* TNT (*pf*-TNT) task on a controls and a couple of patients with focal brain lesions (study reported in Chapter3).

While the patient study was being developed, a stimulation method (tDCS) was used to investigate whether the ability to inhibit unwanted memories could be manipulated. The rationale was to see if these effects could be demonstrated in participants who neurologically normal, and is an intervention with potential clinical implications (reported in Chapter 2). Finally, based on Benoit & Anderson's study (2012) a secondary data set was used to understand the white matter structures underlying the frontal-hippocampal connectivity, to see how they correlated with behavioural performance. This is the study is reported in Chapter 5.

2. The effect of transcranial Direct Current stimulation (tDCS) on the ability to suppress or facilitate specific memories.

2.1 Introduction

Every day, people experience many events that they try to remember, such as the location where they parked their car. However, they may also have experiences that they wish to *forget,* usually because these memories and thoughts generate one or more negative emotion (Anderson, 2003). When encountering such reminders, people often try to inhibit the unpleasant memories that come into awareness. This process, long labelled as "repression" or "suppression" (Freud, 1915; Boag, 2012), is a well-known (defence) mechanism often used to prevent aversive recollections. Recent work has sought to better understand the cognitive control process that underpin the ability to inhibit unwanted thoughts from conscious awareness (Levy & Anderson, 2002), making it almost impossible to retrieve the unwanted memory (Kuhl, Khan, Dudokovic, & Wagner, 2008; Anderson, & Green, 2001; Hertel & Calcaterra, 2005; Anderson & Huddleston, 2012, Hulbert, Henson & Anderson, 2016) - a process that may be impaired in conditions such as post-traumatic stress disorder (PTSD) and depression (Catarino et al., 2015).

Research suggests at least two mechanisms by which unwanted memories may be controlled. When confronted with a reminder, people may attempt to directly *suppress* an unwanted memory (Anderson & Green, 2001; Benoit & Anderson, 2012; Depue, Curran, & Banich, 2007; Hertel & Mahan, 2008;

Freud, 1894); alternately they may attempt to *substitute* a more desirable memory for the unwanted one (Benoit & Anderson, 2012). Importantly, these abilities differ between individuals, where the variability appears to be mediated by differences in executive control, or in mood (Levy & Anderson, 2008; Hertel & Gerstle, 2003; Marzi, Regina & Righi, 2014).

Evidence from functional magnetic resonance imaging (fMRI) studies suggests that a broad prefrontal network mediates the process of direct suppression. These include reports of increased activity (i.e. increased BOLD signal) in the right dorsolateral pre-frontal cortex (DLPFC), together with decreased activity (i.e. reduced BOLD signal) in the hippocampi bilaterally (e.g. Anderson et al., 2004; Benoit & Anderson, 2012, Depue et al., 2015). This has been interpreted as suggesting that the right DLPFC inhibits the hippocampus when people use direct suppression (Benoit & Anderson, 2012; Hulbert, Henson, & Anderson, 2016). Converging evidence from patients with focal lesions suggests that patients with right frontal damage have difficulty *using* the direct suppression method to inhibit unwanted memories, compared to patients with left frontal lesions (see Chapter 2).

The think/no-think task (TNT, Anderson & Green, 2001) is used to study memory inhibition (for more details, see Chapter 1); it is a memory analogue of the motor inhibition task (i.e. go/no-go, Luria, 1966). In this task participants first memorise arbitrary word pairs (e.g. Jogger-Collie), then are shown the left word of each pair and instructed to either think about or suppress ('no-think') the right word. Subsequently, when asked to recall the associated word pairs (memory retrieval phase), participants typically recall more words from the pairs they had thought about, compared to words that they had suppressed

(Anderson & Green, 2001). Memory retrieval in this task is typically tested using two different methods, namely the *same* probe (the left word (cue) from the word pair they learnt before, e.g. Jogger) and the *independent* probe (the category of the response word, followed by the first letter of the right side word, for example 'DOG – C', where they respond with the word Collie).

The independent probe (IP) method (see Anderson & Spellman, 1995) was specifically designed to test the inhibitory account of intentional forgetting (see Chapter 1 for details). Results from either the same or independent probe showed reduced retrieval for 'no-think' words compared to the 'think' condition (e.g. Anderson et al., 2004; Benoit & Anderson, 2012). Most studies report an averaged accuracy from both the retrieval condition (Benoit & Anderson, 2012; Anderson et al., 2004; see also Bulevich, Roediger, Balota, & Butler, 2006). However, some studies report suppression only in the same probe condition (e.g. Catarino et al., 2015). The results from both retrieval methods often indicate level of suppression, where the IP condition is supposedly a stronger indication of suppression compared to the SP condition (Anderson & Green, 2001; Anderson & Spellman, 1995). This suggests that suppression is therefore the result of an inhibitory process of the memory *itself*, and cannot be explained by degraded cue-response associations (Anderson & Spellman, 1995).[1]

To date, studies have only *passively* measured memory inhibition, with brain imaging studies and in patients with neurological (Chapter 4) or psychiatric disorders (Catarino et al., 2015; Hertel & Gerstle, 2003). No attempt

[1] For Experiment 2.1 & 2.2 data for the same and inhibition probe have been analysed separately.

has been made to directly *manipulate* people's ability to use the mechanisms of suppression (using the TNT task). One technique is transcranial direct current stimulation (tDCS), in which low electrical current is delivered to the scalp using two electrodes (anode and cathode). The effects of cathodal or anodal stimulation affects the cortical excitability due to the hyperpolization or depolization of the cortical neurons (Nistche & Paulus, 2000). tDCS is a non-invasive method, with anodal tDCS producing, in general, a facilitatory effect, and cathodal tDCS an inhibitory effect (Dayan et al., 2013). Anodal tDCS has been shown to improve basic skills such as motor learning (Nitsche et al., 2003), and also cognitive abilities such as verbal fluency and working memory (Fregni et al., 2005; Iyer et al., 2005) and emotional processing (Peña-Gómez et al., 2011). Ten minutes of stimulation can affect neural activity and behavioural task performance for up to 40 minutes (Lang et al., 2005; Nitsche & Paulus, 2000). Even though there are a number of studies that support that tDCS can affect cognitive abilities, it is important to keep in mind the limitations of tDCS (Hamilton, Messing & Chatterjee, 2011).

Only two studies have investigated the role of tDCS in retrieval induced forgetting (RIF, Anderson, Bjork & Bjork, 1994). Both these studies stimulated either the right or left DLPFC. Penolazzi and colleagues (2014) suggested that cathodal stimulation to the right DLPFC affected the forgetting of unpractised items in a RIF task. The second tDCS study proposed that individual (or premorbid) differences in RIF performance (i.e. high or low ability) may play an important role in understanding the role of frontal lobe in memory inhibition (Anderson, Davis, Fitzgerald & Hoy, 2015). These studies indicate that cathodal stimulation to DLPFC can impair performance on RIF task; however, there are no

studies of how tDCS can affect motivated forgetting. Data from fMRI studies suggest the DLPFC is engaged when participants directly suppress unwanted memories (Benoit & Anderson, 2012; Gangepain et al., 2014; Hulbert, Henson & Anderson, 2016; Wimber et al., 2015). Applying anodal tDCS (RA-LC) to the right DLPFC (cathodal tDCS to the left, RC-LA) is expected to enhance the ability to suppress unwanted thoughts (relative to cathodal stimulation when applied to the left DLPFC) in the think/no-think task; and whether any effects of tDCS are specific to the type of probe (same versus independent). Studies have shown effects of anodal stimulation (Nitsche et al., 2003; Pirulli et al., 2013) to the left DLPF have shown increase in correct responses (facilitation effects) in a go-no-go task, but this study did not use a cathodal stimulation to the left DLPFC (Boggio et al., 2007). Left hemisphere has been associated with using substitution in memory inhibition (Benoit et al., 2012). The design in this study allows us to see how anodal or cathodal stimulation may affect inhibition or facilitation in the context of memory inhibition.

2.2 Aim and hypothesis

The aims of this study were twofold. First, Experiment 2.1 aimed to replicate the standard effects of inhibition and facilitation of the Think/No-think task (Anderson & Green, 2001; Benoit & Anderson, 2012). Specifically, the hypothesis for experiment 2.1 was that performance (accuracy) for the words in the no-think condition will be worse compared to baseline, and the accuracy for the words in the think condition will be higher than baseline. This should be similar for both retrieval conditions (i.e. independent probe and same probe).

Second, Experiment 2.2 investigated the effect of transcranial direct current stimulation (tDCS) on motivated forgetting. The hypothesis for this study

was that inhibition would be better for the group receiving right anodal, left cathodal (RA-LC) stimulation compared to the group with RC-LA stimulation (Anderson et al., 2015; Penolazzi et al., 2014). In contrast, the facilitation was expected to be better in the RC-LA group compared to the RA-LC group. Research has suggested that memory inhibition (especially using direct suppression) to be a more right lateralised function (Anderson & Green, 2001; Benoit & Anderson, 2012). Based on this premise, the current experiment was designed to see the effect of anodal-cathodal or cathodal-anodal stimulation specifically in the right or left DLPFC. One experimental control condition would be to have a sham condition. However, administering a sham condition has a number of challenges: a) the participants, especially if they have had any experience of tDCS, may know the difference; and b) the design would need to be double-blinded, such that the researcher is not aware of the type of stimulation, until the analysis has been completed (Davis et al., 2013; Ambrus et al., 2010).

As noted in Chapter 1, the ability to inhibit unwanted memories is thought to be right-lateralised (Benoit & Anderson, 2012). Therefore, the main aim of this study was to understand if altering the balance of neural activity between right and left DLPFC made any difference to the individual's ability to inhibit (rather than the difference between stimulation versus sham). Thus, current design need not include a sham condition. The behavioural results (without the sham) have been compared to the behavioural results of the tDCS condition, for the purposes of comparing how stimulation affects inhibition or facilitation compared to no-stimulation (see Results section 2.7).

The methods and results for each experiment (2.1 & 2.2) are reported separately. The behavioural task (Think/No-think) for both experiments was the

same; they differed only in the tDCS that was administered just after the TNT practise task in Experiment

2.3 Experiment (2.1)

Methods

Participants

All participants completed the study in return for partial course credit and/or money. Participants reported no current psychiatric and/or neurological disorders, including history of seizures, or severe migraines. The Bangor University School of Psychology Ethics Committee approved all study procedures. The standard safety procedures (Bangor University stimulation committee) for the use of non-invasive brain stimulation were followed. Written informed consent was taken before participating.

Participants in the Exp. 2.1 (pilot study) completed the behavioural task with no stimulation. Eighteen participants (6 males) aged between 20 to 57 years (mean age = 34.41 years; SD = 11.40) were recruited for the first pilot study.

Materials & Procedure

The Think/No-Think (TNT) Task

Think/No-Think Task. The think/no-think (TNT) procedure has three phases (Benoit & Anderson, 2012; modified from Anderson & Green, 2001, see Figure 2.1). The task began with a "**study phase**", in which participants encoded a series of 54 word pairs. Each pair consisted of a hint word followed by a response word (e.g., "Lawn – Beef"). Participants viewed each word pair for 4 seconds. After viewing the entire list, they were tested using a recall procedure

in which they viewed the hint word, and generated the response word within 3 seconds. They received feedback (saw the correct response word on the screen) regardless of whether their response correct. The 54 word pairs consisted of 12-baseline word pairs (i.e. these word pairs were not used in the think/no-think phase), 12 word pairs each in the think and no-think condition, and 18 filler word pairs (i.e. six word pairs in baseline, think and no think conditions). The 12 word pairs in each of these conditions (i.e. baseline, think, and no think) were counterbalanced across participants. In order to proceed with the experiment, participants met a criterion of 60% correct (i.e. 32 out of 54 words). All study participants met this criterion.

During the "**TNT phase**" participants viewed the hint words and received instructions to suppress the response word for the hint words that were presented in red (no-think condition) and recall the response word for hint words presented in green (think condition). Participants first completed a short practice consisting of 3 no-think and 3 think trials. Participants then completed the TNT phase where 24 hint words (12 think and 12 no-think) were presented 12 times across 6 short blocks. These words were counterbalanced across participants. The 12 hint words each in order of the think and the no-think conditions were randomised across participants.

In the final "**memory retrieval phase**" retrieval for the all the 36 word pairs was tested using both same probe (SP) and independent probe (IP). During retrieval using same probe participants saw the original hint word along with the first letter of the response word (for example Lawn B). While in the independent probe test (IP, Anderson, Bjork & Bjork, 1994), participants saw a category as a cue with the first letter of the response word (for example Meat B).

The presentation sequence during the memory retrieval tests (i.e. same probe – independent probe (SPIP) or independent probe – same probe (IPSP)) was counterbalanced across participants. The procedure is illustrated in Figure 2.1.

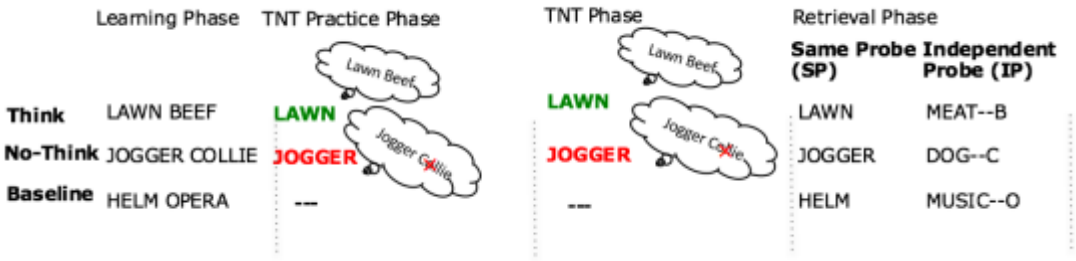


Figure 2.1 Think/No-think task (Exp.2.1)**.** Participants in the pilot study completed the task without any stimulation.

The percentage of correct responses in the think, baseline and no-think words during the final retrieval test were the main data of interest. During the retrieval test, memory was tested using two methods: 1) the *Same Probe* (SP) where participants saw the same left hand side word from the word pair (e.g. LAWN -), 2) the *Independent Probe* (IP) where participants saw a word describing a broader semantic category of the response word with the first letter stem of the response word (e.g. MEAT – B).

Results (Experiment 2.1)

Two separate ANOVAs (repeated measures) for same and independent probe with the three conditions (Think, Baseline, and No-Think) showed a significant for both retrieval condition ($F_{SP(2,58)}$ = 8.359, p = .001, partial eta square = .224; $F_{IP(2,58)}$ = 3.441, p = .039, partial eta square = .106).

Paired t-tests suggested that there was a significant difference between the baseline and no-think conditions for same probe (t_{29} = 3.420, p = .002, two-

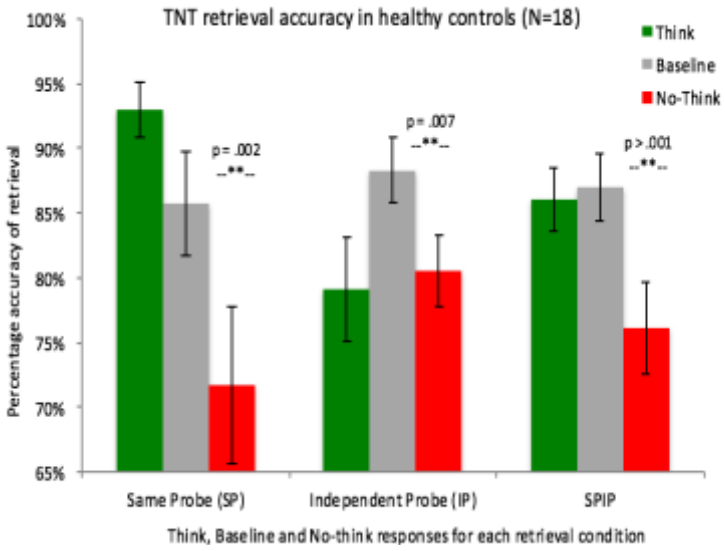


Figure 2.2 The percent accuracy for memory retrieval phase.

tailed), independent probe (t_{29} = 2.901, p = .007, two-tailed), and also when averaged across same and independent probe (t_{29} = 4.354, p > .001, two-tailed, Fig. 2).

2.4 Interim Discussion

The results from the first experiment (2.1), suggested that participants were able to inhibit unwanted memories (performance for the no-think was worse than the baseline). This difference was clear when the retrieval was tested using both same probe (SP) or the independent probe (IP) method. This was empirical evidence that the Think/No-Think effect (for inhibition) is replicable. However, these data showed facilitation effects (i.e. performance for think is greater than baseline) only in the same probe condition.

Following this pilot study, the same methods and procedure for the TNT task was used in the second experiment (2.2) with the only addition being the

tDCS stimulation, which was administered just after the TNT practice task (see Figure 2.3)

2.5 Experiment 2.2 (tDCS Study)

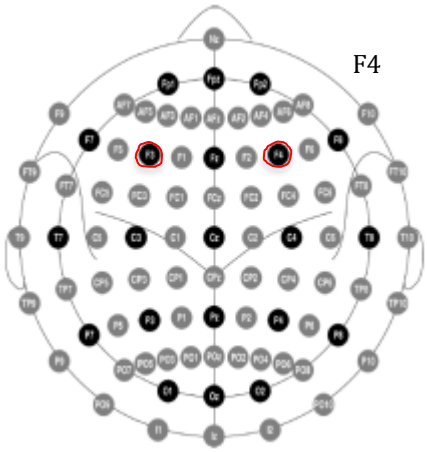
Experiment 2.2 was designed to investigate the role of tDCS in memory inhibition.

2.6 Assumptions of tDCS

In this study the participants were randomly assigned to either of the two groups. The first group received stimulation with the anodal electrode over the right DLPFC (referred to as "Anodal-Cathodal (AC)" group; *n* = 12; mean age = 23.92 years; SD = ±3.53; 3 males), while the second group received stimulation with cathodal electrode over the right DLPFC (referred to as "Cathodal-Anodal (CA)" group; *n* = 12; mean age = 23 years; SD = ±2.37; 5 males).

The right DLPFC electrodes were placed over the F4 (international EEG 10/20 system; Oostenveld & Praamastra, 2001), while the left DLPFC electrodes were placed over the F3. The system for electrode placement (i.e. the point of stimulation) for each individual participant were identified and measured (Oostenveld & Praamastra, 2001). The points of measures (F3 and F4) are based on 10-10 system and is endorsed as the standard of the American Electroencephalographic Society (Klem et al., 1999) and the International Federation of Societies for Electroencephalography and Clinical Neurophysiology (Nuwer et al., 1998). The findings from such stimulation studies (a) would provide evidence that external stimulation methods can modulate this psychological process, and (b) might inform clinical applications (especially in neurological patients and for disorders such as PTSD and depression).

2a



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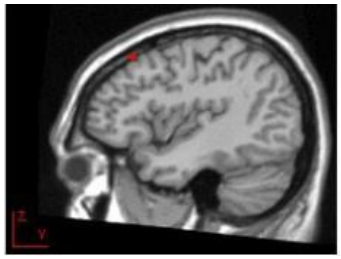

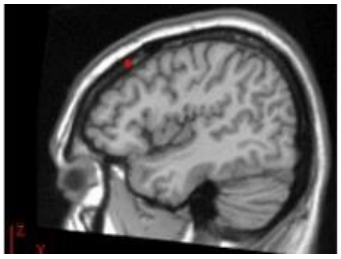

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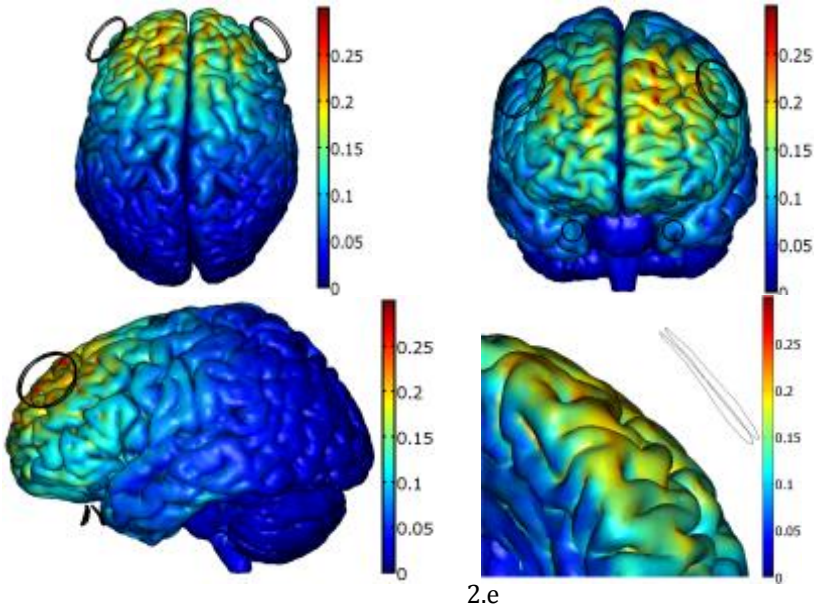

2.e

Figure 2.a Electrodes for the study (size: 5x5 cm, area 9cm^2; current: 2mA) Figure. 2.b. Electrode positions and labels in the 10±20 system. Black circles indicate positions of the original 10±20 system, gray circles indicate additional positions introduced in the 10±10 extension (Oostenveld and Praamastra, 2001). Figure 2.c Ask Helen for the reference of Iconographie. Figure 2.d. Diagram of the magnitude of the electric field stimulated at F3, F4. Figure. 2.e. The magnitude of the electric field is higher in the gyri near the electrodes than in the mesial wall of the hemispheres.

tDCS Methods

Participants

For the tDCS experiment (2.2), a new cohort of twenty-four participants (8 males) aged 18 to 30 years (mean age = 23.46 years; SD = 2.98) were recruited from Bangor University and local community. All participants completed the study in return for partial course credit and/or money. Participants reported no current psychiatric and/or neurological disorders, including history of seizures, or severe migraines. The Bangor University School of Psychology Ethics Committee approved all study procedures. The standard safety procedures (Bangor University stimulation committee) for the use of non-invasive brain stimulation were followed. Written informed consent was taken before participating.

Methods and Materials

The think/no-think (TNT) task (described in Experiment 2.1) was used for this experiment with the sole addition of the tDCS stimulation and relevant questionnaires (see Figure 2.2).

tDCS stimulation parameters

A Magstim DC+ (Witland, Dyfed, Wales) constant current stimulator applied the tDCS. We used two conductive rubber electrodes (5cm x 5cm) placed in sponges saturated with saline to induce the current (Figure 4.1a). The electrodes were located bilaterally over the F3 and F4 electrode position of the 10-10 system (Figure 4.1b; American Electroencephalographic Society; Nuwer et al., 1998). These positions correspond to the left (F3) and right (F4?) DLPFC (Koessler et al., 2009; Oostenveld and Praamstra, 2001). A 2mA current (current

density 0.08mA/cm^2) was applied for 20 minutes after the TNT practice phase of the task. Participants were instructed to rest during the stimulation and the experimenter did not engage in any discussion while the current was applied. The current onset and offset were gradual over an additional 15 seconds at the beginning and end of stimulation to minimise skin sensation. Participants reported non-painful skin sensations throughout the stimulation.

Half of the participants received right anodal - left cathodal (RA-LC) stimulation and the other half received right cathodal-left anodal (RC-LA) stimulation. Participants were randomly assigned to the stimulation conditions. Importantly, the experimenter was blind to stimulation condition throughout the

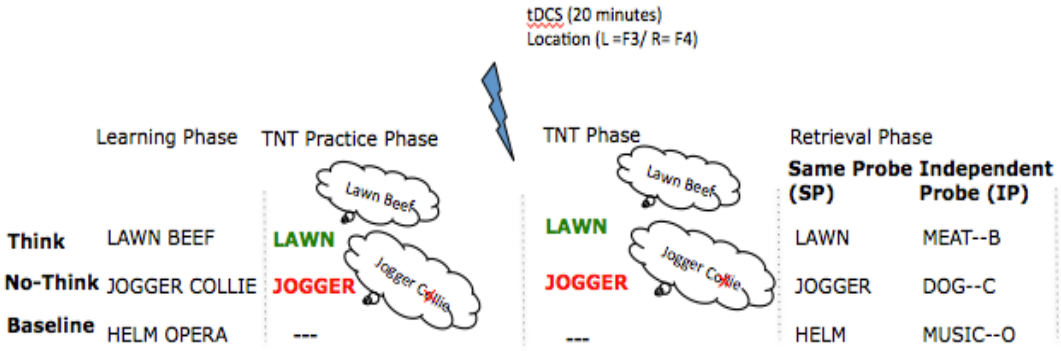

Figure 2.3 Think/No-think task (tDCS Study)**.** Participants in the tDCS study completed the same task (Exp. 2.1) but received stimulation just after the practice phase.

duration of the data collection phase of the study. There were no differences between the stimulation groups (RA-LC: mean age = 23.92 years, SD = 3.53, 3 males; RC-LA: mean age = 23 years, SD = 2.37, 5 males).

Questionnaire (tDCS Study).

All participants completed several questionnaires. The Thought Control Ability Questionnaire (TCAQ, Luciano, Algarabel, Tomás, & Martínes, 2005) before the experiment: a 25-item questionnaire which assesses the individual's perceived ability to exert control over intrusions. Participants indicate whether they agree with these statements (e.g. I am usually successful when I decide not to think about something and I get rid of uncomfortable thoughts or images almost effortlessly) using a 5-point scale from 1 (*completely disagree*) to 5 (*completely agree*). Higher scores on the TCAQ indicate better control ability (Cronbach's α = .825).

The emotion regulation questionnaire (ERQ, Gross & John, 2003):10 statements on how individuals control (i.e. regulate and manage) their emotions (e.g. I keep my emotions to myself and I control my emotions by not expressing them). Participants indicate using a 7-point scale whether they agree or disagree (1 = *strongly disagree*; 7 = *strongly disagree*). The ERQ is designed to assess the individual differences in the use of emotional regulation strategies, i.e. cognitive reappraisal (Cronbach's α = .792) and emotional suppression (Cronbach's α = .871).

The Five Facet Mindfulness Questionnaire (FFMQ, Baer, Hopkins, Krietemeyer, Smith, & Toney, 2006) is 39-item measure of mindfulness, with five subscales: observing (Cronbach's α = .774), describing (Cronbach's α = .925), acting with awareness (Cronbach's α = .885), non-judging of inner experience (Cronbach's α = .921), and non-reactivity to inner experience (Cronbach's α = .809).

The State-Trait Anxiety Inventory (STAI Y-1, Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) is a self-administered questionnaire assessing state and trait anxiety. Items measure the presence (Cronbach's α = .640), or absence of state anxiety (Cronbach's α = .930) and the presence (Cronbach's α = .369) or absence of trait anxiety (Cronbach's α = .827). The Cronbach's α for the anxiety present items was low at .369, however removing item 18 (I took disappointments so keenly that I couldn't put them out of my mind) improved the overall internal reliability of the presence subscale (Cronbach's α = .794).

All questionnaires have high internal reliability measured by Cronbach's α. During and at the end of the session, detailed questionnaires to record subjective experience were administered (see appendix).

Data Analysis (Exp. 2.2)

To examine the effect of stimulation (RA-LC or RC-LA) on the ability to facilitate or supress memory retrieval, the percentage of correct responses (from the retrieval tests) was analysed to see the effect of stimulation (RC-RA or RA-RC) on inhibition and/or facilitation. Two separate 3 x 2 ANOVAs for the same probe and independent probe conditions were used. Factors were the retrieval condition (baseline, think, no-think) and stimulation condition (RA-LC, RC-LA).

Results (Experiment 2.2)

Independent t-tests results confirmed there were no differences at baseline between the RA-LC and the RC-LA group for the independent probe, $t_{(22)} = .678$, p = ns, or for the same probe, $t_{(22)} = 1.05$, p = ns. Table 1 shows the mean percentage correct retrieval for each condition.

Table 1: **Percent correct responses for each condition**

	Same Probe			**Independent Probe**		
Conditions	Think (SD)	Baseline (SD)	No-Think (SD)	Think (SD)	Baseline (SD)	No-Think (SD)
RA-LC	89.65 (9.82)	93.56 (7.45)	86.96 (12.13)	78.81 (14.62)	83.02 (12.28)	73.23(16.21)
RC-LA	96.65 (6.55)	90.18 (8.26)	79.15 (18.09)	82.31(16.67)	79.42 (13.68)	74.17 (19.99)

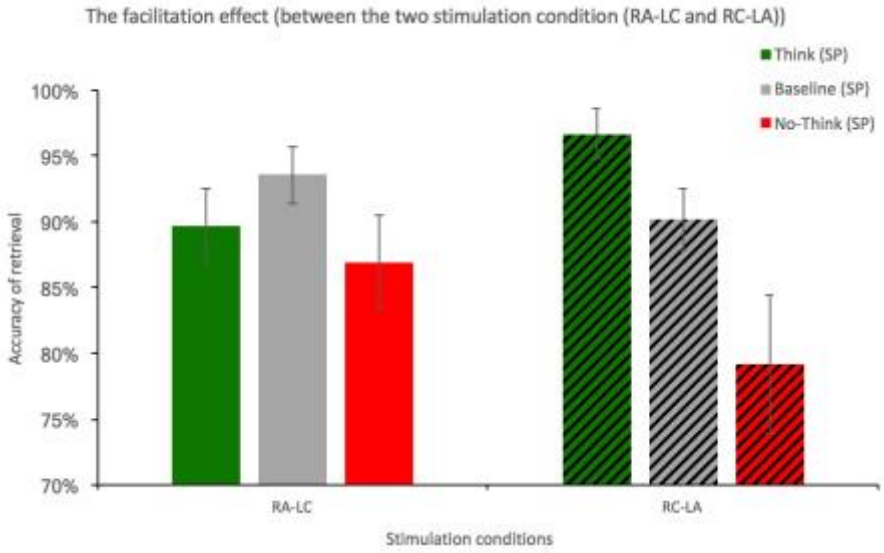

Figure. 2.4a Average performance for think, baseline and no-think condition (between the two stimulation conditions)

To investigate the effect of stimulation on the ability to inhibit (baseline vs. no-think) or facilitate (baseline vs. think), the correct responses from the final retrieval tests for each of the probe type (same or independent) were submitted to two separate 3 (retrieval conditions, i.e. think, baseline, no-think) x 2 (type of stimulation, i.e. RA-LC & RC-LA) mixed ANOVAs. The statistics were based on a-priori assumptions of the inhibition and facilitation effect.

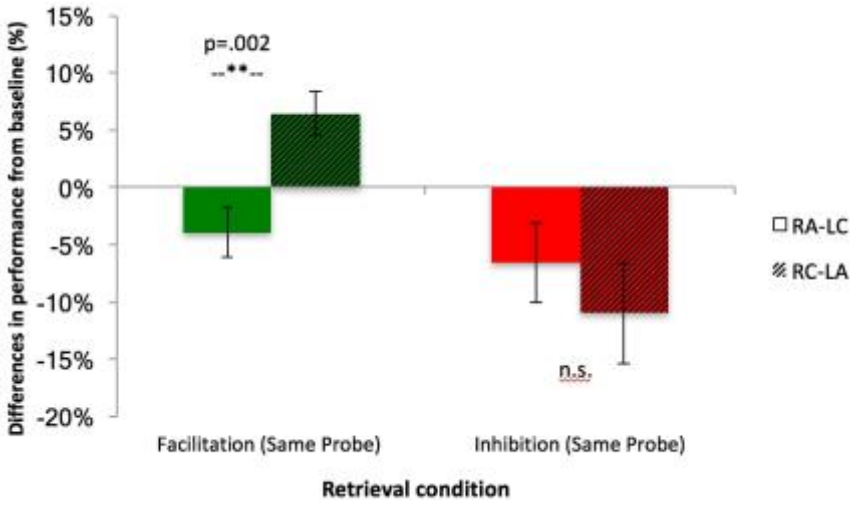

Figure. 2.4b Average performance for facilitation (think minus baseline) and inhibition (baseline minus no-think) for the two stimulation group.

The same probe analysis showed a significant main effect of retrieval condition, $F_{(2, 44)} = 9.104$, $p < .001$, and a significant interaction between retrieval condition and stimulation condition, $F_{(2, 44)} = 4.36$, $p = .02$. The ANOVA on the independent probe results showed no main effect of retrieval condition, $F_{(2, 44)} = 2.28$, ns, nor an interaction, $F_{(2, 44)} = 0.43$, p = ns.

To further examine the interaction between retrieval condition and stimulation condition (in the same probe ANOVA), two post hoc t-tests (using a Bonferroni-corrected alpha value of p = .025) were carried out to examine how the facilitation effect (think minus baseline) and the inhibition effect (no-think minus baseline) differed between the stimulation conditions. The results indicated that the level of facilitation (think minus baseline) was significantly greater in the RC-LA condition compared to the RA-LC condition, $t_{(22)} = 3.48$, $p = .002$, two-tailed, with better facilitation ($t_{(22)} = 3.30$, $p = .007$, two-tailed) in the RC-LA stimulation condition compared to lesser facilitation ($t_{(22)} = 1.74$, p = ns.,

an inhibition like effect) in the RA-LC condition. By contrast, there was no significant difference between stimulation conditions on inhibition (no-think minus baseline in the same probe), $t_{(22)} = 0.79$, p = ns. two-tailed (Figure. 2.4).

The *a priori* hypothesis (specifically for inhibition) was that cathodal stimulation would affect inhibition, specifically more so in the independent probe condition; the results do not support this. The inhibition between the baseline and no-think ($t_{(11)} = 1.803$, p = .099, two tailed, p = n.s.) in the RA-LC condition was trending to be larger than the inhibition in the RC-LA condition ($t_{(11)} = 1.295$, p = .222, two-tailed, p = ns.) though neither of these were significant (for figure see appendix).

Questionnaire results

Scores on all the questionnaires did not differ between participants in the two stimulation conditions, suggesting that the effect of stimulation cannot be explained by the psychometric differences between the participants (See Table 2). Also, all participants were in the high range of the TCAQ score (2 to 125) suggesting that all the participants in the stimulation study had a high thought control ability.

Questionnaire	RA-LC	RC-LA	t-test (p value, 2 tailed)
	Mean (SD)	Mean (SD)	
TCAQ	80.75 (12.48)	79.25 (11.70)	t_{22}= .304 (p = .764)
STAI-I	44.92 (6.08)	45.50 (4.32)	t_{22}= .271 (p = .789)
STAI-II	47.75 (3.37)	48.58 (6.64)	t_{22}= .363 (p = .720)
FFMQ	22.25 (4.20)	21.67 (5.66)	t_{22}= .723 (p = .447)
ERQ-Reappraisal	29.25 (5.92)	30.17 (5.29)	t_{22}= .400 (p = .693)
ERQ-Suppression	14.50 (6.22)	14.67 (6.56)	t_{22}= .064 (p = .950)

Table 2.2 Descriptive statistics for the questionnaires for Experiment 2.2 (tDCS)

2.7 Results (comparing the behavioural results of the experiment without [2.1] and with stimulation [2.2])

Same probe (SP)

Separate 2 x 3 ANOVAs for facilitation (think minus baseline) and inhibition (baseline minus no-think) were conducted for the SP condition with baseline and no-think as within- subject factors and type of stimulation [RA-LC, or RC-LA (Experiment 2.2) or control (Experiment 2.1) as between-subject factors.

The ANOVA for facilitation suggests that there was no main effect of retrieval ($F_{(1,39)}$ = 1.995, p =.166, n.s., Pillai's Trace = .049). There was no difference in the performance (in the facilitation) between the RC-LA stimulation conditions and the pseudo-sham condition (pseudo-sham) condition (t_{28} = -.152, p = .880, n.s.); the difference between the RA-LC and the pseudo-sham condition was trending towards significance, but was not significant with the Bonferroni-adjusted alpha level of .017 (t_{28} = -2.077 p = .049, n.s.). There was also with no interaction $F_{(2,39)}$ = 2.333, p = .110, n.s., Pillai's Trace = .107, see figure 2.5).

The ANOVA for inhibition suggests that there was a main effect of retrieval ($F_{(1,39)}$ = 15.67, p < .001, Pillai's Trace = .287); but, no interaction $F_{(2,39)}$ = .687, p = .509, n.s. see figure 2.5) between the inhibition across the conditions. There is no difference in the performance (for inhibition) between the stimulation conditions and the pseudo-sham condition (RC-LA and the pseudo-sham condition (t_{28} = .457, p = .651, n.s.); the difference between the RA-LC and the pseudo-sham condition was trending significant, but not significant (t_{28} = 1.125, p = .222 n.s.).

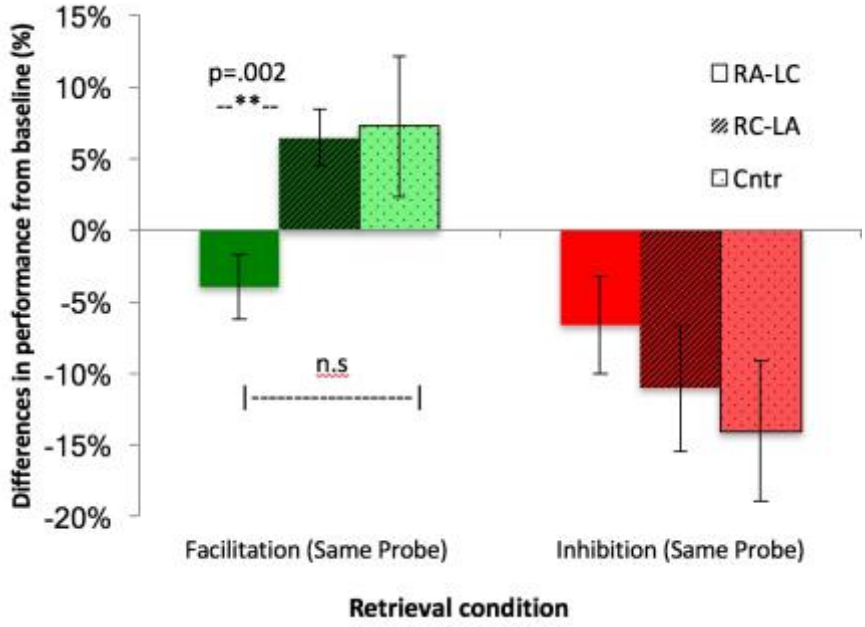

Figure. 2.5 Average performance (Same Probe) for facilitation (think minus baseline) and inhibition (baseline minus no-think) for the two stimulation and the pseudo-sham group.

Independent Probe (IP)

Separate 2 x 3 ANOVA for facilitation (think minus baseline) and inhibition (baseline minus no-think) for IP (baseline and no-think as within and type of stimulation [RA-LC, RC-LA or control] as between factors).

The ANOVA for facilitation suggests that there was neither a main effect of retrieval ($F_{(1,39)}$ = 1.333, p =.255, Pillai's Trace = .033) nor an interaction $F_{(2,39)}$ = 1.411, p = .256, n.s., Pillai's Trace = .067, see figure 2.6). There was no difference in the performance between the stimulation conditions and the pseudo-sham condition (RC-LA and the pseudo-sham condition (t_{28} = 1.719, p = .099, n.s.); the difference between the RA-LC and the pseudo-sham condition was trending significant, but not significant (t_{28} =-0.675, p = .507, n.s.).

The ANOVA for inhibition suggests that there was a main effect of retrieval ($F_{(1,39)}$ = 9.380, p =.004, Pillai's Trace = .194); but, no interaction $F_{(2,39)}$ = .013, p = .780, n.s. see Figure 2.6). There is no difference in the performance between the stimulation conditions and the pseudo-sham condition (RC-LA and the pseudo-sham condition (t_{28} = 0.466, p = .646, n.s.); the difference between the RA-LC and the pseudo-sham condition was trending significant, but not significant (t_{28} = -0.320, p = .753, n.s. Bonferroni correction).

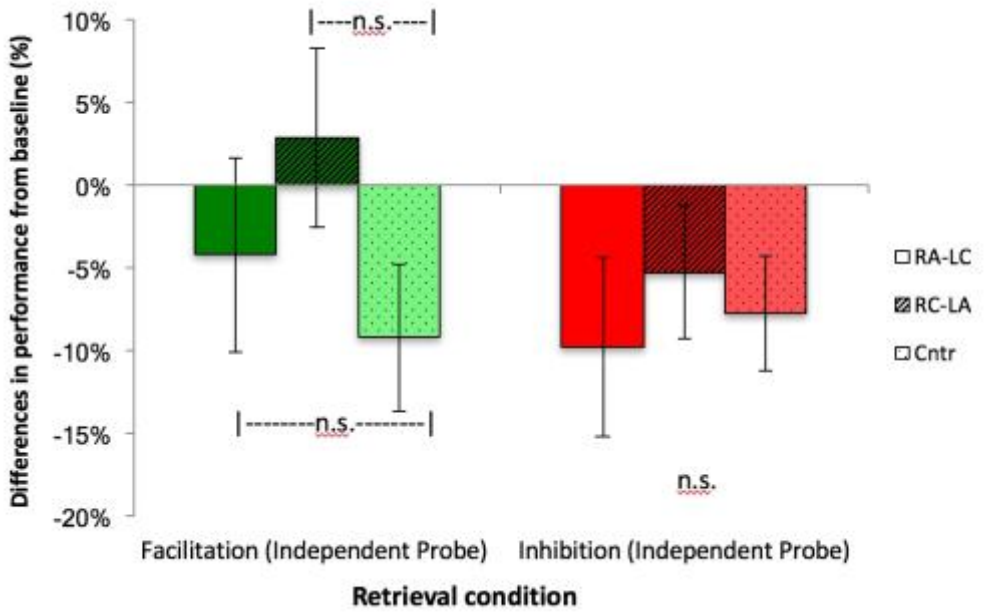

Figure. 2.6 Average performance (Independent Probe) for facilitation (think minus baseline) and inhibition (baseline minus no-think) for the two stimulation and the pseudo-sham group.

2.8 Discussion

Most of the studies using the Think/No-Think task show the expected suppression and facilitation effects (Anderson & Green, 2001; Anderson & Hanslmayr, 2014); however, there have been studies that do not show these effects (Bulveich et al., 2006; Racsmany et al., 2012; see also Hertel & Calcaterra, 2005). Experiment 2.1, therefore aimed to replicate the findings in most

Think/No-Think (TNT) studies (e.g. Anderson & Green, 2001; Anderson et al., 2004; Benoit & Anderson, 2012), before using the task with tDCS (Experiment 2.2) or adapting it to be used in patients with focal lesions (see Experiments in Chapter 3 & 4).

The results from the behavioural (Exp. 2.1) study replicated the TNT inhibition effect, which suggests that engaging in suppression results in lower accuracy on the no-think items compared to the baseline during the final recall (e.g. Anderson & Green, 2001; Anderson et al., 2004; Benoit & Anderson, 2012). Some studies have observed this effect in both types of retrieval (same or independent probe, Benoit & Anderson, 2012). In this study, however, the facilitation affect (i.e. think greater than baseline) was only seen in the same probe condition (similar to that noticed in Caterino et al., 2015). It is important in the future for both behavioural and neuroimaging studies using TNT tasks to discuss both the inhibition and facilitation effect. In addition to this it might be interesting to understand how reaction times across individuals may interact with either inhibition or facilitation effects.

The second experiment (Exp. 2.2) was designed to understand if stimulation to the lDLPFC or the rDLPFC affected inhibition. This experiment used the same procedure from the behavioural study (Exp. 2.1), with the addition of 20 minute tDCS stimulation just after the TNT practice task (see Fig. 2.2 for details). Participants received either RA-LC or RC-LA stimulation to the DLPFC. The design used in this study does not permit us to compare the

behaviour (pseudo-sham) condition to the stimulation condition[2]. The main purpose of this study (Exp. 2.2) was to look at the differences between right (anodal/cathodal) and left stimulation (anodal/cathodal, RA-LC or RC-LA). The study was designed to understand if stimulation of DLPFC (RC-LA or RA-LC) affected inhibition. The results suggested that RC-LA or LA-RC stimulation does not affect the inhibition, in the context of the Think/No-Think (TNT) task.

Performance in the no-think condition was poorest, with highest performance in the think condition, when compared to the baseline. These results are similar to Experiment 2.1 (in this study). Retrieval measures from the same-probe condition (RC-LA stimulation) show that the standard think/no-think effect is observed (Benoit & Anderson, 2012).

Although, it was hypothesised that there would be a difference in facilitation (think minus baseline), it was not expected that facilitation in the RA-LC stimulation would be significantly worse compared to the RC-LA stimulation. The observed facilitation effect in the RA-LC was significantly lower and was opposite to what is normally expected, in the no-think (behavioural) studies (Anderson & Hanlmayr, 2014). Previous research has demonstrated a facilitation effect of anodal stimulation (online) on an implicit and explicit motor learning task (Nitsche et al., 2003), while results from visual studies have shown offline anodal stimulation to show facilitation (Pirulli et al., 2013). These results suggest that given evidence that anodal stimulation may show some facilitation effect, it

[2] A section of results (2.7) does compare the performance between the psudo-sham and stimulation condition, and there seems to be no significant differences between these two experiments.

is often not generalizable across areas. Therefore, this study has demonstrated that anodal stimulation (RC-LA) to the right DLPFC may not improve facilitation, but it does impair facilitation either. Interestingly, cathodal stimulation to the left DLPFC (and anodal to the rDLPF, RA-LC) impairs facilitation. However, none of the studies in a typical TNT task, have focused on the facilitation effect. It would indeed be interesting to see how different stimulation methods, and possibly timings of stimulation affect facilitation in a TNT task and possible also look for any changes in inhibition.

This provides some evidence that anodal stimulation to the right DLPFC and cathodal stimulation to the left DLPFC (RA-LC) may impair the ability to recall the associated word (think condition), when memory retrieval is tested using the same probe (LAWN - __) methods, but does not necessarily affect the ability to inhibit (no-think condition). Contrary to our hypothesis, this suggests that enhancing the activity of right relative to the left DLPFC does not enhance the ability to suppress, but instead impairs facilitation. It would be of interest to see in the future, if these changes correlate with differences in the reaction time.

Functionally, these results related to those of Penolazzi et al., (2014) who showed cathodal stimulation of the right DLPFC during RIF interfered with the inhibitory processes. However, our results suggest that RC-LA stimulation does not affect either inhibition or facilitation, whereas the RA-LC stimulation does impair performance during facilitation (think compared to baseline). One possible explanation of why stimulation did not affect participants' ability to inhibit is that they had a strong ability to control (as shown by the TCAQ questionnaire results, see Table 2.4, in appendix) suggesting that they are high in their ability to suppress. tDCS stimulation may therefore not improve

performance in participants are already over a certain threshold (Anderson et al., 2015). It is well known that stimulation effects are often affected by individual and time/strength of stimulation (Ambrus et al., 2010). Future studies could investigate whether stimulation may affect participants with low scores differently and/or possibly use a between-subject design.

The RA-LC stimulation affects the underlying cognitive process such that even when they make an effort (confirmed from evidence in the post-study questionnaires) when confronted with the reminder to 'bring to mind' the word pair, they still are unable retrieve the right hand side words. The recall of the paired word was impaired (rather than facilitated) relative to baseline in the think condition after RA-LC stimulation. It is possible that RA-LC tDCS weakened the association between the cue and response words in the think condition. Racsmány et al. (2012) suggest that it is the associations between the cue and response words, rather than the response words themselves, that are inhibited in the no-think condition. Indeed, other work suggests that dorsolateral prefrontal cortex is specifically involved in associative memory (Blumenfeld & D'Esposito, 2010) and exerts modulatory control over the hippocampus (Woodcock et al., 2015). However, it is not clear why RC-LA tDCS did not affect associative memory in this experiment as expected. Another possible explanation for this is that the RA-LC stimulation improves inhibition, such that it prevents learning even when participants are actively engaging in thinking about the relevant word pair in the think condition.

The fact that tDCS only affected retrieval in the same probe trials suggests that there may be separate cognitive processes underlying retrieval during the same probe and independent probe conditions. It is argued that measuring

retrieval using independent probe (IP) during a TNT task is better indication of the underlying inhibition process (Anderson & Bjork, 1995) than using the same probe. The results from this study show a trend in the expected direction, that is right anodal (left cathodal) stimulation seems to still allow people to actively inhibit unwanted information compared to right cathodal (left anodal) stimulation (where there is lesser difference between baseline and no-think), suggesting that right DLPFC might have an important role in the process of inhibition (Penolazzi et al., 2014). It is of interest to note that when both right and left DLPFCs are stimulated (RA-LC or RC-LA) tDCS does seem to affect the underlying cognitive process in the IP method of retrieval. It is beyond the scope of this study to comment on the underlying process of retrieval and why tDCS acts differently on these retrieval methods. Future studies are needed to disentangle how the processes underlying motivated forgetting are affected by stimulation.

Why is the evidence then not as strong as expected in this particular study? The results indicate that right anodal stimulation (RA-LC) differently affects the ability to actively retrieve memories compared to the RC-LA condition. All the participants in the stimulation group had a high TCAQ score. This suggests that they had a higher ability to control their thoughts (Catarino et al., 2015). Based on prior tDCS research (Anderson, Davis, Fitzgerald & Hoy, 2015) in retrieval induced forgetting, stimulation is known to differently affect people based on their premorbid disposition. There is further evidence that tDCS positively affects participants who are below a certain threshold (Anderson, Davis, Fitzgerald & Hoy, 2015; Bradman, Stinear & Byblowm 2011). Therefore, as most participants in the tDCS experiment in this study are already high in their ability

to inhibit unwanted information, anodal stimulation does not appear to improve this ability, while cathodal stimulation to the right DLPFC and anodal stimulation to left DLPFC does not significantly impair the inhibition.

The present results (Experiment 2.2) are consistent with several other studies which have failed to find think/no-think effects on recall using independent probes (Algarabel, Luciano, & Martínez, 2006; Bulevich et al., 2006; Wessel, Wetzels, Jelicic, & Merckelbach, 2005). More recent studies (Racsmány et al., 2012; Catarino et al., 2015) have reported found the usual think/no-think effect when the same cue words (same probes) were used at retrieval. One of the limitations of this study is the absence of a sham condition. Hence, it is difficult to conclude (from the stimulation conditions alone) whether there was some effect of the RC-LA stimulation or whether this stimulation just displays the expected effect in a Think/No-Think task (Anderson & Green, 2001).

This study is the first to address the role of tDCS in motivated forgetting, using current stimulation. The main interest was to see how stimulation affects our ability to suppress or inhibit unwanted memories. Stimulation did not affect inhibition by did significantly affect ability to facilitate. This results support a recent tDCS study which did not find evidence for DLPFC stimulation to improve performance on a stop-signal task (Stramaccia, et al., 2015). The stop-signal task is often considered to be the motor analogy of the TNT task. The result from the tDCS (in this thesis) does provide some evidence, which can be followed up in future studies. It is beyond the scope of this study to conclude whether the effect of stimulation on facilitation is an independent effect, or indeed an overarching effect of inhibition (from the rDLPFC). Future studies can be designed to answer this specific question.

Overall, it may be concluded that when people are generally high in their pre-morbid ability to suppress information, tDCS affects the facilitation process rather than the inhibition or suppression. Moreover, this effect can only be seen in retrieval measured using the same probe condition. Although the current findings are not entirely in line with the general claim in memory inhibition literature that independent probe is a better measure of inhibition (Anderson & Green, 2001; Anderson et al., 1994), it does support the argument that executive functions affect the ability to inhibit (Levy & Anderson, 2008)

3. Developing the Patient friendly TNT (*pf*-TNT)

3.1 Introduction

The ability to forget unwanted information is equally as important as remembering relevant information. Neuroimaging and behavioural studies over the recent decades have suggested that the ability to inhibit unwanted experiences is an active cognitive process (e.g. Anderson & Green, 2001; Hertel & Calcaterra, 2005; Anderso & Huddleston, 2011) that in turn impairs the retention of the suppressed memory (Benoit & Anderson, 2012; Bergström et al., 2009). This ability to purge unwanted memories, when confronted with the reminder (evidenced by neuroimaging research) is suggested to be a more right lateralised function (Benoit and Anderson, 2012; Anderson & Hanslmayr, 2014), implying that right DLPFC is involved in this cognitive process. An interesting question that remains to be answered is whether the right DLPC is critical to this process of motivated forgetting. Only neuropsychological studies in lesion patients can answer this question (Rorden & Karnath, 2004; Bub, 2002). In order to test the TNT paradigm in patients with focal lesions (see Chapter 4), it is important to adapt this task to make it patient friendly.

Development of the patient friendly adaptation of the *direct suppression* TNT proceeded through a number of changes. Principally focused on: 1) modification to the experimenter script, based on the procedures used in a previous TNT study with older adults (Murray et al., 2011; Murray et al., 2015); 2) modification of the timings in the task; and 3) modification to the number of word pairs presented at the learning stages.

The *pf*-TNT was initially piloted with a sample of older adults (Pilot Experiment 1 (PE1), n=7). After completing the PE1, this first version of the task was tested on a single patient (high functioning) with focal neurological lesion (Pilot Experiment 2 (PE2), Patient MJ). Based on MJ's performance and comments provided by MJ at the end of the session, this version was further modified. This modified patient friendly version was then piloted in a further small group of patients with focal brain lesions (Pilot Experiment 3 (PE3, n=5). This version was then re-tested on Patient MJ, to ensure she was able to complete the task. It was this version that has been used in the final experiment on patients with focal unilateral frontal lesions (see Chapter 4 for more details).

3.2 Methods

All participants gave written consent, as approved by School of Psychology, Ethics Committee (Bangor University), the Local Research Ethics Committee, North Wales region or the Cambridge Psychology Research Ethics Committee (CPREC, Cambridge University). All participants received a small token of £6 per hour for their time in all studies.

Participants

Pilot Experiment 1 (PE1): TNT Pilot in healthy older adults

Seven right-handed volunteers participated in this study. They either responded to advertisements or were a part of the community panel within Bangor University and had expressed interest to participate in research. They all reported no history of psychiatric or neurological disorder. The seven participants (two males, mean age: 40.86 years, range: 24 – 62 years) completed the modified TNT task with instructions for *direct suppression.*

Pilot Experiment 2 (PE2): TNT Single Case Study (Patient MJ)

MJ (55-year-old, female) was the first patient to complete a brief cognitive assessment followed by a TNT task in the same (first) session. Participant MJ had a focal lesion to her left frontal lobe following a stroke, ten years ago. Post stroke, MJ had some difficulties with speech, and she no longer reported these. She reported some continuing difficulties with her ability to do mental calculations, especially when using cash for transactions during her shopping. She does not have any difficulties in her activities of daily living and continues to drive. She is keen on gardening and takes interest in activities around her home. MJ completed the TNT tasks that were adapted in healthy controls (Experiment PE1).

Pilot Experiment 3 (PE3): TNT in patients (n = 6) with focal lesions.

Five patients (Mean age = 53.83, Std. Dev = 9.89, DH, SB, JM, PP and WK) from the Cambridge Cognitive Neurosciences Research Panel (CCNRP), MRC-CBU and patient MJ were recruited for this study. Patients had focal unilateral lesions due to brain surgery (N =3) and stroke (N = 3).

3.3 Procedure

The Think/No-Think procedure (Benoit & Anderson, 2012) was adapted based on the studies in older adults (Murray et al, 2011; Murray et al., 2015). Older participants have been reported to need longer presentation speeds to match the performance in younger adults (Murray et al., 2011; Murray et al. 2015). Based on age-related declines in speed of processing the presentation times and time taken to respond were increased from the original study (Salthouse, 1996).

Participants completed all three phases (as in Benoit & Anderson, 2012; see Figure 2.1) for all the three experiment (PE1, PE2, and PE3). Which were (1) the Learning Phase; (2) Think/No-Think (TNT) phase; and (3) the Memory Retrieval Phase. In the *Learning Phase*, participants encoded fifty-four word pairs (e.g. LAWN-BEEF; BEACH-AFRICA).

Pilot Experiment 1 (PE1): TNT Pilot in healthy older adults

Thirty-six of the fifty-four word pairs were the critical pairs (i.e. used in the main TNT Phase) and 18 were filler pairs (i.e. some of these words were used in the practise task). The fifty- four word pairs were divided into three lists (A, B, C) of 18 words each (in Benoit & Anderson, 2012)[1]. Each word-pair in this study was presented on the screen for up to 4 seconds (compared to the 3.3 seconds.). After the initial presentation of the word-pair list (e.g. A), the participants would then complete a *cued recall.* In cued recall, they would see the right hand (referred to as hint word) on the screen and they had to respond with the left hand (known as the response word). The hint word would be on the screen for up to 6 s. After which irrespective of their answer, they would then receive feedback, and only the correct response word (e.g. AFRICA) would be displayed on the screen for 2 sec. (compared to 1 sec. in healthy adults) in BLUE. They were instructed to reinforce their learning during this phase. If they correctly learnt 12 out of 18 word pairs or after they completed two cycles of the cued recall, participants proceeded to the next list (e.g. B then C). Compared to Benoit and Anderson's (2012) study, where participants completed the cued recall for

[1] In Benoit & Anderson (2012) participants were shown all the 54 word pairs in one long list.

all the 54 word pairs until they reached a 50% criterion or a maximum of three times, before going on to the criterion test phase. After all the three lists of words (in this study) were completed, participants proceeded to the *criterion phase*. In this they were presented with the hint word (just like before) and they had to respond with the response word, but they did not receive any feedback in this phase.

There was no change made in the *TNT Phase*. Eighteen of the 54 word pairs were the baseline and thus were not presented during the TNT phase. These 18 words pairs were counterbalanced across participants. During the *TNT Phase* they received instructions for *direct suppression* (Benoit & Anderson, 2012; Bergström et al., 2009). Some of the words were presented in GREEN (think condition) - when they saw the word in GREEN they were asked to covertly recall the word pair, and keep it in mind for the entire time the green hint word was on the screen. For words that appeared in RED (no-think) they were instructed to avoid thinking of the word that went with it. If it did come to mind, they were asked to "push it out of mind" and keep it out the entire time; they then were instructed to focus their attention back to the red hint word on the screen[2].

Finally, participants had to remember all the right hand (or response) words irrespective of the condition (think, baseline, or no-think). The reminders were presented on the screen for a maximum of 3.3 s (ISI: 1.1 s). Response was coded as correct only if participants recalled the word while the cue was

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[2] The instructions for task (for the study participant and the experimenter) were read from a detailed script at all times (the instructions are not available in the public domain, please email the author for more details).

onscreen. Retrieval was measured using same probe (SP) or independent probe (IP) test; the order was counterbalanced across participants. In the SP test original reminders were used as a probe (e.g. BEACH - ___). While, in the IP test participants were cued with a semantic category of the memory and the first letter (e.g. CONTINENT-A for AFRICA)- used to test if forgetting generalised to novel cues (Anderson, 2003). Participants were debriefed at the end of the study and they completed a detailed questionnaire on the difficulty they had to suppress each word, and the strategies they used.

Pilot Experiment 2 (PE2): TNT Single Case Study (Patient MJ)

The procedure for the study in patient MJ was exactly that employed for healthy controls (PE1).

Pilot Experiment 3 (PE3): TNT in patients (n = 6) with focal lesions.

For each instruction patients were shown flash-cards of the screen, to help them visualise the actual experiment. Instead of handing them a copy of instructions to follow along (Benoit & Anderson, 2012).

Learning Phase: Participants were shown the word pairs for the first time for up to 6s compared to the 4s in EP1 and EP2. After which participants during the *cued recall*, they were shown the left hand (hint word) and had to respond with the response word within 4s (compared to the earlier TNT studies that had a time limit of 3.3 sec). Irrespective of the answer, participants saw both the pairs on the screen for up to 2s (in healthy controls, this is 1 sec.). The words were presented in BLUE one above the other, and we also the shade of blue was changed in order to increase the contrast, reducing any other details that may

affect learning. Participants had to reach a 65% criterion (12 out of 18 words) or complete a maximum of 4 learning cycles (in older adults this has been maximum of 2 cycles). After which, they continued to the next list (e.g. B or C) where the procedure was identical to the above.

Each of the list (A/B/C) was broken down to show only the 18 word pairs (@ 6 s). After participants completed the *cued recall* for all the three lists (i.e. A/B/C) they entered the *criterion phase* (part of the learning phase).

In the *criterion phase* they saw only the left hand (or the hint word) and had to verbally respond with the right hand (or the response word). All the fifty-four words from lists A, B and C were randomly presented. They did not see the correct response, nor did they receive any feedback from the experimenter. No participant was excluded from the study during these phases from the study.

TNT Phase: The TNT phase has six short blocks and in this study, participants received a questionnaire after every two blocks (compared to once in healthy

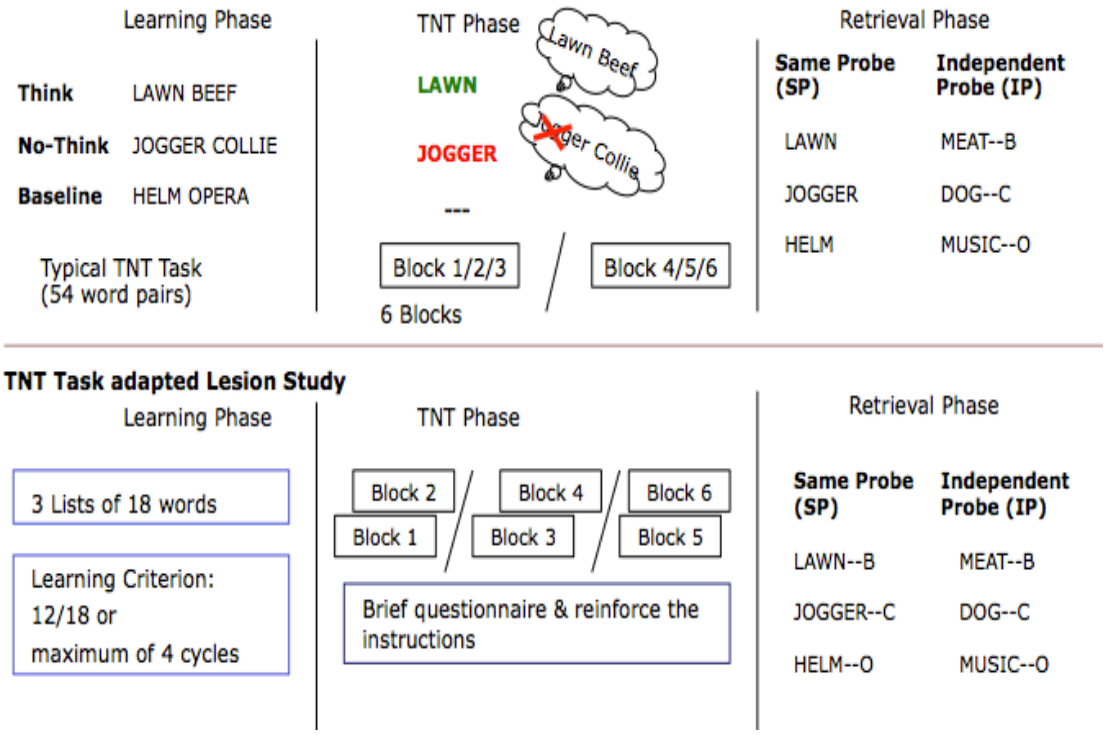

Figure 3.1 Comparing the original TNT with the adapted TNT task

controls). During these breaks experimenter checked to see if participants remembered the task, ensured that they were not tired and repeated the instructions briefly (see Figure. 3.2). There were no changes made to the TNT phase (from Benoit & Anderson, 2012) with respect to the timing or inter-stimulus-interval.

Retrieval phase: Participants were tested using the same probe (SP); in this version participants were presented with the first letter of the response word, as a cue during the same probe (e.g. BEACH – A, the correct response would be AFRICA in healthy controls this cue was not given for the same probe). They were also tested using an independent probe (IP) where participants were given a sematic category cue and the first letter of the response word (e.g. CONTINENT – A, for AFRICA). The time allowed for participant's response was set to 6s compared to the 4s in the original study (from Benoit & Anderson, 2012), no changes were made to inter-stimulus-interval.

3.4 Results

Pilot Experiment 1 (PE1): TNT Pilot in healthy older adults

Based on existing studies of TNT it was hypothesised that performance on the no-think condition will be worst compared to the baseline, which would be lower than the think conditions. This would especially be true, when retrieval is measured using independent probe (IP) test compared to retrieval measured using the same probe (SP) test.

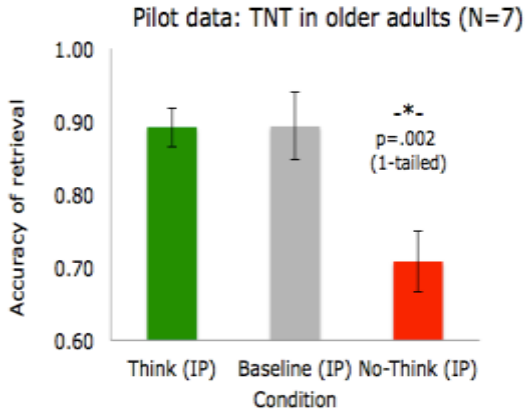

Figure 3.2 Think, baseline and no-think scores for the independent probe (IP) test.

A repeated measures ANOVA with Condition (Baseline, Think, & No-Think) and Probe (IP, IP, & SPIP) as within subject factors was performed. There was a main effect of Condition ($F_{2,12} = 5.294$, $p = .022$, $\eta^2 = .469$). Paired sample t-tests were performed to confirm *a priori* hypothesis. These tests were

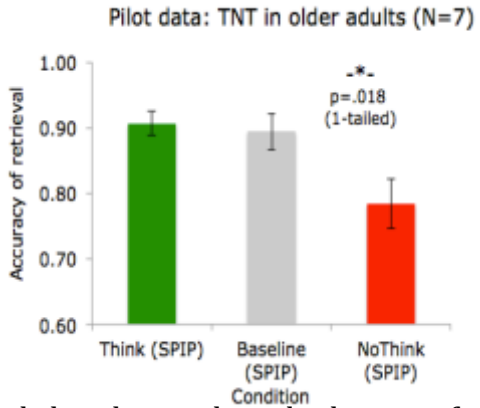

Figure 3.3 Think, baseline and no-think scores for the same /independent probe (SPIP)

specifically investigated the inhibition effect (baseline > no-think, due to memory control) and the facilitation effect (and think > baseline). The results confirmed that inhibition effect (Baseline > No-Think) was true for retrieval during IP (t_6 =

4.351, p = .002 (1-tailed)) and SPIP (t_6 = 2.708, p = .018 (1-tailed)) probe, but not in the SP.

Pilot Experiment 2 (PE2): TNT Single Case Study (Patient MJ)

Patient MJ was the first patient to be tested using the standard instruction to be administered the TNT Task. Unfortunately, patient MJ not only found it difficult to follow the instructions, but was unable to follow along the printed script that was provided to her. The usual procedure used to deliver the instructions in a TNT task is to read the instructions, while the participant follows the written script that is handed to them (personal communication regarding the procedure followed in Benoit & Anderson, 2012).

MJ found the instructions difficult, and was not able to learn any words. After the first 18 word pairs were presented, during the first cued recall, she was only able to learn 2 out of 18 words. She found learning the words pairs quite distressing and we had to discontinue the TNT task with MJ. After which we spent time to understand her difficulties, and the reason she found it difficult to complete the task. Based on this the TNT task was modified (see methods for Experiment 3, in this chapter).

MJ's performance on verbal fluency was below normal (with 10 words on verbal fluency (P), and 11 words in the category fluency (animal). Patient MJ remember 2 out of 3 words on three-word recall of ACE. Patient MJ has more attentional and executive problems. Which is in line with the expected profile of patients with frontal lesions. However, on a day-to-day basis MJ reported she was able to carry on with her activities of daily living including able to manage her basic shopping. Her autobiographic memory was not impaired and she was able to remember events from her past. MJ was scanned as a part of this study

(see Figure 3.4) which indicates that there is clear focal lesion, with some mild atrophy of the cortical regions in the brain. The clinical neurologist reported no significant clinical abnormality on these scans (these were compared to MJ's scan from three years ago).

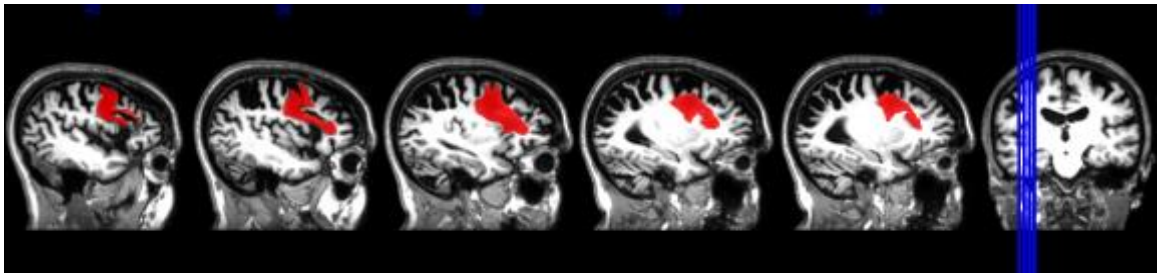

Figure 3.4 T1 scans with location of the lesion drawn (in red) for patient MJ

Pilot Experiment 3 (PE3): TNT in patients (n = 5, plus Patient MJ).

Five patients with left lesions, and one patient with tumour in the right frontal region participated in this study. The sixth participant was MJ, we wanted to check if the modified instructions were clear compared to the previous procedure (EP2). The aim of this study was twofold. First, it was expected that patients with right lesions will be unable to inhibit the words (in the no-think condition), especially if the lesions overlapped with the regions of interest (e.g. right DLPFC or right MFG). Second, we wanted to ensure that all participants were able to complete the task within the second session.

The performance across conditions (think, baseline and no-think) for type of retrieval (IP, SP and IPSP) were averaged for five participants and plotted separately for Patient MJ (as she had been tested before).

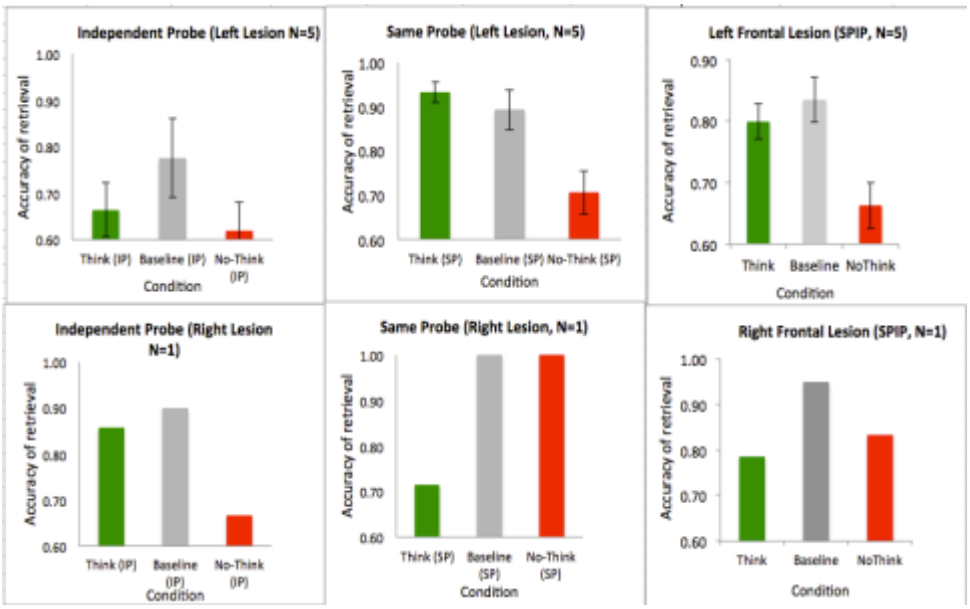

Figure 3.5 Percentage accuracy of retrieval shown for Think, baseline & no-think (SP, IP, SPIP)

In this study, the patient with right lesion in this (WK) did not have the tumour excised, hence the results show that WK was able to inhibit unwanted memory (i.e.no-think < baseline).

3.5 Summary of the pilot studies

This pilot study provides clear the evidence that patients with frontal lesions can indeed engage successfully in suppressing unwanted memory, using the direct suppression method. The effect of inhibition (i.e. lower performance in no-think compared to baseline, e.g. Anderson & Green, 2001; Benoit & Anderson, 2012) seen in a small sample size (N=5) of patients with left lesions was a promising line of evidence, and motivation to continue with this line of research (see Chapter 4 for the main study).

In line with existing think/no-think results (e.g. Anderson et al., 2004; Anderson & Green, 2001; Benoit & Anderson, 2012) the results from the adapted version for TNT (in healthy controls) mirrored most results in the literature (Schmitz et al., 2016; Gagnepain, Henson, & Anderson, 2014; Benoit & Anderson, 2012; Anderson et al. 2004; Murray et al., 2015). The performance on the No-Think condition was significantly lower than baseline items (i.e. words they had not seen during the TNT phase) in the IP test (a more accurate measure of suppression, see Graph 2.1) and in the averaged SPIP results. The inhibition effect (i.e. baseline minus no-think) was 18.5% (for IP) and 11 % for SPIP conditions. The was no significant facilitation effect across for any of the tests. The performance on the think condition was not significantly greater than the performance at baseline condition during the retrieval across IP and SP conditions. The main contribution of the first study (PE1) is that the modifications in the timing did not affect the inhibition effect (no-think < baseline), especially on retrieval tests using an independent probe.

The task was then tested on a single patient MJ (PE2), who could be considered to be high function with minimal cognitive impairment/s. The results from PE2 suggested that she was unable to complete the task. The amount of time spent on explain the task instructions suggested that the standard procedure for delivering the instructions may be difficult for patients with lesions to follow. This may be because patients with focal frontal lesions find it difficult to pay attention (Wilkins, Shallice, & McCarthy, 1987; Lezak, 2012; Bidet-Caule et al., 2014; also see Szczepanski & Knight, 2014 for a review), or because they find it difficult to switch between tasks (Shallice and Burgess,

1991). In this case, the difficult may be that patients find it difficult to read along with the instructions, whilst the experimenter was reading them out.

The TNT task is demanding, and requires cognitive effort. Some of the identified issues from this study which were modified included: the procedure for delivery of instructions; the automaticity of the task; the timings for the learning phase, and the procedure in the TNT Phase. The study also suggested that completing the TNT task in the second session helped the participant engage in the task better.

Modifications in the delivery method of the instruction.

Patients with frontal lesions often find it very difficult and demanding to understand the instruction while reading along. Keeping this in mind the protocol was accordingly changed. The experimenter rote-learned the scripted instructions, and repeated it slowly to the participant (while referring to the script if required).

The experimenter used flash cards that represented the stimuli on the screen. Using the flash cards, the experimenter explained the process to the participant. This procedure of delivering the instructions was used across all the phases (i.e. Learning Phase, TNT Phase and the Memory Retrieval Phase).

Most TNT tasks are programed to continue on audio trigger. This was disabled for the patient study, especially as any interference could set off the trigger during the testing in their homes (for example coughing, door bell, or the dog). Participants were tested in their homes, or in the Unit (MRC CBU), based on their preference.

Each of the word pairs in the final study (PE3) was changed to 6s in the compared to the 4s (PE1). Also patients had up to 6 seconds to give an answer in the memory retrieval phase (compared to 4 seconds in Benoit & Anderson).

During the cued recall (in MJ) only saw the right hand or the response word which appeared after the hint word disappeared from the screen (as in the standard TNT tasks). This was changed to ensure that during feedback participants saw both hint and response words, which were displayed in the centre for the screen. Irrespective of their response, the word pairs were displayed for up to 2 seconds (compared to 1 second in Benoit & Anderson, 2012).

The results from these adaptions suggest that patients with focal lesions were indeed able to follow the instruction, and sustain the required attention to complete the study. The current pilot not only included patients like DH, MJ, PP & SP who had minimal executive function deficits and were quite high functioning in their day-to-day lives, but also, patients like WK who was not very high functioning and patient JM who had severe amnesia. Patient JM was unable to learn the word pairs, but was able to maintain the attention for the entire study.

The results from the TNT behavioural data in this pilot study supports the existing literature (e.g. Anderson et al., 2004; Benoit & Anderson, 2012; Levy & Anderson, 2012) that when participants engage in thought suppression they inhibit the unwanted memories, which in turn are impaired. On the final test of retrieval performance for the no-think items (where participants engaged in the direct suppression) is lower than baseline. This is evidently more when retrieval is tested using the independent probe method (Anderson, 2003) compared to retrieval measured using the same probe test.

The results from this study not only support the existing literature, but also the hypothesis for the primary study (Chapter 4) in this thesis, that patients with left focal lesions can effectively engage in suppressing unwanted memories if they use the method of direct suppression. Finally, the results from this pilot study provide support of successful adaptation of the main TNT design for testing patients with focal neurological lesions. The series of three experiments provided empirical evidence to suggest that the final adapted version, method and accompanying instructions (see Chapter 4, for more details) were robust to be used in patients with focal lesions.

3.6 Discussion

This is the first study to our knowledge that has adapted the TNT task for use with patients who have focal neurological lesions. Based on prior studies in older adults, a number of changes in the presentation time and method of instruction were made, to ensure that the TNT task was patient friendly (Murray et al., 2011; Murray, Anderson and Kensinger, 2015).

Adaptations to designing a patient friendly TNT task

Firstly, being a cognitively demanding task, the TNT instructions are difficult for any patient with lesions to follow. Secondly, the task takes between sixty to ninety minutes in healthy adults, and anywhere up to 120 minutes or more in patients with focal lesions. No previous studies have adapted any version of the TNT in patients with focal lesions, hence, three pilot studies tested methods used in the Learning Phase, after which the patient friendly version was finalised.

The first change addressed the method of delivering instructions. Using flash cards combined with explicit instructions is the ideal method for patients,

compared with the usual method of asking participants to follow a complex script of instructions. The task was less automated, avoided the use of voice trigger to proceed with the display of words. In the Learning Phase, patients saw a smaller list of word pairs, instead of a long list of 54 word pairs. This allowed participants to engage in the task. The time for display for each word pair was increased from 3.4 seconds to 6 seconds, to compensate for any attention deficits (Murray et al., 2011). No changes were made to the TNT Phases, while minimal changes to the Learning Phase and the Retrieval Phase were required to successfully adapt the TNT in patients with focal lesions. These changes included: 1) In the Learning Phase, participants in the patient-friendly TNT task (*p*f-TNT) received three lists (of 18 word pairs) instead of a long list with 54 word pairs. 2) Participants saw the word pairs for 6 seconds compared to 3 seconds in most TNT studies (Anderson et al., 2004; Benoit & Anderson, 2012); 3) While in the retrieval phase participants were given up to 4 seconds to respond compared to the 3 seconds in Benoit & Anderson (2012); 4) Finally, in the Same Probe condition patients saw the stem of the right hand side word, to keep the probe between the Same and Independent probe retrieval conditions identical.

Inhibitory deficits have been reported in older adults with no known pathology or disorders (see Hasher, Zacks, & May, 1999 for review), with some interest in understanding whether these deficits extend to memory suppression, as it may be important from a clinical perspective (Depue, Burgess, Willcutt, Ruzic & Banich, 2010; Kupper, Benoit, Dalgeish & Anderson, 2014; Joorman, Hertel, LeMoult & Gotlib, 2009). This patient friendly Think/No-Think (*pf*-TNT)

task has been used to test 34 patients with focal neurological lesions (reported in Chapter 4).

The literature suggests that providing older adults with effective strategies, may reduce age-related cognitive deficits (Buckner & Logan, 2002; Naveh-Benjamin, 2000; Naveh-Benjamin, Brav & Levy, 2007). Similarly, one might argue that when patients with focal lesions are provided with explicit instructions and strategies, they may be able to engage in the task and effectively suppress unwanted memories (Murray, Kensinger, & Anderson, 2015; Murray et al., 2011). In contrast, empirical studies have reported older adults' failure to show a suppression induced forgetting effect (henceforth referred to as SIF). This has often been attributed to the reduced ability to inhibit information (Hasher & Zacks, 1988; Levy & Anderson, 2008), a decline in lateral prefrontal functions (Grieve, Clark, Williams, Peduto & Gordon, 2015), or due to the difficulty of choosing effective strategies, which tends to be a resource-demanding process (Anderson et al., 2011; Murray, Kensinger, & Anderson, 2015; Buckner & Logan, 2002). This *pf*-TNT task allowed us to empirically test whether there are laterality differences in the ability to directly supress unwanted memories (this method has been used to test patients with focal lesions, see Chapter 4 for details).

4. Neuropsychology of motivated forgetting: Insights from patients with focal neurological lesions[1].

4.1 Introduction

To forget an important task at hand can be quite distressing. Often forgetting has been considered to be a negative process. However, under some circumstances, memory losses can be useful, for example, in the face of a negative event. Forgetting may also be *adaptive*, in cases when we encounter a reminder of an unpleasant experience, we may *wish* to forget that specific memory (see Levy and Wagner, 2007 for a review). This may be achieved by excluding a memory from awareness directly, a process that appears to require cognitive effort (Anderson & Green, 2001; also see Benoit & Anderson, 2012).

Within the memory inhibition literature, this process is often seen to have several advantages. For example, inhibiting unwanted memories may simply help us to concentrate on what we want to do, protect us from experiencing negative emotions, or may help to preserve our sense of self (Anderson, 2005; Catarino et al., 2014). This kind of process is also argued to be shaped by some

[1] All the behavioural data for Chapters 3 and 4 have been collected by SS. The MRI images have been acquired as part of the MRC-CBU panel and SS assisted in the collection of 3 scans. The lesions for each of the patient had been traced by Facundo Manes (FM), however, SS learnt the process of lesion mapping and retraced the lesions of the 18 participants as a learning process (but used the lesion maps created by FM for the analysis). SS used MRIcro to create the RoI and completed the RoI analysis independently (modifying a script provided by DM at the MRCCBU).

form of internal motivation, usually where there is an *intention* to forget (Bjork, 1989), referred to as 'motivated forgetting[2]' (Anderson & Hanslmayr, 2014).

Historically, labelled as 'repression'[3] (Freud, 1915a/1963), the ability to push unwanted memories out of awareness has been reported in the clinical literature for over a century (Chu, Frey, Ganzel, & Matthews, 2014; also see Holmes, 1990; McNally, 2003; for historical review see Erdelyi, 2006). Since Freud defined repression, it is often used in the context of forgetting, generally associated with inhibition of powerful traumatic experiences from the past (Feldman-Summers & Pope, 1994; Freyd, 1994). Forgetting associated with day to day memory loss has been attributed to either 'the slip of the tongue phenomena' or 'thought-avoidance' (Freud, 1911). Before Freud formally defined it, Herbart (1824-25, c.f. Erdelyi, 2006) had introduced the essence of repression as, "inhibition of ideas by other ideas" (pp 500), where the idea of repression was not necessarily linked with trauma.

The concept of inhibiting unwanted memories has been reported extensively (but usually anecdotally) in a range of clinical populations (Bartlett, 1932/1995; Brandt & van Grop, 2006; Markowitch et al., 1998; Cassel &

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[2] Motivated forgetting refers to an active process, i.e. an intention of forgetting an unwanted memory. Successful forgetting is usually argued to be achieved through a process of memory control, through inhibition (or suppression) of the memory, or substituting the unwanted memory with another memory (Benoit & Anderson, 2014).

[3] Repression and suppression have been used as synonyms in clinical literature. One view maintains that repression is an unconscious process while suppression is a more intentional, goal-directed process to exclude memories from awareness (Erdelyi, 2006). Freud (1915a/1975/1963) defined repression as, "*the essence of repression lies simply in the function of rejecting and keeping something out of consciousness*" (p. 147, emphasis in the original).

Humphreys, 2015). Much of the most powerful clinical documentation has been on what is known as functional or psychogenic amnesia. In this regard, there has been a long-standing debate in the clinical literature as to whether 'repression' is a conscious (explicit) process and possibly that 'suppression' may be more of an unconscious (implicit) process[4] (e.g. Vaillant, 1998, also see Boag, 2006). Typically, it has often been regarded as a dysfunctional process (e.g. Kihlstrom, 2002), though, it has been difficult to test the concept empirically.

Recently, there has been an interest to understand the cognitive processes underlying active forgetting (Anderson and Green, 2001; Anderson et al., 2004). These studies use cognitive experiments in a non-traumatic setting, to study the mechanisms which underpin such forgetting (Anderson & Green; Hulbert, Henson & Anderson, 2016). One could indeed argue that these studies may not necessarily address the processes underlying repression from the clinical context (see Eldrelyi, 2006 for a review). Unfortunately, there has been no converging evidence from both the clinical (Freud, 1915) and cognitive perspective until recent times (Anderson, 2006; Anderson & Levy, 2002; Bjork & Bjork, 1994; Erdelyi, 2006).

In spite of the lack in converging evidence of the causes of active forgetting, there is an overall consensus that an underlying *motivation* drives what we *wish* to forget (Anderson & Green, 2001; Breuer & Freud, 1895/1955;). There appears to be growing evidence about the mechanisms which may address the issue of

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[4] The modern psychoanalytical literature maintains the difference (Erdelyi, 2006), we do not discuss the unconscious or conscious nature of repression (or suppression). In this study and across the thesis we refer to the process of memory inhibition as an active process, with some underlying motivation (with occasional reference to it as suppression).

whether the clinical and experimental processes represent the same phenomenon (Anderson & Green, 2001; Anderson et al., 2004; Anderson & Levy, 2006; Hulbert, Henson & Anderson, 2016).

Think/no-think task

The literature suggests that in addition to any *motivation*, there may a number of cognitive mechanisms to help achieve forgetting (Anderson & Bjork, 1994; Anderson & Green, 2001; Anderson et al., 2004, Hulbert, Henson & Anderson, 2016). How can motivated forgetting be assessed in an empirical setting? Anderson & Green (2001) proposed the Think/No-Think (TNT) task as an experimental model to empirically test this process. This approach enables us to ask questions such as a) what is the cognitive process underlying motivated forgetting? b) What are the neural mechanisms underlying motivated forgetting?

The Think/no-think task (TNT, Anderson & Green, 2000) was developed to investigate the ability to actively suppress unwanted information in an empirical setting. The task is a memory analogue of the well-known go/no-go task (Luria, 1966). Participants learn word pairs (Anderson & Green, 2001) or picture pairs (Catarino et al., 2015) during an initial learning phase. They then either respond (*Think* trials) or suppress (*No-Think* trials) when faced with a reminder – which is the right-hand side word or picture from the learned pairs (see Mostofsky & Simmonds, 2008). During the TNT task participants inhibit a memory (during the no-think trial) instead of inhibiting the motor response (during the *No-go* trial) in a Go/No-Go task.

The TNT task has three phases: The Learning Phase, the TNT phase, and the (Memory) Retrieval phase (see Method section for more details). In the retrieval phase the accuracy for three conditions (think, no-think and baseline) is of

primary interest. The classic experimental result would be for lowest accuracy performance for the No-think trials, compared to better performance on the baseline, with the best accuracy on the Think trials. The decreased performance on the No-Think item, compared to the baseline, is known as the 'Suppression' effect. Increased performance on Think items compared to the baseline is known as the 'Facilitation' effect (Anderson et al., 2004; Benoit & Anderson, 2012; Anderson & Hanslmayr, 2014). These effects have been replicated in dozens of studies (e.g. Anderson et al., 2004; Benoit & Anderson, 2012), however the interpretation of these findings have been contested (Bulevich et al., 2006; Hertel & Calcaterra, 2005).

Mechanisms of motivated forgetting

Inhibition has been the most well-known cognitive process underpinning motivated forgetting (Anderson & Hanslmayr, 2014). Of the forty-one published papers on the topic, thirty-nine have used the direct suppression method which suggests that people inhibit the unwanted memory, such that this process prevents the memory from coming into awareness (e.g. Anderson & Green, 2001; Anderson et al., 2004). This is especially true, when people *actively* choose to control (i.e. stop) a memory from coming to mind (Anderson & Green, 2001; Anderson et al., 2004; also see Chapter 1 for a more details) often requiring an inhibitory control, which suggested to be modulated by the executive functions. Control often refers to the ability to override prepotent responses to inappropriate cues (Craik, 1947; Logan & Cowan, 1984; Luria, 1966; Shallice, 1982). It has long been argued that during memory suppression there is an executive - control process that directly *targets* the memory representation (Kuhl & Anderson, 2008; Levy & Anderson, 2002; Anderson et al., 2004; Depue,

Banich, & Currran, 2006; Bjork, Bjork, & Anderson 1998; Bjork, 1989; Geiselman, Bjork, & Fishman, 1983). Recent evidence has challenged this claim, suggesting that the control is not over the *specific* memory, but instead aimed at the (memory) system in general (Hulbert, Henson, & Anderson, 2016). What then of the neurobiological substrate of this specific process?

Motivated forgetting: Insights from neuroscience

Neuroimaging studies have identified the right prefrontal regions, DLPFC and the hippocampus to be specifically engaged during the TNT task (Anderson et al., 2004, Anderson & Benoit, 2012, Hulbert, Henson & Anderson, 2016). Most of the studies investigating the role of pre-frontal cortex (PFC) has often investigated the role of PFC from a motor control, attention or emotional-social perspective (Szczepanski & Knight, 2014). A large literature does make reference to the role of pre-frontal cortex, especially the ventrolateral prefrontal cortex (VLPFC) in context of inhibition and retrieval (Aron et al., 2015). However, only limited studies have investigated the role of dorsolateral pre-frontal cortex (DLPFC) in inhibition of unwanted memories (Anderson & Hanslmayr, 2014; Depue et al., 2015).

While it is clear that there is a functional connectivity between the frontal and hippocampal structure, neuroimaging evidence may not be sufficient to identify whether the right DLPFC orchestrates this inhibition, and/or only plays an essential role in the inhibition process.

Motivated forgetting in patient populations

No published study has ever investigated the TNT task in patients with focal lesions. Nevertheless, it has been investigated across eight clinical

populations: depression (Joormann, Hertel, Brozovich and Hertel, 2005; Joormann, LeMoult, Hertel & Gotlib, 2009), anxiety (Marzi et al., 2014; Waldhouser et al., 2011), repressors (Hertel & McDaniel, 2010; Kim et al., 2007), schizophrenics (Salame & Danion, 2007), dysphorics (Hertel & Mahan, 2008), low and high dissociators (Wessel et al., 2005), a patient with functional amnesia (Tramoni et al., 2009) and in post-traumatic stress disorder (PTSD, Caterino et al., 2015). These study results are highly variable. Some studies suggest that certain psychiatric conditions do not significantly affect the ability to supress (Hertel & Mahan, Tramoni et al.; Wessel et al., Hertel & Hayes, 2015), but high levels of trait anxiety may influence the ability to exert cognitive control over unwanted memories (Marzi et al., Waldhouser et al.). While, other conditions like PTSD or schizophrenia (Catarino et al., Salame & Danion) does impair the ability to inhibit unwanted information. These finding though interesting, provide us with limited information about the neurocircuitry, but arguably might (indirectly) implicate neuromodulators if deficits are sensitive to medication.

Of much greater interest is the only published lesion study measuring memory inhibition (Conway and Fthenaki 2003). This study does not use TNT, but instead used 'item method directed forgetting' and 'retrieval induced forgetting' (RIF, Anderson & Bjork, 1994)[5]. This study suggests the right DLPFC

[5] In a RIF paradigm participants study a list of categories. The study phase is followed by the 'retrieval practice phase' in which a subset of items are recalled to the category cues, (e.g. Fruit – O___?) for only some categories. Retrieving selective items is known to cause inhibition of unpractised items from the practised categories which is observed in the poor recall rates of the items relative to recall of the items from the unpractised categories and to the practised items themselves.

mediates the long-term memory, and the right frontal regions support inhibition. The inhibition process underlying the RIF paradigm is more implicit, compared to the Think/No-Think (TNT) task where inhibition is a more of an explicit process. Thus, the evidence from Conway and Fthenaki[6] is important, but may be insufficient to explain the neural mechanisms underlying the process of motivated forgetting (a more explicit process of inhibiting).

In addition, while helpful, this study does have a number of limitations. The participants in this study (Conway and Fthenaki 2003) had lesions due to arterio-venous malformation (AVM) or acquired head injury (with a small sample size). Both of these causes make it difficult to map the exact lesion locations (Kertesz, 1983). Also, patients with AVM have a pre-morbid pathology. This study is the only published study in the literature, and with its limitations, there is a need for future studies with a larger sample size, and in patients with more easily identifiable focal lesion (Anderson & Hanslmayr, 2014). An ideal sample in neuropsychology lesion studies would include patients with lesions

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[6] The results from experiments 1 & 2 (Conway & Fthenaki) suggested that patients with right frontal lesions recalled more TBF (To Be forgotten) words that (To Be Remembered) words while the performance of patients with left frontal lesions were similar to that of the controls. While, results from the Experiment 3 indicated that patients with lesions to frontal lobe did not show disrupted inhibition in RIF, while patients with lesions to the left temporal lobe did not show the usual RIF patterns. Conway & Fthenaki (2003) suggested that inhibition during RIF is triggered by selective attention process, and results (automatically) as a consequence of attentional focus. The first two experiments in Conway and Fthenaki's study (2003) used the item method directed forgetting (DF, Basden et al., 1993) task in which the items or lists were paired with a cue to forget or remember. Both the to be remembered (TBR) and to be forgotten (TBF) items were later tested using a recall and recognition test. While, in a third experiment they used the retrieval induced forgetting (RIF, see Anderson & Spellman, 1995).

caused by a stroke, or tumour excisions (Kertesz, 1983), instead of, patients with brain injury.

In summary (also see Chapter 1) most empirical studies investigating the neural networks of motivated forgetting come from neuroimaging studies in healthy controls (Anderson et al., 2004; see Anderson & Hanslmayr, for a review), or studies in patients with psychiatric disorders (Murray et al., 2015; Streb et al., 2016, Dalgeish et al., 2014). Clearly, there is lack of evidence from lesion studies. Today, converging evidence from lesion studies supporting neuroimaging evidence are necessary to fully understand any cognitive function and their underlying neural mechanisms (Bub, 2000; Rorden & Karnath, 2004).

Laterality in Motivated forgetting

More recently literature has focused on possible *lateral* differences in the frontal regions, and their control over the hippocampus (Benoit & Anderson, 2012). Only one study appears to have demonstrated two distinct neural mechanisms supporting different strategies to control memory: direct suppression, and thought substitution (Benoit and Anderson, 2012). This line of argument is further supported by an ERP study. The study (Bergström et al.) reported that when participants engaged in direct memory suppression there was reduced activation in the centro-parietal positivity, often linked to the process of recollection. This suggested a dissociation between inhibitory and non-inhibitory (substitution) processes (Bergström et al., 2007).

Direct suppression is suggested to involve a more right lateralised network, specifically with right DLPFC (and ~BA 9/46) inhibiting the hippocampus (Hulbert, Henson & Anderson, 2016; Anderson et al., 2004; Depue et al., 2007; Benoit & Anderson, 2004; Levy & Anderson, 2012; Schmitz, Guo,

Ferreira & Anderson, 2016; see also Conway and Fthenaki, 2003). In contrast, thought substitution seems to be a more left lateralised process. Increased activation in the left pre-frontal regions seems to have a correlated increase in the hippocampal activity (Benoit & Anderson; Karpicke & Roediger, 2008; Wimber et al., 2009). Benoit and Anderson (2012) suggest that these are two distinct neural mechanisms which support the memory inhibition strategies (direct suppression or thought substitution).

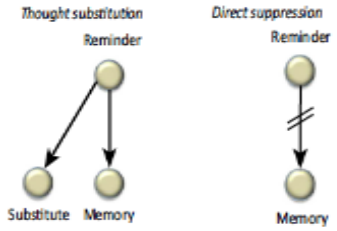

Figure 4.1 Direct suppression and thought substitution involve distinct networks that both cause forgetting, but have differing effects of the hippocampus (cited from Anderson & Hanslmayr, 2014).

Limited number of neuroimaging and cognitive studies may not be definitive evidence to support this dissociation (Price & Friston, 2002). Modern cognitive neuroscience ideally requires multiple evidence using different methods to understand the underlying mechanisms of any cognitive process. Converging evidence from patients with unilateral frontal lesions would essentially provide evidence to whether is it right or left DLPFC that is essential to direct suppression. This provides a novel opportunity to test the role of laterality in patients with frontal lesions. The present study, to our knowledge, is the first study that has investigated motivated forgetting using the *direct suppression* method, employing the Think/no-think task (TNT) in patients with focal lesions. The primary hypothesis for this study compared to patients with

left frontal lesions (LFL) who *will* be able to engage in direct suppression, performing at levels no different from controls, patients with right frontal lesions (RFL, especially to regions of right DLPFC (BA 44~46)) will not be able to inhibit unwanted memories using the direct suppression method.

4.2 Methods

Participants

This study was approved by the North Wales Research Ethics Committee (REC) – West and was approved by the Cambridge Psychology Research Ethics Committee (CPREC No. Pre.2014.27). Seventeen individuals with left unilateral lesions (9 males, mean age = 61.82 (10.55) years) and right unilateral lesions (10 males, mean age = 60.35 (11.87) years) were recruited from the Cambridge Clinical Neurosciences Research Panel (CCNRP), MRC Cognition and Brain Sciences Unit. All of the patients lived in their own homes and had expressed an interest in participating in research.

A *priori* sample size with a maximum of 24 in each of the left and right frontal lesion group was decided[7]. This was based on sample sizes of previous neuroimaging studies using the Think/No-Think task (Anderson et al., 2004; Benoit & Anderson, 2012; Catarino et al., 2015; Gangepain et al., 2014). It was difficult to recruit 24 participants in each group, based on the time constraints it was agreed that the recruitment for this study will stop, after all potential participants from the CCNRP were contacted by October 2015. Interim analysis was done when with a total of 23 participants and recruitment for the current

study stopped when data was collected from 34 participants (17 patients with left and right frontal lesions) based on sequential analysis (Lakens, 2014).

All patients in this study had a unilateral frontal lesion caused by cerebro-vascular accident (infarction or haemorrhage) or tumour resection (see Appendix for details). The existence of a structural MRI scan or consent to be scanned as part of this study was one of the inclusion criteria[8]. Any documented memory impairments, colour blindness, difficulties in using a computer, and/or inability to participate in long sessions, reported in the CCNRP database, acted as other exclusion criteria. Participants were randomly assigned to either morning or afternoon tests session to match the influence of circadian rhythms and optimal time of day for mental processes including inhibition on age (e.g. Anderson, Reiholz, Kuhl, & Mayr, 2011; May & Hasher, 1998; Hasher, Chung, May & Fung, 2002).

Procedure

The study was designed to be completed in three sessions, but some patients (n = 2) needed additional sessions to complete all the measures. The first session included a clinical interview with the patient and in some cases interaction with a significant carer. If participants or their carers indicated any signs of early onset memory impairment they were excluded from the study (n = 2) after the first session. Further, if participants did not report any memory impairments but were unable to learn a list of words (mild to moderate

[8] Any patients who had aneurysm clips and/or could not have a scan due to any reason participated in the pilot study and were excluded from the study.

impairments in recall and recognition scores), from the Wechsler Memory Scale (WMS -III, word list) administered during the first session they were excluded from the study (no participants were excluded on this criterion).

Each participant completed three sessions[9]. In the *first session*, following a brief clinical interview, participants then completed eleven neuropsychological tests (Appendix A for more details). In the *second session* participants completed the Think/No-Think task, a set of task related questionnaires[10] , the thought control ability questionnaire (TCAQ, Luciano et al., 2005), and Speilberger's State and Trait Anxiety Inventory (STAI – I & II). In the *third session* all participants completed the executive tasks of inhibition, shifting and updating (paper-pencil or computer-based tasks, Miyake, et al., 2000; 2008) and the stop-IT task (Verbruggen & Logan, 2008). During the study participants also competed the Five-Facet Mindfulness Questionnaire (FFMQ, Baer et al., 2006), the Emotional Regulation Questionnaire (ERQ, Gross & John, 2003), the DEX – self-Questionnaire (Burgess, Alderman, Wilson, Evans, & Emslie, 1996), Beck Depression Inventory (BDI-II Beck, Steer & Brown, 1996), and the Hamilton Anxiety Depression Scale (HADS, Zigmond & Snaith, 1983).

Materials: *Patient friendly*-Think/No-Think (*Pf*-TNT) Task

The TNT task (Anderson & Green, 2001; Benoit & Anderson, 2012) has three phases (i.e. the learning phase, the TNT phase and the memory retrieval

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[9] For the purposes of this PhD only TNT task (Session 2) and data from some neuropsychological measures has been reported (from Session 1). Remaining neuropsychological measures (Session 1) and other executive tasks (Session 3) were neither analysed nor have been discussed in this thesis.

[10] This is a questionnaire that is not available in public domain and is given to a researcher after he/she has received the training to administer the TNT task.

phase). The *Pf*- TNT task was administration in patients with neurological lesions after few initial pilot experiments (see Chapter 3 for more details). The pilot experiments confirmed that patients were able to compensate for the reduced speed of processing, working memory and potential executive impairments known to be associated with frontal lobe lesions.

Learning Phase

The Learning Phase for patient friendly version was divided into three blocks (i.e. 18 word pairs in each block) instead of the traditional method, where all the fifty-four word pairs were shown in one block. Each of the three blocks had total of 18 word pairs, which included twelve critical word pairs[11] (i.e. 4

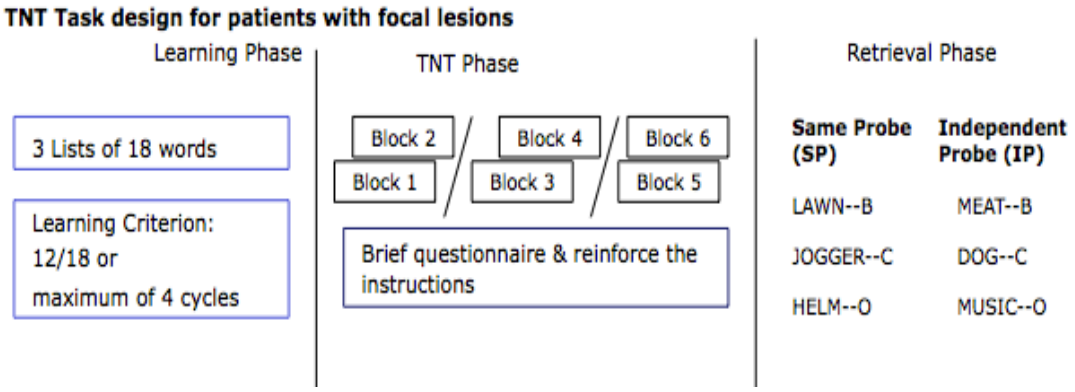

Figure 4.1 The adapted LesPat design of TNT in patients with focal lesions. See section on material, for more detail notes about the adaptation of TNT in patients.

Think, 4 No-Think, 4 Baseline), and six filler pairs[12] (2 Think, 2 No-Think, 2 Baseline).

[11] Critical words refer to the words that are used in the actual TNT task across the baseline, think or no-think condition.
[12] Filler words refer to the words that are used during the TNT practice phase.

During the learning phase participants saw eighteen word pairs (e.g. LAWN BEEF), each pair was shown on the screen for 6 seconds[13] (inter-stimulus-interval [ISI]: 600 ms) which is slightly longer than in most TNT studies (Anderson et al., 2004). After the patients had seen all 18 word pairs from the first block, they completed a cued recall test[14] for the eighteen words from that block.

During the recall phase, participants were presented with the left hand word (referred as the 'hint word') and were asked to overtly recall the right hand word (known as the 'response word',) which was shown for up to 6s (like in Benoit & Anderson) after a reminder offset and a 600 ms ISI (Benoit & Anderson), irrespective of their responses, participants saw both the cue and the response word one above the other[15] on the screen in BLUE for 2 seconds. The hint word and response word were presented together in the centre of the screen above each other, to ensure minimal eye movement. During this 2 seconds all participants were instructed to use this opportunity to reinforce their learning. After all the three blocks (and their associated cued recall tests) participants completed the criterion test.

Criterion Threshold in the Pf-TNT

In contrast to the most TNT studies in healthy controls (Anderson et al., 2004; Benoit & Anderson), participants were *not excluded* if they did not meet

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[13] In Benoit & Anderson (2012) the words were shown for 3.4 seconds
[14] In other TNT studies all the 54 words are shown in one block and the cued recall test is completed up to three times or until the participant reaches the threshold (i.e. correctly learns 18 out of 36 critical words)
[15] In Benoit & Anderson (2012) participants only saw the response word in blue without the original word and only for 1 second.

reach a minimum criterion of 65% on each of the blocks (i.e. 8 out of the 12 critical word pair). Instead, if they did not meet the criterion (i.e. got less than 8 out of 12 word pairs), they completed additional criterion learning phases, continuing until they either achieved the minimum criterion of eight, and/or had completed a maximum of four attempts.

This restriction (of excluding participants based on a criterion measure) was not adhered to in this study, because a) there are no prior TNT studies in patients with lesions, making it impossible to arbitrarily define a cut-off threshold; b) more importantly, a motivation for this study was to understand whether patients with focal lesions could successfully engage and perform this task.

During the criterion test, as in Benoit & Anderson (2012) they saw the *hint word* and had to respond with the *response word* as in the learning phase, but (in criterion tests) did not receive any feedback, each of the word was presented for up to 3.3. seconds (ISI: 1.1 s). Participants then proceeded to the TNT Practice phase, which was identical to the original study (Benoit & Anderson, 2012).

TNT Phase

Only in the TNT phase participants were told that some of hint words (left hand side word) would appear in either green or red colour. For the words that appeared in GREEN (Think words), participants were asked to "bring to mind the word pair", just like they have done until now. They were then instructed that when the hint word (i.e. the left hand side word from the word pair) appeared in RED (no-think conditions) they should "not bring the response word (the right hand side word from the word pairs) to mind", and they received detailed

instructions (Bergstrom et al., 2009; Benoit and Anderson, 2012), based on the script for TNT (not available in public domain, but given during training). All participants completed the short TNT practice phase, followed by a task-related diagnostic questionnaire. After which all participants had a break between 5 to 15 minutes (to replicate the procedure used for neuroimaging and tDCS studies of TNT). After the break, they received additional instructions, and continued the TNT Phase.

Participants were informed in the instructions that each of these words would be repeated up to 12 times and that this phase would have six short TNT blocks with short breaks (up to 1 minute, for rest) after trials 1 and 3. They had a slightly longer break (including the rest) after blocks 2 and 4, where they completed the diagnostic questionnaire, instead of twice (Benoit & Anderson) [16]. After every two blocks (block 2 and 4) participants were briefly reminded of the instructions. The suppress (words that appeared in red) and recall (words presented in green) conditioned were pseudo randomly presented. Each reminder was shown for 3 s and the ISI was jittered (≥ 0.5 s; mean ± SD: 2.3 ± 1.7), during the ISI, a fixation cross appeared (Benoit & Anderson, 2012). After the participants completed the TNT phase, they completed the Memory Retrieval phase. As in all TNT studies, the participants were not informed before about this memory test.

[16] In Benoit and Anderson's study (2012) participants filled this questionnaire after the practice task and then only once after three blocks. In this study we changed the procedure to completing the questionnaire after 2 blocks and twice during the study as this would also help remind participants of the instructions.

Memory Retrieval Phase

Immediately after the TNT phase, the memory for all 54 word-pairs (e.g. LAWN BEEF) was tested using two approaches: 1) The *Same Probe* (SP) method, where they saw the original Hint word, paired with the first letter stem of the Response word (e.g. LAWN – B); 2) the *Independent Probe (IP,* Anderson 2003*)* method, where they saw a word describing the broader semantic *category* of the response word, again, together with the first letter stem of the response word (e.g. MEAT – B). The presentation sequence during the memory retrieval tests (i.e. same probe – independent probe (SPIP) or independent probe – same probe (IPSP)) was counterbalanced across participants. The hint word (i.e. the left hand side word) was presented one at a time, on the screen, until a response was given or for a maximum of 4 s (ISI: 1.1. s) after which the word disappeared from the screen and the next word was presented. The task was completed after all the 54 words pairs were tested using the SP and IP methods. All participants then completed a detailed study related questionnaire (Benoit & Anderson, 2012, Catarino et al., 2014). This questionnaire captures in detail the strategies participants engaged in, when they saw a red word and they had to not-think about the respective response word.

Randomization parameters for TNT Task

The 54 word-pair list (Benoit & Anderson, 2012) was used in this study. There were 36 'Critical' words (12CThink, 12CNoThink, 12CBaseline) and 18 'Filler' words (6FThink, 6FNoThink, 6FBaseline). For the learning phase, the 54 word-pairs were divided into 3 blocks of 18 words (i.e. 4CThink, 4CNoThink, 4CBaseline, & 2FThink, 2FNoThink, 2FBaseline). Each of the Blocks was pseudo-

randomized, using the Blocked Randomized list method. Further, average serial positioning across the blocks was calculated, with the average between 9 and 10.

The hypothesis for this study are: (1) patients with LFL will be able to suppress unwanted memories using the direct suppression method compared to the patients with LFL. (2) Patients with lesions to the right PFC, especially to regions around the rDLPFC will not be able to suppress unwanted memories using direct suppression.

4.3 Demographic and other measures

Right and left unilateral frontal lesion patients were recruited from the CCNRP panel. The exclusion criteria for this study were: a) incapacity to give consent (assessed using guidelines of the Mental Capacity Act, 2005 Code of Practice; pp. 40); b) current neurological disorder or illness (e.g. multiple sclerosis, Parkinson's disease, dementia) assessed during clinical interview, neuropsychological assessment, and/or self-report; c) substantial language impairment (aphasia, anomia, especially, if it affects comprehension) assessed during the first session. Any patients who had a recent (below 6 months) injury were tested after at least 12 months.

Various questionnaires and neuropsychological measures were assessed in session 1, to understand if there were any major differences in the mood or cognition (NART and predicted Full-IQ) between the two groups. There were no significant differences between the two groups (see Table 4.1 for details). Patients were recruited from the MRC-CBU panel (which specifically recruits

patients with very focal lesions) and are very –well matched between the two groups for this study[17].

Table 4.1 Table showing the various measures between the two patient group.

Measures	LeftfrontalLesion Mean (Std)	RightFrontalLesion Mean (Std)	T-Test (Sig. 2 tailed)
Age	61.82 (10.55)	60.25 (11.87)	.690
BDI	8.82 (6.78)	9.25 (6.48)	.855
HADS_D	3.29 (3.00)	3.62 (3.22)	.726
HADS_A	4.94 (3.77)	5.43 (3.54)	.700
TCAQ	74.18 (31.64)	74.69 (31.31)	.963
ERQ_Reappraisal	26.06 (6.88)	24.50 (7.63)	.542
ERQ_Suppression	15.94 (6.06)	12.93 (4.90)	.129
STAI-1	47.06* (9.94)	45.25 (12.70)	.651
STAI-2	45.29 (3.84)	43.19 (12.01)	.497
FFMQ	121.73 (38.14)	133.87 (12.70)	.237
NART (Errors)	13.93 (5.59)	14.06 (7.65)	.958
Predicted_FIQ	102.53 (38.84) Average	116.06 (6.37) High Average	.179

4.4 Results (Behavioural)

This study was designed to answer five main questions (1) Can patients with (unilateral) left frontal lesions (LFL) suppress unwanted memories? (2) Can patients with (unilateral) right frontal lesions (RLF) suppress unwanted memories? (3) Is there a significant difference between patients with LFL and RFL a) in the ability to supress unwanted memories and b) in the ability to recall memories? (4) Whether the size of lesion correlates with the ability to suppress? (5) What are the specific lesion locations in patients with impaired performance on inhibition measured by TNT?

[17] The details of the executive measures and the neuropsychological assessments have not been included in this thesis.

Question 1: Can patients with left frontal lesions suppress unwanted memories?

Same and Independent Probe (SPIP)

Patients with LFL recalled 90% of the word pairs in the Think and 84% in

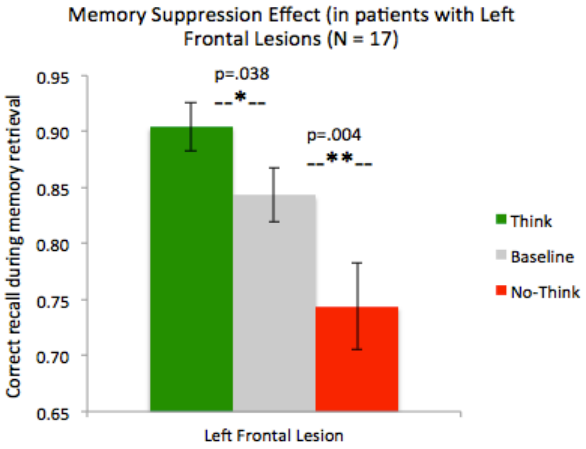

Figure 4.3 Retrieval performance (Think, Baseline & No-Think, SPIP) in patients with Left frontal lesions.

the Baseline conditions respectively (M_{LFL_Think} = .904, SD = .089; $M_{LFL\_Baseline}$ = .843, SD = .099). In contrast, they recalled 74% of the word pairs in the No-Think condition ($M_{LFL\_No\text{-}Think}$ = .743, SD = .159, Figure 4.3).

A one by two ANOVA with retrieval conditions (i.e. Baseline and No-Think)[18] as within participant factors showed a main effect of inhibition ($F_{(1,16)}$ = 11.229, p =.004, partial Eta Square = .412)[19], suggesting that patients with left

[18] Based on a-prior assumptions that check for the inhibition and facilitation effect in TNT (e.g. Benoit & Anderson, 2012) the literature reports separate ANOVA for inhibition and facilitation, instead of an omnibus ANOVA with all the three conditions (think, no-think and baseline).

[19] To account for any variance within the groups non-parametric equivalent statistics were also calculated (p = .007, Wilcoxon Signed Rank Test).

frontal lesions can inhibit unwanted memories using the direct suppression method.

Performances across the Independent and Same Probe

Patients with left frontal lesion were able to inhibit unwanted memory using direct suppression across independent and same probe (see figure 4.4).

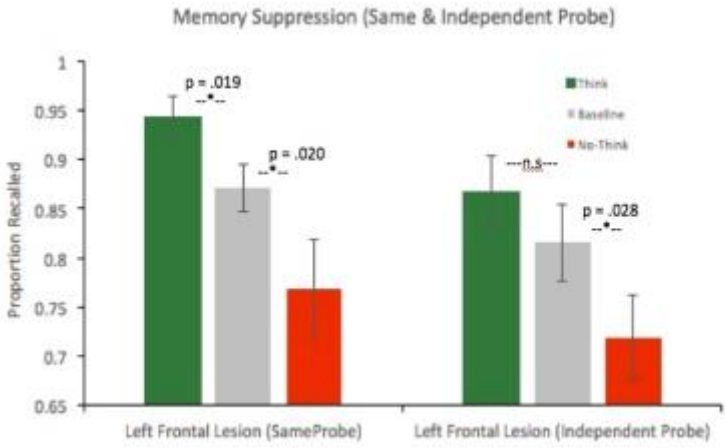

Figure 4.4 Retrieval performance (Think, Baseline & No-Think, SP & IP) in patients with left frontal lesions.

Question 2: Can patients with right frontal lesions suppress unwanted memories?

Patients with RFL recalled 93% of the word pairs in the Think, 88% in the Baseline and 86% in the No-Think conditions (M_{RFL_Think} = .939, SD = .054; $M_{RFL\_Baseline}$ = .882, SD = .113; $M_{RFL\_No\text{-}Think}$ = .868, SD = .099). One participant was excluded from the analysis, as his performance was two standard deviations

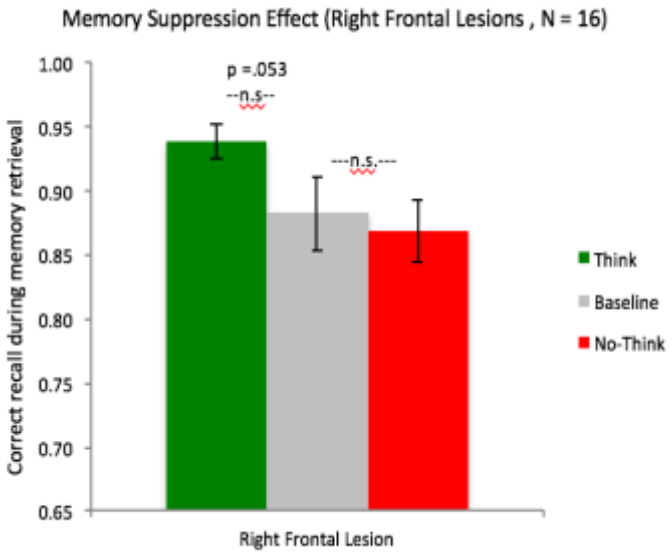

Figure 4.5 Retrieval performance (Think, Baseline & No-Think, SPIP) in patients with Right frontal lesions.

outside the mean (for the inhibition condition)[20]. The results for the RFL group have been reported on data from sixteen participants[21].

A one by two ANOVA with retrieval conditions (i.e. Baseline and No-Think) as within participant factors showed no main effect of inhibition ($F_{(1,15)}$ = .242, p = .630 (n.s.), partial Eta Square = .0.16)[22]. These results suggest that patients with RFL are *unable* to inhibit unwanted memories using the direct suppression method.

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[20] BH's performance was .357 (M = .033, SD = .137). The inhibition scores (Baseline minus No-Think) were calculated averaging the performance on both same and independent probe retrieval tasks.

[21] The statistics for the group including this patient is provided in Appendix B (Chapter 4) for this chapter.

[22] To account for any variance within the groups non-parametric equivalent statistics were also calculated (p = .594 (n.s.), Wilcoxon Signed Rank Test).

Performances across the Independent and Same Probe

Patients with right frontal lesion were not able to inhibit unwanted memory using direct suppression across independent and same probe (see figure 4.6).

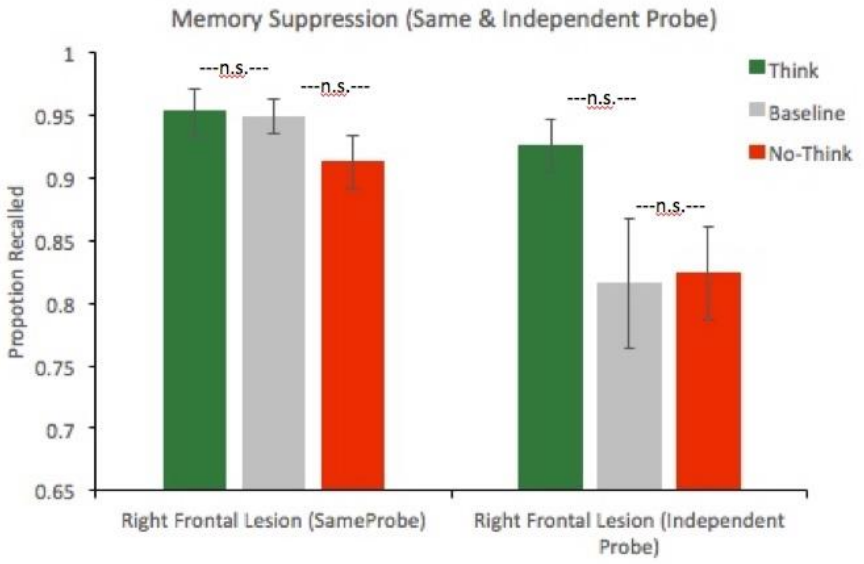

Figure 4.6 Retrieval performance (Think, Baseline & No-Think, SP & IP) in patients with right frontal lesions.

Question 3a: Is there a significant difference between patients with LFL and RFL in the ability to supress unwanted memories

The LFL group showed suppression effect of approximately 9% compared with the RFL group who showed only 1% ($M_{LFL\_Inhibition}$ = .099, SD = .122; $M_{RFL\_Inhibition}$ = .014, SD = .112).

A two by two mixed ANOVA with retrieval conditions (as calculated in the literature, for Baseline and No-Think) as within participant factors and the lesion site (left or right) as between participant factors showed a significant main effect of inhibition ($F_{(1,31)}$ = 7.663, p = .009, partial Eta Square = .198) and a significant

interaction effect of inhibition x site ($F_{(1,31)} = 4.389$, $p = .044$, partial Eta Square = .124)[23].

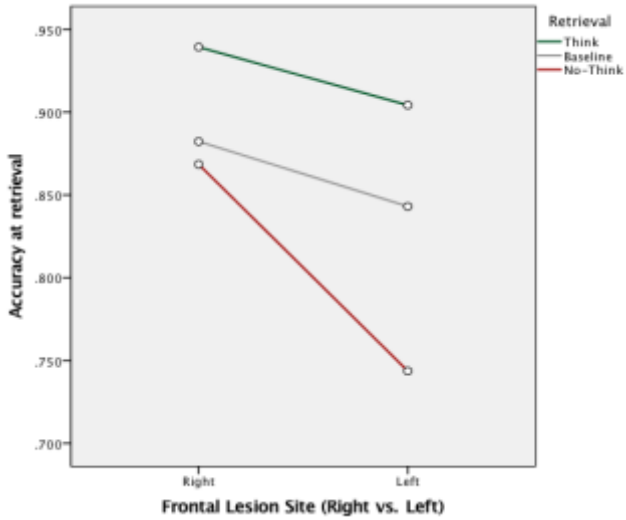

Figure 4.7 Performance for each of the retrieval measures (Think, No-Think, & Baseline) across both in patient groups (Left & Right).

To test the interaction independent t-tests were completed post-hoc (see Figure 4.7). The results suggests that the left frontal patients are able to inhibit unwanted memories (difference between baseline and no-think conditions) significantly better than the right frontal patients ($t_{(31)} = -.2.095$, $p = .022$ (1-tailed[24])).

All participants completed the Thought Control Ability Questionnaire (TCAQ, Luciano, Algarabel, Tomás, & Martínes, 2005, Cronbach's $\alpha = .802$).

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[23] To account for any variance within the groups non-parametric equivalent statistics were also calculated ($p = .037$, Mann-Whitney U)

[24] We used 1-tailed statistics, based on the *a-priori* hypothesis that patients with left lesions will be able to suppress, while patients with right frontal lesions will be unable to suppress or inhibit unwanted information (using the direct suppression method, Benoit & Anderson, 2012)

Independent T-test between the LFL and RFL groups suggest that there is no difference in their perceived thought control ability ($t_{(27)}$ = .243, p = ns., 2-tailed; M_{LFL_TCAQ} = 84.07 (15.92) M_{RFL_TCAQ} = 85.36 (12.25)).

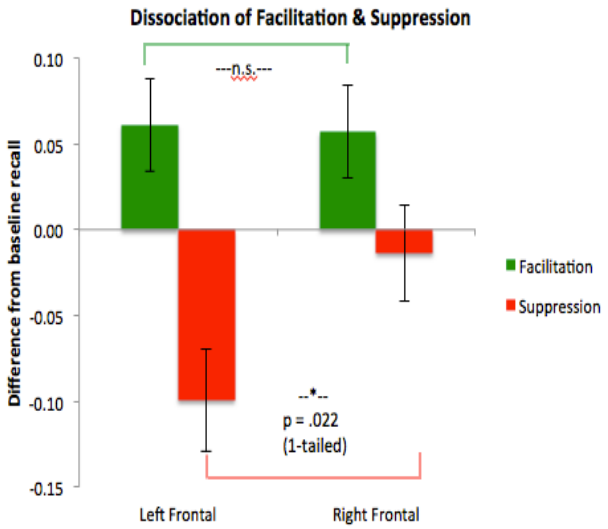

Figure 4.8 Graph showing the facilitation effect (that is baseline – think) and inhibition effect (no-think minus baseline) in patients with Left & Right frontal lesions.

Question 3b: Is there a significant difference between patients with LFL and RFL in the ability to recall memories (facilitation effect)?

The LFL and RFL groups showed around 6% of the facilitation effect ($M_{LFLPFaclitation}$ = .061, SD = .112; $M_{RFL\_Facilitation}$ = .057, SD = .108).

A two by two mixed AVONA with retrieval conditions (i.e. Baseline and Think) as within participant factors and the lesion site (left or right) as between participant factors showed a significant main effect of facilitation ($F_{(1,31)}$ = 9.487, p=.004, partial Eta Square = .234) but no significant interaction effects ($F_{(1,31)}$ = .012, p = .915 (n.s), partial Eta Square = .000, Figure 3.6).

4.5 Methods (Lesion Analysis)

Procedure

A neurologist (FM) or the author[25] used MRICron to trace the lesion on each participant's structural (T1) scans. These scans were then normalised to MNI space using SPM 08 or SPM 12. Lesion sizes for a subset of participants (N=18) were calculated using MATLAB Scripts[26] (Karnath, Berger, Küker, & Rorden, 2004). The T1 images of the remaining 16 participants were not available for this analysis. The RoI for the right and left DLPFC were drawn using spherical maps with centre coordinates based on previous research (Benoit &

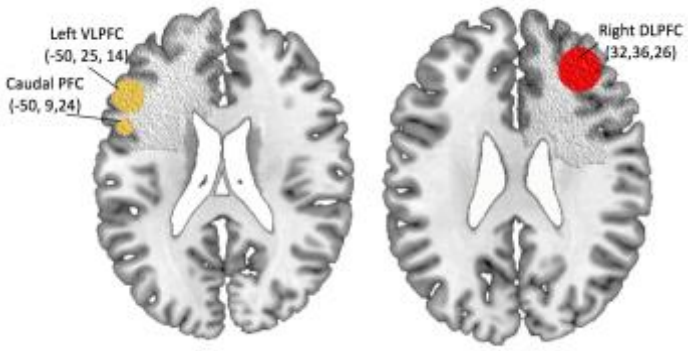

Figure. 4.9 Shaded area is a representation of the lesions across participants with unilateral frontal lesions. The centre coordinates of the three regions of interest (RoI) are listed (Benoit & Anderson, 2012; Badre & Wagner, 2007; Wimber et al., 2008).

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[25] All participants (except for MJ – pilot study) were recruited from the Cambridge Cognitive Neurosciences Research Panel (CCNRP), MRC Cognition and Brain Sciences Unit. 14 scans used in this thesis were traced by a neurologist (Facundo Manes, FM); remaining 3 scans that FM had not traced, were traced by the author (SS).

[26] The scripts for normalisation methods, and the RoI analysis, was provided by Daniel Mitchel, MRC CBU – but were modified by SS for this study. Prof. Chris Rorden provided some input and explained the process of RoI analysis.

Anderson, 2012; Badre and Wagner 2007; Wimber et al., 2008, see Figure 4.9)[27].

It was hypothesised that at a behavioural level, participants with right frontal lesions (RFL) would be unable to inhibit using the direct suppression method compared to participants with left frontal lesion (RFL). However, within the lesion analysis method, we hypothesised that within the RFL group, participants who had a lesion in areas around right DLPFC or lesions to possible white matter tracts connecting the frontal-hippocampal regions would be worse at inhibition in contrast to participants who had a more anterior-frontal or orbito-frontal lesions (see Figure 4.9 for the average lesion area across the participants in this study and the regions of interest).

4.6 Results (Lesion Analysis)

Question 4: Whether the size of lesion correlates with the ability to suppress.

To assess for any differences between the left and right frontal lesions paired sample t-tests were completed. The total volume of lesion (mL) between the right ($M_{RightLesionVol}$= 48.83, (59.18)) and left ($M_{LeftLesionVol}$= 39.37, (70.70)) frontal lesions were not significantly different ($t_{(13.700)}$ = .303, p = .767 (2-tailed)). Correlations between the total lesion volume and the ability to inhibit were calculated. There was no significant correlation for either the left (r = .200,

[27] The RoI masks were created by SS and then verified by Michael Anderson. These masks have also been used in another MPhil Study Investigating Retrieval Induced and Directed Forgetting in Patients with focal lesions (Berit Brummerloh, University). The Peak coordinates for the right DLPFC RoIs are: x = -50, y = 25, z = 14.

n = 8, p = .636 (n.s.)) or right (r = -.037, n = 10, p = .919 (n.s.)) frontal lesion group (see Table 4.2 for details of the lesions).

Both of these results suggest that it is indeed the specific region of interest that may be driving the ability to inhibit and not necessarily the size of the lesion.

Table 4.2. Details of lesions

Lesion Laterality	PID	Age	Aetiology	Lesion Area (cc)	Inhibition (SPIP)
Left Hemisphere	2182	43	Subarachnoid haemorrhage, aneurysm		18.75%
	539	73	Tumour resection	18.789	18.82%
	2751	61	Tumour resection	3.365	15.15%
	944	61	Meningioma excision	25.009	12.27%
	1946	67	Tumour resection	213.017	16.67%
	2675	57	Tumour resection	24.001	**-9.28%**
	321	71	Tumour resection		16.67%
	2349	68	Tumour resection	17.042	**-3.57%**
	2603	37	Spontaneous deep frontal haematoma	12.513	4.16%
	2867	52	Tumour resection		15%
	2781	68	Tumour resection	66.376	33.33%
	3043	70	Tumour resection		**-13.89%**
	611	67	Tumour resection		2.78%
	3030	51	Tumour resection		13.64%
	913	73	ACoA aneurysm	1.394	21.43%
	2950	68	Haemorrhage		11.91%
	2399	64	Infection drained by surgery		**-8.33%**
Right Hemisphere	812	67	Tumour Resection (Meningioma)	3.754	-9.72%
	2907	43	Tumour Resection		**4.17%**
	2948	68	Tumour Resection	22.942	**2.83%**
	2957	68	Meningioma excised	176.981	-1.25%
	1973	74	Tumour Resection	27.543	-22.22%
	735	54	Tumour Resection	114.726	-0.76%
	2298	44	Tumour Resection	88.719	-9.09%
	1745	70	Tumour Resection		**13.636**
	2837	70	Tumour Resection		-2.08%

1701	72	Tumour Resection	40.069	**25%**
175	64	Tumour Resection	2.991	0.00%
2585	62	Infarct		**35.71%**
2196	62	AVM Bleed		**10.00%**
2825	43	Tumour Resection		0.00%
2629	68	Ischemia		**6.67%**
3089	39	Tumour Resection		**14.02%**
119	58	AVM Bleed	0.78	-4.54%

Note (Table 4.2): The shaded rows indicate the patients from either group, whose individual performance differed from the group direction. However, as the current TNT is not suitable to measure individual performance, therefore for the purposes of this thesis, the data was analysed to measure group differences.

Question 5: Whether all patients with lesions to the right hemisphere have impaired performance on inhibition measured by TNT or is the lesion to specific regions (rDLPF or superior frontal) that affect behaviour?

The behaviour performance for inhibition within the RFL group was used to answer this question. There was a significant difference in the ability to inhibit unwanted memories with the RFL group ($t_{(15)} = 4.40$, $p = .001$ (2-tailed)). Eight participants showed some inhibition ($M_{RFL\_SPIP\_Inhibition} = .139$ (.11)) compared to 9 participants who were unable to suppress unwanted memories effectively ($M_{RFL\_SPIP\_Inhibition} = -.060$ (.07)).

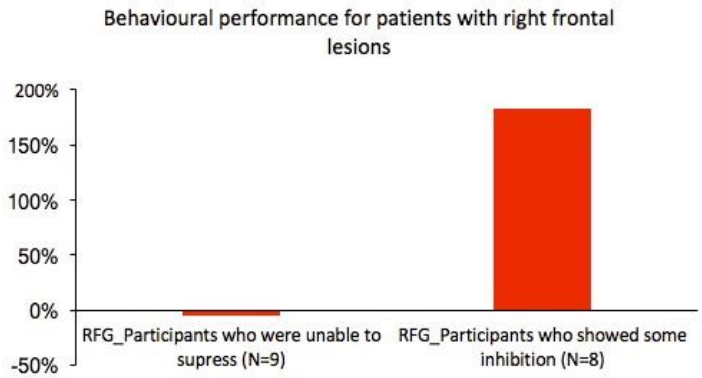

Figure. 4.10a. Graph showing the behavioural difference in participants with right frontal lesions (RFL) who were able or unable to inhibit unwanted memories.

Based on this behavioural results, the lesion areas of these patients were compared to the RoI (rDLPFC). Based on the regions of the lesion and the area of lesion described by the radiographers[28], the results suggest that most of the patients who had a more posterior frontal/small or large inferior frontal lesions (see Figures 4.10c) compared to the other nine participants performed better at inhibition than those who had a more dorsolateral frontal, superior frontal and more medial frontal lesion (see Figures 4.10b)[29].

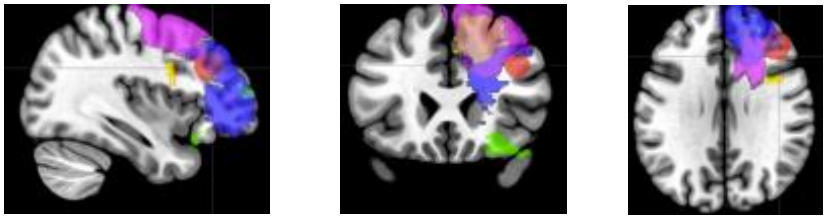

Figure. 4.10b. An example of lesion location from eight (out of nine) participants with right frontal lesions (RFL) who were unable to inhibit unwanted memories.

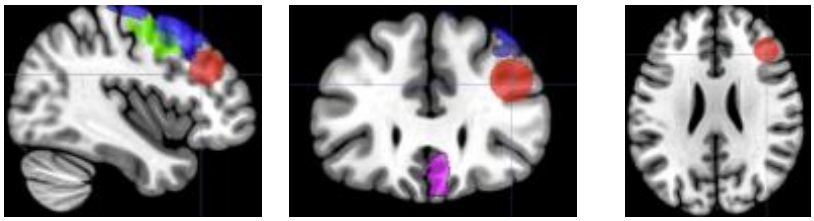

Figure. 4.10c. An example of lesion location from three (out of eight) participants with right frontal lesions (RFL) who were able to inhibit unwanted memories.

[28] The lesion maps were drawn by FM (for 7 patients), SS independently drew the lesion map and compared it to the original maps by FM for the process of learning. SS drew the maps for the remainder 1 patient.

[29] For the purposes of the thesis, a simple RoI was undertaken using a MATLAB script, due to small number of scans available (SS performed the lesion analysis and created the visualizations using MRIcroGL).

4.7 Discussion

Many studies of TNT using advanced neuroimaging techniques have hypothesised a possible causal relationship between frontal and hippocampal structures (Benoit & Anderson, 2012; Gangnepain et al., 2014; Levy & Anderson, 2012). Benoit and Anderson's study has provided the (first) neuroimaging evidence for unique neural networks underlying separate memory control processes (i.e. direct suppression and thought substitution). However, there was no empirical evidence of the TNT task being used in patients with focal lesions. One of the few contributions of this study is that the TNT task (with some adaptations, see Chapter 3 for more details) has been successfully adapted for use in patients with focal lesions. The results from Chapter 3 suggest that, given explicit instructions, patients with unilateral frontals lesions (left or right) are able to complete the task (for details on the adaptions, refer to Chapter 3). The methods in this study ensured that participants learnt all the words in the criterion-phase or saw the word list up to a maximum of four times to account for over-learning effects. In spite of possible overlearning, it is interesting that behavioural data shows that patients with left frontal lesions are able to inhibit unwanted memories better at a group level compared to patients with right frontal lesions. Future studies, could need to ensure that: a) all participants are equally exposed to the words, and b) that the rate of initial learning could be considered as a co-variate in the final analysis to account for any over-learning effects. In addition to this, it might be of interest to collect the time of response for each learning phase.

Lateral differences in memory inhibition

The current data suggest that patients with right frontal lesions (RFL) indeed are unable to suppress unwanted memories, using direct suppression, compared to patients with left frontal lesions (LFL). Within the RFL group, patients with lesions to regions around the rDLPFC are impaired in the ability to suppress unwanted memories compared to patients who have lesions to the inferior or middle right frontal lobe.

Can it be argued that these laterality effects are caused by specific lesions to the regions of interest rather than the size of the lesion? The data suggests no correlation between the behavioural performance and the lesion size in both RFL and LFL groups.

Interestingly, the data supports the argument that lesions to specific regions and networks do affect the ability to inhibit unwanted memories. Patients with lesions to the RFL (in and around rDLPFC) are significantly unable to suppress unwanted memory compared to patients with either left focal lesions or lesions to other right frontal regions which do not include the rDLPFC. This is the first lesion study evidence that it is indeed the right pre-frontal cortex (especially regions around BA46/9) is essential to engage in inhibition using the direct suppression methods. These results do support existing neuroimaging evidence that suggest a right lateralized network is engaged during direct suppression (Anderson et al., 2004; Benoit & Anderson, 2012; Depue et al., 2007 Gagnepain et al., 2014; Levy & Anderson, 2012; Wimber et al., 2015).

Compared with the existing literature, the results suggest patients with RFL (in the inferior frontal region) show abnormal stopping during the stop-signal paradigm (Logan et al., 1984; see also Criaud & Boulinguez, 2013; Aron et

al., 2003) indicate that thought right laterization is necessary for inhibition, the focal regions of interest underlying motor and memory inhibition may not necessarily be the same. This is further supported by studies that implicate regions such as the right operculum regions in response inhibition (Rubia et al., 2001, 2003; see also Li et al., 2006). One possible reason for these differences within the right hemisphere could suggest that there may be some over lapping regions between memory and motor inhibition, but some regions that are unique to memory or motor inhibition. Based on these data it seems that lesions to specific focal regions (especially the rDLPFC ~ BA46/9) and regions around DLPFC (including areas that connect the rDLPFC to the hippocampus) are essential for one to engage in direct suppression. The results suggest that it is indeed the right pre-frontal regions, especially around the dorsal lateral PFC regions (including areas in and around the BA46/BA9 regions) are essential for inhibiting unwanted memories, rather than laterality alone.

One of the limitations in this study is the lack of diffusion tensor imaging from patients. White matter microstructures in patients with focal lesions in future studies could provide the opportunity to do more detailed analysis of the specific networks underlying memory and motor inhibition.

Individual Differences

The averaged results show a clear dissociation between the right and left lesion groups. As discussed above one of the main reasons for this difference is lesions to specific frontal networks, especially in patients with right frontal lesions. Evidence for this comes from patients with RFL are significantly able to inhibit the unwanted memory, especially if the lesions are outside the rDLPFC regions (especially not in the BA46/9 regions). Are these differences also

supported by other factors or specific individual differences? A sample size of 17 participants in one group, limits the investigation of individual factors that may that may impair or improve the ability to supress unwanted memory. Additionally, the limited access to imaging data in patients of this study has not allowed us to do advanced regression analysis aimed at understanding the individual differences within patients.

The current design of the TNT task has been often used to discuss the individual differences in the literature (Norren & MacLeod, 2014). However, this task has been originally conceived to understand group effects of memory inhibition. Evidence using same task to support individual differences without accounting for other differences or adapting the task should be treated with caution. The performance on TNT tasks, at this point, may not be a holistic representation of the individual's ability to inhibit unwanted memory. More empirical evidence correlating the performance on this task with everyday ability and also understanding this process when people may confront emotional memories are necessary to understand who memory inhibition may work at an individual level.

Future studies in patients with a larger sample size may allow us to explore possible individual differences that might predict individual performances on memory inhibition tasks. Studies have access to better neuroimaging data (including DTI) in patient groups may help us understand the neural networks underlying these individual differences.

Clinical Implications

The current study has provided answers two main questions that not only support existing gaps in the memory inhibition literature, but also provide some

fundamental evidence that can be applied into clinical settings, possibly into models that may support cognitive rehabilitation. The *first main impact* was that both high or low functioning patients can be tested using this method. The ability to test individual patients on the TNT task might allow us to compare the empirical performance with everyday difficulties in memory inhibition that they may experience in. However, the design, in its current form, is time consuming to be able to extend it into a clinical setting. Also, the design is not suitable for individual comparisons.

However, future studies should aim at standardizing this task to extend it within the clinical framework. It these test that can be normed to compare individual performance, it can indeed be a tool to support clinical rehabilitation.

From a clinical point of view, it would be interesting to see if the ability to inhibit unwanted memories in the task informs patient's choices in life. If yes, then lesions to the underlying network, may affect the person's resilience. Individual's might continue to engage in strategies of direct suppression when in fact the neural mechanisms may be impaired, thus affecting their ability to cope with life stressors. When faced with a neurological disorder or event, patients do not receive information about which of these mechanisms are used to inhibit unwanted memories. Often unpleasant memories are almost automatically inhibited, generally motivated by a bigger goal, for example well-being and resilience. For example, a patient with lesion to right DLPFC would have normally use suppression to forget any unpleasant memory in her or his life. After a stroke or a tumour resection, patients are often unaware that a) one of the specific network underlying the ability to inhibit unwanted memory is now impaired. B) They have always suppressed or inhibited any unwanted memory

when faced with a reminder. After the focal lesion, with the neural mechanism is impaired, not being aware of this they still engage in the cognitive process of memory inhibition as this is what they have learnt to do. Not being able to successfully forget the event, even after having tried, they are not only disturbed faced with the reminder, but also are frustrated as they realise that are unable to forget! This may often lead to feeling low and anxious, commonly diagnosed as (comorbid) depression and/or anxiety.

During debrief for this study, participants have often felt understanding the mechanisms of memory inhibition has helped them understand their cognitive process. Extending this awareness in the community is one of the goals for future research avenues for this study. This study suggests that there are avenues for future research, these are discussed in the final discussion (Chapter 6).

5. Frontal-hippocampal pathways underlying inhibitory control of unwanted memories.

5.1 Introduction

When confronted with unwanted memories from the past, one often strives to limit awareness of these memories, by stopping its retrieval (Anderson & Green, 2001; Anderson et al., 2004). Recent evidence suggests that during retrieval suppression, the right lateral prefrontal cortex suppresses the hippocampal activity which is known to support retrieval (Anderson et al., 2004; Benoit & Anderson, 2012; Depue, Curran & Banich, 2007; Depue, Orr, Smoker, Naaz & Banich, 2015; Anderson & Ghetti, 2013). Often referred as suppression induced forgetting (SIF), over the last decade, evidence for this has been provided by various neuroimaging and behavioural experiments (Anderson & Hansylmyer, 2014; Depue, Curran & Banich, 2007; Depue, Orr, Smoker, Naaz & Banich, 2015; Anderson & Ghetti, 2013). SIF is commonly assessed using the think/no-think (TNT) task (Anderson & Green, 2001).

The neural processes underlying the ability to stop unwanted memories from coming into awareness, has often been compared to that of action stopping (Levy & Anderson, 2012; Depue et al., 2015). The anatomical pathways of action stopping have been well studied compared to the pathways underlying the lateral pre-frontal hippocampal connections that are assumed to support retrieval suppression (Schmidt, Leventhal, Mallet, Chen, & Breke, 2013; Aron, Robbins & Poldrack, 2014; Anderson, Bunce, & Barbas, 2015).

Right Lateral prefrontal cortex.

Retrieval suppression is known to engage a strong right lateralized set of regions, including the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLOPFC), posterior middle prefrontal gyrus (pMFG) and the insula (Anderson & Hanslymyer, 2014; Anderson, Bunce, & Barbas, 2015; Levy & Wagner, 2011). Imaging studies have consistently shown activations in the right DLPFC, often extending across the anterior-posterior length of middle frontal gyrus (Brodmann's area (BA) 9 and 46; Anderson et al., 2004; Benoit & Anderson, 2012; Gangepain, Henson & Anderson, 2015). Although, some studies have shown activation in the anterior right DLPFC (towards the posterior region of BA10, near the border of BA9/46). These neuroimaging studies suggest that the activation in the DLPFC is often in the anterior BA9/46/10 areas (Anderson et al., 2004; Depue et al., 2007). Based on this evidence it has been suggested that individual differences in SIF effect may be predicted by the activation in these anterior DLPFC regions (Anderson et al., 2004; Depue et al., 2007). Behaviourally, it has been suggested that the differences in working memory capacity may predict the individual differences underlying retrieval induced forgetting (Anderson, Bjork & Bjork, 1994; Levy & Anderson, 2007).

Though most reports focus on the right DLPFC activations, there is evidence from right VLPFC (BA44 and 45) and bilateral insula activations during retrieval suppression (Benoit et al., 2015). These regions have been known to be engaged during inhibitory control over action (Aron et al., 2014). It has been proposed that both VLPFC and the DLPFC may play critical roles in retrieval suppression, but currently there has been no efforts to identify the functional contributions of these individual areas (Anderson, Bunce & Barbas, 2015).

Controlling retrieval by redirecting the retrieval process instead of inhibiting it is known to activate regions of the left VLPFC and the caudate VLPFC regions instead of the right prefrontal regions (Hertel & Calcaterra, Bergström et al., 2009; Benoit & Anderson, 2012). In contrast when participants were instructed to not generate alternative thoughts, but asked to focus on the reminder whilst stopping retrieval there was engagement of the right DLPFC and VLPFC but not left prefrontal cortex (Benoit & Anderson, 2012). Finally, a within-subject comparisons of motor control, emotional regulation and retrieval suppression, suggests that a supramodel inhibition mechanisms in the right anterior DLPFC is activated across these tasks. Evidence from connectivity analyses suggest that these right anterior DLPFC regions negatively couple with the hippocampus during retrieval suppression (Benoit & Anderson, 2015; Benoit et al., 2015; Gangnepain, Henson & Anderson, 2015).

Subcortical structures

During retrieval suppression activity in the basal ganglia, specifically in regions of the right caudate and putamen have often been reported (Benoit & Anderson, 2012), but no one has really investigated the role of basal ganglia structures in memory inhibition. A recent meta-analysis across Stop-Signal tasks (SST) and Think/No-Think (TNT) has proposed common critical regions within the right caudate and putamen in inhibition, when compared with studies of go/no-go tasks (Guo et al., 2016). Basal ganglia structures have been reported in previous studies, along with the striatal pathways that are known to underpin motor inhibition responses, when stopping a prepotent motor response (Chambers, Garavan & Bellgrove, 2009; Zandbelt & Vink, 2010; Wiecki & Frank, 2013).

Studies that assess memory inhibition (using TNT tasks) have reported reduced hippocampal activation in the no-think conditions (Anderson & Benoit, 2012). Reduction in hippocampal activity by itself may not necessarily indicate down-regulation (Benoit & Anderson, 2012; Depue et al., 2007). However, DLPFC activation during the no-think trial has been negatively correlated with hippocampal activity (Depue et al., 2009; 2010). Further evidence comes from studies that suggest that reduction of hippocampal activity predicts later SIF (Benoit & Anderson, 2012; Depue et al., 2007). Finally, connectivity analysis has corroborated this top-down modulatory influence of the right prefrontal regions (especially the DLPFC) on the hippocampus (Benoit & Anderson, 2012; Benoit et al., 2015; Gangepain et al., 2015).

Evidence from neuroimaging literature thus suggests, during retrieval suppression there is a top-down modulation, with increased activation of the right prefrontal cortex (especially in the right DLPFC) with regional suppression of the mnemonic activity in the hippocampus. Given the empirical evidence supporting a functional connectivity between right prefrontal and the hippocampal regions, what then of the anatomical structures that underpin the inhibitory control of unwanted memories?

The prefrontal-hippocampal structural connections

Neuroimaging evidence propose that PFC may exert inhibitory control on the mnemonic representations within hippocampus or indeed that these frontal regions inhibit a systemic suppression that reduces hippocampal activity (Anderson, Bunce, & Barbas, 2015; Hulbert, Henson & Anderson, 2016). Indeed, underlying these functional coupling, there may be anatomical structures

underlying memory control that may be slightly different from those necessary for motor control (Anderson, Bunce & Barbas).

Lack of empirical evidence from human studies defining the prefrontal-hippocampal connective, makes it further difficult to predict how these structures may be critical for memory suppression (Anderson, Bunce & Barbas, 2015). One recent study investigated the white matter structures underlying memory inhibition, emotional regulation and motor inhibition (Depue et al., 2015). The results from Depue and colleagues suggest that the cingulum bundle is critical for memory suppression. Specifically, that the functional anisotropy of the cingulum bundle (CB) predicted the increase of the right anterior medical frontal (aMFG) – hippocampal pathway compared to the inferior fronto-occipital fasciculus (iFOF)-uncinate (UNC) and the anterior limb of the internal capsule (ALIC) which correlated with emotional regulation and motor inhibition respectively. Although, the Depue and colleagues (2007) work is a significant step in the right direction, suggesting that it may be a MFG-Hipp pathway that is critical for memory inhibition, additional studies replicating their findings in memory inhibition are necessary. These studies need to address specifically the mechanisms and the white matter connectivity to understand how prefrontal structures like the DLPFC, VLPFC orchestrating subcortical structures like basal ganglia and the hippocampus during memory suppression.

Cingulum Bundle

The cingulum bundle has been proposed to connect the medial frontal gyrus and the hippocampus (Schmahmann & Pandya, 2006; Catani et al., 2002, 2013). One study suggests that it is this MFG-hippocampal pathway that is critical in predicting memory inhibition, however, it is unlikely that this pathway

alone can contribute to memory inhibition (see Anderson, Bunce and Barbas, 2015). What then of the connectivity between MFG and DLPFC areas and how are these prefrontal networks connected to the subcortical structures within basal ganglia connectivity.

Based on anatomical findings in non-human primates, Anderson and colleagues (2015) have attempted to bridge the gap of prefrontal-hippocampal connectivity underlying memory suppression. Keeping in mind the various constraints (those that have not been evaluated in Depue et al., 2015), two possibly pathways have been put forth (Anderson, Bunce & Barbas, 2015).

Entorhinal gating hypothesis

In the first proposed hypothesis, the anterior cingulate cortex (ACC) is suggested to mediate the influence of the lateral prefrontal cortex on memory (Anderson, Bunce & Barbas, 2015). This hypothesis proposes that within the ACC area 32, the powerful paravalbumin (PV) neurons preferentially synapses with inhibitory neurons (Bunce et al., 2013). Two pathways have been suggested to mediate memory suppression. Transmission may be enhanced by attentional signals from mPFC, facilitating the transfer of signals from entorhinal to the perirhinal cortices (Paz, Buer & Pare, 2007; Anderson, Bunce, & Barbas, 2015). In contrast, the ACC can inhibit this transmission via its innervation of PV neurons, thereby obstructing the necessary activity underlying recollection in the hippocampus (Anderson, Bunce & Barbas, 2015; also see Depue 2012).

The thalamo-hippocampal modulation hypothesis

The second pathway proposes the idea that the ACC may modulate hippocampal process actively, rather than merely gating the input. Based on primate literature, PFC regions have been known to share connections with

midline nuclei of the thalamus including the reuniens nucleus (Barbas, Henion & Dermon, 1991; Dermon & Barbas, 1994). However, the strongest connection of the RE is with the ACC in mFC (Barbas, Henion & Dermon, 1991).

The ACC signals are positioned to affect hippocampal dynamics via the RE interactions with distinct inhibitory and excitatory post-synaptic targets (Anderson, Bunce & Barbas, 2015). Recent evidence suggests that projections from ACC to RE are critical in controlling the specificity with which memories are encoded (Ito, Zhangm, Witter, Moser, & Moser, 2015; Xu & Sudhof, 2013), especially in the context of traumatic flash back memories.

Motivation for the current study

Prefrontal-hippocampal structural connectivity has not been well characterised, especially in the context of mechanism for memory inhibition. Further evidence is necessary to support the current evidence from one study (Depue et al. 2015) and/or the two proposed hypothesis (that may be speculative). This study aimed to investigate whether the white matter connections underlying DLPFC and hippocampus (via the caudate nucleus) correlated with inhibition measures (see section on TNT for more details of the task).

The current study proposed two white matter tracts that may predict memory inhibition. The first tract was hypothesised to connect the rDLPFC to the caudate nucleus, which would be part of the anterior thalamic projections (Guo et al., 2016). While the second tract was expected to connect the caudate nucleus to the hippocampus and would be part of the fornix (Catani et al., 2002; Catani et al., 2013).

5.2 Methods

Thirty-six participants were recruited from MRC –Cognition and Brain Science Unit (CBU) student and community panel. They all reported to have no psychiatric and/or neurological disorders, and gave written informed consent, approved by the MRC-CBU Ethics committee.

The current study explored white matter connectivity (using Diffusion Tensor Imaging) in 36 individuals, who completed the TNT task. Eighteen of these participants used the direct suppression method while the others used the thought substitution method. The fMRI data from this study has been published (Benoit & Anderson, 2012). The researcher (SS) was blind to the memory control method (i.e. direct suppression or thought substitution) used by the participant.

Think/No-Think task

The think/no-think task used in this study is identical to the one reported by Benoit and Anderson (2012; please see Chapter 1 for a more detailed description of the Think/no-think task). The TNT task has three main phases. 1) In the Learning Phase participants are shown fifty-four word pairs. They have to learn these word pairs, such that, when they see the left hand word, they need to respond with the right hand word. 1a) In the Substitute study phase, eighteen participants received substitute memories for a subset of these reminders (left hand words). All participants in this study had to meet a criterion threshold of 65% (36 out of 54 words), to continue with the study 2) Think/no-Think (TNT) Phase: after a brief practice phase, all participants completed the TNT phase. In this phase they were instructed to suppress the right hand side word, when the left hand side words appeared in red (12 words, referred to as the No-Think condition). When the right hand side word appeared in green, they were asked to

recall the right hand side word and keep it in mind for the entire duration the word was on the screen (12 words; referred to as the Think condition). 12 other words from the learning phase were not shown in this phase and formed the baseline condition. 3) Retrieval Test Phase: In this phase memory was tested for all the word pairs. In the same probe (SP) test, participants saw the left hand side word (that they had seen during the learning phase) and had to respond (orally) with the correct right hand side word. Memory was also tested using an independent probe (IP). In the IP condition, participants were presented with a semantic category and the first letter of the right hand side word. For example, if the right hand side word was beef, they would be shown: Meat__B. This method is proposed to be a better measure of inhibition compared to the SP test (Anderson & Spellman, 1995). At the end of the session, detailed questionnaires were administered to record subjective (see Appendix E).

Scanning Parameters

Scans were acquired in the 3.0–Tesla Siemens TIM Trio MRI scanner using a Head Matrix 12 element head coil at the MRC CBU, Cambridge. A high resolution T1 anatomical scans, and a Diffusion Tensor Imaging sequence were acquired for each participant. The functional scans (T2* weighted scans had also been acquired, results from which have already been published, Benoit & Anderson, 2012).

Anatomical

Anatomical images were acquired using T1 weighted, 3D, TFE volume acquisition with a TR/TE1/delta TE = 16/4.5/2.2 msec., the voxel size = 0.699 x

0.699 x 0.699 mm, 220 slices in the transverse orientation with AP fold–over direction were taken.

Diffusion Tensor Imaging [DTI][1]

The DTI was based on single–shot echo planar imaging [EPI] sequence. The TE = 70 msec., voxel size = 2 x 2 x 2 mm, slice thickness of 2 mm, DELTA= 34 msec., delta= 21 msec., 64 high directional resolutions, b–factor=2, in the ascending order, with a max b–factor of 800 with maximum gradient were imaged for all participants. The data was converted from DICOM to NIFTI using MRI Convert (http://lcni.uoregon.edu/~jolinda/; version 2.0, rev. 216) and then analysed using FSL (version 4.8.1). The DTI measures were correlated with the behavioural performance.

Diffusion MRI pre-processing

The data was converted to NIFTI from the DICOM format (Dicom2nifit, MRICron, Li, Ashburner, Smith & Rorden 2016). The processing pipeline included motion and eddy current correction (Anderson and Sotiropoulous, 2016; Graham, Drobnjak & Zang, 2016).

Probalistic Tractography (analysis undertaken, but not reported in this thesis).

Initially, all the data (36 participants) were analysed using the probabilistic tractography method[2]. The results were not significant, based on verbal

[1] The DTI data was collected as part of the Benoit & Anderson (2012) study. Only the raw scans (DCM images) were provided to SS. SS converted the images to .nii and independently did all the pre-process and relevant analysis using probtrax and deterministic approaches.

discussions with the experts in the field (Catani, M, 2016), it was decided that deterministic tractography was a better analysis for this data set.

Dissection of the frontal-hippocampal connections in human brain (deterministic tractography)

Diffusion Tensor Estimation

StarTrack (Version 1, NatBrainLab) was used to create the diffusion tensor estimation. The diffusion data was then processed using a spherical deconvolution approach based on the damped Richardson Lucy (SD- dR, Dell' Acqua et al., 2010). Whole brain tractography was performed selecting brain voxels with at least one fibre orientation as a seed voxel (Catani et al., 2012; Mori & vanZijl, 2002) to identify the two tracts of interest. In regions with crossing white matter bundles, the algorithm follows the orientation vector of least curvature as described in Schmahmann and colleagues (2007). Deterministic tractography was preferred over probilistic, as this was an exploratory study to identify specific white matter tracts underlying memory inhibition (Tournier, Mori, & Leemans, 2011). All data processing was performed using software developed with MATLAB (The Math Works, Inc., Natick, MA, provided by Natbrainlab, London). Visualization was performed using Trackvis (www. trackvis.org).

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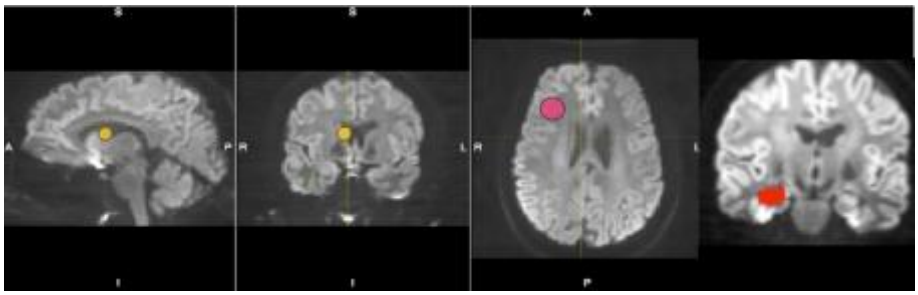
[2] The pre-processing and main pipeline analysis using FSL was undertaken by the author Shanti Shanker (SS). The values for Mean Diffusivity (MD), Radial Diffusivity (RD) and Fractional Anisotropy (FA) for the tract between DLPFC and the hippocampus did not significantly correlate with individual's behavioural performance. Nor was the tractography across participants consistent (due to artefacts and crossing fibres), hence this analysis was discontinued (results not included in the thesis) and the data was analysed using deterministic tractography (reported in this Chapter, independently analysed by SS).

Regions of Interest[3]

Virtual dissections were performed in Trackvis using three RoIs to isolate two separate tracts (Catani & Thiebaut de Schotten, 2008). The details of the RoIs used are: 1) A 5 mm sphere was placed in DLPFC. 2) A 3 mm sphere was placed near the tail of the caudate nucleus, such that, the RoI was able to pick up the tracks of the anterior thalamic radiation. 3) The right hippocampus for each participant was manually traced in MRICron, this image was then loaded as a right hippocampal mask (see below for an example from one participant).

The same RoIs were used to trace the white matter tracts from the human connectome project (Sotiropoulos et al., 2013), as the quality of the images were superior to the ones acquired in this study.

[3] The protocols used to identify the regions of interest were: (a) **the DLPFC** which was based on the regions that have been identified in the literature as DLPFC (Badre and Wagner, 2007; Benoit & Anderson, 2012) and correlated by the white matter atlas (Catani and Thiebaut de Schotten, 2012). The same identification method was followed across all participants. To reduce any bias, a spherical RoI was used in this study; b) **The caudate nucleus mask**, was based on anatomical landmarks for the caudate nucleus. A spherical RoI was used across all participants (Catani and Thiebaut de Schotten, 2012); c) **the right hippocampal mask** was individually traced for each participant (SS underwent training to understand this process with Dr Ana Catarino, in Michael Anderson's Lab).



The 3mm sphere: placed at the tail of the caudate nucleus.
The 5 mm sphere: placed in the right DLPFC (based on anatomical landmarks)
The right hippocampal mask drawn in each individual.

Figure 5.1 Example of regions of interest used in this study.

5.3 Results (Deterministic Tractography)

Frontal-hippocampal connectivity

In each participant, diffusion weighted values for the two white matter tracts were calculated. The first tract was hypothesised to connect the DLPFC regions to the caudate nucleus, which was part of the anterior thalamic projections. While, the second tract connected the caudate nucleus to the hippocampus and appears to be part of the fornix (see figure 5.2). The number of tracts and the mean diffusivity measure for each of these tracts was calculated using Trackvis). Individual participants showed evidence of both the tracks that were hypothesised. Similar tracts were also seen in the Human connectome dataset.

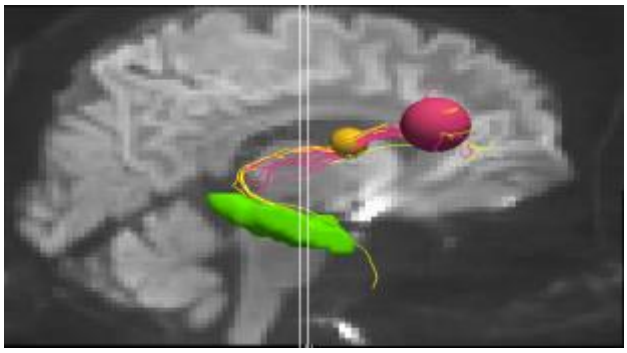


Figure 5.2 Example of the two tracts in one participant. Also visible is the three RoIs that were used for the seed based tractography.

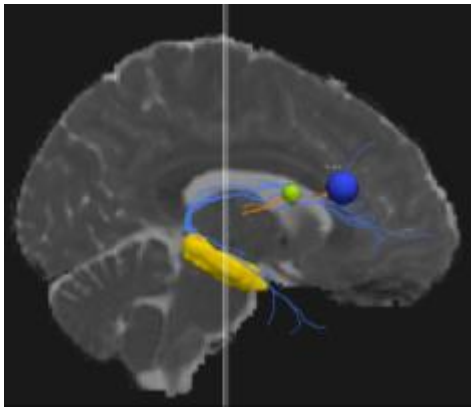


Figure 5.3. The two tracts (orange tract: connecting the DLPFC to the caudate nucleus; blue tract: connecting the caudate nucleus to the hippocampus) from the human connectome data set.

Correlation between individual performances and tractography

The performance on no-think was significantly below baseline (t_{35}= 5.761, p > .000) when averaged across both test conditions (SP and IP; see Figure 4.4), suggesting a significant inhibition effect, irrespective of the method of memory control (thought substitution or direct suppression) used. This behavioural data has been reported in Benoit & Anderson (2012).

There was no correlation between the diffusivity values (HARDI DWI) of the tract 1 (which is part of the anterior thalamic projections, r = -.187, p = .274 (n.s.) or tract 2 (part of the fornix; r = -.200, p = .241 (n.s.)) and the behavioural measure of inhibition (i.e. baseline minus no-think conditions. These results suggest that both these tracts of interest may not be critical for memory suppression.

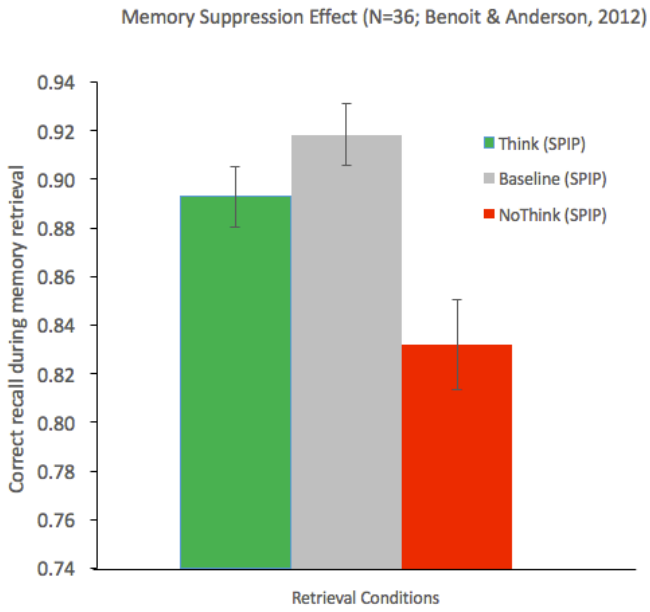


Figure 5.4. Graph showing correct recall across the three retrieval conditions.

5.4 Discussion

The primary aim of this study was to investigate possible anatomical connections underlying functional activity of memory suppression. The hypothesis to identify tracts of interest was based on the imaging results that identified these regions during functional connectivity (Benoit & Anderson, 2012; Gangenpain, Henson & Anderson, 2015). To ensure that the tract was indeed present, the same RoIs were used to virtually dissect this in the Human Connectome DTI dataset. These results also show minimal connectivity,

resembling the tracts seen in thirty-six participants of this study. The results suggest that these specific white matter tracts connecting the rDLPFC and the hippocampus via the caudate nucleus does not correlate with behavioural inhibition. These results do not support the possibility that direct connections from the right DLPFC modulate the hippocampal activity during memory inhibition.

This study did not contribute to predicting the structural connections underpinning memory inhibition for at least reasons: a) although the functional regions crucial for memory inhibition have been identified, there are no empirical evidence (in human) that suggest a particular white matter tract that may connect these functional regions; b) although one study has identified the cingulum bundle to be of importance (Depue et al., 2015), that alone does not connect the functional regions that have been identified in memory inhibition, especially using the TNT task (Benoit & Anderson, 2012).

However, this is a first step in the direction of bridging the gap, suggesting that the rDLPFC may not necessarily have a direct connection to structures within the basal ganglia. Based on results from Depue and colleagues' further investigation of these results might be interesting. One possible future direction would be to identify each tract of interest and correlate them individually with the behaviour. This analysis would take considerable time and effort and is not within the remit of this PhD thesis, given the lack of time and resources. However, this analysis is planned to be considered in the future using the current data set. Specifically, virtually dissection of the cingulum in each of these participants (Catani et al., 2002), along with identifying specific short connections with the prefrontal cortex connecting the rDLPFC with the MFG or

the ACC (Catani et al., 2012; Anderson, Bunce and Barbas, 2015) might allow further understanding the frontal-hippocampal structural pathways. Parallel post-mortem dissections of the specific tract will allow us to confirm the findings from in-vivo studies using DTI.

The next chapter of this thesis will briefly tie together relevant discussions across the three empirical studies of this thesis and provide a general overview of the limitations, and future directions.

Acknowledgement: "Data were provided [in part] by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University."

6. Discussion

The primary aim of this thesis was to bridge the gap between the empirical findings from neuroimaging studies of suppression induced forgetting (using the Think/No-Think task, Anderson & Green, 2001) to neuropsychology, using a number of techniques: such as tDCS, DTI, and patients with unilateral frontal lesions.

6.1 General summary

As regards to the patient work, the two central ideas in this thesis were: a) to create the *patient-friendly* TNT (*pf*-TNT) task (adapted from the TNT task in Benoit & Anderson, 2012), b) To investigate whether the ability to suppress unwanted memory (using direct suppression) would be impaired in patients with right frontal lesions compared to those with left frontal lesions. Overall, this thesis concludes that the *pf*-TNT task can be administered to adults with focal-frontal lesions. At a group level, it does suggest that a majority of patients with right frontal lesions are indeed unable to supress compared to those with left frontal lesions. However, though this provides strong evidence of laterality. Future work, using voxel based lesion (VBLM) may well address the specific network within the right frontal region that may affect suppression-induced forgetting (SIF).

Based on the evidence that tDCS may be of potential benefit in patients with stroke, or those who may impaired cognitive control, another study (in healthy controls) aimed to understand if suppression-induced forgetting (SIF) is affected by cathodal-anodal or anodal-cathodal stimulation to the right DLPFC.

Anodal-cathodal or cathodal-anodal stimulation to the right DLPFC, especially in healthy participants with a high perceived thought control ability does not seem to affect inhibition. However, anodal-cathodal stimulation seems to affect facilitation. The current experiment is not robust enough to address the cause underlying the changes in facilitation, but this provides an interesting avenue for future research.

A finally study investigated the frontal-hippocampal connectivity using DTI. The proposed direct connection between the right DLPFC to the hippocampus via the caudate nucleus does not seem to correlate with the ability to inhibit (using either direct suppression or thought substitution strategies). The results from this final chapter suggests that there may be one, or more than one, indirect connection from the frontal regions of the brain to the hippocampus.

The next section will briefly revisit the three main contributions of this thesis, the general limitations, and the possible future direction.

6.2 Direct-suppression is more right lateralised

Neuroimaging work indicates that suppressing retrieval engages the right dorsolateral prefrontal cortex (DLPFC), a region critical for inhibitory control (e.g. Anderson et al., 2001; Benoit & Anderson, 2012; Depue et al., 2007; Hertel & Calcaterra, 2005; Hulbert, Henson & Anderson, 2015). Previous accounts of Think/No-Think (TNT) have proposed that a network of frontal regions (right DLPFC, Pre SMA) engage in top-down control of subcortical systems, especially the hippocampus (Anderson et al., 2004; Benoit & Anderson, 2012; Gangepain et al., 2014). A recent magnetic spectroscopy study (Anderson, Schmitz, Correia,

Ferreira & Prescott, 2016) has further supported the role of GABAergic processes supporting the fronto-hippocampal network when engaging in SIF. Neuroimaging evidence suggests that when engaging in direct suppression there is increased activation in the right DLPFC, with down regulation of activity in the hippocampus as a result of inhibition (Benoit & Anderson, 2014; Anderson et al., 2004; Gangepain, Henson, & Anderson, 2015).

Taken together these data suggest a lateral asymmetry in the neural mechanism underlying motivated forgetting. However, there has been no lesion work that has tested this possibility. Using the patient friendly TNT task, this was the first study that has aimed to address this gap in the literature, by empirically testing the role of the right hemisphere in memory suppression when using the direct-suppression method (Chapter 3 & Chapter 4).

Human lesion study has been a critical method in investigating laterality differences, and specifying the causality underlying neuro-cognitive functions (Bub, 2000; Kertesz, 1983; Rorden & Karnath, 2004). Thirty-four patients with unilateral frontal lesions (17 right lesions) completed the *pf*-TNT task. The results suggest that patients with lesions to the *left* frontal lobe *were* able to suppress unwanted memories using directly suppression. Those with *right* frontal lesions were significantly worse. This effect was found when memory was tested using both the Same and Independent probe methods.

These findings are an important conformation, using different neuroscientific method, which support the existing neuroimaging evidence (Benoit & Anderson, 2012; Bergstrom et al., 2009; Gangepain, Henson & Anderson, 2015; Depue et al., 2015).

Electrical stimulation is another method used to investigate laterality (Penolazzi, et al., 2014). Published studies investigate the role of tDCS during retrieval induced forgetting RIF, (Anderson, Bjork & Bjork, 1994) which suggests that cathodal stimulation over the rDLPFC abolishes the RIF effect, but did not affect the retrieval-induced facilitation (FAC; Anderson, Davis, Fitzgerald & Hoy, 2015). Interestingly, no one has reported a study investigating the effects of tDCS during the TNT tasks. In one experiment (Chapter 2) participants received right anodal-left cathodal, or right cathodal-left anodal stimulation to the DLPFC, before the TNT task. The results from this tDCS study suggests that RA-LC or RC-LA stimulation does not significantly impair nor facilitate the process of suppression induced forgetting.

However, the performance in the Think Condition (also what is known as the facilitation affect) was significantly worse in the RA-LC stimulation compared to the RC- LA stimulation. The study in this thesis does not directly support the laterality effect in inhibition, but suggests that RA-LC stimulation does not affect inhibition, but does impair the accuracy of the facilitation (i.e. the items that are practiced). One possible conclusion for this failure to replicate the laterality effect in inhibition (seen in retrieval induced forgetting) using tDCS could be, that some process or mechanisms may also be unique to each of these types of forgetting. This could be one possible avenue for future research.

6.3 Can direct-suppression be modulated?

A previous tDCS study using the RIF paradigm, suggests, that premorbid ability may be an important factor to consider (Anderson, Davis, Fitzgerald & Hoy, 2015). In addition, there is evidence from tDCS studies in other cognitive

domains which indicate that electrical stimulation may not be effective in participants who are above a certain threshold (Metuki, Sela & Lavidor, 2012). As discussed previously (in Chapter 2), all participants in this study had a high perceived ability of thought control (as measured by the Thought Control Ability Questionnaire, Luciano, Algarabel, Tomás, & Martínes, 2005). Higher scores indicate that participants may be better at thought suppression (Catarino, et al., 2015).

The results from the tDCS study (Chapter 2) suggests that electrical stimulation of the rDLPFC in participants with high premorbid ability of perceived control does not impair or facilitate the suppression-induced forgetting. Thereby proposing that electrical stimulation may not modulate direct-suppression, especially in participants with high perceived thought control ability. Further studies, especially in healthy participants with lower TCAQ scores, and in patients (who may have low memory suppression ability, Catarino et al., 2015; Joormann et al., 2005) is necessary to get a more complete picture of whether memory suppression can be modulated. This is the first study using stimulation in with the TNT paradigm, and clearly more studies need to replicate these findings to confirm whether electrical stimulation does or does not modulate our ability to suppress unwanted memories.

6.4 Structural connections underlying motivated forgetting?

The final contribution of this thesis was to explore the neuroanatomical structures (in-vivo) connecting the frontal regions, especially the DLPFC to the hippocampus (Chapter 5). Based on existing neuroimaging evidence (Benoit & Anderson, 2012; Anderson et al., 2015) there is a suggestion that there may be

possible structural links between the DLPFC, possibly via the anterior thalamic projections. One hypothesis is that this network may be routed through the basal ganglia, most probably from head of the caudate nucleus via the caudate tail and the globus pallidus (Anderson et al., 2016; Catani et al., 2002) to the hippocampus. Other neuroimaging data (including DTI) suggests that a subset of the well-known white matter bundles (i.e. the cingulate bundle and the uncinate fasciculus) may be critical to mnemonic control (Depue et al., 2014).

The current study identified a small number of white matter microstructures that connects the DLPFC, via the basal ganglia, to the hippocampus. The current results suggest that these specific direct tracts do not correlate with behavioural measures of inhibition. This implies that further investigations are necessary to identify the white-matter tract underlying the frontal-hippocampal pathway that is critical for memory inhibition.

6.5 Limitations

One of the main limitations of this thesis is the limited sample size, in both the lesion study (Chapter 3, N=34) and the tDCS study (Chapter 2, N= 42). Given the limited resources within the PhD setting a considerable time was spent in getting ethics approvals, and adapting the tasks for the given patient population, placed a limit on sample size. Each session with patients (Chapter 3) lasted between two and three hours. With each participant completing at least three sessions, the study was time-consuming. The **first** session included a brief clinical interview and the TNT task was always completed on the **second** visit. As part of the protocol the patient was tested in their home, which warranted additional travel time.

Previous neuroimaging studies have typical sample sizes of 18 – 24 participants (Anderson & Benoit, 2012; Anderson et al., 2004). Behavioural data was collected from 17 patient participants in each condition (total sample of 34 patients) was used in this thesis. However, not all patients had undergone MRI scans, thereby limiting the ability to perform a voxel based lesion analysis for the lesion study (Chapter 3). However, attempts are being made to acquire all the neuroimaging data before the study is prepared for a manuscript.

Another limitation, relating to ecological validity, was that a basic well-tested variant of the TNT task (i.e. word pair) was used throughout this thesis. Illustrating the stimuli with either autobiographical experiences or personally relevant pictures may have more effect, compared to using a more generalized word pair or picture list (Salas, Radovic, Turnbull, 2011). However, this would reduce the experimental control. The experimentally optimised decision was to replicate the well-established findings of the TNT task (with word pairs) in patients with focal lesions in the first instance.

Having additional studies, using a different stimulation protocol for the tDCS experiment, might produce a more robust effect. Additional experiments might warrant a sham condition, and/or other control region (e.g. left orbitofrontal region), instead of left DLPFC when stimulating the right DLPFC. Discussions with an expert in this field (Andrea Antal, personal communication, March 2015) led to suggestions of reducing the stimulation intensity, and time to get more robust results.

Finally, the current study using diffusion tensor imaging only investigated one of the three possible frontal-hippocampal connections. It is necessary to investigate all the tracts of interest in one study, using both probabilistic and

deterministic approaches. Corroborating the existence of this tract in a larger anatomical data set (e.g. human connectome project) and further replicating this tract through post-mortem tractography would be a useful approach. Multiple methods are critical, especially as these tracts support higher cognitive functions, and one cannot base it on evidence from primate studies.

6.6 Future directions

The evidence from this thesis does indeed suggest that participants with right frontal lesions are unable to supress unwanted information (using direct suppression as a strategy) compared to participants with left frontal regions. The immediate follow-up study based on this evidence would be to investigate whether participants with left frontal lesions may find it difficult to use the *thought substitution* as a strategy to inhibit unwanted memory. Combining empirical evidence from both these studies will provide evidence of laterality differences proposed by neuroimaging studies (Benoit & Anderson, 2012; Hulbert, Henson & Anderson, 2015) in patients with focal lesions.

Another proposed study would aim to investigate how failure to control unwanted thoughts in patients with focal frontal lesions may indeed impair their resilience in every-day life. This study might extend the empirical findings from the lesion study, using the TNT paradigm, to an everyday ability to regulate unwanted thoughts. Therefore, it would possibly inform the literature on whether training to inhibit unwanted memory translates to improving this ability in everyday life.

Another important issue that needs to be addressed in future is the standardization of the Think/No-think task and the RIF task. To measure

memory suppression ability in the clinical context, these tasks must be reliable over time, and one must be able to use it to predict individual differences. Both the TNT (Anderson & Green, 2001) task and the retrieval induced forgetting (RIF, Anderson, Bjork & Bjork, 1994) task were designed to study mechanisms underlying forgetting from a cognitive perspective. There are issues with the reliability of these tasks, as participants may switch strategies over time (Ben, 2016; Potts et al., 2012). Though researchers used these tasks to understand the individual differences underlying memory suppression (Levy & Anderson, 2008; Noreen & MacLeod, 2014) the task was not created for these purposes. From a clinical point of view, almost all tests focus on how memory is *impaired*. It is essential to design an ideal task measuring memory inhibition or *forgetting.* This clinical version should not only house the idea of the current TNT and/or RIF, but should take half the time to complete.

Finally, it would be interesting to investigate how memory suppression is affected in various neurodegenerative disorders (e.g. Pick's disease, Parkinson's disease (PD) or in patients diagnosed with early mild cognitive impairment (MCI) or Alzheimer's disease (AD). It would be especially useful to understand how time (and possibly other factors) facilitates or impairs the ability to selectively forget. An example of this would be to: a) to test patients within the first 6 months of having experienced a stroke, and follow them for a period of two to three years; or b) compare how inhibition of memories is effected in a group of patients with Pick's disease (frontal variant) compared to patients with lesions due to surgery or stoke (non-degenerative); or c) investigate how patients with early cognitive impairments perform on memory inhibition, and follow-up to see how many eventually are diagnosed with AD.

In a clinical setting patients often report that they try to inhibit unwanted memories, but are unable to suppress it. During debriefing, patients who were unable to engage in direct suppression often reported that they "*tried to push the memory, but it kept coming back*" - clearly suggesting that the process is somehow present, but the mechanism that underlies this process (i.e. the frontal-hippocampal pathway) may be impaired. Translating that anecdote into empirical knowledge, and perhaps encouraging patients to strategically learn or increase the use of thought substitution to inhibit unwanted memories, might not only help them carry on their lives, but actually could be considered a possible rehabilitation strategy given to patients with focal lesions.

6.7 Conclusion

The evidence from this thesis employs three different methodologies using the TNT paradigm. Findings from the lesion study (Chapter 3) highlight the necessary and selective role of the right DLPFC in enabling inhibitory control over memory and support the broader role or right-PFC in inhibitory control (Anderson et al., 2004). Results from the tDCS study (Chapter 2) suggest that electrical stimulation may not improve one's ability to inhibit unwanted memories, especially when individuals may have a high perceived thought control ability. Finally, results from the diffusion imaging study (Chapter 4) provides evidence that white matter tracts connecting the DLPFC to the hippocampus via the basal ganglia do not correlate with behavioural measures of inhibition. These results can inform applied clinical and rehabilitative work in memory inhibition, some of which have been discussed in the section on future directions (section 6.6).

In conclusion, this thesis is an example of how a cognitive experimental method can be adapted, using a range of neuropsychological approaches. It is hoped that converging evidence will help translate this research into a more practical paradigm, and possibly inform rehabilitation strategies in the future.

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8. Appendix A (Chapter 2)

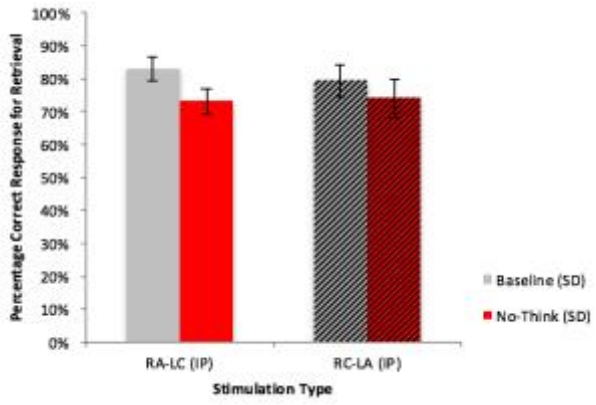

Figure 8.5. Performance on baseline and no-think conditions for both stimulation conditions (RA-LC, RC-LA) in the independent probe condition.

Table 8.3. Percentage correct response for retrieval condition (think, baseline, and n-think) across same and independent probe for pilot experiment (2.1) and the tDCS experiment (2.2).

	Same Probe			**Independent Probe**		
Conditions	Think (SD)	Baseline (SD)	No-Think (SD)	Think (SD)	Baseline (SD)	No-Think (SD)
Experiment 2.1	93.00 (9.23)	85.72 (17.23)	71.71 (25.95)	79.12 (16.97)	88.29 (10.77)	80.56 (11.71)
RA-LC (Exp. 2.2)	89.65 (9.82)	93.56 (7.45)	86.96 (12.13)	78.81 (14.62)	83.02 (12.28)	73.23(16.21)
RC-LA (Exp. 2.2)	96.65 (6.55)	90.18 (8.26)	79.15 (18.09)	82.31(16.67)	79.42 (13.68)	74.17 (19.99)

Table 8.4. Data from the post-task questionnaire

Post-task Questions	Range	RA-LC Mean (SD)	RC-LA Mean (SD)
Q1	0 to 4	4 (0.00)	3.79 (0.40)
Suppression Index **	0 to 100 %	69.44 (18.26)	69.97 (12.32)

1. For the Hint words presented in Green, how often did you try to think of the associated RESPONSE word as fast as possible?

Never		Half of the time		Always
0	1	2	3	4

** Suppression Index is calculated for each participant. In the Think/No-Think Phase each participant saw 12 words that appeared in RED (the words were counterbalanced across participants). After the experiment, participants had to specify what percentage of the trials were they completely able to prevent the response from coming to mind (see below for an example). Finally, the suppression index across all participants from each of the stimulation condition was calculated.

provided. Also, please put an X next to the words that you think you just didn't learn, and so you didn't have to try at all.

	Never able to avoid thinking about it (0%)	(25%)	Able to avoid around half of the time (50%)	(75%)	Always able to avoid thinking about it (100%)
SERVANT	0	1	2	3	4
OFFICER	0	1	2	3	4
VAULT	0	1	2	3	4
GLOW	0	1	2	3	4
NAPKIN	0	1	2	3	4
HUG	0	1	2	3	4
JOURNEY	0	1	2	3	4
DECISION	0	1	2	3	4
ANTLER	0	1	2	3	4
NEEDLE	0	1	2	3	4
HIVE	0	1	2	3	4
NAIL	0	1	2	3	4

9. Appendix B (Chapter 4)

Session 1 (Neuropsychological /Clinical Measures)	
	Clinical Interview
Cognitive Measures	Addenbrooke's Cognitive Exam (ACE) - III
Memory	Word List (WMS-III)
Verbal Fluency	Letter Fluency (FAS)
	Semantic Fluency (Animals/Fruits)
Premorbid intelligence	NART (Optional)
	Cattell (Optional)
Executive Tests (Neuropsychology)	Digit Symbol
	Stroop (from DKEFS)
	Trail Making Test (TMT) A & B
	Digit Span (Forward/Backward)
Other Measures	Design Fluency (Filler)
	DEX- Self Questionnaire
	Beck Depression Inventory- II
Session 2 (Think No-Think Task and related Questionnaire)	
Questionnaires	Emotional Regulation Questionnaire (ERQ)
	Thought Control Ability Questionnaire (TCAQ)
	Spielberg Trait Anxiety Inventory (STAI 1 & 2)
Think No-Think (TNT) Task	See below for more details
	Post Task Questionnaires
	Five Facet Mindfulness Questionnaire (FFMQ)
	Hamilton Anxiety and Depression Scale (HADS)
Session 3 (Executive Tasks, based on Miyake et al., 2001)	
Inhibition	STOP –IT (V et al.,
	Antisaccade
	Arrow-Tone Task
Switching	Number- Letter
	Plus Minus
Updating	Keep Tract
	Letter Memory
	Tone Memory

Table 9.1

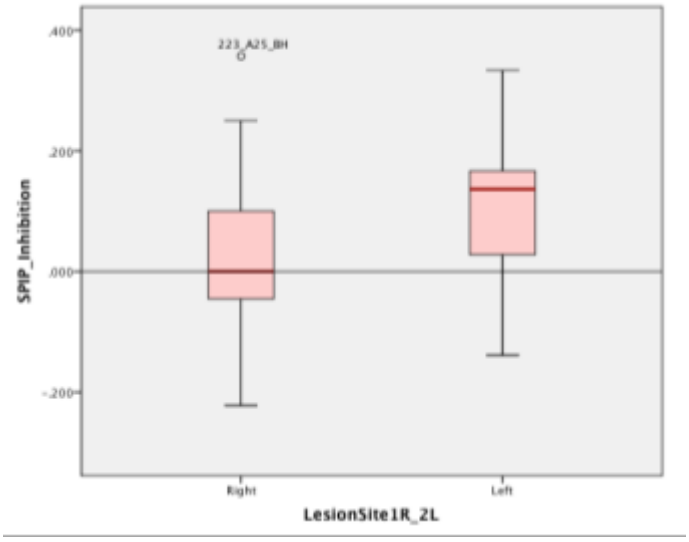

Figure 9. 1 Graph showing the facilitation effect (that is baseline – think) and inhibition effect (no-think minus baseline) in patients with Left & Right frontal lesions. Patient 223_A25 is an outlier.

10. Appendix C: Ethics Approvals etc.

Ethics Approval: BCUHB R&D and NISHR, RES, North Wales

GIG CYMRU NHS WALES | Bwrdd Iechyd Prifysgol Betsi Cadwaladr University Health Board

Panel Arolygu Mewnol Y&D
R&D Internal Review Panel

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28th October 2013

Dear Mrs Shanker

Re: Confirmation that R&D governance checks are complete / R&D approval granted

Study Title	Neuropsychology of executive function and attention: The mechanisms underlying 'motivated forgetting' in patients with focal lesions
IRAS reference	129417
REC reference	13/WA/0304

The above research project was reviewed at the meeting of the BCUHB R&D Internal Review Panel

The Committee is satisfied with the scientific validity of the project, the risk assessment, the review of the NHS cost and resource implications and all other research management issues pertaining to the revised application.

Thank you for responding to the Committee's request for further information.

Thank you for responding to the Committee's request for further information.
The R&D office considered the response on behalf of the Committee and is satisfied with the scientific validity of the project, the risk assessment, the review of the NHS cost and resource implications and all other research management issues pertaining to the revised application.

The R&D office considered the response on behalf of the Committee and is satisfied with the scientific validity of the project, the risk assessment, the review of the NHS cost and resource implications and all other research management issues pertaining to the revised application.

The Internal Review Panel is pleased to confirm that all governance checks are now complete and to grant approval to proceed at Betsi Cadwaladr University Health Board sites as described in the application.

The documents reviewed and approved are listed below:

Document:	Version	Date
R&D Form – 129417/502434/14/342	-	19/09/2013
SSI Form – 129417/502435/6/521/220956/281294	-	13/09/2013
R&D Checklist	-	-
SSI Checklist	-	-
Permissions signature sheet – Dr Elghenzai	-	17/09/2013
Protocol	1.0	29/07/2013
Study Summary	-	-
Advert - Control	1	29/07/2013
Invitation letter via Clinician	2.0	19/09/2013
Invitation letter - Pts Support Group	2.0	19/09/2013
Invitation letter – Participant panel - Control	2.0	19/09/2013

Email Invitation letter for participant panel - control	2.0	19/09/2013
Participant Information Package – Control	2.0	19/09/2013
Participant Information Package - Patient	2.0	19/09/2013
Professionals' Information Sheet	1.0	29/07/2013
Consent Form – Tracked & Clean	3.0	17/10/2013
Scanning Information & Consent Form	2.0	19/09/2013
Appointment Card	1	29/07/2013
List of the Measures	1.0	29/07/2013
Detailed measures for 3 sessions	1.0	29/07/2013
Questionnaire - Demographic Screen	2.0	19/09/2013
Questionnaire - BDI	1.0	29/07/2013
Questionnaire - STAI form	1.0	29/07/2013
Questionnaire - Hospital Anxiety & Depression Scale	1.0	29/07/2013
Questionnaire - Emotion Regulation Questionnaire	-	-
Questionnaire - TCAQ	1.0	29/07/2013
Questionnaire - Between Task questions	1.0	29/07/2013
Questionnaire - TNT Post Task Questions	1.0	29/07/2013
Questionnaire - MR Scanning form	1.0	29/07/2013
Questionnaire – ACE-R	A(2005)	-
Questionnaire - Frontal Assessment Battery - FAB	1.0	29/07/2013
Debrief form	1.0	29/07/2013
SL5 Favourable opinion with additional conditions	-	23/09/2013
SL44 Acknowledgement of documents submitted in compliance with additional conditions	-	26/09/2013
SL31 Acknowledgement of a minor amendment 13-WA-0304-AM01 (Shanker)	-	28/1/2013
UMAL Indemnity Insurance - BU	-	11/07/2013
SOP - Lone worker	1	29/07/2013
CV – CI - S Shanker	-	-
CV – Dr M Bracewell	-	-
CV – Professor O Turnbull	-	-

Please ensure that you have a valid research passport from Human Resources before commencing the field work for this study.

All research conducted at the Betsi Cadwaladr University Health Board sites must comply with the Research Governance Framework for Health and Social Care in Wales (2009).
An electronic link to this document is provided on the BCUHB R&D WebPages.
Alternatively, you may obtain a paper copy of this document via the R&D Office.

Attached you will find a set of approval conditions outlining your responsibilities during the course of this research. Failure to comply with the approval conditions will result in the withdrawal of the approval to conduct this research in the Betsi Cadwaladr University Health Board.

If your study is adopted onto the NISCHR Clinical Research Portfolio (CRP), it will be a condition of this NHS research permission, that the Chief Investigator will be required to regularly upload recruitment data onto the portfolio database.
To apply for adoption onto the NISCHR CRP, please go to:
http://www.wales.nhs.uk/sites3/page.cfm?orgid=580&pid=31979.
Once adopted, NISCHR CRP studies may be eligible for additional support through the NISCHR Clinical Research Centre. Further information can be found at:http://www.wales.nhs.uk/sites3/page.cfm?orgid=580&pid=28571 and/or from your NHS R&D office colleagues.

To upload recruitment data, please follow this link:
http://www.crncc.nihr.ac.uk/about_us/processes/portfolio/p_recruitment.
Uploading recruitment data will enable NISCHR to monitor research activity within NHS organizations, leading to NHS R&D allocations which are activity driven. Uploading of recruitment data will be monitored by your colleagues in the R&D office.
If you need any support in uploading this data, please contact wendy.scrase2@wales.nhs.uk or

sion.lewis@wales.nhs.uk

If you would like further information on any other points covered by this letter please do not hesitate to contact me.

On behalf of the Committee, may I take this opportunity to wish you every success with your research.

Kind regards

Rossele Roberts

Dr. Mike C Jackson
Associate Director of R&D
Chairman IRP-West

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Part of the research infrastructure for Wales funded by the National Institute for Social Care and Health Research, Welsh Government.
Yn rhan o seilwaith ymchwil Cymru a ariannir gan y Sefydliad Cenedlaethol ar gyfer Ymchwil Gofal Cymdeithasol ac Iechyd, Llywodraeth Cymru

NISCHR
Gwasanaeth Moeseg Ymchwil | RES | Research Ethics Service

Pwyllgor Moeseg Ymchwil Cymru 5
Wales Research Ethics Committee 5
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26 January 2015

Dear Mrs. Shanker

Study title:	**Neuropsychology of executive function and attention: The mechanisms underlying 'motivated forgetting' in patients with focal lesions.**
REC reference:	**13/WA/0304**
IRAS project ID:	**129417**

This study was given a favourable ethical opinion by the Committee on 23 September 2013.

Research Ethics Committees are required to keep a favourable opinion under review in the light of progress reports and any developments in the study. You should submit a progress report for the study 12 months after the date on which the favourable opinion was given, and then annually thereafter. Our records indicate that a progress report is overdue. It would be appreciated if you could complete and submit the report by no later than one month from the date of this letter.

Guidance on progress reports and a copy of the standard NRES progress report form is available from the Health Research Authority website.

The Health Research Authority website also provides guidance on declaring the end of the study.

If you fail to submit regular progress reports – which is a condition of the favourable ethical opinion – the REC may wish to consider suspending or terminating its opinion.

13/WA/0304 Please quote this number on all correspondence

Yours sincerely
Rossela Roberts

Dr Rossela Roberts
Research Ethics Service Manager

E-mail: rossela.roberts@wales.nhs.uk

GIG CYMRU NHS WALES | Bwrdd Iechyd Addysgu Powys | Powys Teaching Health Board

Cynhelir Cydweithrediad Gwyddor Iechyd Academaidd y Sefydliad Cenedlaethol ar gyfer Ymchwil Gofal Cymdeithasol ac Iechyd gan Fwrdd Addysgu Iechyd Powys

The National Institute for Social Care and Health Research Academic Health Science Collaboration is hosted by Powys Teaching Health Board

Ariennir gan Lywodraeth Cymru
Funded by Welsh Government

11. Appendix D: Publications and Abstracts

11.1 First Author Publications (In preparation)

Shanker, S., Turnbull, O.H., Anderson, M.C. (In preparation). Neuropsychology of motivated forgetting: Insights from patients with focal lesions.

Shanker, S., Bracewell, M., Turnbull, O.H., Anderson, M.C., & Morgan, H.M (In preparation). The role of dorsolateral prefrontal cortex (DPFC) in thought suppression: a transcranial Direct Current Stimulation (tDCS) study.

Shanker, S., Anderson, M.C., Turnbull, O.H., Bracewell, M.R., & Robert, C. (In preparation). Motivated forgetting after stroke: how an empirical model feeds into everyday living?

11.2 Co-authored Publications (Appendix E)

Turnbull, O.H., Bowman, C.H., **Shanker, S**., and Davies, J.L. (2014). Emotion-based learning: insights from the Iowa Gambling Task. *Frontiers in Psychology*, 7 (172). Doi:10.3389/fpsyg.2014.00172

11.3 First author abstracts

Shanker, S., Turnbull, O.H., Bracewell, M.R., & Anderson, M.C. The Right, but Not the Left Prefrontal Cortex is Necessary for the Suppression of Unwanted Memories. *International Conference of Memory, 2016, Budapest, Hungary.*

Shanker, S., Turnbull, O.H., & Anderson, M.C. Motivated forgetting: Insights from patients with focal lesions. *Wednesday Lunch Seminars, Michaelmas Term, November, 2014*

Shanker, S., Amritwar, A., Sharma, A. Redesigning the wheel: adapting therapy in neurological patients. *17th Neuropsychoanalysis International Congress, July 2014, New York.*

Shanker, S and Turnbull, O.H. Wishful forgetting: the cognitive mechanisms of repression. *14th Neuropsychoanalysis International Congress, August 2013, Cape Town*.

12. Emotion-based learning: Insights from the IGT (Appendix E)

Oliver H. Turnbull, Caroline H. Bowman**, Shanti Shanker**, and Julie L. Davies

A re-print of published paper is attached

frontiers in
PSYCHOLOGY

REVIEW ARTICLE
published: 21 March 2014
doi: 10.3389/fpsyg.2014.00162

Emotion-based learning: insights from the Iowa Gambling Task

Oliver H. Turnbull*, Caroline H. Bowman, Shanti Shanker and Julie L. Davies

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Interest in the cognitive and/or emotional basis of complex decision-making, and the related phenomenon of emotion-based learning, has been heavily influenced by the Iowa Gambling Task. A number of psychological variables have been investigated as potentially important in understanding emotion-based learning. This paper reviews the extent to which humans are explicitly aware of how we make such decisions; the biasing influence of pre-existing emotional labels; and the extent to which emotion-based systems are anatomically and functionally independent of episodic memory. Review of literature suggests that (i) an aspect of conscious awareness *does* appear to be readily achieved during the IGT, but as a relatively unfocused emotion-based "gut-feeling," akin to intuition; (ii) Several studies have manipulated the affective pre-loading of IGT tasks, and make it clear that such labeling has a substantial influence on performance, an experimental manipulation similar to the phenomenon of prejudice. (iii) Finally, it appears that complex emotion-based learning can remain *intact* despite profound amnesia, at least in some neurological patients, a finding with a range of potentially important clinical implications: in the management of dementia; in explaining infantile amnesia; and in understanding of the possible mechanisms of psychotherapy.

Keywords: emotion-based learning, intuition, prejudice, psychotherapy, episodic-memory

INTRODUCTION

Over the last few decades, there has been a growing interest in the cognitive and/or emotional basis of complex decision-making (e.g., Bechara et al., 1994; Damasio et al., 1996; Rogers et al., 1999; Manes et al., 2002; Turnbull et al., 2003; Bowman et al., 2005; Peatfield et al., 2012). This interest was, in large part, inspired by the well-established finding that neurological patients with lesions to ventromesial (VM) frontal lobes often showed normal intelligence, with near or near-to-normal performance on a range of "executive" tasks (e.g., Bechara et al., 2000b). However, in spite of these domains of preservation, such individuals often displayed difficulties in learning from past mistakes, with real life manifestations such as entering repeatedly into inappropriate relationships, and unsuitable business agreements. Such decisions may immediately seem rewarding, but typically prove to be counter-productive in the long run, often leading to career termination and financial losses (Damasio et al., 1991; Bechara et al., 2000a). Notably, such individuals display failures in using emotional feedback from previous situations (i.e., the punishing consequences of impulsive actions) in the guidance of their future choices.

Measuring these decision-making failures in the real-world is challenging, both ethically and methodologically. The Iowa Gambling Task (IGT) was developed as a simple neuropsychological tool to tap into such deficits in emotional-processing, which might be associated with complex decision-making difficulties, as observed in individuals with frontal lobe lesions (Rolls et al., 1994; Damasio et al., 1996; Lezak et al., 2012). In a poetic turn of phrase, patients with VM lesions were argued to have "myopia for the future" (p. 217), where their focus was on the *immediate* outcome of decisions, with an apparent indifference to the long-term consequences of their actions (Bechara et al., 1994; Bechara, 2005).

A key element of the recent complex decision-making literature has been the role of *emotion* (Bechara et al., 1994; Damasio et al., 1996; Rogers et al., 1999; Manes et al., 2002), and indeed its ability to drive emotion-based learning (EBL) during complex decision-making (Damasio et al., 1996; LeDoux, 1996, 2000; Turnbull et al., 2003, 2006). EBL systems are known to facilitate insights about the possible outcome of complex decisions, based on prior experience of the emotional consequences of actions, with particular objects and/or agents (Claparède, 1951; Johnson et al., 1985; Tranel and Damasio, 1993; Bechara et al., 1994; Damasio et al., 1996; Rogers et al., 1999; LeDoux, 2000). The role of emotion in such decision-making is supported by studies of patients with VM frontal, amygdala, and insular lesions (e.g., Bechara et al., 1997, 1999, 2003; Clark et al., 2008), as well as studies measuring skin-conductance changes (e.g., Bechara et al., 1996, 1997, 1999; see also Suzuki et al., 2003). Importantly, (see below) this class of memory (or learning) appears to be independent of the episodic memory systems of the medial temporal lobe (Claparède, 1951; Tulving and Schacter, 1990; Turnbull and Evans, 2006; Evans-Roberts and Turnbull, 2011).

THE IOWA GAMBLING TASK

The IGT (Bechara et al., 1994) has become the key experimental paradigm in evaluation of emotion-based decision-making, especially when humans are faced with emotion-mediated information, ambiguous contingencies, and uncertain consequences

(e.g., Rogers et al., 1999; Manes et al., 2002; Bowman and Turnbull, 2004; Happaney et al., 2004). The IGT has been extraordinarily influential, with Bechara et al.'s (1994) original paper having already acquired over 3000 citations on a Google Scholar search for this paper (November 2013). The spread of influence is also remarkably diverse, spanning a range of theoretical, and clinical papers in psychiatry (e.g., Cavedini et al., 2002; Evans et al., 2005; Must et al., 2006), psychology (e.g., Schmitt et al., 1999; Blair et al., 2001), neuropsychology (Turnbull and Evans, 2006; Torralva et al., 2007), and neurology (e.g., Bechara et al., 1999; North and O'Carroll, 2001; Cavedini et al., 2002; Anderson et al., 2006).

A number of psychological variables have been investigated as potentially important in understanding the nature of these EBL systems. The most prominent of these are (i) the extent to which we are explicitly aware of the basis of such decisions; (ii) the biasing influence of pre-existing emotional labels in complex decision making; and (iii) the extent to which EBL systems are anatomically and functionally independent of episodic memory systems. Each of these issues are briefly reviewed in this article.

DECISION-MAKING OUTSIDE AWARENESS

An important element in our understanding of the nature of emotion-based-learning, and the factors that drive learning on the IGT in particular, is the question of conscious awareness. The Iowa group have argued that the IGT is extremely complex in nature (Damasio, 1994, pp. 205–222), and that participants do not appear to explicitly understand the contingencies of the game (Bechara et al., 1994, 1996, 1997, 2000b). In analyzing this issue, it is important to keep in mind the definition of "awareness" used by the original Iowa group (e.g., Bechara et al., 1997) – an issue which may explain some of the emergent controversies amongst IGT researchers.

Bechara et al. (1997) explored how participants "conceptualized" the task, by which they appear to have meant the broad understanding of the contingency values on the IGT, and the types of (explicit) strategies used on the task. In their study, they asked participants (patients with VM lesions and neurologically normal controls) two questions: "(i) Tell me all know about what is going on in this game? (ii) Tell me how you feel about the game" (Bechara et al., 1997, p. 1293). In other words, they sought a definition of "awareness" which emphasized formal but also general (and, arguably, rational or cognitive) understanding, as well as broadly based feelings about the task. An initial phase of task awareness was labeled as the "*hunch*" period, where neurotypical participants experienced conscious, but poorly formed impressions about the task (Bechara et al., 1997). During this period, neurotypical participants reported "liking" or "disliking" certain decks, often guessing the general contingencies of the decks. During a later phase of the task, most neurotypicals reached a "conceptual" period – developing a better awareness of the rewarding nature of the decks. Notably, after encountering losses on specific decks, (neurotypical) participants developed pre-decision anticipatory skin conductance responses (SCRs). While, neurological patients did not generate these anticipatory SCRs, nor did they tend to enter the "*hunch*" period. In the later periods most neurological patients were unable to shift their pattern of choice away from the "bad" decks though many did develop a conceptual awareness. However, Bechara et al. (2000a, p. 301) reported some instances of the famous "knowing versus doing" dissociation, (first noted by Teuber, 1964) where "... patients "say" the right thing but "do" the wrong thing". Even more paradoxically, they reported that some neurotypical participants did *not* reach the conceptual period in that they did not describe an awareness regarding which decks were good and which were bad, *yet* they still made increasingly advantageous choices over time (Bechara et al., 1996, 1997).

In sum, they appear to suggest that conscious awareness on the task, and good performance are unrelated. The Iowa group explained the "unconscious" (unaware) nature of these decisions in terms of the somatic marker hypothesis (SMH; ; Damasio, 1989a,b, 1994; Damasio et al., 1991, pp. 205–222; Bechara et al., 2000a), where "bodily" (i.e., extra-cerebral) systems play a role in facilitating decisions (Bechara et al., 1997). This proposition has received some experimental support (Bechara et al., 2000a), but it has also attracted criticism (Tomb et al., 2002; see Dunn et al., 2006 for a review).

Further support for advantageous decision-making occurring *outside* of explicit awareness, might be argued to come from the "BLINK" task (Peatfield et al., 2012). An analog of the classic IGT, BLINK is some 25 times faster to complete than the conventional computerized IGT (Bechara et al., 1999). Here, individual decisions are presumably so rapid that little opportunity arises for conscious awareness to develop, thus meeting the criteria for "fast and frugal" decision-making (Gigerenzer, 2004). Notably, in spite of the rapid response rate on the BLINK paradigm, participants show IGT-like performance (see Peatfield et al., 2012 for a detailed discussion of BLINK).

In recent years, Bechara's claim of advantageous decision-making outside of awareness has been shaped by a series of papers which suggest that *some* forms of conscious awareness *are* available to participants on the IGT. The first of these more formal investigations was reported in Maia and McClelland's (2004) study, based on a structured questionnaire that assessed participants' knowledge of the IGT. Maia and McClelland probed the general awareness of task contingencies, without asking participants to specify the cognitive details underlying their understanding. Importantly, most participants who made advantageous choices, and thus showed preference for one or more of the decks, also demonstrated conscious feelings about the decks. Indeed, by the end of Block 1 (i.e., 20 card selections made) participants were able to report basic affective properties of decks, and by 50 card selections, the majority of participants could correctly report "good" decks. Such understanding would readily correspond to participants' decision preference (see Maia and McClelland, 2004).

Their results suggested that when behaving advantageously, participants not only had access to some explicit knowledge about the "goodness" or "badness" of the deck, but also had reportable knowledge that was well placed to facilitate choice (Maia and McClelland, 2004, p. 16078). Maia and McClelland (2004) therefore claimed that participants playing the IGT *did* have access to explicit awareness about the contingencies of the game. They argued that this resulted from the self-paced nature of the task, which allowed ample time for deliberative reasoning, and also that the outcomes of choices were presented

in a clear numerical form, which aided explicit tracking and learning of the incentive nature of each deck (at least to *some* degree – though see Peatfield et al., 2012 above). Thus, Maia and McClelland (2004) posited a degree conscious awareness of the task in participants, albeit of a different form of awareness to that proposed by Bechara et al. (1997). Indeed, this difference was captured by asking participants probing questions about the task, rather than by assessing notoriously difficult-to-verbalize and general feeling. Therefore, Maia and McClelland's (2004) quantitative method successfully examined explicit awareness, but failed to tap affectively mediated *qualitative* knowledge (feelings) about the game that may indeed facilitate favorable choices. Importantly, Maia and McClelland (2004) suggests multiple source of information might possibly guide the choice during complex-decisions.

Further, empirical support on the question of awareness, comes from the work of Bowman et al. (2005). In this study, participants quantitatively rated the "goodness/badness" of each deck after each twenty-card block. Bowman et al.'s (2005) data suggested that participants could explicitly report affective evaluation (i.e., the relative goodness/badness) of the task objects, even during the "pre-hunch" phase (Bechara et al., 1997). In fact, participants showed obvious awareness of the "valence" of the decks, even following the *first* 20 trials of the task. Other studies (e.g., Evans et al., 2004; Cella et al., 2007) using the same method of tracking task subjective awareness, confirm these original findings, and indeed extend them to a psychiatric population (Evans et al., 2005). However, Turnbull et al. (2007) confirmed, in neurotypicals, that dissociations do occur between explicit deck ratings and behavioral choices on the IGT – suggesting that participants can and do actively ignore explicit knowledge regarding the incentive values of their choices, in favor of implicit emotion-mediated knowledge, especially in situations where varying sources of information come into conflict.

Thus, it appears that explicit (emotion-mediated)-knowledge of incentive values of choice is available *much* earlier than originally claimed by Bechara et al. (1997). This form of awareness is also a type substantially different in quality to that encountered during explicit cognitive approaches to decision making (Gilhooly and Murphy, 2005). The descriptions of these decisions emphasize the fact that the non-cognitive choices are, in contrast, poorly formed ("a hunch") and laden with affect ("a gut feeling"). It is perhaps this knowledge that subserves the phenomenon that has been long described as "*intuition*" (see also Kahneman and Tversky, 1973; Stanovich and West, 2000; Kahneman, 2003; Turnbull et al., 2003, 2005).

INTUITION?

We are therefore faced with an interesting, and under-investigated, phenomenon, whereby humans are aided in navigating complex and uncertain problem-spaces, via the awareness of emotion-based signals – presumably derived from prior experience of objects and/or agents. (Kahneman et al., 1982; see Kahneman, 2003) have long described the properties of such *intuitive* responses as being fast, rapid, explicit, effortless, and emotionally laden. Stanovich and West (2000) have proposed a similar dichotomy (e.g., Hogarth, 2001; Myers, 2002). Both seek to discriminate between systems underpinning "intuition" versus "reasoning" (Kahneman, 2003). One approach (intuition; or System 1) generates an overall and apparently imprecise general impression of objects or situations, through an involuntary process sometimes described as *natural assessment* (Tversky and Kahneman, 1983). This phenomenon emerges without intention or effort, and could not (they argued) be verbalized explicitly. In contrast, the reasoning pathway (System 2) is involved when more formal *judgements* are made, even if these are not overtly expressed (Kahneman, 2003; for more on this in relation to the IGT see Bechara, 2005; Cella et al., 2007; Stocco et al., 2009). However, such reason-based decisions were always intentional and explicit.

"*Intuitive*" is therefore a label which appears to capture a decision process reflecting imprecise and emotion-based impressions. We have argued that such EBL systems may pre-empt or guide reason-based choice, when faced with settings involving combinations of a complex problem space; high levels of uncertainty and ambiguity; and laden or infused with affect. Interestingly, this literature potentially links to emotion-based systems of the sort found in psychiatric disorders (Evans et al., 2005), or neurological disorders of emotion regulation (Fotopoulou et al., 2004) – where both groups show impaired understanding in the form of delusional beliefs. These affectively laden biases may perhaps appear without conscious awareness, and lack explicit understanding, even when producing successful outcomes (Damasio, 1994, pp. 187–189; Turnbull et al., 2007).

In sum, one *form* of conscious awareness *does* appear to be readily achieved during the IGT, but this is in the sense of an emotion-based impression: "How much do I like this object?" (Bowman et al., 2005; Evans et al., 2005), though this may also explain why Bechara et al. (1997) report that optimal IGT decision-making operates outside of formal *cognitive* scrutiny.

PRE-EXISTING AFFECTIVE BIAS ON THE IGT

The IGT is usually regarded as a good simulation of the complexity of real-world decision-making, given that it involves exploratory decisions under both risk *and* ambiguity (e.g., Brand et al., 2007), with shifting contingencies over time. Although other tasks may provide a better psychological dissection of the decision-making processes (e.g., Fellows, 2004; Dunn et al., 2006, 2010; Brand et al., 2007), the IGT is typically regarded as affording an ecologically rich and complex problem space (Damasio et al., 1991; Bechara et al., 1994). Of particular interest is the "balance," or trade-off, between cognition and affect, as a measure of adaptive task performance (e.g., Manes et al., 2002; Fellows and Farah, 2005; Dunn et al., 2006, 2010; Cassotti et al., 2011). For instance, affective states appear to especially underpin adaptive decisions in the early "opaque" and ambiguous period of the IGT, with the latter phase of the task (as discussed above) more readily informed by conscious awareness of the incentive properties (e.g., Maia and McClelland, 2004; Bowman et al., 2005; Dunn et al., 2006; Brand et al., 2007; Wagar and Dixon, 2007; Stocco and Fum, 2008).

What then of the fact that humans are often biased or predisposed – toward objects, even before they first encounter them? And how does this bias shift over time? Notably, the IGT involves an intrinsic affective *shift,* where initially learned

associations require reversal for adaptive behavior on the task (Fellows and Farah, 2005). In many ways, such pre-existing affective biases might be regarded as the psychological foundation of prejudice – for example where humans express a pre-existing negative evaluation, in the absence of knowledge of the object's intrinsic properties (e.g., Allport, 1954/1979). Overcoming such biases clearly requires reversal of an affectively laden association. Notably, such social biases are understood to be both common and well-established, with the potential to linger outside full awareness (Devine, 1989; Amodio et al., 2003; Gregg et al., 2006). Indeed, the notion that most objects rapidly and automatically evoke affective states is now well-established (e.g., Zajonc, 1980; LeDoux, 1996; Ito and Urland, 2003; Cunningham et al., 2004). Therefore, an ecologically valid *starting* point for the IGT would be a set of objects which are affectively laden, rather than neutral.

A relevant distinction, and one often stressed by the social cognition literature, is that affect can be sourced from an evaluation of the features of the target itself (*integral affect*), or influenced by the background mood state or another unrelated source (*incidental affect*, Pham et al., 2001; Mussweiler and Bodenhausen, 2002; Finucane et al., 2003). Thus, integral affect may result from actual, perceived, or even imaginary characteristics of the decision targets – i.e., with a focus or the object itself. In contrast, incidental affect is sourced from temporary mood states, trait affective states (e.g., anxiety), or transferred from other diffuse sources distinct from the target object (e.g., Cohen et al., 2008).

How might these sources of affect influence complex decision-making? It is likely they are incorporated into an online affective state, which is readily placed to infuse and bias choices (Damasio, 1994; Finucane et al., 2003; Cohen et al., 2008). Here, the literature is patchy in its coverage. The influence of "incidental" affect on judgment and decision-making has been well-studied, suggesting that there are gains in the flexibility and openness of problem-solving in positive mood states (e.g., Isen, 2001), and risk-aversion in states of anxiety (e.g., Raghunathan and Pham, 1999). Indeed, *incidental* affect appears to have important impacts on IGT performance (Schmitt et al., 1999; Carter and Smith-Pasqualini, 2004; Suhr and Tsandis, 2007). However, the primacy (e.g., Zajonc, 1980; LeDoux, 1996) and importance of *integral* (object biased) affect for judgement and decision-making has been less well-investigated (Pham et al., 2001; Finucane et al., 2003). Surprisingly, only a few studies (Hinson et al., 2006; Davies and Turnbull, 2011; Aïte et al., 2013) have assessed integral affective bias in decision-making paradigms like the IGT – although questions of this sort are highly relevant for human social decision-making (e.g., Bechara et al., 1994).

Notably, real-world social behavior involves encountering agents and objects that develop, and ultimately come to *possess*, ambiguous and ambivalent characteristics (e.g., Cacioppo and Berntson, 1994; Cunningham et al., 2003). Thus, an appraisal of a well-known individual (e.g., Tony Blair, Barack Obama, Lance Armstrong, Edward Snowden) may well evoke both negative and positive evaluations, potentially resulting in a net-weighted (heuristic-based) attitude (e.g., Van Harreveld et al., 2004). Ecologically rich paradigms such as the IGT have only recently been employed to examine the impact of affective biases in complex and dynamic decision-making (Hinson et al., 2006; Davies and Turnbull, 2011; Aïte et al., 2013). The following section presents an overview of this research.

INSIGHTS FROM TASKS INVOLVING AFFECTIVE BIAS

Given the proposed primacy of emotion-based processes (Bechara et al., 1994, 1997), it is perhaps surprising that only three studies have examined affective bias within IGT-style decision-making. While each study uses different variants of the IGT, and a range of affective biases, the data are broadly consistent – demonstrating that pre-existing bias readily impacts complex decision-making (Hinson et al., 2006; Davies and Turnbull, 2011; Aïte et al., 2013).

Using a three-deck variant of the IGT, Hinson et al. (2006) invoked affective bias, by associating task decks with emotional words, which varied according to deck incentives. In the incongruent condition, the "good" deck was labeled with negative words, and "bad" deck labeled with positive words (with the associations reversed for the congruent condition). Additionally, a third "neutral" deck was labeled with emotionally neutral words. As one might predict, incongruent affective bias impaired performance, while congruent bias enhanced decision-making. Thus, the use of stable emotional landmarks from the outset of the task readily biased IGT-style decision-making.

The SCR data collected during the experiments (Hinson et al., 2006) were used to examine the development of discriminating anticipatory SCRs. Incongruent affective bias was found to hinder the development of these physiological markers – with little discrimination in differential SCRs across the three decks. However, in the congruent condition, these anticipatory markers appeared to selectively distinguish between bad deck choices from both good and neutral options. These responses are often viewed as an index of decision biasing "somatic markers" (Bechara et al., 1997). However, in this study the somatic signals produced no causal influence on decision behavior, merely acting as one index of adaptive decision-making (Hinson et al., 2006).

Building on these findings, Davies and Turnbull (2011) investigated features of the classic Gambling Task potentially influenced by affective bias – expanding the topic to include features such as sensitivity to punishment cues (Dalgleish et al., 2004), and the dynamic tracking and weighting of overall deck attitudes (e.g., Van Harreveld et al., 2004; Bowman et al., 2005) that were not explored in the Hinson et al. (2006) experiments. The Davies and Turnbull (2011) tasks introduced affective bias using visual stimuli that were either non-social (International Affective Picture System; Lang et al., 2001) or more socially salient, in the form of racially diverse faces (Tottenham et al., 2009). To control for individual variation, the stimuli were also customized for each participant, by pre-evaluation. As in the Hinson et al. (2006) studies, there was a growing preference for selections from the advantageous decks. Importantly, affective bias altered selection in both congruent and incongruent conditions; especially both experiments demonstrated that affective labels impaired selection behavior specifically under *incongruent* conditions. Additionally, the study (experiment 2) also showed a clear influence of affective bias on *subjective* ratings of task objects over the task.

This sparks the question of *how* such decision-making is changed. Congruency did not influence shifts from the frequently punishing decks, nor did it alter preferences for decks with lower loss frequency. Also, decoupling subjective evaluation data to absolute deck ratings showed that weighting of deck attitudes were unaltered by the congruency manipulation. However, incongruent association *selectively* modulated evaluation of the disadvantageous decks. Indeed, consolidating the importance of awareness of the affective nature of the punishing bad decks, subjective awareness of their incentive nature was strongly associated with adaptive task performance (cf. Maia and McClelland, 2004; Bowman et al., 2005). Such dissociation between deck ratings suggests that deck attitudes in general were not influenced by affective bias. Instead it appears that sensitivity to *accumulating* losses is a major driving force in IGT decision-making (Christakou et al., 2009; Weller et al., 2007, 2010; cf. Dunn et al., 2010).

PRE VERSUS POST-DECISIONS

Both of the above studies (i.e., Hinson et al., 2006; Davies and Turnbull, 2011) introduced affective bias at the *decision* level. In contrast, a recent study (Aïte et al., 2013) suggests that placing affective stimuli during the *post-decision* (feedback stage) phase of decision-making also affects performance on IGT. Here, the ability to make an advantageous choice increases when the emotional context is congruent with the feedback, while this is impaired in an incongruent condition. Indeed, facial emotion appears to carry intrinsic incentive value (Shore and Heerey, 2011); therefore presenting bias during the feedback phase should modulate the net decision feedback. For example, providing a reward of $10 with a smile would provide more positive reinforcement than the same reward with a fearful face.

The findings of Aïte et al. (2013) are thus consistent with affective bias influencing the decision process via a range of plausible pathways and mechanisms – both affective and cognitive (e.g., Hinson et al., 2002, 2006; Dunn et al., 2006, 2010). Incongruent affective bias again leads to a robust impact on IGT decision-making (cf. Hinson et al., 2006; Davies and Turnbull, 2011). This would be consistent with the observations made by Davies and Turnbull (2011), and further imply that affective bias within IGT variants disrupts adaptive shifting of decision behavior in the face of changing contingencies (i.e., reversal learning).

A notable inference derived from this study surrounds the use of additional supporting feedback the IGT (and other decision-making paradigms) often present additional feedback with affective value (e.g., smiley faces). Such feedback probably *consolidates* reinforcement of primary incentive feedback, potentially complicating task interpretation (Shore and Heerey, 2011). However, as highlighted by Aïte et al. (2013), the use of such feedback may be unhelpful methodologically, and should therefore be discouraged in IGT experiments.

In sum, a modest number of studies have manipulated the affective loading of IGT tasks – with positive and negative biases, and pre or post-decision influences. All make it clear that affective labeling has a substantial affect on performance, biasing outcome in the direction of the emotion-based influence. Psychophysiological data showed that anticipatory SCRs did not appear to be an important (or necessary) indicator of good decisions. Finally, the awareness of accumulating loss was found to be critical for adaptive task performance (cf. loss aversion; Weller et al., 2007, 2010). In demonstrating these effects, the studies show a useful analogy for the biases of prejudice in everyday decision-making, while demonstrating the flexibility of the IGT as a research tool.

DISSOCIATING EPISODIC MEMORY AND EMOTION-BASED LEARNING

The remarkably rich literature on the IGT has been a central source of evidence for the role of the frontal lobes in EBL (e.g., Bechara et al., 1994, 1997; Rogers et al., 1999; Bowman and Turnbull, 2004). Indeed, Bechara et al. (1997) original paper especially emphasized the role of ventromedial pre-frontal cortex (VMPFC). A later set of studies narrowed the focus, to investigate which specific frontal regions (right or left, dorsal or lateral, or ventral or medial) played the most significant role in EBL (e.g., Rogers et al., 1999; Duncan and Owen, 2000; see Manes et al., 2002; for a detailed discussion).

However, this focus on the frontal lobes, and thus on executive functions, has potentially ignored the role of other brain areas, and indeed other classes of psychological ability. An especially interesting question is the relationship between EBL and episodic memory. In this section of the paper, we will present evidence from lesion (e.g., Damasio et al., 1996; Bechara et al., 1998; Turnbull and Evans, 2006) and neuroimaging studies (e.g., Patterson et al., 2002; Fukui et al., 2005), to understand the relationship between these key psychological systems.

EMOTION-BASED LEARNING AND EPISODIC MEMORY

The neurobiology of EBL is far less well understood than that mediating episodic memory. However, an introductory survey of likely brain regions might include a full range of subcortical emotion systems (e.g., Panksepp, 1986, 1998; Davidson and Irwin, 1999; LeDoux, 2000; Rolls, 2000; Calder et al., 2001; Phan et al., 2002; Bechara et al., 2003; Berridge, 2003; Patterson and Schmidt, 2003; Adolphs et al., 2005), as well as the connection between these systems and pre-frontal cortex, in many cases through the VM frontal lobes (Davidson and Irwin, 1999; Bechara et al., 2000a; Bechara, 2004; Anderson et al., 2006).

Consistent with this, studies also suggest that certain emotional-learning processes clearly involve medial prefrontal cortex (e.g., Lane et al., 1997; Reiman et al., 1997). A meta-analysis of neuroimaging studies, for example, suggest that medial prefrontal cortex is involved in emotion-based tasks, while the anterior cingulate and insula are involved when tasks have both emotional and cognitive load (see Phan et al., 2002).

However, lesion-study and imaging findings have suggested that *episodic* memory systems (Tulving, 1972, 1983) particularly include the medial *temporal* lobes and associated structures (e.g., Zola-Morgan et al., 1986; McDonald and White, 1993; Schacter et al., 1995; Nyberg et al., 1996; Schacter et al., 1996; Rugg et al., 1997; Clark and Squire, 1998). In principle, if EBL and episodic memory systems are anatomically independent (Tranel and Damasio, 1993) it should be possible to disrupt one system and leave the other intact.

Evidence of such intact EBL has long been reported, notably in a classic patient with amnesia (Claparède, 1951). In this well-known

report, Claparède concealed a pin in his palm, before shaking the hand of an amnesic patient. On the day following this painful episode, the patient refused to shake the physician's hand, despite having no conscious recollection of the incident (Claparède, 1951; for review see Eichenbaum and Cohen, 2001). Modern and systematic evidence for the claim comes from the work on the profoundly amnesic patient, Boswell (Tranel and Damasio, 1990, 1993; Feinstein et al., 2010). In the experiment (Tranel and Damasio, 1993), Boswell engaged in inter-personal encounters with stooges who played a "good," "neutral," or "bad" character in their interactions. After a week, Boswell was shown sets of photographs that included the face of one of the individuals, and an unfamiliar face, and was asked to "Pick the person you would like best?" (p. 83). Naturally, Boswell had no explicit memory of any of the individuals (tested with a free or cued recall). However, when asked to make a forced-choice response, Boswell chose the "good" character almost 80% of the time, and virtually never chose the bad character (Tranel and Damasio, 1993).

What of *complex* learning tasks that also have a reward-based element? Interestingly, some studies have reported relatively normal performance by amnesic patients on the Wisconsin Card Sorting Test (WCST; e.g., Leng and Parkin, 1988; Shoqeirat et al., 1990), and the probabilistic "Weather Prediction" Task (WPT; Knowlton et al., 1994, 1996). A plausible hypothesis is that these tasks also have an emotion-based preference – given that the experimenter provides "correct" or "incorrect" feedback after each trial.

COMPLEX EMOTION-BASED LEARNING

Empirical evidence from such studies (see also Johnson et al., 1985; Tranel and Damasio, 1989, 1990, 1993) thus suggests that capacity to learn *complex* emotional valence may be retained in profoundly amnesic patients. However, many of reports of the sort described above relate to relatively *simple* patterns of emotional valence learning (uniformly good versus uniformly bad, e.g., Tranel and Damasio, 1993; Feinstein et al., 2010), rather than the more sophisticated patterns of valence which characterize everyday life (e.g., Barraclough et al., 2004). As noted earlier, it is precisely this complicated pattern of reward and punishment that the IGT was designed to assess (Bechara et al., 2000a).

In this context, Turnbull and Evans (2006) measured the IGT performance of a profoundly amnesic patient (SL) who had suffered a posterior cerebral artery stroke, producing profound amnesia. On the IGT, SL performed at a comparable level to controls, across a 3-week period, where each week his performance was no different to (or in one case much better), than controls. This learning was also seen despite the fact that the reward-contingency pattern was shifted between sessions (c.f. Fellows and Farah, 2003), and that SL was unable to explicitly recall any aspect of the previous sessions, or recognize the examiner – evidence suggesting that EBL was preserved.

Thus, complex EBL can remain intact despite profound amnesia – though this effect is not universal. Turnbull and Evans (2006) patient may have been a relatively rare example of such a powerful dissociation. Gutbrod et al. (2006) report patients with lesions to the basal forebrain ($N = 5$) or medial temporal lobe ($N = 6$) who performed the IGT. Here two patients *did* develop a behavioral preference, though the other nine patients performance remained at chance. In a further study, Gupta et al. (2009) investigated five patients who had bilateral hippocampal damage, and reported that no patients developed a preference for advantageous over disadvantageous choice.

Further evidence of preserved implicit EBL has been reported in patients with Alzheimer's disease (AD), another pathology targeting the medial temporal lobe (e.g., Winograd et al., 1999; Blessing et al., 2006). For example, Evans-Roberts and Turnbull (2011) investigated EBL using the IGT in a patient with dementia of the Alzheimer's type – who had profound impairment of both verbal and visual recent episodic memory, and completed the Gambling task over three weeks (as in Turnbull and Evans, 2006). Mr. A again performed consistently above chance, an effect which seems unlikely to be a result if the more "liberal" response bias of Alzheimer's patients (Budson et al., 2006).

An interesting related finding was the remarkably good performance, in SL's recognition of paired-associate items (Turnbull and Evans, 2006). He had comprehensively failed to bring even a single one of these pairs to conscious recall on any his 40 previous exposures to the pairs, but nevertheless appeared to have encoded at least some aspect of a memorial linkage between them. One explanation might be that he had stored some emotional marker associated with each pair ("rose–bag," good; "elephant–glass," bad). Another possibility might be that the previously tested items had acquired some positive emotional valence through the "mere-exposure" effect (Zajonc, 1980; see Turnbull and Evans, 2006 for detailed report of SL).

These data support the growing evidence that there are multiple memory systems in the brain, especially supporting an anatomical and functional dissociation between episodic (e.g., Schacter and Tulving, 1994; Schacter et al., 2000) and emotion-based memory (Tranel and Damasio, 1993; Damasio, 1994; Panksepp, 1998; see Eichenbaum and Cohen, 2001; Phan et al., 2002 for reviews). These findings are consistent with performance of amnestic patients in other non-declarative memory and learning system (e.g., motor learning). The evidence clearly suggests that EBL systems appear to encode more sophisticated patterns of valence learning than have previously been reported, and sustain these over substantial periods of time, especially in patients with "hippocampal" amnesia (Turnbull and Evans, 2006).

CLINICAL IMPLICATIONS

These findings have a range of potentially important clinical implications. For example the Evans-Roberts and Turnbull (2011) study on preserved EBL in dementia clearly supports claims from the "person-centered" literature (e.g., Kitwood, 1997; Sabat and Collins, 1999) – that in spite of progressive memory loss (Blessing et al., 2006) patients with AD are able to learn and retain emotion-based knowledge. Unfortunately, the behavior of many of those who care for patients with AD is less than optimal (Sabat and Collins, 1999). Such carers may hold the opinion that they can perhaps speak critically of such patients, because they will inevitably forget the experience. The systematic findings reported above suggest that patients with AD may retain emotion-based memories, which may have direct impact on interpersonal relationships with

patients with memory loss, both in a personal and therapeutic context.

In addition, the finding of preserved emotional learning in the face of profound amnesia is of some interest in the context of infantile amnesia. It is well established that humans have poor, or non-existent, episodic memory for the first few years of life (Freud, 1905; Dudycha and Dudycha, 1941; Sheingold and Tenney, 1982 for review see Pillemer and White, 1989). Indeed, there is some consensus that the earliest adult autobiographical memories are for events that occurred between 2.5 and 4 years of age (Waldfogel, 1948; Wetzler and Sweeney, 1986; Bruce et al., 2000; MacDonald et al., 2000).

Some researchers posit that language development plays a crucial causal role in such childhood amnesia (Allport, 1937; Schachtel, 1947; Simcock and Hayne, 2002; see also Hayne, 2004 for a review). While, modern neuroscientific accounts of the phenomenon stress especially the late development of hippocampal (conscious) memory systems (for further discussion, see Yovell, 2000; see also Jacobs and Nadel, 1985; Turnbull and Evans, 2006). However, surely these children are learning from this period of early childhood? It is now clear that infants *do* process a well-developed capacity for learning of *emotional* valence in relation to objects, for example, the quality of attachment relationships with specific adults (Winnicott, 1960; Bowlby, 1969; Ainsworth et al., 1978; Ainsworth, 1985; Fonagy et al., 1991a,b). The empirical evidence from childhood amnesia studies suggests EBL systems might be available to infants possibly much before the hippocampus-based systems develop.

Interestingly, this issue may also be important for our understanding of the mechanisms of psychotherapy. It has been suggested that aspects of the therapeutic alliance might (for example) be mediated by emotion-based non-episodic memory systems (Turnbull et al., 2006). In principle, this topic could be investigated through the study of neurological patients with amnesia in a psychotherapeutic setting (Turnbull et al., 2006). In a report of a patient with severe and stable amnesia, Mr. N (see Kaplan, 1994, pp. 590–624 for details), there is at least some evidence that the patient shows therapeutic gains from the interaction with the therapist (Turnbull et al., 2006). Moore et al. (2012) report a similar finding. These preliminary data suggest that during psychotherapy the interpersonal properties of the therapeutic relationship may still exist in patients with profound amnesia, suggesting that the therapeutic alliance may be mediated by a class of memory system that is separate to that of episodic recall.

CONCLUSION

Summarizing the literature over the last two decades, it is evident that EBL, in the face of a complex ambiguous decision-making landscape, is an important psychological process that occurs rapidly, and is remarkably flexible. This specific form of learning contributes to the scientific understanding of psychological phenomena such as intuition, prejudice that were long ignored, and often difficult to define functionally.

For much of its history, psychological science focused on rational choice, rather that the less well-specified and emotion-based intuitive aspects of human choice (Gilhooly and Murphy, 2005). These later systems are clearly enormously important for human beings, and this paper has reviewed our growing understanding of range of important issues: the flexibility of theses systems, their access to conscious awareness, their relationship to episodic memory, their role in prejudice, and a number of potentially important implications for psychotherapy and care of the elderly. However, this strand of research is clearly still only in the early stages of development, and we anticipate a range of future discoveries on this scientifically important topic.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 20 December 2013; accepted: 10 February 2014; published online: 21 March 2014.

Citation: Turnbull OH, Bowman CH, Shanker S and Davies JL (2014) Emotion-based learning: insights from the Iowa Gambling Task. Front. Psychol. ***5****:162. doi: 10.3389/fpsyg.2014.00162*

This article was submitted to Decision Neuroscience, a section of the journal Frontiers in Psychology.