Salience Network and Default Mode Network dysfunction after traumatic brain injury

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Statement of Publications

The results from chapters 3 and 4 have been published in:

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Statement of originality

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Abstract

It is now widely accepted that cognitive control depends on the integrated operation of large-scale distributed brain networks. Recent methodological advances allow both structural and functional connectivity (FC) within these networks to be studied non-invasively *in vivo.* These approaches hold the promise of dramatically extending our understanding of the impact of traumatic brain injury (TBI) on cognitive control, which has the potential to help determine strategic targets for the rehabilitation of individuals with TBI.

In the current thesis, structural and functional magnetic resonance imaging is combined to test the general hypothesis that *cognitive deficits after TBI arise from functional disconnection within brain networks that mediate cognitive functions.* Of particular interest are the interactions between two brain networks known as the Salience Network (SN) and the Default Mode Network (DMN). These networks are thought to be important for cognitive control however, how these networks interact during cognitive control is limited.

This thesis largely investigates the effect of TBI on network interactions that accompany changing motor control. Functional MRI of the Stop Signal Task (SST) is initially used to study response inhibition. In healthy subjects, FC between the right anterior insula (rAI), a key node of the SN, and the DMN transiently increased during stopping. This change in FC was not seen in a group of TBI patients with impaired cognitive control. Furthermore, the amount of damage to the underlying white matter tract negatively correlated with the strength of FC between the networks.

These findings are confirmed in a second group of TBI patients. In the second group,

switching rather than inhibiting a motor response: (1) was accompanied by a similar increase in network FC in healthy controls; (2) was not seen in TBI patients; and (3) tract damage after TBI again correlated with FC breakdown. I also replicate this pattern of structure-function in a group of elderly participants who demonstrate similar cognitive control impairments as the TBI group.

The findings show that FC between the rAI and DMN increases with cognitive control, and that the ability to efficiently regulate the FC between the rAI and DMN can be predicted by the structural integrity within a remote brain network previously proposed to be involved in switching between internally and externally directed attention. This work provides evidence for a model of cognitive control where the SN is involved in the attentional capture of salient external stimuli and signals the DMN to reduce its activity when attention is externally focused. It also identifies DMN dysfunction as underlying various cognitive deficits after TBI, and confirms the relevance of white matter damage in the development of brain dysfunctions after TBI.

List of abbreviations

BOLD   blood oxygenated level dependent

dACC   dorsal anterior cingulate cortex

DAI   diffuse axonal injury

DMN   Default Mode Network

DTI   diffusion tensor imaging

EV   explanatory variable

FA   fractional anisotropy

FC   functional connectivity

fMRI   functional magnetic resonance imaging

GLM   general linear model

PCC   posterior cingulate cortex

PPI   psychophysiological interaction

preSMA   pre-supplementary motor area

rAI   right anterior insula

rIFG   right inferior frontal gyrus

ROI   region of interest

RT   reaction time

SN   Salience Network

SSD   stop signal delay

SST   stop signal task

SSRT   stop signal reaction time

StC   correct stop trial

SwC   correct switch trial

TBI   traumatic brain injury

TBSS   tract-based spatial statistic

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Table of participants

Group	Functional imaging paradigm	Number of participants (n)	Mean age in years (± SD)	Used in which chapters
TBI Group 1	Stop Signal Task	57	36.7 ± 11.5	3
TBI Group 2	Motor switch and cognitive switch Paradigms	30	37 ± 11.9	4, 6
Control Group 1	Stop Signal Task	25	34.2 ± 9.6	3
Control Group 2	Motor switch and cognitive switch Paradigms	20	28.5 ± 8.7	4, 6
Old	Stop Signal Task	29	69.5 ± 4.6	5
Young	Stop Signal Task	33	28 ± 3.7	5
Control Neuropsychology	NA	26	35.4 ± 11.1	3, 4, 6
Control DTI	NA	30	37.2 ± 8.9	3, 4, 6

1. Introduction

1.1 A general introduction to traumatic brain injury

1.1.1 Definition

Traumatic brain injury (TBI) is widely recognised as an affliction of humankind (Aron et al., 2003; Floden and Stuss, 2006; Li et al., 2006; Granacher, 2007). It can be defined as an "*alteration in brain function, or other evidence of brain pathology, caused by an external force*" (Dove et al., 2000; Monsell, 2003; Hampshire and Owen, 2006; Menon et al., 2010). To break this definition down; an "alteration *of brain function*" refers to clinical signs such as loss of consciousness, loss of memory or alteration in mental state at the time of the injury. "*Other evidence of brain pathology*" can include visual, neuroradiological, or laboratory confirmation of brain damage. An "*external force*" that can cause a TBI include events where the head is struck by an object or the head strikes an object, sudden acceleration/deceleration movement of the head or a foreign body penetrating the head (Simon, 1969; Simon and Small, 1969; Menon et al., 2010) or from a blast (MacDonald et al., 2011; Baxter et al., 2013).

1.1.2 Epidemiology

According to the World Health Organization, TBI is one of the major causes of death and disability among people under the age of 40. An estimated 10 million people worldwide experience a TBI every year (Mesulam and Mufson, 1982; Mufson and Mesulam, 1982; Hyder et al., 2007), with around 235 per 100,000 individuals affected each year in Europe. This accounts for approximately one million hospitalizations (Craig, 2002; 2003; Tagliaferri et al., 2006). TBI affects approximately 1.6 million people annually in the United States (US), accounting for 52,000 deaths and 80,000

patients suffering from permanent neurological impairment (Sosin et al., 1996; Ullsperger and Cramon, 2001; Ham et al., 2013b). The highest incidence of TBI is among individuals aged between 15 and 24 (Thurmann et al., 1998; Holroyd et al., 2004; Ridderinkhof et al., 2004), with a second peak in adults over 75. Children aged 5 or younger are also more at risk (Vogt, 1993; Langlois et al., 2006; Vogt, 2009a). In the United Kingdom (UK), 30% of the 115,000 estimated people suffering a TBI per year are less than 15 years old (Thornhill et al., 2000; Vincent et al., 2006; Margulies et al., 2009; Leech et al., 2012a). Overall, males are approximately twice as likely as females to sustain a TBI (CDC, 2001), which is perhaps due to males engaging in risk-taking behaviour more often.

1.1.3 Causes

In the UK, falls (22-43%) and violence/assaults (20-50%) are the most common cause of TBI, followed by road traffic accidents (RTAs) (~ 25%) (NCCAC, 2007). The rates of fall-related TBI are highest among children and adults over 75, with the rate of both RTA and assault highest among adolescents (CDC, 2004; Fox et al., 2005; Rutland-Brown et al., 2006; Leech et al., 2011). RTAs include accidents involving motor vehicles, bicycles and pedestrians and account for a greater proportion of the more severe cases of TBI. Death and disability resulting from RTAs are likely to become a more common occurrence due to the increase in motor vehicle accidents associated with economic growth in low and middle income countries (Murray and Lopez, 1997; Gusnard and Raichle, 2001; Hampson et al., 2006; Hahn et al., 2007).

Alcohol considerably increases the risk of injury, with risky behaviour, falls and violence common factors contributing to many adult TBIs. A study performed in California estimated that 55% of adults diagnosed with a TBI had a positive blood

alcohol concentration test (Kraus et al., 1989; Koch et al., 2002; Hagmann et al., 2007; 2008; Johnston et al., 2008; Lawes et al., 2008; Greicius et al., 2009). Several studies in European countries also observed high percentages (24-54%) of TBI cases related to alcohol consumption (for a review, see Tagliaferri et al., 2006). Sports and recreational activities also account for an important number of TBIs. For instance, approximately 300,000 sports related head injuries occur each year in the US (Thurmann et al., 1998).

1.1.4 Consequences

TBI often results in long-term physical, cognitive, behavioural and emotional impairments and therefore represents one of the most disabling injuries (Langlois et al., 2006). Approximately 5.3 million Americans (2% of the US population) live with TBI related long-term disabilities (Binder et al., 2005). A study on the incidence and outcome of TBI in a Western European urban centre estimated that 40% of TBI survivors continue to have persistent disabilities (Maegele et al., 2007).

The direct and indirect annual costs of TBI have been estimated as $56billion in the US and €64.1billion in Europe for the year 2010 (Gustavsson et al., 2011). TBI therefore represents an important economic challenge for health care systems (Gustavsson et al., 2011). The increase in survival rates following TBI and the fact that it largely affects relatively young people mean long-lasting impairments that increase the requirement for rehabilitation (Patel et al., 2005). TBI results in a highly relevant medical and socioeconomic burden for modern societies, and a major healthcare concern with growing challenges to policy makers, healthcare systems, social care providers and clinicians (Murray and Lopez, 1997).

1.2 Pathophysiology and classification of TBI

Brain trauma initially results in mechanical distortion of the brain tissue. Generally, brain damage following a TBI can be described as focal (such as a contusion or laceration) or diffuse (such as diffuse axonal injury or an ischemic injury). This classification of injury is based on clinical and neuroradiological evaluation (Silver et al., 2005).

1.2.1 Focal injury

1.2.1.1 Description

Focal brain injuries mainly result from inertial forces, such as objects striking the head or the brain striking the inside of the skull, causing visible structural disruption of neural tissues (Ommaya and Gennarelli, 1974) (***Figure 1.1***A). They principally consist of vascular injury and non-haemorrhagic focal lesions that result in haemorrhages and contusions in the cortical grey matter (Gennarelli et al., 1998). They most commonly occur when the brain contacts a dural ridge or bony protuberance (Granacher, 2007) and thus have characteristic locations, such as the orbitofrontal cortex and temporal poles, as well as the lateral and inferior surfaces of the temporal lobes (Gentry et al., 1988) (***Figure 1.1***B). Gentry and colleagues studied a group of 40 TBI patients and observed that nearly half of the contusions were located in the temporal lobes, with a higher prevalence in the temporal pole and around the sylvian fissure, and another third occurred in the frontal lobes, particularly around the frontal poles (Gentry et al., 1988). DiMaio and Vincent have previously reported that contusions evolve over time, and as time progresses, blood products seep into the adjacent cortex, resulting in the degeneration of structures around the

contusion (DiMaio and Vincent, 2001).

1.2.1.2 Clinical imaging assessment

Focal injuries produce areas of highly reduced regional cerebral blood flow and increased blood product (Gentry, 1994), and in general, can be easily identified using computed tomography (CT) and magnetic resonance imaging (MRI). In emergency care, CT is the most common imaging technique used for assessing TBI, and magnetic resonance imaging (MRI) at a field strength of 1.5 Tesla is occasionally used for further assessment (Lee et al., 2008). CT provides a rapid assessment of structural brain injuries and an accurate means of diagnosing intracranial haematomas. It is commonly used due to its availability, as well as it being faster and cheaper than MRI. However, CT is known to underestimate the severity of many forms of cerebral injury such as non-haemorrhagic cortical contusions (Gentry et al., 1988).

A more sensitive imaging tool in detecting traumatic lesions during the acute phase of injury is MRI (Paterakis et al., 2000). T1 and T2-weighted MRI is the most commonly used MRI sequence to identify focal lesions, which typically manifest as areas of decreased signal intensity (***Figure 1.1***C). T1-weighted MRI is good for structure whereas T2-weighted MRI is more sensitive for pathology (detailed information about MRI is presented in Chapter 2).

1.2.2 Diffuse axonal injury

1.2.2.1 Description

Diffuse axonal injury (DAI) is the most common pathologic feature of TBI (Gentry et

al., 1988). The modern day understanding of DAI was first defined by Sabina Strich, who described diffuse degeneration of the brain's white matter in patients with severe post traumatic dementia (Strich, 1956). In contrast to contusions, DAI can occur in the absence of impact forces and is thought to be the result of rapid head acceleration-deceleration that is commonly produced by RTAs as well as, in some cases, falls and assaults (Adams et al., 1989) (*Figure 1.1*D). These abrupt head movements can lead to the stretching and deformation of axons (Povlishock and Katz, 2005) (*Figure 1.1*E). Various studies have observed that some neurons are more susceptible to DAI than others. For example, axons can be more easily damaged when they change direction (Grady et al., 1993; Povlishock et al., 1993) and larger neurons are more vulnerable to injury (Yaghmai and Povlishock, 1992). The brain is more vulnerable if it is moved laterally rather than in the anterior-posterior direction, as Graham and colleagues suggest that the brain tolerates movements in the sagittal plane better (Graham et al., 2002). DAI can appear throughout the deep and subcortical white matter and is particularly common in midline structures, such as the corpus callosum (Povlishock and Katz, 2005). It is also generally more concentrated in frontal areas of the brain (Gentry et al., 1988; Wilberger et al., 1990). In addition, axons are more easily injured in areas of the brain where a change in tissue density occurs, such as at the subcortical grey-white matter interface (Grady et al., 1993; Povlishock et al., 1993).

1.2.2.2 Clinical imaging assessment

Diffuse axonal injury is extremely difficult to detect noninvasively and is poorly defined as a clinical syndrome (Smith et al., 2000) however, with the advancements of MRI sequences, DAI is becoming more detectable (Granacher, 2007). DAI is often accompanied by small haemorrhages, or so-called microbleeds, that are not

necessarily visualised with routine radiological examinations such as conventional MRI T1-weighted images (Onmaya and Hirsch, 1971) (***Figure 1.1***G). The most sensitive imaging technique available to identify microbleeds is susceptibility weighted imaging (SWI) (Akiyama et al., 2009) (***Figure 1.1***F). Susceptibility weighted imaging is a modified magnetic resonance technique that allows the visualisation of small amounts of altered blood and blood product by accentuating their magnetic properties (Haacke et al., 2004). Susceptibility weighted images have become a marker for DAI, with the extent of SWI identified haemorrhages shown to correlate with initial severity of injury, duration of coma and long-term outcome measured at 6 to 12 months after injury, as well as specific neuropsychological deficits (Tong et al., 2004; Babikian et al., 2005). However, examination of microbleeds alone underestimate the true extent of DAI, as some DAI may be non-haemorrhagic (Gentry, 1994; Paterakis et al., 2000).
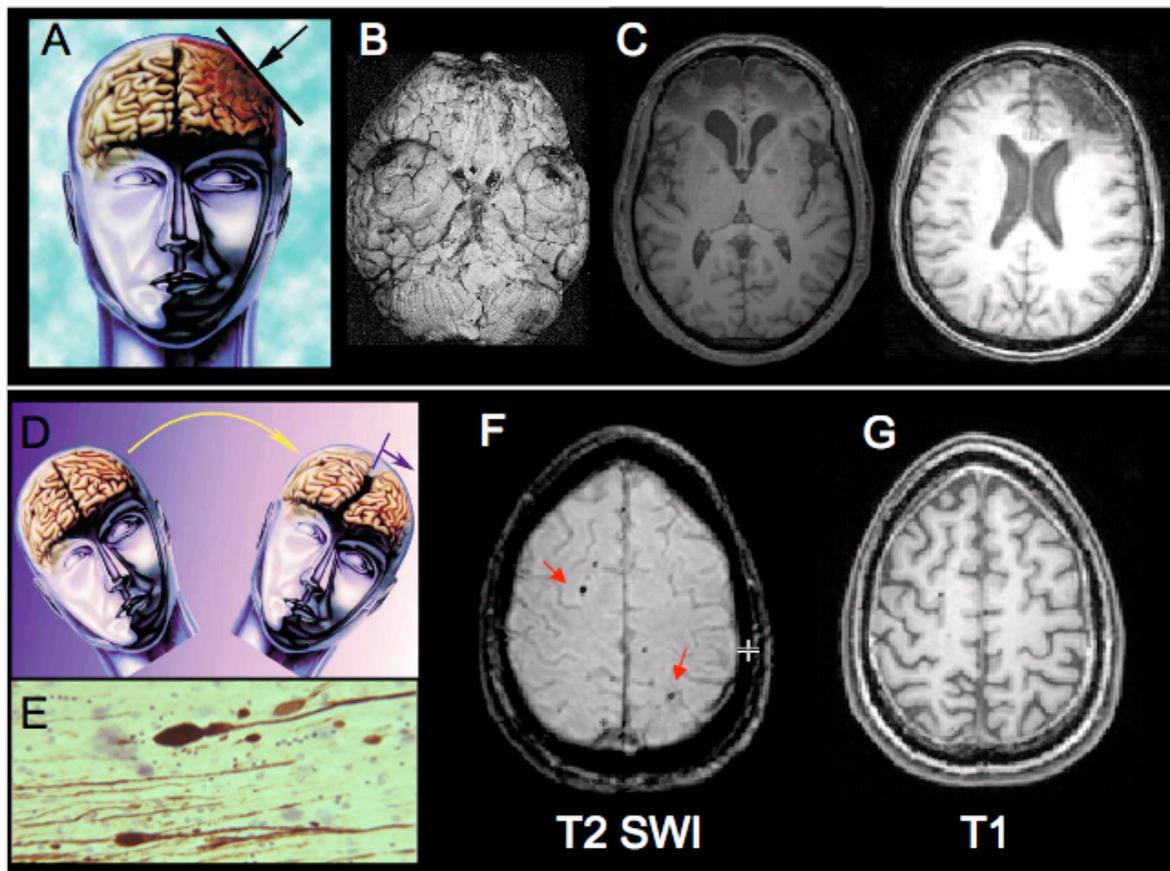
Figure 1.1: Pathophysiology of traumatic brain injury (TBI). A) Focal cortical contusions: Schematic mechanism for focal brain injury resulting from a contact force and formation of a subdural haematoma due to focal vascular disruption (adapted from Smith and Meaney, 2000), B) Post-mortem brain picture showing the typical fronto-temporal contusions pattern (Gentry et al., 1988), C) MRI T1 images of frontal contusions in two TBI patients, D) Diffuse axonal injury (DAI): schematic representation of DAI mechanism, where abrupt rotational acceleration/deceleration of the head results in the deformation of the whole brain and axonal pathology, especially in midline structures (adapted from Smith and Meaney, 2000), E) Axonal bulbs demonstrating the characteristic discrete region of swelling at the terminal stump of disconnected axons (adapted from Smith and Meaney, 2000), F) DAI is often associated with microbleeds in the white matter. They can be visualised as dots of hypointense signal on MRI T2 SWI (susceptibility weighted imaging), but are much less visible on the same axial view on T1 images (G).

1.3 Cognitive control

The current thesis focuses on cognitive control impairments after TBI. Terms such as

cognitive control or 'frontal lobe functions' have been used extensively in the past but

are challenging to define and measure (Cicerone et al., 2006). Cognitive control

refers to the processes that allow the production of goal-directed behaviour, such as monitoring for situations where automatic actions need to be suppressed or changed (conflict monitoring), inhibiting or changing those actions (inhibitory control), monitoring performance outcome (performance or error monitoring) and adjusting behaviour when needed (switching). Deficits in cognitive control strongly determine the functional outcome following a TBI (Granacher, 2008) and the work presented in the current thesis focuses on response inhibition and switching as two mechanisms of cognitive control. These deficits contribute to the persistent disability following TBI (CDC, 2001; Castellanos et al., 2010) and response inhibition and switching deficits are impairments that are commonly reported by TBI patients.

Cognition is analogous to a computer; it is the information processing aspect of behaviour. Cognition, according to (Lezak, 2004) is organised in a systematic way, with brain receptors and sensory systems selecting and classifying the input information. This input information is then stored and retrieved through the memory and learning portions of cognition, with thinking occurring during the mental organisation of all the stored input information. The expressive output portions of cognition are the means through which information is communicated or acted upon (Lezak, 2004). All this forms the basis of human cognition and, dependent upon neurological impairment, damage to any portion of this system may alter cognition. Neuropsychological testing allows health professionals to gain insight into which portion is impaired using a variety of different tests. This is discussed further in section 2.2 below.

TBI patients often have difficulties using flexible or novel approaches when facing new or complex situations, but tend to perform quite well, at least initially, on simple,

automatic or well-rehearsed tasks (Stuss et al., 1989; Park et al., 1999). These impairments in goal-directed behaviour are particularly evident under conditions of high response conflict or when inappropriate, prepotent response tendencies need to be overridden (McDonald et al., 2002; Perlstein et al., 2006). TBI patients also often demonstrate impairments in conflict detection and resolution as well as performance monitoring. For instance, they have been found to detect and correct significantly fewer errors than controls (Hart et al., 1998; O'Keeffe et al., 2004). O'Keeffe and colleagues also observed that the decrease in error detection in TBI patients was associated with decreased electrodermal activity, indicating the level of autonomic arousal, following errors (O'Keeffe et al., 2004).

1.3.1 Response inhibition

The ability to stop in response to an external stimulus requires a multitude of components, including processing the perceptual cues that indicate one to stop; the attentional capture of this cue; and the outright response inhibition (Logan, 1994; Li et al., 2006). To inhibit a prepotent or habitual response is important for the behavioural flexibility required in everyday life. Impairment in inhibitory control can lead to risky and dangerous behaviours, such as failing to stop and look before crossing a street. A recent meta-analysis reported strong evidence for inhibitory control deficits in TBI patients (Dimoska-Di Marco et al., 2011). Such impairment may be due to an inability to maintain a sufficiently high vigilance level (Robertson et al., 1997). It may also be due to limited attentional resource or deficits in attentional factors other than vigilance.

The theory of response inhibition is focused on how a process is controlled (Logan et al., 1984). This control can be understood in terms of the interactions between an executive system and a subordinate system. The executive system forms intentions and issues the commands or steps that are required to realise those intentions, while the subordinate system interprets and executes these commands (Logan et al., 1984). As discussed above, there are a series of commands that are required to successfully inhibit a response however, the act of control that is the focus of the work presented in this thesis is the ability to inhibit actions when they are no longer required. This ability can be studied using neuropsychological tasks. This is discussed further below.

1.3.1.1 Investigating response inhibition

Neuropsychological testing is principally used to measure various specific aspects of a patient's mental ability and/or personality. The 'measurement' of human behaviour can be divided into two subcategories: cognition and emotionality (Granacher, 2007). Response inhibition can be measured using neuropsychological tasks such as the 'go/no-go' or the stop signal task (SST). In the current thesis, the SST is used to investigate response inhibition deficits.

The SST quantifies the ability to inhibit an unwanted response by measuring the latency of control even when the act of control (inhibiting) is not directly observable, as well as measuring the presence and duration of the ballistic component of inhibiting (components that cannot be inhibited once they begin). In the SST, participants are given a primary motor task to perform. The primary motor task is a basic choice reaction time task where participants are required to respond to left or

right facing arrows with the appropriate button press. These are known as 'Go' trials. Unexpectedly, and typically on 20% of trials, the participants are presented with a 'stop' cue, during which they are required to inhibit their response. The 'stop' cue (also known as the stop signal) serves to capture the attentional processing of an unexpected event that signifies the importance of inhibitory processing (Sharp et al., 2010). A comprehensive background of the SST is provided in Chapter 2.

The SST has a higher load on inhibitory control than other tasks that aim to test inhibitory processes, such as the go/no-go task (Rubia et al., 2003). This is because rather than measuring selective inhibition that can be planned beforehand as in a go/no-go task by careful, selective attention to the stimuli, the SST measures the withholding of a triggered motor response that may already be triggered for execution (Rubia et al., 2001). The task mimics every day situations where behavior must be inhibited suddenly and unexpectedly, such as performing emergency braking in a car after seeing a young child running across the road.

1.3.1.2 The neural basis of response inhibition

Functional magnetic resonance imaging (fMRI) has previously been widely used to examine response inhibition (Rubia et al., 2003; Chevrier et al., 2007; Aron et al., 2007). Previous neuroimaging studies using the SST have shown that a set of brain regions including the preSMA; the right inferior frontal gyrus (rIFG); and the right anterior insula (rAI); and the subthalamic nucleus are particularly involved during response inhibition (Aron et al., 2003; Floden and Stuss, 2006; Li et al., 2006). However, the specific contributions these brain regions make to the stopping process itself are still unclear.

Neuroimaging work carried out by Katya Rubia in 2003 attempted to delineate the multitude of processes involved in motor response inhibition, such as the perceptual processing of the stop signal; the attentional capture of the cue; and the actual inhibiting of the motor response (the outright inhibition) (Rubia et al., 2003). In their study, Rubia and colleagues used the SST to fractionate these mechanisms, notably, outright inhibition. Their brain activation results, when contrasting successfully inhibited stop trials with unsuccessfully inhibited stop trials, showed activity in the right lateralized region of the inferior prefrontal cortex (PFC), within the IFG/anterior insula. On unsuccessful stop trials, they found activity in the rostral anterior cingulate cortex, with further activation clusters in the medial PFC (Rubia et al., 2003).

Despite this finding, Sharp and colleagues argued that the literature still failed to delineate the distinct cognitive processes that are involved in stopping, such as the response inhibition itself from the attentional capture of an unexpected event and the error processing when the inhibition fails (Sharp et al., 2010). Sharp and colleagues proposed that the network activated during stopping, which included the right inferior frontal gyrus/anterior insula (rIFG/rAI) is directly responsible for simply processing the stop signal. They go on to hypothesize that the pre-supplementary motor area (preSMA) is responsible for the actual inhibition of a response. To test this hypothesis, they modified the standard SST to include a high-level control condition in the form of an unexpected continue signal. In essence, this allowed them to distinguish the brain regions that are active during response inhibition and the attentional capture triggered by the stop signal (Sharp et al., 2010).

Sharp and colleagues reported similar activations to previous stopping literature, such as that in Rubia Katya's study above, in that the right anterior insula/inferior frontal gyrus (rAI/IFG) and middle frontal gyrus, bilateral inferior, middle and superior frontal gyrus, right supramaginal gyrus were involved during stopping and a failure to stop resulted in activity in the rostral anterior cingulate cortex. As hypothesized, they found that the preSMA is specifically activated during response inhibition, especially with peak activations within the medial and lateral parts of the preSMA. Activity was also shown laterally into the right middle frontal gyrus but noticeably, no activity was shown in the rAI/IFG specific to response inhibition. Importantly, activity in the rAI/IFG during stopping was similar to the activity seen when participants successfully performed continue trials.

Sharp and colleagues' finding was corroborated by work carried out by Adam Hampshire et al in 2010 (Hampshire et al., 2010). Hampshire et al addressed the uncertainty surrounding the rIFG and whether this region is specifically involved in inhibitory control, or is more generally involved in the detection of salient or task relevant cues. They tested the hypothesis that the rIFG would be recruited whenever an important cue was detected regardless of the subsequent response and despite the increased difficulty associated with response inhibition. Their results, again using the SST, supported this hypothesis in that it revealed that the rIFG is recruited when important cues are detected, regardless of whether that detection is followed by the inhibition of a motor response; the generation of a motor response; or no external response at all.

Despite these findings, Adam Aron argues that the 'right inferior frontal cortex' (rIFC; which includes the right inferior frontal gyrus, right anterior insula and the pars opercularis, orbitalis and triangularis) is critical for response inhibition. Although the rIFC is not well defined in their ten-year review (Aron et al., 2014), they propose that the rIFC is best characterised as a brake, which can be turned on in different modes (e.g. to outright inhibit a response), and in different contexts (e.g. by a stop signal). To properly engage a response inhibition process, a task must require the stopping of a response that is already initiated and Aron argues that much research now shows that the rIFC is activated by, and is critical for, outright stopping (see Bari and Robbins, 2013 for a review).

Aron also addresses Sharp et al's finding that the rIFG/rAI is important for attentional detection rather than for inhibition (Sharp et al., 2010), based on their use of 'continue' trials in the SST. As discussed above, Sharp and colleagues compared stop trials with continue trials (trials where the participant processes but ultimately ignores the continue cue and keeps responding) and found that both types of trials (stop and continue trials) equivalently activated the rIFC (which includes the rAI) and hence concluded its function is attentional detection.

1.3.2 Task switching

Task switching is the ability to switch efficiently between different tasks (Hayden et al., 2010). It is a common day-to-day cognitive control function, which requires executing one task consistently and then suddenly reconfiguring mental resources in order to execute another task (Miller and Cohen, 2001). Similarly to stopping, switching requires the attentional capture of unexpected stimuli; the monitoring of errors; inhibition of the previous task set; and the outright reconfiguration of mental

resources to perform a novel task. The origin of task switching is credited to the psychologist Arthur T. Jersild (Jersild, 1927; Monsell, 2003; Jersild, 2011). Jersild timed his students working through a list of items (such as basic math problems like subtraction and addition) where they either had to repeat one task or alternate between two. Jersild compared the time difference between blocks where his students repeated a task, against when his students alternated between tasks. Jersild found that students who simply repeated a task performed better in terms of accuracy and speed than students who had to switch between tasks (Jersild, 1927; Monsell, 2003). This basic phenomenon became known as a switch cost. This is discussed further below in section 0.

1.3.2.1 Investigating task switching

This "switching" behaviour has been studied using 'task switching' paradigms. Although task switching was neglected as a research topic for a period of time after Jersild's findings, the phenomenon has regained popularity since the 1990's and much progress has been made (Monsell, 2003). These paradigms capture two core features of goal directed behaviour (Ruge et al., 2005) in that they measure: 1) flexibility by implementing frequent changes to repeat behaviour, i.e. task switches; and 2) anticipation by giving notice for when the upcoming task can be prepared in advance, either by a short interval (little or no advanced preparation) or a long interval (advanced preparation). The current thesis focuses on the former (task switches) feature of goal-directed behaviour.

Typically in a task switching experiment, a participant is pre-trained on two or more simple tasks afforded by a set of stimuli. In essence, each task requires the individual

to attend to and classify different elements of the stimuli, retrieve the relevant information from memory and execute the action accordingly. The participant is then presented with some stimuli and must perform one of the tasks on each series of trials. The task switch can occur in a variety of ways:

1) During a pre-specified task sequence where participants are given a short sequence of trials (e.g., colour-shape-colour).

2) Within an intermittent-instruction paradigm where a task is occasionally interrupted by an instruction that indicates which task to perform.

3) Within an 'alternating-run paradigm,' a task alternates every N trials, where 'N' is constant, therefore we can compare task-switch and task repetitions in a trial.

4) During a 'task-cueing paradigm' where a task is unpredictable and a task cue appears either with or before stimulus.

In recent years, the cost of switching tasks has been isolated on a trial-by-trial basis by contrasting a task-repeat trial (where a trial in which the task has just repeated, these trials are referred to in the current thesis as Go trials) against a task switch trial (Rogers and Monsell, 1995) (a trial in which the current task has switched to a new task, these trials are referred to in the current thesis as switch trials). The advantage of this type of experiment design is the flexibility it allows the researcher to examine trial effects, such as the timing between different trial components (e.g. the interval between the previous response and occurrence of the next task cue versus the interval between the task cue and target stimulus) (Braver et al., 2003). Furthermore, it allows a more accurate link between switch costs and neural processes that are involved in reconfiguring task-set (Braver et al., 2003).

Based on how the task switches occur, participants are asked to switch between tasks in various ways:

1) Stimulus switching denotes a switch between stimulus rules, such as switching between a red circle and a blue triangle based on a different rule.

2) Response switching denotes switching between response rules, such as switching from pressing the left button to the right button when you see the switch cue.

3) Cognitive set switching denotes switching between task rules, such as the Wisconsin Card Sorting Task (Berg, 1948).

The existence of multiple and distinct switch types most likely contributes to variations in our ability to cope with a constantly changing environment and understanding their neural bases is a goal of the current thesis. Therefore, the work presented in this thesis focuses on switching between response rules (which is referred to as a motor switch in the current thesis, as set out in Chapter 4) and also switching between task rules (which is referred to as a cognitive switch in the current thesis, as set out in Chapter 6).

1.3.2.2 Basic phenomena of task switching

Results from the task switching literature have yielded some common basic phenomena (Monsell, 2003) which will be discussed below.

The switch cost

The ability of flexibly shifting between competing tasks to meet new environmental demands leads to a prolongation of reaction times (RT) at the transition between tasks (Jersild, 1927; Monsell, 2003). In essence, the switch cost is the phenomenon that arises when a participant's behavioural performance on a switch trial is worse (slower) than their performance on a baseline task (responses can take around 500ms longer to initiate on switch trials with error rates higher after a task switch). Switch costs reflect the elevated control necessary to counteract the tendency to repeat the previously performed task (Ruge et al., 2005).

Recent work has found this "switch cost" to be attributable to multiple cognitive factors, including the overcoming of "proactive" interference from the previous task set (Allport, 1994; Yeung et al., 2006) and "the engagement of time-consuming control processes that allow the selection (and/or de-selection) of context-appropriate stimulus–response contingencies ("task set")" (Rogers and Monsell, 1995; Monsell, 2003). The stimulus-response (S-R) contingencies refer to responses to stimuli in a particular set with a pre-specified response (Sakai, 2008). A switch cost is elicited because the brain goes through a mental 'gear-changing' process to reconfigure itself to another rule (Monsell, 2003). This "task set reconfiguration" results in a cost of time and resources, which happens prior to task-specific processes.

The preparation effect

It is thought that switch costs are often reduced with prolonged preparation intervals. This is known as the preparation effect, whereby when a participant is given advanced notice of a task switch, the switch cost is reduced.

The residual cost

Despite preparing for a switch, advanced notice of a task switch does not always eliminate the switch cost entirely. Although there would possibly be a reduced switch cost given advanced notice of the upcoming switch, a task switch still results in a long-term, lingering switch cost. This lingering switch cost is known as the residual cost. It has also been found that extensive practice does not always eliminate this residual cost either (Hayden et al., 2010).

1.3.2.3 The neural correlates of task switching

The neural responses associated with performance deterioration during task switching has shown medial and dorsolateral frontal cortices subserving these executive processes (DiGirolamo et al., 2001). This switching cost has been theorized to result from high-level cognitive control processes "that are not inherent to the component operations of either task when performed alone" (DiGirolamo et al., 2001).

There is strong evidence that the rAI/IFG plays a role in task switching (Dove et al., 2000; Monsell, 2003; Hampshire and Owen, 2006). In line with the inhibitory literature discussed above, the rAI/IFG could account for the role played in attentional task switching, in that the rAI/IFG facilitates the task switch by inhibiting the previously attended task, thereby allowing attention to shift away to another task (Hampshire et al., 2010). It could be predicted from this account, that when switching attention away from a previously routine response, a much greater degree of inhibition would be necessary in order to overcome the pre-potent stimulus-response mapping and

switch to a new stimulus-response mapping. These findings best fit with a role for the rAI/IFG in reconfiguring a representation of the currently attended input.

However, as discussed above, there are various ways in which a switch can occur. Previous task switching neuroimaging literature (see Sakai, 2008 for a review) suggests that the brain may utilise a variety of different regions to accommodate different switching mechanisms. Previous literature has focused little on multidimensional switch tasks, where an individual not only has to switch between stimuli (for example, switch between an odd/even number rule and a red/blue colour rule) but also between stimulus-response mappings (for example, switches between the responses of the number and colour rules).

Kim and colleagues carried out one study of particular interest to the work presented in the current thesis (Kim et al., 2011). They designed an experiment that induced a variety of switches in one paradigm in order to investigate which brain regions contribute to different types of switches (Kim et al., 2011). They recruited sixteen healthy participants to take part in an experiment specially designed to independently measure the neural responses of three switch types (stimulus, response and set switches) as described in section 1.3.2.1 above.

From their analysis, they identified specific prefrontal cortex (PFC) regions of brain activity that were preferentially activated for each switch type. They showed an anterior-to-posterior gradient of activation, across the lateral and medial frontal cortex, based on the switch type. They found that activity for cognitive set switching was most anterior, with more posterior activity (than the cognitive set switch) resulting from the response switch. The most posterior activity was found during

stimulus switching. Essentially, as switches became more abstract (cognitive set switching → response switching → stimulus switching), brain activity became more posterior.

Furthermore, their conjunction analysis (which identifies common regions that are active between the switch types) showed activity in the inferior frontal junction (IFJ: see **Figure 1.2**). This finding suggests that IFJ contributes to the core cognitive processes generic to task switching (Kim et al., 2011), which include representing and updating task sets (Miyake et al., 2000).

Previous studies support the role of the IFJ in representing and updating task sets from previous studies. Imaging studies have shown more activity in this region, which is located more dorsal/superior to the inferior frontal gyrus (IFG) (Petrides, 2000). The IFJ, located in the posterior fronto-lateral cortex, has been identified as an important region of task switching and the task switching literature has revealed the most consistent overlap in activation across studies (Derrfuss et al., 2005). Brass and colleagues argue that the role of the IFJ has been overlooked as researchers have focused on the mid-DLPFC in task switching (Brass et al., 2005).
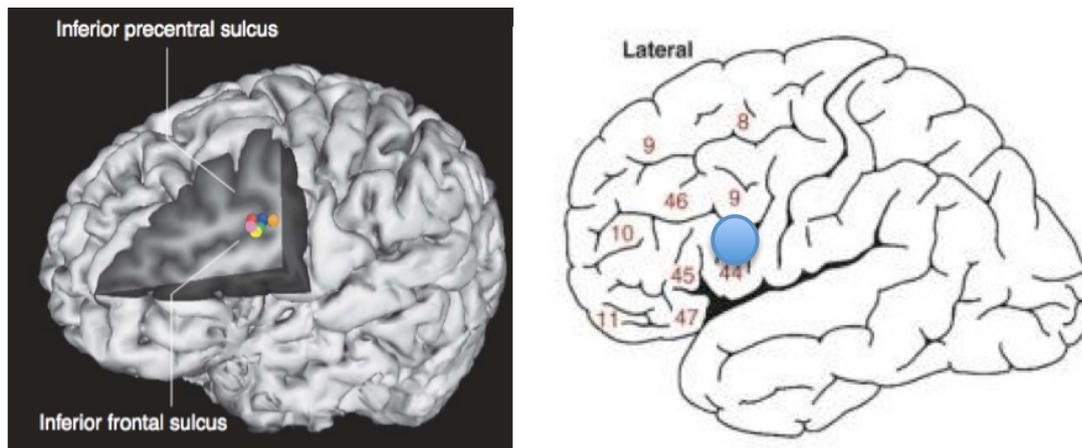
Figure 1.2: Sagittal view of brain regions involved in task switching. *The dots in this lateral view of the human brain represent the inferior frontal junction: at the junction of the inferior precentral sulcus and the inferior frontal sulcus. The location of the inferior frontal junction is also seen between the premotor and prefrontal cortex and includes parts of BA 6, 9 and 44. (Left image taken from Brass et al., 2005).*

1.4 Attention

Attention is "the sine qua non of sensory input to the brain" (Granacher, 2007). Although the research forming the basis of this thesis focuses on task switching and response inhibition, they both critically depend on attentional processes. Attention deficits are a prominent aspect of cognitive dysfunction after TBI and include an inability to concentrate, greater distractibility, and difficulty performing more than one task at a time (dual tasking) (Whyte et al., 1995; Bate et al., 2001; Azouvi et al., 2004; Dockree et al., 2006). Therefore, poor performance in switching and stopping tasks in TBI patients could arise from attention deficits, as attention deficits are often associated with confusion, fatigue and an increased time and effort to perform even simple tasks (McKinlay et al, 1981; Azouvi et al., 2004; Cantor et al., 2008). Niemann and colleagues proposed that attention deficits could be divided into three main types: (1) sustained attention; (2) selective attention; and (3) energetic aspects of attention that encompass concepts such as effort, fatigue and motivation (Niemann et al., 1996)

1.4.1 Sustained attention

Sustained attention can often be termed 'vigilance' (Granacher, 2007), and refers to the ability to maintain concentration on a task over a continuous period of time (Granacher, 2007). This is distinct from 'divided attention,' which refers to the "ability to attend to two or more task simultaneously" i.e. to multitask (Granacher, 2007). Vigilance can be divided into two distinct components; 'vigilance level' and 'vigilance decrement over time' (Parasuraman, 2000; Sarter et al., 2001). A decrease in vigilance level often leads to lapses in attention, which are associated with momentary increases in reaction time (RT) or response errors (Robertson and Garavan, 2004). Vigilance decrement corresponds to the inability to maintain attention that is directed towards an external goal over a sustained period of time, which is characterised by increased RT and/or response errors with time spent on a task (Mackworth, 1948).

1.4.2 Selective attention and attentional resource

Selective attention is the ability to set priorities in information processing to make optimal use of limited attentional processing capacity (Niemann et al., 1996). This is directly linked to the idea of attentional resource or capacity limitation, which suggests that attention processing capacity is limited (Kahneman, 1973). As a consequence, allocating additional resources to a task can improve performance on that task, but only at the cost of reducing the resources available for other concurrent tasks (Luck et al., 1996).

1.5 Brain networks involved in cognitive control

Prior to the advancements of neuroimaging, neuropsychological and neuroscience researchers proposed models of cognitive functions by drawing largely upon lesion studies (this is discussed later in the chapter in section 1.6.3.1).

As imaging techniques became more accessible and advanced, researchers began to focus on the underlying neural structure of cognitive functions through model-based task-activation in fMRI studies. However, one major limitation of these approaches is that they attribute the function of one brain region in isolation from the rest of the brain. That is, in the case of fMRI studies, the neural correlates of a particular task are often localized to one active brain region. However, the function of any brain region cannot be understood in isolation, but should also be investigated in conjunction with the knowledge about the other regions with which it interacts. For instance, He and colleagues reviewed evidence from translational neuroscience research supporting the idea that normal brain function depends on the synchronisation of regional activity within large-scale, distributed brain networks (He et al., 2007). Their conclusion is that "a network perspective is fundamental to appreciating the pathophysiology of brain injury" (He et al., 2007). This idea is particularly relevant to TBI because the mechanism of TBI often revolves around DAI. The effect of TBI on cognitive functions most likely arise because of the way it affects the structural connections between distinct brain regions, which work together as part of a brain network.

1.5.1 What are brain networks?

As revealed by fMRI, brain networks correspond to the spontaneous fluctuations of the fMRI signal, where activity from one part of the brain is temporally correlated with other spatially distinct parts of the brain. Brain networks have been of interest since the 1960s when Norman Geschwind set about investigating brain connections in order to explain the neural basis of language disorders (Geschwind, 1965)Since then, brain networks have been at the forefront of modern day neuroscience since it was first noted that, even when a participant was at 'rest' during an fMRI scan, the BOLD signal from one part of the motor cortex was temporally correlated with other parts of the same functional network (Biswal et al., 1995). Following this finding, researchers have found several other correlated temporal patterns of activity in the 'resting brain' (Smith et al., 2009), and although these activations are from the same source, they can be fractionated from a single fMRI dataset (Xiong et al., 1999). This is because each network has different temporal characteristics (Beckmann et al., 2005), which are robust enough to be detected even while the participant is asleep (Fukunaga et al., 2006) or under anaesthesia (Vincent et al., 2007).

The value of such network-based research also has the potential to be of great clinical value by providing sensitive markers of disease (Greicius et al., 2004). For example, Greicius and colleagues used a brain imaging technique called independent component analysis (ICA) to isolate a brain network called the DMN (see below) in a group of thirteen participants with mild Alzheimer's disease (AD), while they performed an episodic memory-processing task in the scanner. They found that the AD group, compared with an age-matched elderly control group showed decreased DMN activity in the posterior cingulate cortex (PCC) and

hippocampus, suggesting that disrupted connectivity between these two regions accounts for the posterior cingulate hypometabolism (Greicius et al., 2004).

Cognitive control has traditionally been associated with functioning of the frontal lobes (Miller and Cohen, 2001). However, in recent years, results from both resting state and task based fMRI studies have described models of cognitive control that stretch beyond the frontal cortex. These results include the existence of large-scale brain networks (Cocchi et al., 2013), that work in parallel to dynamically adjust and control behaviour. The network's functional anatomy is assumed to be consistent across resting-state and task contexts (Harrison et al., 2008; Smith et al., 2009). One influential model about network function in cognitive control surrounds the relationship between the DMN and the SN, which is the focus of the current thesis and is discussed further below.

1.5.2 The Salience Network

The term 'Salience Network' was first used by Seeley and colleagues to describe a set of paralimbic structures, most prominently the anterior cingulate cortex (ACC) and bilateral anterior insular cortices (Seeley et al., 2007) (**Figure 1.3**). These regions are found to be co-activated (Dosenbach et al., 2006), and FC studies have shown these regions form a functionally connected network both during task and at rest (Seeley et al., 2007; Sridharan et al., 2008). Menon and Uddin propose that the SN is "sensitive to salient events, and that its core function is to mark such events for additional processing and initiate appropriate control signals" (Menon and Uddin, 2010). Dosenbach and colleagues have shown that the regions of the SN show sustained activity across a variety of tasks and conditions and in response to various forms of

internal or external salient stimuli (Dosenbach et al., 2006). The magnitude of activation of these regions (especially the ACC and anterior insula) appears to be proportional to the perceived saliency of a stimulus (Mouraux et al., 2011). However, the subcomponents within the SN appear to play a distinct role, which is discussed further below.
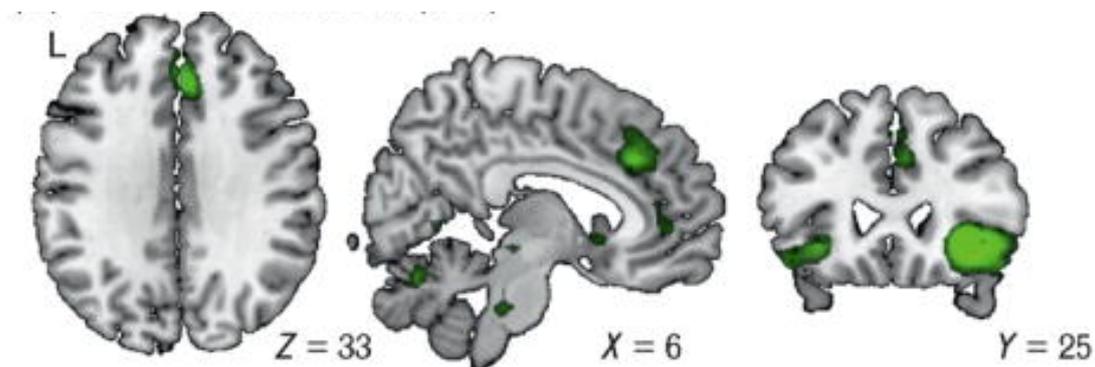
*Figure 1.3: **The Salience Network (SN).** A map of the SN, which illustrates the anterior cingulate cortex found at the front part of the cingulate cortex, which lies immediately above the corpus callosum, as well as bilateral insula. (Image adapted from Ham and Sharp, 2012).*

1.5.2.1 Nodes of the Salience Network

The anterior insula cortex

A key region of great interest to the current thesis is the role of the anterior insula cortex. Recent studies suggest a central role of the anterior insula in human perception, cognition and attention (Brass and Haggard, 2010; Mouraux et al., 2011; Menon and Uddin, 2010). More recent FC work (Ham et al., 2013a) suggests a role for the insula to be a prominent node in signalling high level environment events. It has also been proposed to be primarily involved during introspective-autonomic and emotional processes such as pain, stress, hunger or enjoyable feelings (Peyron et al., 2000; Blood and Zatorre, 2001; Craig, 2002).

In one study conducted by Ham and colleagues (Ham et al., 2013b), they used a technique to infer the causal relationships between brain regions, known as dynamic causal modelling (DCM). They applied DCM to investigate the relationship between nodes in the SN after errors. They scanned thirty-five healthy controls on performance of the Simon task (Simon, 1969; Simon and Small, 1969). This task had two conditions (congruent and incongruent), which produced two distinct error types. Neural activity associated with errors was investigated using fMRI. Their DCM analysis showed that input into the SN was most likely via the rAI for both error types and that the rAI was the only region intrinsically connected to both other nodes of the SN (the left AI and the dACC). They concluded that the rAI, not the dACC, drives the SN after errors on an attentionally demanding task (Ham et al., 2013b).

Sridharan and colleagues found that the rAI plays a critical and causal role in switching between the DMN and an attentional network that they refer to as the 'executive network' (EN) (see section 1.5.6) (Sridharan et al., 2008). They scanned eighteen healthy controls while they participated in an auditory task involving listening to classical symphonies and found right lateralized activity in the insular cortex during 'movement transitions'. These are the most salient parts of the piece. The activations they found in the SN in response to movement transitions were accompanied by deactivation of the DMN. Furthermore, they also carried out a latency analysis, which revealed early activation of the rAI relative to the EN and DMN. They did this by identifying differences in the latency of the event-related fMRI responses across the entire brain. Their method allowed them to estimate the peak latency of the BOLD response at each voxel by modelling the canonical

haemodynamic response function (a discussion on the BOLD response is provided in Chapter 2) (Sridharan et al., 2008). This analysis revealed that the fMRI signal in the rAI peaked earliest, followed by the dACC, compared to the signal in the nodes of the EN and DMN. This finding indicates that the neural responses in the rAI precede the EN and DMN.

Sridharan and his colleagues then carried out a Granger Causality Analysis (GCA) (Sridharan et al., 2008). Briefly, GCA detects causal interactions between brain regions by assessing the predictability of signal changes in one brain region, based on the time course of responses in another brain region. GCA assumes that if one time-series looks like a time-shifted version of the other, then the one with temporal precedence has caused the other. Sridharan and colleagues found that the rAI had the highest number of 'causal outflow' connections (the number of connections going out from the rAI to other brain regions), the lowest number of 'causal inflow' connections (the number of connections coming into the rAI from other brain regions) and the shortest path length among all regions. Essentially, they found significant direct or indirect causal influences from the rAI to all of the regions in the EN and DMN. The most striking finding from their work was that they demonstrated how robust their findings were by replicating them in two other independent fMRI experiments – a visual oddball attention task and in resting state fMRI. These results suggest that the rAI acts as an outflow hub at the junction of other large-scale brain networks, notably the DMN. However, the Granger causality analysis used by Sridharan and colleagues has a number of limitations (see (Smith et al., 2011), as this technique also brings with it some technical issues in that it fails to take into

consideration the latency differences in neural response across different brain regions, as well low-sampling rates and noise (Wen et al., 2013).

Structural connectivity of the insula cortex

Current understanding of structural connections of the insula has previously been obtained from careful tracer studies in animals, such as the monkey (Mesulam and Mufson, 1982; Mufson and Mesulam, 1982) and cat models (Craig, 2002; 2003), followed by lesion studies (see Ibañez et al,. 2010). By contrast, the structural connections of the human insula are currently poorly understood (Menon et al., 2010) however, DTI studies of white matter microstructure and pathways are now beginning to provide new information about the structural connectivity of the human insula.

A recent study used a technique called K-means clustering for connectivity-based segmentation of the insula using DTI (Nanetti et al., 2009). K-means clustering is an iterative technique, which divides the voxels of a seed region into 'k' non-overlapping clusters of voxels; the experimenter then decides the value of 'k' based on functional and anatomical considerations. Nanetti and colleagues found that the proportion of voxels that can be attributed to a cluster is relatively low in the insula, suggesting a high level of heterogeneity in this cortical region compared to the supplementary motor area (Nanetti et al., 2009). Progress in non-invasive mapping of white matter pathways around the insula cortex using DTI has been limited, however, rapid progress is being made in this area using better data acquisition techniques and improved analytic methods for fibre tracking (Wedeen et al., 2008). For example, white matter pathways between the insula and the posterior parietal cortex (Uddin et

al., 2009) and the ACC have been demonstrated (van den Heuvel et al., 2009), and more recently by Bonnelle and colleagues (Bonnelle et al., 2012).

1.5.2.2 The anterior cingulate cortex

A number of studies have suggested that the rostral anterior cingulate cortex (rACC) might be involved in error detection, whereas more dorsal ACC/preSMA may monitor for conflict (Ullsperger and Cramon, 2001; Ham et al., 2013b). A wide range of functional imaging studies and theoretical models has suggested that the ACC plays a prominent role in action selection (Rushworth, 2008). Although the preSMA is not a direct node of the SN, it has also been implicated in various executive functions, such as changing or stopping movements plan and the ACC node has been proposed to extend into the preSMA (for review, see Nachev et al., 2008).

One theory of ACC function states that the dorsal ACC (dACC) monitors performance and signals the need for behavioural adaptation (Holroyd et al., 2004; Ridderinkhof et al., 2004). Electrophysiological studies have identified a very early response to errors (80–110 ms) in the form of an error-related negativity (ERN) component, which is thought to arise from the dACC (Debener et al., 2005). It is proposed that activity in the dACC signals the need for increased cognitive control (Ridderinkhof et al., 2004), and interactions between the dACC and lateral prefrontal structures implement subsequent behavioural changes (Ridderinkhof et al., 2004).

More generally, the medial prefrontal components of the SN have shown to be implicated in response regulation (Roelofs et al., 2006), as they are thought to influence attentional processing in favour of task-relevant behaviours and implement

some adjustments in situations where behaviour needs to be adapted, changed or stopped (Roelofs et al., 2006). There is also evidence that the ACC is involved in a number of other functions, such as identifying the motivational relevance of external events; sustaining the level of effort needed for the execution of attentional tasks (Mesulam, 1981); or self-regulation (Posner et al., 2007).

1.5.2.3 The role of the Salience Network

One influential model of SN function that has been proposed by Vinod Menon and his team, suggests that the SN facilitates the detection of important environmental stimuli, which engages the brain's attentional and higher-order control processes while disengaging other systems that are not immediately task relevant (Menon and Uddin, 2010). This might constitute one brain mechanism through which the SN can regulate and guide behaviour by acting as a transient circuit breaker, which integrates bottom-up/top-down and emotional/autonomic state processing (Critchley et al., 2004). Chronometric techniques and dynamical systems analysis suggest that the SN, and the rAI in particular, plays a critical and causal role in switching between other brain networks, notably the DMN, across task paradigms (Menon and Uddin, 2010). Critically, Menon's model suggests that once a stimulus activates the rAI, the SN will have preferential access to the brain's attentional and higher-order control resources (Menon and Uddin, 2010) (**Figure 1.4**).

Taken together, the SN's roles include: (1) bottom–up detection of salient events; (2) switching between other large-scale networks to facilitate access to attentional resources when a salient event is detected; (3) interaction of the anterior insula with

other regions to modulate autonomic reactivity to salient stimuli; and (4) strong functional coupling with the anterior cingulate cortex that facilitates rapid access to the motor system. Within the framework of the model described here, Menon and Uddin suggest that the rAI plays a more prominent role in the detection of salient stimuli, whereas the dACC plays a more prominent role in modulating responses in the sensory, motor, and association cortices. Taken together, as part of a functionally coupled network, the rAI and dACC help to integrate bottom–up attention switching with top–down control and biasing of sensory input. This dynamic process allows us to filter through many different incoming sensory stimuli and adjust the gain for task-relevant stimuli (Yantis, 2008).
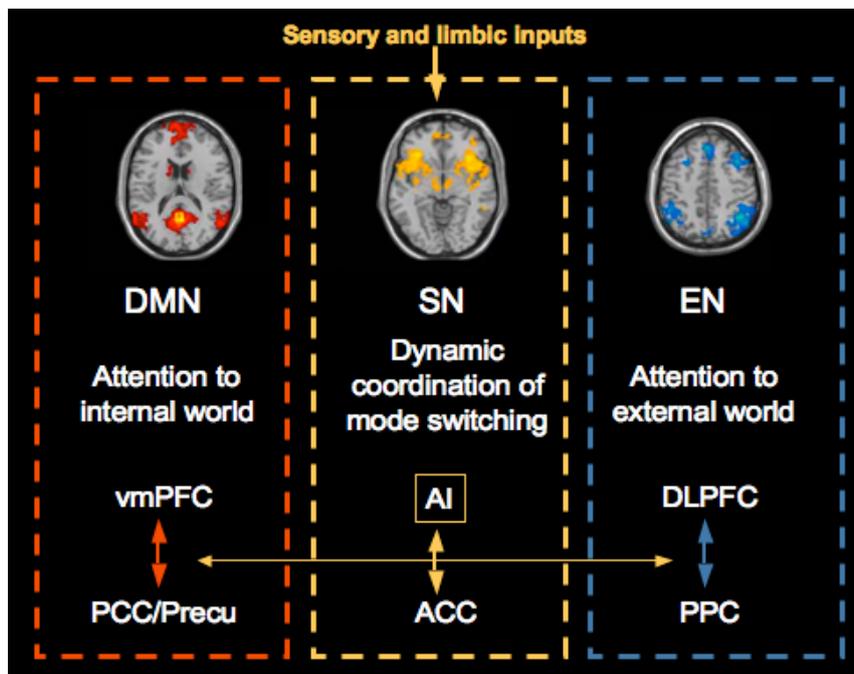
Figure 1.4: Brain networks dynamic. *According to Sridharan and colleagues, based on external sensory and internal limbic inputs, the Salience Network (SN) acts a transient circuit breaker and dynamically coordinates the switching between Executive (EN) and Default Mode (DMN) Networks, allowing attention to be directed either to the external or the internal world (Adapted from Menon and Uddin, 2010).*

1.5.3 The Default Mode Network

When the brain is at rest, i.e. not actively engaged in a cognitively demanding task, brain regions show spontaneous neuronal activity and synchronised behaviour, particularly within a range of low fMRI BOLD signal frequency oscillations (0.01–0.1 Hz) (Biswal et al., 1995). Most of these patterns of FC have been shown to support a specific cognitive function (De Luca et al., 2006; Damoiseaux et al., 2006), and show a close correspondence with the patterns of brain activation observed during task-dependent cognitive activity (Smith et al., 2009). This work corroborates the idea that the FC of intrinsic connectivity networks is a result of "synchronized, intrinsic neuronal activity across well-established 'hard-wired' networks, and not the consequence of external cardiac and respiratory cycles" (Shmueli et al., 2007). Although the role of intrinsic connectivity networks is not fully understood, they reflect the wiring of the brain, where regions that 'wire together fire together'. It has been suggested that intrinsic connectivity networks maintain functional integrity by reinforcing the synaptic connections that sub-serve the network's typical functioning during active states (Pinsk and Kastner, 2007).

One resting state network of particular interest is the DMN (**Figure 1.5**). The term 'Default Mode Network' was first proposed by Raichle and colleagues to describe a set of brain regions that exhibit higher metabolic activity at rest rather than during performance of externally oriented cognitive tasks and show strong FC at rest (Raichle et al., 2001; Gusnard and Raichle, 2001). The DMN consists of the following nodes (Buckner et al., 2008): 1) the precuneus and posterior cingulate cortex (Precu/PCC); 2) the inferior parietal lobes (IPL); 3) the ventromedial prefrontal cortex (vmPFC); 4) the superior frontal gyrus; 5) the anterior portions of inferior temporal

cortex and 6) the medial temporal cortex (parahippocampal gyrus and hippocampus). Amongst these, the midline structures (the Precu/PCC and the vmPFC); and the bilateral IPL are the most commonly reported and form what is thought of as the DMN. The PCC in particularly is thought to constitute a core node of the network (Fransson and Marrelec, 2008) and is discussed further below.
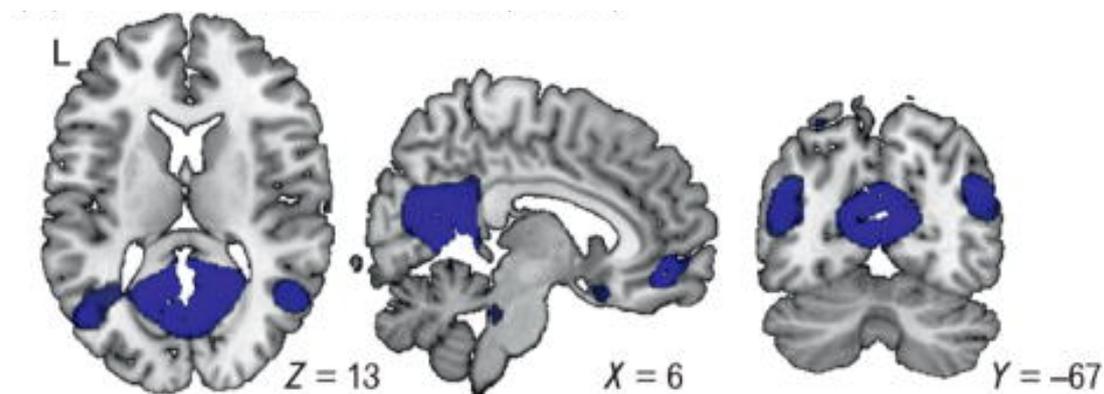
Figure 1.5: *The Default Mode Network (DMN).* *A map of the DMN that illustrates the posterior cingulate cortex/precuneus (Brodmann areas 23 and 31) found at the back part of the cingulate cortex, which lies immediately above the corpus callosum, as well as the ventromedial prefrontal cortex (vmPFC) located more anteriorly. (Image adapted from (Ham and Sharp, 2012).*

1.5.3.1 Nodes of the Default Mode Network: the posterior cingulate cortex

The PCC is situated in the medial part of the inferior parietal lobe and lies within the posteromedial cortex, which also includes the precuneus (Parvizi et al., 2006). Vogt had proposed a major subdivision of the PCC which includes the mid-cingulate region, that contains a motor field with direct corticospinal projections (Vogt, 1993; 2009b). In line with Vogt's model, the PCC consists of Brodmann areas 23 and 31 and is bounded mainly by "the marginal ramus of the cingulate sulcus, inferiorly by the corpus callosum, posteriorly by the parieto-occipital sulcus and anteriorly by Brodmann area 24 in the mid-cingulate region" (Leech and Sharp, 2010).

One of the most striking physiological features of the PCC is that the cerebral blood flow and metabolic rate within the PCC and adjacent precuneus are on average approximately 40% greater than other brain regions on average (Raichle et al., 2001). This high rate of metabolism in the PCC is responsive to cognitive state (e.g. whether a demanding cognitive task such as making a perceptual decision and motor response is required). However, fluctuations in perfusion produced by changes in cognitive state are relatively small compared to the high levels of baseline activity (Raichle et al., 2001) but even when a task results in a relative fall in PCC activity, the region still shows consistently higher levels of blood flow compared with almost all other brain regions (Pfefferbaum et al., 2011).

The structural connectivity of the PCC is closely related to its FC with other brain regions (Leech et al., 2011). In keeping with its extensive structural connectivity, the PCC shows a complex pattern of FC (Vincent et al., 2006; Margulies et al., 2009; Leech et al., 2012a), which provides evidence for its interaction with distinct intrinsic connectivity networks across the brain (Leech et al., 2012a). This is discussed further below in section 1.5.4.

1.5.3.2 The role of the Default Mode Network

Perhaps the most dominant current theory of DMN function is that it is directly involved during internally directed thought (Buckner et al*.*, 2008). One early hypothesis was that the DMN plays a role in supporting the semantic elements of 'stimulus-independent' thought (Binder et al., 1999). Activity in the DMN was higher when subjects reported more 'stimulus-independent' thoughts, a state where mental activity is unconstrained by external stimuli. Binder and colleagues therefore

proposed that the DMN is continually involved in the conceptual processing associated with this type of 'freewheeling' mental activity (Binder et al., 1999). In this state, semantic knowledge is retrieved, maintained in awareness and manipulated for the purposes of problem solving and planning. Furthermore, several studies have reported that the magnitude of DMN deactivation contributes to task performance, and might reflect task engagement and difficulty (McKiernan et al., 2003; Hester et al., 2004; Weissman et al., 2006; Li et al., 2007; Zhang and Li, 2010). Binder et al's influential hypothesis suggests that the DMN supports internally directed cognition and shows increased activity when individuals retrieve autobiographical memories or plan for the future, as well as during unconstrained 'rest' when activity in the brain is 'free-wheeling' (Leech and Sharp, 2013). Weissman and colleagues found that a failure to deactivate the DMN during externally directed attention tasks resulted in lapses of attention (Weissman et al., 2006).

A related account is that the DMN supports internally directed thought more generally than stimulus-independent (Buckner et al., 2008). Previous studies have shown that the DMN increases in activity when participants attend to internally driven cognitive processes and reduces its activity when an external task-based focus is required (Gusnard and Raichle, 2001; Raichle et al., 2001). As a result, the DMN has been associated with introspective attentional orientation related to 'mentalization' and emotional processing (Gusnard et al., 2001). During a task that requires attention to be externally directed, 'stimulus-independent thoughts' are often incompatible with goal-directed activity, and may represent a potential source of cognitive task interference (Sonuga-Barke and Castellanos, 2007). This idea is supported by work carried out by Mason and colleagues, who demonstrate an association between

stimulus-independent thoughts during task performance with both DMN activation and participants' reports of their subjective experiences of 'mind wandering' (Mason et al., 2007).

A broad internal focus of attention occurs in the freewheeling cognitive state, which is usually thought of as accompanying participants at 'rest' during an fMRI scan (Leech and Sharp, 2010). 'Resting state' fMRI and FC analyses show that activity across and within the DMN is relatively high, whereas the ventral PCC shows an anticorrelated pattern of activity to other brain networks, such as the dorsal attention network (Fox et al., 2005; Leech et al., 2011) (the dorsal attentional network is briefly discussed below).

The DMN is also implicated as a key network for both arousal and awareness (Boly et al., 2009b). Relatively high levels of DMN metabolism and FC are associated with the normal conscious state. In contrast, in low states of arousal and awareness, including deep sedation, DMN activity measured by both absolute blood flow and FC is reduced (Fiset et al., 1999). DMN metabolism and connectivity is also low in the vegetative state and increases as patients regain consciousness (Heine et al., 2012). Activity in the DMN is also sensitive to changes in awareness associated with sleep. Stepwise reductions of connectivity between the posterior nodes of the DMN and prefrontal nodes track the changes in vigilance level that occur in different sleep states (Samann et al., 2011). Connectivity analyses suggest that the reduction in consciousness level observed with propofol sedation is associated with a loss of the normal top-down cortico-cortical communication from the dACC to the DMN (Boly et al., 2012). Hence, alterations in arousal and awareness across many different states

are associated with changes in the neural activity of the DMN and its interactions with other brain regions.

However, other evidence suggests that the DMN plays a more direct role in regulating the focus of attention (Gusnard and Raichle, 2001; Hampson et al., 2006; Hahn et al., 2007), by potentially controlling the balance between internally and externally focused thought (Leech et al., 2011). In addition, activity in the DMN varies with arousal state, and its interactions with other brain networks may be important for conscious awareness (Vogt and Laureys, 2005).

1.5.4 Default Mode Network activity is anticorrelated with Salience Network activity

Coordinated activity between the DMN and the SN is important for efficient cognitive function; and a major challenge is to understand how these networks dynamically interact (Leech and Sharp, 2010). During cognitively demanding tasks where attention needs to be directed to external information, activity is seen to increase in the SN and decrease within the DMN in a tightly coupled way (Fox et al., 2005; Seeley et al., 2007; Cocchi et al., 2013). This produces an anticorrelated pattern of activity over time between the DMN and SN (Leech and Sharp 2010). This anticorrelation has been proposed to reflect the dichotomy between tasks that require the balance of internally oriented attentional modes versus externally oriented attentional modes (Fransson, 2005). As the attentional demands of a cognitive task increase, the anticorrelation becomes more pronounced, and the strength of the

anticorrelation has been found to be associated with more consistent behavioural performance (Kelly et al., 2008).

Kelly and colleagues used an active Erikson flanker task and hypothesized that a strong negative correlation (where r ~= − 1, will indicate that the relationship between the activity of the DMN and that of another task positive network is nearing 180° antiphase) would be associated with more consistent (less variable) performance. By contrast, a weaker negative correlation (indicating the likelihood that the two networks are sometimes simultaneously active) would be associated with greater behavioural variability (Kelly et al., 2008). Furthermore, Kelly and colleagues also expected that this link would be more evident under the more attentionally demanding incongruent condition of the Erikson flanker task, which was expected to increase the requirement to regulate activity between the networks. They found that the strength of the negative correlations between the DMN and the task positive networks were significantly related to individual differences in the variability of flanker task response times (Kelly et al., 2008).

The above findings suggest that the DMN and the SN serve distinct functions that are critical for attention. In keeping with this idea, it has been proposed that increasing attention when needed during task performance may be achieved by distinct neurobiological mechanisms; either by predominantly boosting fronto-parietal activity (i.e. regions of the SN), by predominantly deactivating DMN, or by a combination of the two (Lawrence et al., 2003). A recent study suggested that the two main nodes of the DMN do not show the same patterns of anticorrelation with some task positive networks (Uddin et al., 2009). That is, resting-state activity within the vmPFC

appeared negatively correlated with activity in regions of the dorsal attention network (DAN) (discussed briefly below), whereas activity in the PCC was more negatively correlated with activity in regions of the SN (Uddin et al., 2009). This would explain why the SN and DAN both appear to be anticorrelated with the DMN, whereas the SN and DAN are, in fact, functionally distinct networks (Seeley et al., 2007).

1.5.5 Other networks involved in cognitive control

The DAN and the ventral attention network (VAN) are two other task positive networks that have been proposed by Corbetta and Shulman (Corbetta and Shulman, 2002). Although the focus of this thesis is on the interaction between the DMN and the SN, I provide a brief summary of these two networks in context of task anticorrelation with the DMN.

The DAN describes a system of fronto-parietal regions often active during visual-attention tasks. Core regions of this network include parts of the dorsal frontal cortex, along the precentral sulcus, close to or at the frontal eye field (FEF), and regions of the dorsal parietal cortex, particularly the intraparietal sulcus (IPS) and superior parietal lobule (Corbetta and Shulman, 2002). The VAN on the other hand, has been found to be strongly activated by target detection, particularly when the targets occur at an unexpected location, or during the "detection of low-frequency or salient events" (Corbetta and Shulman, 2002). This network is made up of the right inferior frontal cortex (IFC) (comprising the inferior frontal gyrus (IFG), the anterior insula (AI), and the frontal operculum) and posteriorly the right temporo-parietal junction (TPJ). Interestingly, these regions have also been found to form one of the resting state networks (Fox et al., 2006), and the VAN has been proposed to act as a circuit

breaker of on-going cognitive activity when salient stimuli are detected (Corbetta and Shulman, 2002). However, results from previous neuropsychological and neuroimaging studies revealed that a right lateralized fronto-parietal network anatomically close to the VAN was also involved in modulating and maintaining vigilant or sustained attention (Posner and Petersen, 1989; Paus et al., 1997). To explain this apparent discrepancy, Coull proposed that this network might provide the neuroanatomical location for the functional interaction between stimulus-driven attention and internally maintained sustained attention (Coull et al., 1998).

1.5.6 Complexities of the network approach (nomenclature of networks)

There is still no recognised and standard nomenclature for the networks presented above. This is probably at the heart of a lot of confusion in the field currently. For instance, one group will discuss a 'core' or 'task-control' network (Dosenbach et al., 2006) while the other will refer to the same network as the 'salience' network (Seeley et al., 2007), or in pain related research as the 'pain network.' An even more important source of confusion comes from studies using the same term to describe distinct networks.

As an example, the 'executive network' (EN) (also named 'executive control' or 'central executive' network) has generally been used in studies investigating FC using independent component analysis (ICA, see Chapter 2 for description of the technique) to refer to a frequently observed component generally comprising a set of bilateral fronto-parietal brain regions (Beckmann et al., 2005; Seeley et al., 2007). Therefore, in some studies, the EN may encompass the VAN and the DAN (De Luca et al., 2006); be limited to the DAN (Sridharan et al., 2008); or be further split into

right and left subcomponents (Habas et al., 2009).

In the current work, I refer to two networks as they have been described above: the default mode network (DMN) and the salience network (SN).

1.5.7 The "fallacy of the task positive network"

Another confusing term that is frequently used to refer to a set of brain regions that typically shows activation during most attention-demanding cognitive tasks is the 'task-positive network' (TPN) (Fox et al., 2005; Kelly et al., 2008). While some regions (generally comprising regions of the SN as well as the VAN and DAN) often exhibit an increase in activity during cognitive tasks, regions of the DMN show a decrease (Gusnard and Raichle, 2001). Those who refer to the 'task-positive network' thus encompass the SN and the VAN/DAN as one functional network. This can be confusing in the context of FC studies as it is difficult to infer the direction of the change in activity. Nonetheless, in the context of model-based task-activation fMRI it can be useful to refer to the 'task-positive' regions, as opposed to the brain regions that exhibit decreased activation ('task-negative') such as the DMN. In this thesis, I refer to the regions that show positive activation during task fMRI as 'task-positive' regions.

1.5.8 Overlapping regions

It is not uncommon for the networks discussed above to share common nodes; as this might be a sign that they are hub regions that integrate functionally distinct brain networks. For instance, when investigating resting state FC of the DAN, Fox and colleagues noticed that the frontal eye fields (FEF) and intraparietal sulcus (IPS) are

also functionally connected with the preSMA (Fox et al., 2006). However, the preSMA is potentially a region that spans more than one network as it is also functionally connected to regions of the SN. One possible explanation is that the SN and the DAN may interact via the preSMA. Similarly, the right anterior insula appears to be related to both the SN and the VAN, and might constitute the locus of functional interaction between the two networks. Furthermore, Leech and colleagues found that the neural activity within the PCC has a highly complex structure (Leech et al., 2012). They fractionated the PCC to its subcomponents, revealing functionally distinct but spatially overlapping subregions of the PCC, suggesting a complex functional organisation of the PCC (Leech et al., 2012). Furthermore, they showed that the relative deactivation of the PCC found with performance on the choice reaction time task was isolated to signals originating in dorsal PCC. These signals echoed activity in frontoparietal networks that, given their spatial locations, are likely to be involved in attentional control (Leech et al., 2012). This suggests that the dorsal PCC has greater communication with attentional systems during periods without a focused task, possibly reflecting the PCC's role in maintaining a broad attentional focus. Such overlapping nodes, which span more than one distinct network, are not necessarily problematic when defining networks based on ICA, as is the case in the work presented in the current thesis.

1.6 Structural connectivity of large-scale brain networks

1.6.1 An overview of diffusion tensor imaging principals

Brain regions constitute large groups of spatially segregated neuronal populations. These are interconnected via bundles of long-distance axons forming white matter tracts, which enable the transport of large amounts of information between distinct

brain regions. Recent advances in magnetic resonance imaging (MRI) physics have led to the development of diffusion tensor imaging (DTI). DTI can identify how axons are organised in the brain by allowing the *in vivo* exploration of anatomical connectivity in the human brain, and then estimating the integrity of white matter tracts in a completely non-invasive way (Le Bihan et al., 2001). Briefly, in an unrestricted environment, water molecules diffuse freely in any direction (isotropically). However, in the white matter, diffusion is restricted by the cell membranes and myelin sheath, and diffusion therefore tends to be oriented in the same direction as axons (hence, anisotropically). Any alterations in the microstructure of white matter tracts provokes a change in diffusivity (Le Bihan et al., 2001). DTI can be used to infer the orientation of white matter tracts in the brain, as well as their structural integrity by measuring the direction of diffusivity. This technique is now becoming widely used for the evaluation of DAI (Arfanakis et al., 2002; Sidaros et al., 2008; Sugiyama et al., 2009).

A variety of measures have been developed to quantify white matter integrity using DTI. The most commonly used are fractional anisotropy (FA), and radial, axial and mean diffusivity (MD). Although the way in which these map to pathological changes is uncertain, FA is believed to relate to the degree of myelination and axonal density and/or integrity (Song et al., 2002; Arfanakis et al., 2002). Axial diffusivity measures diffusivity parallel to axonal fibers and has been proposed to reflect pathology of the axon itself. In contrast, radial diffusivity measures diffusivity perpendicular to axonal fibers and appears to reflect myelin abnormalities, either dysmyelination or demyelination, and might for instance be a useful marker of Multiple Sclerosis (MS) (Song et al., 2002). In this thesis, FA has been used as a validated marker of white

matter integrity after TBI (Mac Donald et al., 2007).

1.6.2 Relationship between functional and structural connectivity

This thesis combines both functional and structural connectivity measures to investigate cognitive control after TBI. By combining DTI with FC analysis, a number of studies have observed a direct association between functional and structural connectivity in the human brain (Guye et al., 2008; Damoiseaux and Greicius, 2009). For example, resting state FC has recently been compared with structural connectivity in three clinical case studies of patients with compromised inter-hemispheric white matter connections (Damoiseaux and Greicius, 2009). The studies converge to indicate that the strengths of resting state FC and structural connectivity are positively correlated. In keeping with that, almost all functionally linked regions of the DMN, the SN, and other task positive networks have been found to be structurally interconnected (van den Heuvel et al., 2009). Conversely, structurally connected brain regions exhibit stronger and more consistent resting state FC than structurally unconnected regions (Honey et al., 2009). This supports the notion of an overall link between structural and FC at a whole-brain level.

In 2009, Greicius and colleagues demonstrated that white matter pathways that connect regions of the functionally active DMN exist (Greicius et al., 2009). Their work suggests that there is an important role for the cingulum bundle in connecting the active regions of the DMN. Furthermore, Lowe and colleagues have recently demonstrated in multiple sclerosis patients that disease related decreases of FC between left and right primary motor regions are associated with the structural integrity of interconnecting corpus callosum tracts (Lawes et al., 2008). Johnston and

colleagues have reported that a section of the corpus callosum results in complete loss of inter-hemispheric FC during rest (Johnston et al., 2008), suggesting that the underlying white matter that connects the two hemispheres play an important role in functional synchronization. Taken together, these results suggest a direct link between structural and FC in the human brain (Koch et al., 2002; Hagmann et al., 2007; 2008; Johnston et al., 2008; Lawes et al., 2008; Greicius et al., 2009).

1.6.3 The impact of TBI on brain function: a review of the literature

TBI produces a complex combination of focal lesions and DAI that taken together are likely to have a devastating impact on cognitive functions. In this next section, I will separately review the studies investigating the effect of lesions and those looking at the effect of DAI on cognitive impairment post TBI.

1.6.3.1 'Lesion oriented' TBI studies

The impact of focal lesions on specific cognitive functions

Previous neuropsychological studies have often associated impairments in specific cognitive function with lesions in particular regions of the brain; this is based on two major assumptions. The first one being specific functions are supported by specific parts of the brain (Brodmann, 1960), and the second is that brain injuries disrupt this localized function, giving rise to corresponding behavioural deficits (Broca, 1863). The logic of this lesion based approach is 'if a patient cannot do X, then the execution of X must depend on the lesioned area'. As seen earlier in this chapter, lesions resulting from TBI tend to have characteristic locations in the frontal and temporal lobes. Previous studies have particularly focused on frontal lobe lesions,

mainly due to the critical role that this brain area plays in cognitive functions (Stuss, 2011). Stuss and colleagues, who over a number of years have provided detailed investigations of the relationship between focal damage in the frontal lobe and cognitive function (Shallice et al., 2007; Stuss, 2011) have shown that lesions to the superior, medial frontal structures, including but not limited to the ACC, affected a cognitive effort or 'energization' system. This resulted in a decreased ability to initiate a response and maintain performance overtime. They propose that lesions in this area of the brain may underlie the 'abulic' symptom often observed in TBI, and typically associated with slowness of processing, lack of activity and initiative, apparent disinterest and lethargy (Stuss, 2011; Zappalà et al., 2012). Lesions to this part of the brain would thus appear to relate to the deficits in the energetic aspects of attention described previously. In contrast, lesions to the left dorsolateral prefrontal cortex (DLPFC) affected task setting (task setting is the ability to set a stimulus-response relationship), while those to the right DLPFC affected monitoring (Stuss and Alexander, 2007; Shallice et al., 2008). Right frontal lesions have also often been associated with sustained attention deficits (Wilkins, 1987; Rueckert and Grafman, 1998) and inhibitory control impairment (Dimitrov et al., 2003; Aron et al., 2004). In addition, lesions to the ventro-medial/orbital PFC have been associated with a failure of emotional and behavioural regulation, and corresponding pathological behaviours such as impulsivity, childishness or aggressive and abusive behaviour (Stuss, 2011).

However, the problem with the lesion approach is that it leaves out the connectivity damage. Although these 'localisationist' approaches have been important in the evolution of modern clinical neuroscience, the emergence of new theories of the brain as being organised into large-scale networks proposes that the transfer of

information between distinct regions also plays a critical role in efficient cognitive control. Therefore, the study of lesions alone is unlikely to explain the full extent of cognitive deficits after TBI. Owing to the way DAI affects axonal connections, its impact on cognitive function and its high incidence (found in almost three quarter of patients with moderate and severe TBI; Skandsen et al., 2010), studies investigating the relationship between cognitive deficits and DAI appear important.

Furthermore, the presence of only one localized focal lesion is rarely observed in TBI patients, who are more likely to present with a combination of focal and diffuse injury. The most carefully designed lesions studies on TBI have claimed they had excluded subjects with evidence of DAI (e.g. Stuss et al., 2001). This is important because DAI can cause cognitive dysfunctions in the absence of focal injury, and these may be difficult to distinguish from those produced by focal injury alone (Stuss and Gow, 1992; Levine et al., 1998). However, it is only relatively recently that it has been possible to assess the true extent of DAI using DTI, and most previous studies did not have the advantage of this technique to characterize DAI. This might explain, at least in part, why studies of lesions' effects on cognitive functions in supposedly pure TBI groups have yielded such inconsistent results and have often failed to find clear relationships between lesion locations and neuropsychological performance (Levin et al., 1991; Ponsford and Kinsella, 1992; Anderson et al., 1995; Cockburn, 1995; Leblanc et al., 2006; Power et al., 2007). For instance, a study of 136 children who experienced TBI showed that deficits in inhibition were not related to lesion characteristics (Leblanc et al., 2005).

1.6.3.2 Diffuse axonal injury oriented TBI studies

Evidence for white matter tract damage post TBI

Using DTI as an imaging technique, persistent changes in white matter structure after TBI have been found to correlate with injury severity, and to predict functional outcome better than patients' initial clinical state or focal lesion load (Azouvi, 2000; Sidaros et al., 2008). Reduced FA has been reported, even in the absence of observable lesions in standard structural MRI (Nakayama et al., 2006). Increases in radial and axial diffusivity have also been observed, suggesting damage to both myelin and axons (Tisserand et al., 2006; Nakayama et al., 2006; Lo et al., 2009). Frontal and temporal white matter structures such as the anterior corona radiata, the uncinate fasciculus, the superior longitudinal fasciculus, the fronto-occipital fasciculus, as well as commissural fibers of the corpus callosum, are the most frequently damaged following TBI (Niogi et al., 2008). However, as TBI produces a complex pattern of axonal injury at variable locations across individuals, studies have previously not always been entirely consistent regarding the identification of the damaged tracts after TBI, which makes it difficult to identify consistent white matter disruption at the group level (Kinnunen et al., 2010). However, DTI may provide a more sensitive measurement of DAI compared to other neuroimaging techniques (Arfanakis et al., 2002), and recent work has shown consistent findings regarding white matter damage (Sharp et al., 2014) (**Figure 1.6**).
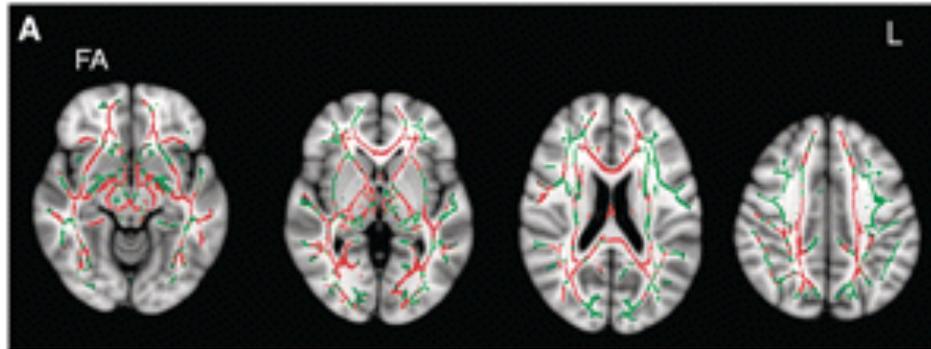
Figure 1.6: Widespread white matter disruption following TBI. *Axial slices illustrating the regions of the white matter skeleton where fractional anisotropy (FA) is significantly lower in TBI patients compared to controls (these tracts are highlighted in red) (adapted from Kinnunen et al. 2010).*

1.6.4 Relationship between white matter and cognition

Recent studies have shown that the severity of cognitive impairment following TBI may correlate with the amount of white matter damage, as assessed by DTI. Whole brain mean FA has been found to correlate with executive, attentional, and memory cognitive measures as well as reaction time (Kraus et al., 2007; Niogi et al., 2008). Other studies have looked more closely at how damage to specific tracts relates to cognitive impairment (Salmond et al., 2006; Lipton et al., 2009; Levin et al., 2010). In one study, impairments in executive functions have been found to relate to the structural integrity of frontal white matter (Lipton et al., 2009; Levin et al., 2010) and thalamo-cortical connections (Little et al., 2010).

A recent paper showed specific relationships between white matter integrity of the fornix and memory functions, as well as integrity in the left superior frontal white matter and executive functions (Kinnunen et al., 2010) (**Figure 1.6**). Other studies suggest that the integrity of the corpus callosum and the cingulum bundles maybe

critical for cognition. Wilde and colleagues reconstructed the corpus callosum of ten TBI patients and found a significant correlation between memory and concentration scores and FA within this tract (Wilde et al., 2008). They went on to study a further 43 TBI patients and found that lower cognitive performance on a flanker task (measuring interference and conflict processing) and the Sternberg task (measuring working memory) were associated with decreased FA within the cingulum bundles (Wilde et al., 2010).

1.6.5 Limitations of DTI studies

DTI appears to be a promising tool in TBI research. However, there are some limitations that should be taken into consideration when using this technique. First, the inclusion of subjects with large focal lesions may affect the measure of diffusion and create challenges for the DTI analysis (Hunter et al., 2012). Second, appropriate normative data are required since white matter structure is highly age-related (O'Sullivan et al., 2001; Andrews-Hanna et al., 2007). In this thesis, the FA measures were corrected for age, and all results were replicated within a subgroup of TBI patients with no evidence of focal lesions.

1.7 Deficits after TBI

1.7.1 Cognitive control deficits after TBI

Following a TBI, patients often suffer from a variety of disabling physical, cognitive, social, emotional and behavioural impairments (Whitnall et al., 2006). All of these

factors dramatically burden an individual and their families (McKinlay et al., 1981; Marsh et al., 1998; Coetzer et al., 2011). As already noted, It is thought that brain regions that are affected by TBI, namely frontal brain systems including the prefrontal cortex, the frontal lobes, anterior lobe structures, anterior temporal lobes and the anterior cingulate, regulate higher order cognitive control mechanisms (Granacher, 2007). Despite the heterogeneity in the cause, severity, and distribution of pathology in TBI, common neuropsychological and cognitive deficits are frequently observed. The lack of a unifying causative explanation for the occurrence of such deficits limits the development of effective treatment strategies to improve cognitive recovery in TBI patients. The current thesis focuses on specific cognitive control deficits that patients report problems with after TBI, namely response inhibition and task switching. These deficits contribute to the persistent disability following TBI (CDC, 2001; Castellanos et al., 2010). However, I will also include a brief review of related cognitive problems reported by patients, such as attention deficits.

Patients commonly complain of cognitive deficits post injury, and many patients live with sustained changes in their cognitive state for the remainder of their lives (McKinlay et al., 1981; McAllister, 1992; Millis et al., 2001). A common switching example is pulling a door that should be pushed. When pulling the door doesn't work, one must switch the initial approach and try the opposite manoeuvre. However, there may be an occasion where one fails to switch and retries the incorrect manoeuvre again. This perseverative type of behaviour is hallmark of patients with prefrontal cortex (PFC) damage in the brain. TBI patients with damage in the PFC epitomize this inability to flexibly switch between tasks, as they often exhibit perseverative behaviour and reduced cognitive flexibility in tasks that require switching, especially

between different categorization rules, such as the Wisconsin Card Sorting Test (Dreisbach and Goschke, 2004). Without the ability to flexibly reconfigure cognitive sets, rules, applications and response dispositions of the real world, we would be unable to adapt to the changing circumstances around us, and would suffer from perseveration and behavioural rigidity (Dreisbach and Goschke, 2004). It is this ability to efficiently and flexibly adjust behaviour on a moment-to-moment basis that is a typical hallmark of human behaviour (Braver et al., 2003).

Cognitive deficits after TBI also include information processing speed (Stuss et al., 1989), memory (Levin et al., 1986; Christodoulou et al., 2001; Vakil, 2005) and attention (Whyte et al., 1995; Dockree et al., 2004; Azouvi et al., 2004). Research on the cognitive sequelae of TBI have shown that these cognitive deficits often prevent patients from resuming previous activities, such as returning to work, and also contribute to psychosocial, educational, and vocational problems (Strangman et al., 2005). Thornhill and colleagues followed up patients one year after their TBI. They estimated that approximately half of the patients were in a worse financial position than pre-injury, whilst one third of were no longer employed (Thornhill et al., 2000). Furthermore, the impact of a TBI is thought significantly to affect a patient's capacity to participate in and benefit from rehabilitation due to cognitive problems (Ruttan et al., 2008).

Bonnelle and her colleagues carried out a study on 57 patients who had suffered a TBI in order to understand how the SN corresponds with efficient inhibitory control (Bonnelle et al., 2012) using the SST. As a group, the TBI patients showed an expected pattern of neuropsychological impairment, with evidence of slow

information processing speed, impaired inhibition, and reduced cognitive flexibility (Bonnelle et al., 2012). Furthermore, accuracy on Go trials was high for both groups, although patients were less accurate than controls. As discussed above, the SST provides a measure of the efficiency of an individual's inhibitory processing, known as the stop signal reaction time (SSRT). Bonnelle et al found that patients elicited a significantly greater SSRT than controls. The pattern of patients' performance on the task as a whole suggests that SSRT abnormalities were related in part to attentional impairments. This study is further expanded upon below in relation to the neural basis of inhibition impairment.

1.7.2 Attention deficits after TBI

TBI patients often suffer from sustained attention deficits, which manifest themselves as increased distractibility, poor concentration and a decreased ability to maintain attention focused over a long period of time; suggesting both a decrease in vigilance level and a decrement over time (Stuss et al., 1989; Whyte et al., 1995; Robertson et al., 1997; Dockree et al., 2004). Such deficits can have a considerable impact on patients' recovery and adjustment, and may be highly connected to impairments in other cognitive functions; particularly since anterior brain injury is so common in TBI (Grancher, 2007). For example, the magnitude of TBI patients' deficits in sustained attention has been related to impairments in error awareness (McAvinue et al., 2005).

It has been suggested that when an error is more impulsive it may be more easily monitored, whereas when an error is characterised by attentional drift, subsequent error-processing mechanisms may fail to engage (O'Keeffe et al., 2007). Robertson

and colleagues showed sustained attention deficits can affect inhibitory performance (Robertson et al., 1997) using a Sustained Attention to Response Task (SART). In the task, subjects have to respond to all numbers except one for which they have to withhold their response, and Robertson and colleagues found that impairments of sustained attention might account for a number of cognitive dysfunctions observed following TBI.

Evidence for this decreased attentional resource concerning TBI patients comes from studies investigating dual-task performance. TBI patients frequently struggle to perform more than one thing at a time, especially when the tasks require important cognitive control operations. In general, this type of attentional deficit tends to manifest under conditions of high cognitive load rather than when the tasks are relatively simple and automatic (Park et al., 1999; Brouwer et al., 2002; Azouvi et al., 2004). A reduced ability to allocate attention according to task demands due to limited resources is likely to have a major impact on the efficiency of patients to perform complex cognitive tasks and could explain, at least in part, deficits in other cognitive functions. Understanding the neural mechanisms underlying such a deficit may give greater insight into other types of cognitive impairments frequently observed in this clinical population.

1.7.3 Neural deficits after TBI

There is a growing body of research that demonstrates how TBI is associated with altered patterns of brain activation during tasks that require high levels of cognitive control. The inability to regulate the balance of internal versus external attention appears to be important in a range of clinical disorders. For example, the inability to

deactivate the DMN (either the result of local damage or through modulating fronto-parietal brain networks such as the SN) during externally focused tasks may result in distracting internally focused information processing. This may impair a range of executive abilities in TBI and normal ageing and is also consistent with a range of psychiatric symptoms in schizophrenia and depression (Leech and Sharp, 2010).

Recent work has consistently shown abnormalities in the DMN following TBI (Kim et al., 2010; Bonnelle et al., 2011; Mayer et al., 2011; Sharp and Ham, 2011; Sharp et al., 2011; Bonnelle et al., 2012). As already observed, head injuries frequently produce DAI, which disconnects brain regions and produces cognitive impairment (Kinnunen *et al.*, 2010). This is associated with reduced metabolism within the DMN (Nakashima et al., 2007). Bonnelle and colleagues studied the clinical significance of these abnormalities by investigating patients TBI who performed a simple choice reaction time task (Bonnelle et al., 2011). TBI often leads to impairments of sustained attention, and they observed that cognitive performance declined over time in their patients. They found that behaviour was normal at the start of the experiment, but slower and more variable by the end. The pattern of FC from the PCC/precuneus to the rest of the DMN predicted this decline in performance, and importantly this predictive information was present in the initial period of the experiment, when behaviour was normal. They also investigated the structure of the cingulum bundles, which connect the PCC to the anterior part of the DMN. They found that increasing damage to the right cingulum bundle was correlated with impairments of sustained attention. These results suggest that disruption of structural and functional connectivity within the DMN contribute to impairments of sustained attention.

Patients with TBI can also have difficulty switching from relatively automatic to controlled responses, and this can result in perseverative behaviour (Sharp et al., 2010). As in healthy ageing, this cognitive problem was associated with a failure of task-dependent deactivation within the DMN (Bonnelle et al., 2012). Bonnelle and colleagues studied this using the SST. A subgroup of patients with TBI showed impaired motor inhibition, which was related to a failure to rapidly deactivate the DMN (Bonnelle et al., 2012). As in healthy individuals (Weissman *et al.*, 2006), this pattern suggests that the inability to maintain efficient control of DMN function is associated with lapses in the moment-to-moment regulation of attention (Bonnelle et al., 2012). The extent of this DMN abnormality in patients with TBI was strikingly predicted by the structural integrity of the white matter tract connecting the right anterior insula (rAI) to the pre-supplementary motor area/dorsal anterior cingulate cortex (preSMA/dACC), core nodes of the SN. To further test for the specificity of this tract connecting the rAI to the preSMA/dACC, Bonnelle et al carried out the same tractography pipeline to derive FA measures on all the tracts that connect the regions that were activated during response inhibition, as based on their fMRI findings. These included: the 1) preSMA to the left anterior insula; 2) the right cingulum bundle, which connects the ventromedial prefrontal cortex (vmPFC) to the PCC; 3) the more marginally left cingulum bundle again connecting the vmPFC to the PCC; 4) the rIFG to the preSMA; 5) rIFG to the right temporo-parietal junction (rTPJ); and 6) the right frontal eye fields to the right intraparietal sulcus. They found that FA in these tracts were significantly lower in patients than controls. Furthermore, using a binary logistic approach, they classified patients into those who did and those who did not deactivate their DMN based on the integrity of these white matter tracts and found that the rAI-preSMA/dACC was the only tract that remained significant in their model.

The relationship between the integrity of the rAI-preSMA/dACC tract and DMN deactivation was not a result of focal brain damage, nor was it due to the overall amount of white matter damage, as Bonnelle et al report that was no relationship between average whole-brain white matter FA and DMN activity (Bonnelle et al., 2012).

The above results suggest that interactions between the SN and the DMN are important for the rapid re-allocation of attentional resources (Bonnelle et al., 2012). Behavioural impairments after TBI can be the result of a failure to efficiently control DMN activity, which is associated with attentional lapses. This in turn has been shown to result from damage to the integrity of the SN, notably the tract connecting the rAI to the preSMA-dACC (Leech and Sharp, 2012). Furthermore, this finding supports a model of cognitive control, in which responses of the SN to unexpected events trigger changes in other large-scale networks, including deactivation of the DMN (Leech and Sharp, 2013).

1.7.4 Changes in functional connectivity following TBI

The architectural organisation of the brain into spatially distributed brain networks may suggest that damage to the white matter is likely to disrupt the synchronisation between regions that are connected via the damaged pathways. This damage then could lead to changes in coordinated network function. Changes in one network function may affect the function of other connected networks (Bonnelle et al., 2012). However, only a few studies have investigated FC changes after TBI and their results are not always consistent.

One of the more consistent findings reported across the few TBI studies investigating FC is that DMN function appears particularly impaired after TBI; and that increased DMN FC is associated with recovery and better cognitive performance (Leech and Sharp, 2013). A recent study investigated resting state FC during brain injury recovery in ten TBI patients (Hillary et al., 2011). Changes in the DMN and a 'goal-directed' network (comprising the ACC and dorsolateral PFC) were observed between 3 and 6 months post-injury, with increased connectivity seen in the DMN and decreased connectivity seen in this 'goal-directed' network. They also found increased FC between both networks and the insula cortex, which is interesting considering the proposed role of this region in dynamically coordinating activity between the two networks (Sridharan et al., 2008). However, the study failed to find any significant relationship with changes in behavioural performance, thus the relationship between network connectivity and behaviour is still poorly understood. A recent study found that TBI patients with higher resting state DMN FC had less cognitive impairment and less evidence of diffuse axonal injury within the adjacent corpus callosum compared to patients who had lower resting state DMN FC (Sharp et al., 2011).

Other studies investigating TBI patients at a single time-point have reported reduced resting state connectivity within the DMN relative to controls (Boly et al., 2009a; Vanhaudenhuyse et al., 2010). Changes have also been observed within the EN. For instance, the dorsolateral PFC has been found to be decoupled from other task-positive brain regions in TBI patients performing semantic memory task, specifically under conditions where strategic control is needed (Strangman et al., 2009).

Brain network abnormalities after TBI have been widely observed in resting-state fMRI, which is acquired in the absence of a specific task (Sharp et al., 2014). Both increases and decreases in FC have been observed in a number of networks, including the DMN and SN (Mayer et al., 2011; Sharp et al., 2011; Stevens et al., 2012a). Several studies have reported that these abnormalities correlate with cognitive impairment (Tang et al., 2011; Caeyenberghs et al., 2014). Furthermore, studies using electroencephalography (EEG) and magnetoencephalography (MEG), which provide higher temporal resolution than fMRI, have also demonstrated disrupted FC after a range of severities of TBI (Castellanos et al., 2011; Tarapore et al., 2014).

Alongside the DMN, network abnormalities have been observed in other brain networks after TBI. For example, increased activation is frequently seen in nodes of brain networks involved in the control of cognitively demanding tasks (Rasmussen et al., 2008; Kasahara et al., 2011). These changes are not always associated with impaired behavioural performance, suggesting that they might represent compensatory increases in cognitive control (Kim et al., 2009). Reduced connectivity has also been observed within the motor network during performance of a simple motor task and disruptions to FC between the right and left inferior frontal gyri correlate with behavioural performance on a working memory task (Kasahara et al., 2010).

Abnormalities of FC have been demonstrated in patients with altered states of consciousness following TBI (Cauda et al., 2009). Disruption of FC to brain networks, particularly within the DMN has been reported across a range of states, including

anaesthesia (Biswal et al., 2010) and coma (Norton et al., 2012). Metabolic activity and FC in the DMN, and in particular the PCC seems to be particularly sensitive to states of awareness and arousal, and is also reduced in patients in the vegetative state (Laureys et al., 1999). More subtle abnormalities of awareness after TBI are associated with abnormal SN function, where after TBI, patients frequently show persistent problems with self-awareness (Ham et al., 2014). This manifests as problems monitoring their own behaviour, which is associated with reduced FC from the dACC to other parts of the SN. In general, the prognostic potential of these observations have been demonstrated by studies showing that DMN connectivity predicts recovery from coma (Norton et al., 2012), and identification of these network abnormalities provides a possible target for novel treatments (Sharp et al., 2014).

1.8 Ageing

Age-related cognitive impairment is an important cause of disability in older adults. By the year 2030, it is expected that there will be 1 billion adults aged 65 world-wide, compared to 500 million at present (National Institute on Ageing, 2007). This has major implications for both individuals and society. Adults aged 85 and older have a dementia rate of nearly 50% (Hebert et al., 2003), with a very high cost to affected individuals and families, as well as to limited medical resources. Even in the absence of disease, ageing is associated with varying degrees of cognitive decline, especially within the domains of memory, speed of processing and cognitive control (Park and Reuter-Lorenz, 2009).

Cognitive control declines with age; and impairments of cognitive control are an important component of this decline (Hasher L, and Zacks, R. T, 1988). Similarly to

TBI, one aspect of cognitive control that older adults demonstrate deficits in is response inhibition. However, perceptual speed and general 'slowing down' accounts for nearly all of the age-related variance on a broad range of cognitive tasks (Salthouse, 1996; Salthouse et al., 1991). In neuropsychological timed tests of executive function, such as the Stroop and Trail Making Tests, older adults, similarly to TBI patients, take significantly longer to complete the tasks (Ashendorf et al., 2008; Graf et al., 1995). Although this is a well-established phenomenon in cognitive ageing, the increased time to complete some cognitive control tests has been shown to result from a decline in the ability perform the task, rather than the general 'slowing down' that is ubiquitously found in ageing behaviour (Brink and McDowd, 1999; West and Alain, 2000). As a result, preservation of cognitive function is therefore becoming increasingly important to healthy ageing. A key challenge within research has been to understand the neurobiological causes of age-related decline in cognitive impairment.

1.8.1 Brain imaging in ageing

The frontal ageing hypothesis was first introduced by Albert and Kaplan (1980). This hypothesis states that frontal lobes are particularly vulnerable to age-related deterioration and predicts that functions largely dependent on frontal regions of the brain decline with increasing age, while functions that are largely independent of frontal lobes remain relatively spared. Thus cognitive function involving frontal regions of the brain such as response inhibition will be most adversely affected by increasing age (West, 1996; Wingfield and Tun, 2007). This localisationist view of cognitive decline with increasing age receives support from a wide variety of

research domains, including structural and functional neuroimaging (Giorgio et al., 2010; Grady, 2000; Salat et al., 2004; West and Alain, 2000).

Efficient cognitive control between brain regions relies on the integrity of white matter tracts (Deary et al., 2010; Neubauer and Fink, 2009). Structural MRI studies in the ageing brain have demonstrated that white matter integrity has a non-linear relationship with age, showing an increase in integrity until middle age where it plateaus and then decreases (Walhovd et al., 2005; Giorgio et al., 2010). A decrease in white matter integrity in older adults has also been demonstrated predominately in frontal white matter (Bergfield et al., 2010).

MRI and DTI studies of white matter in the ageing brain have shown reduced white matter integrity and altered white matter microstructure with increasing age (Salat et al., 2005). It is unclear whether these observed structural changes are uniform across the brain, or whether accelerated white matter degeneration is localized to particular brain regions, as would support the frontal-ageing hypothesis (Salat et al., 2005). However, white matter micro-structural measures show some evidence for greater damage in anterior regions than posterior regions (Raz et al., 1997; Salat et al., 2005).

Reduced white matter integrity is negatively associated with increasing age (Pfefferbaum and Sullivan, 2003; Sullivan et al., 2010; Vernooij et al., 2008; Zhang, 2010). This reduced integrity is thought to represent lower axonal packing (Beaulieu and Allen, 1994), axonal damage (Lehmann et al., 2010) and/or loss of axonal fibres (Aboitiz et al., 1996; Moseley et al., 1990). Although these observed changes in white matter integrity are only indirectly linked to the cellular makeup, decreased integrity

reflects micro-structural damage that is thought to be the primary cause of white matter disconnection within networks that support cognitive performance (O'Sullivan et al., 2001; Bennett et al., 2010). This disconnection of white matter pathways is due to age-related white matter damage (O'Sullivan et al., 2001), which results in inefficient cognitive control (Madden et al., 2009).

Post mortem studies have demonstrated demyelination throughout the white matter in the ageing brain, suggesting widespread disconnection of white matter tracts. Animal studies have led to the suggestion that the increase in myelin production that has been observed in middle age is sub-optimal; with the increased myelin showing greater susceptibility for splitting and therefore being micro-structurally damaged (Lazzarini, 2004, Peters, 2002). It is possible that, from middle age onwards, cognitive decline may be due to a reduction in white matter volume with widespread white matter damage.

A key hypothesis for age-related cognitive decline is that activity within brain networks becomes less co-ordinated as individuals age (Damoiseaux et al., 2008) and the disruption to the co-ordinated activity across the brain networks is mediated by cortical "disconnection" due to damage to white matter fibres (O'Sullivan et al., 2001). To date, the DMN is the most comprehensively studied brain network in ageing (Andrews-Hanna et al., 2007, Damoiseaux et al., 2008, Teipel et al., 2010, Chen et al., 2009). However, the impact of reduced functional and structural connectivity within other networks, together with the impact of this functional-structural connectivity within other brain networks on cognitive control has not been assessed (Andrews-Hanna et al., 2007, Onoda et al., 2012).

Previous work has found that there is reduced FC across the anterior to posterior regions of the DMN in ageing, associated with cognitive decline (Damoiseaux et al., 2008; Onoda et al., 2012). Ageing is also associated with reduced FC within other large-scale brain networks, notably the SN (Onoda et al., 2012). Furthermore, this reduced FC was associated with measured decreases in individual cognitive abilities (Onoda et al., 2012). Investigations into white-matter changes in individuals aged from middle age onwards may contribute to the understanding as to why the accelerated cognitive decline is found within this age group.

1.9 Thesis objectives

1.9.1 Aims

Cognitive control is necessary for goal-directed behaviour. This behaviour includes the ability to initiate and stop an action, as well as monitor and switch behaviour when needed. The current thesis investigates the neural basis of these mechanisms, with particular interest in stopping an unwanted response and switching from an established task to a new task. The neural bases for cognitive decline are complex and its explanation by a single factor, such as frontal lobe damage is likely to be over-simplistic (Greenwood, 2000). Instead, the emphasis in this thesis is on brain networks, which are composed of groups of neurons in the brain that work together to perform a broad range of mental processes and so guide and control behaviour (Bressler and Menon, 2010). These networks are functionally and structurally coherent and a disruption to brain tissue can alter their coherence and hence have a severe impact on cognition (Andrews-Hanna, 2007).

In light of the above, it therefore seems more appropriate to relate cognitive functions to properties of a network rather than specific brain regions. The SN helps to generate a state of heightened physiological awareness of salient stimuli and investigating potential disruptions to these processes may help to better understand brain mechanisms underlying psychopathology in several neurological injuries, including TBI and healthy ageing. This thesis therefore examines how brain networks dynamically interact when a participant stops a prepotent response or switches to a new response. Studying these mechanisms in the healthy brain will then inform us regarding how the brain is affected post TBI. The goal of the current research is to identify brain network interactions that can explain cognitive impairment following TBI; and this will be done using structural and functional neuroimaging techniques. Furthermore, the current thesis proposes that age-related white matter damage to the connections of the SN might explain uncontrolled network activity, providing a mechanism for age-related behavioural impairments in cognitive control. An objective of the current work is to investigate cognitive deficits in ageing, and to assess the structural and functional connectivity of the ageing brain.

1.9.2 Hypotheses

This thesis combines functional and structural neuroimaging data with behavioural and cognitive measures to test a set of specific hypotheses based on the work reported in this chapter. The current thesis investigates how TBI impairs network connectivity, with particular interest in the dynamic interactions between the DMN and the SN. Furthermore, it investigates whether structural damage after TBI and in

healthy ageing impairs these dynamic interactions between the DMN and SN. As a result, the following hypotheses will be tested:

(1) Demanding cognitive operations, such as stopping (as tested using the SST), and switching (as tested using a task switching paradigm), will be accompanied by increased FC between the rAI, a key node in the SN, and the DMN in healthy controls;

(2) Patients who have suffered a TBI, who also demonstrate impairments of response inhibition and task switching, will fail to show this change in FC between the rAI and the DMN.

(3) The amount of damage to the white matter tract connecting two key nodes of the SN, namely the rAI to the preSMA and dACC will inversely correlate with FC between the rAI and DMN during stopping and switching in both the TBI groups and the elderly population.

(4) Furthermore, a group of healthy elderly participants who also demonstrate response inhibition impairments will also demonstrate similar brain network dysfunction as the TBI patient group.

2. Methods

In this chapter, I will describe information about participants and methods, as well as introduce the main concepts for the analytical tools used in this thesis. I first briefly present some information about patients' recruitment and the classification of their injury severity, with further demographic details presented separately in each results chapter. I also present the battery of neuropsychological tests used to assess cognitive function in the patient groups. I then introduce the behavioural paradigms that have been used for the functional imaging studies, as well as the behavioural and cognitive measures that are associated with them. This is followed by a presentation of the general principles of MRI, and a description of functional MRI and DTI techniques. I next introduce the methods I have used to process and analyse the functional and structural imaging data. Finally, I lay out the scanning protocol and scanning parameters used in the studies presented in this thesis.

2.1. Participants

2.1.1. Patient recruitment

Patients were all at the post-acute/chronic phase post-injury, i.e. they were recruited for the study more than two months after their injury. They were referred into their local TBI service because of persistent cognitive problems and were invited to participate in our research program. Exclusion criteria were as follows: neurosurgery, except for invasive intracranial pressure monitoring; history of psychiatric or neurological illness prior to their head injury; history of significant previous TBI; anti-epileptic medication; current or previous drug or alcohol abuse; or contraindication to

MRI. In the results chapters, the participant group is described and I have provided all relevant clinical details for the patient groups.

2.1.2. Classification of TBI severity

The Mayo Classification System was used to classify TBI severity, on the basis of available indicators (Malec et al., 2007). These included trauma-related neuroimaging abnormalities; Glasgow Coma Scale (GCS), which measures the level of consciousness and level of neurological functioning using numbers from 3-15, with lower GCS scores indicating a more severe loss of consciousness); PTA (post-traumatic amnesia); loss of consciousness; and specified post-concussive symptoms. According to this system, cases of TBI can be classified as: moderate to severe (strong evidence of definite brain trauma); mild (weaker evidence of probable TBI); or symptomatic (only equivocal documented evidence of the occurrence of possible TBI) (Malec et al., 2007). A patient will be classified with moderate to severe TBI if one or more of the following criteria apply: death due to TBI; loss of consciousness of more than 30 min; PTA of more than 24 hours; GCS of less than 13 in first 24 hours; evidence of haematoma, contusion, penetrating TBI, subarachnoid haemorrhage; or brain stem injury. A TBI patient will be classified as mild (probable) TBI if none of the above criteria applies and if one or more of the following criteria apply: loss of consciousness of less than 30 minutes; PTA of less than 24 hours; depression; basilar or linear skull fracture (dura intact). Finally, a patient will be classified as symptomatic (possible TBI) if none of the previous criteria applies and if at least one of the following symptoms is present: blurred vision; confusion; daze; dizziness; focal neurological symptoms; headache and nausea. The classification of each patient used in this thesis is provided in the relevant chapters.

2.1.3. Control groups

Independent control groups were used for the functional and structural imaging studies. They were all age-matched with the study relevant patients groups. The controls had no history of neurological or psychiatric disorder, which was assessed via a medical history check and details; details are presented in their relevant chapters.

2.2. Neuropsychological assessment

A detailed neuropsychological battery was used to assess cognitive function. This battery has been previously used to assess cognitive function after TBI (Kinnunen et al., 2010; Bonnelle et al., 2012) and has been found to be sensitive to impairments after TBI. Current verbal and non-verbal reasoning ability was assessed using the Wechsler Test of Adult Reading and the Wechsler Abbreviated Scale of Intelligence Similarities and Matrix Reasoning subtests (Wechsler, 1999). Verbal Fluency, Letter Fluency and Colour-Word (Stroop) tests were administered from the Delis-Kaplan Executive Function System to assess cognitive flexibility, inhibition and set-shifting (Delis et al., 2001). The Trail Making Test (forms A and B) was used to further assess executive functions (Reitan and Wolfson, 2004). Working memory was assessed via The Digit Span subtest of the Wechsler Memory Scale-Third Edition (WMS-III) (Wechsler, 1997). The Logical Memory I and II subtests of the WMS-III were included as measures of immediate and delayed verbal recall. The People Test from the Doors and People Test battery was used as a measure of associative learning and recall (immediate and delayed) (Baddeley et al., 1994).

Table 2.1: Neuropsychological tests and their cognitive components.

Cognitive Domain	Cognitive Subset	Cognitive test
Intellectual ability	Pre-morbid intelligence	Wechsler Test of Adult Reading (WTAR)
	Verbal	WAIS Similarities
	Non-verbal	WAIS Matrix reasoning
Memory	Working memory	WAIS Digit span
	Associative	People Test, Logical memory parts I and II (immediate recall)
		People test, Logical memory parts I and II (delayed recall)
Executive function	Cognitive flexibility	D-KEFS Colour word interference test (Stroop)
	Alternating switch cost	D-KEFS Trail Making Test B/A
	Word generation fluency	D-KEFS Letter fluency F+A+S total
Processing Speed	Visual search complex	D-KEFS Trail Making Test A (s) + Trail Making Test B (s)
Cognitive impairment screen		Mini Mental State Examination (MMSE)

The neuropsychological tests used in this thesis and the cognitive domains they test are described above. WAIS = Wechsler adult intelligence scale, D-KEFS = Delis-Kaplan executive function system, s = seconds.

2.2.1. The Delis-Kaplan Executive Function System

The Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001) is a set of standardised tests for comprehensively assessing higher-level cognitive function, in both children and adults. The tests were designed to assess mild brain damage and in particular mild frontal-lobe involvement (Swanson, 2005). The D-KEFS comprises nine tests that measure a wide range of verbal and non-verbal executive functions. The particular sub-tests used in the current thesis to predict specific cognitive decline include measures of processing speed and mental flexibility via the D-KEFS Trail Making Tests A and B and the D-KEFS colour word interference test (Stroop) (described below).

2.2.1.1. Trail making tests A and B

The Trail Making Test (TMT) (**Figure 2.1**) is a neuropsychological test of frontal lobe function in particular the dorsolateral prefrontal cortex and the medial prefrontal cortex (Moll et al., 2002). The test is administered in two parts: Part A (TMT A) which assesses visual scanning, numeric sequencing, and visual-motor speed; and Part B (TMT B) which tests cognitive demands including visual-motor, visual spatial abilities, working memory and mental flexibility. A more pure indicator of executive function can be obtained by subtracting the TMT B score form the TMT A score (TMTB – TMTA) (Sanchez-Cubillo and Perianez, 2009). This sensitive measure of switching flexibility has been administered outside of the scanner in the current work. The TMT A and TMT B have long been validated as a test of organic brain injury (Reitan, 1958). However, the test can be more skewed towards better educated individuals as studies have found that education level is a variable that affects TMT scores (Tombaugh, 2004).
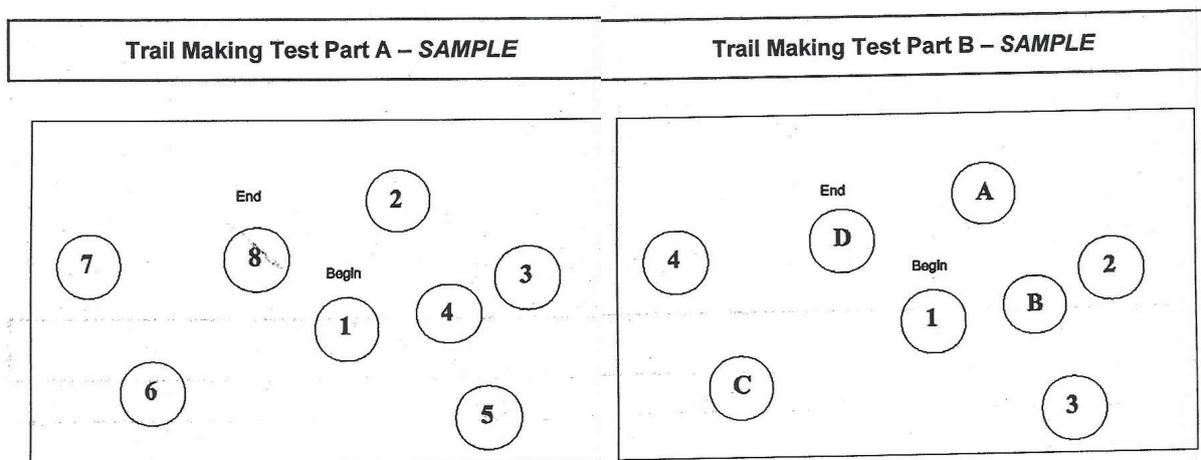
Figure 2.1: Trail Making Test A and B. *In part A of the test (left), the participant is required to draw lines to connect the numbers in ascending order. In part B (right), the participant is required to draw lines to connects the circles in ascending order, but with the added task of switching between the numbers and letters (i.e. 1-A-2-B-3-C-4-D, etc.). The participant is instructed to do this as quickly and as accurately as*

possible, without lifting the pen from the paper. The participant is timed while they connect the trail. An error is pointed out to the participant and errors affect the participant's score in that the correction of errors is included in the time to complete the task.

2.2.1.2. Colour-word interference test (Stroop test)

The colour-word interference test is based on the Stroop effect (Stroop, 1935), which evaluates both inhibition and cognitive flexibility. The test measures the ability to inhibit an over-learned verbal response (i.e. reading printed words) to generate the conflicting response of naming the dissonant ink colours in which the words are printed (**Figure 2.2**). It was designed to evaluate both cognitive flexibility and ability to inhibit perseverative and unplanned impulsive verbal responses. Successful behaviour during the Stroop test (inhibition) requires engagement of attentional networks in the brain, which commonly include the dorsolateral prefrontal cortex, anterior cingulate cortex, and posterior parietal cortex (Chen et al., 2012).
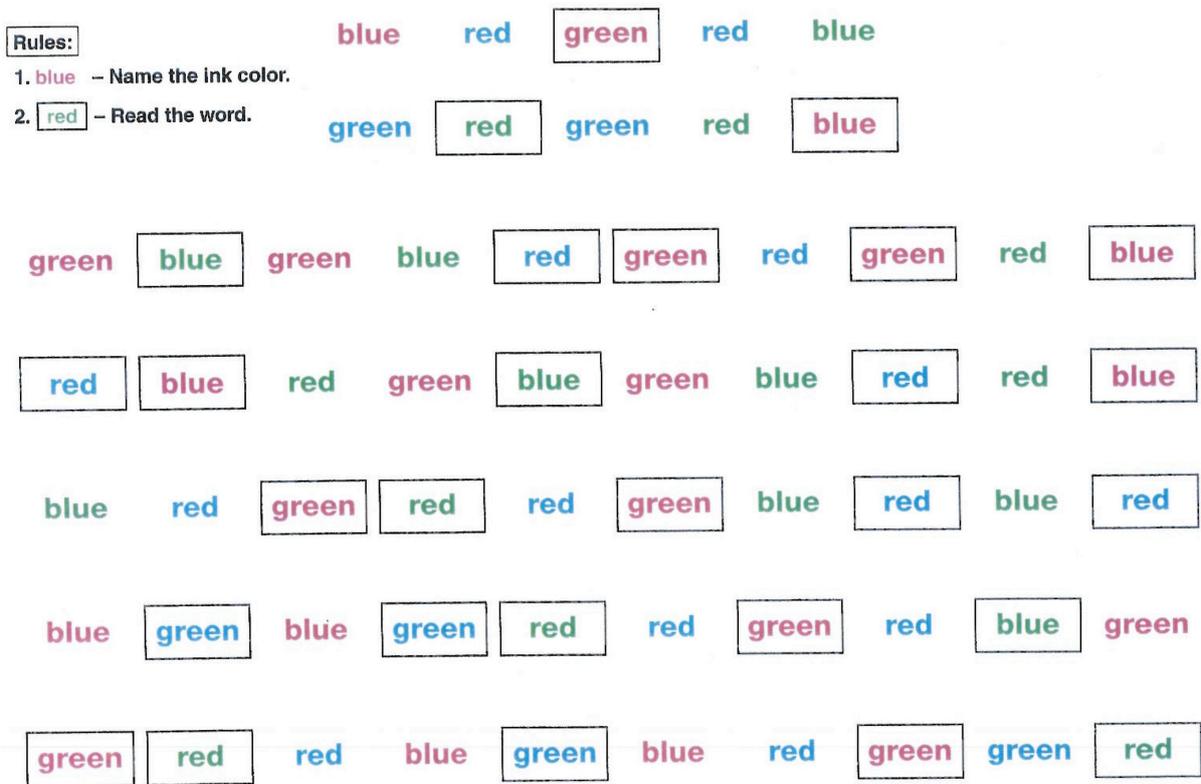
Figure 2.2: The colour-word interference test (Stroop test). *The colour-word interference test comprises four parts. First, participants are timed as they name colours and second they are timed as they read words. Third, they are required to say aloud the name of the ink that the word is printed in (the response for the first two words above would be red and blue). Fourth, they are required to switch between naming the ink colour and reading the word, as this figure above depicts. Under this rule, if a box surrounds the word they are required to say the word (e.g., for the third word in this test, the correct answer would be green).*

2.3. Neuroimaging analysis pipeline

A high level overview of the neuroimaging methodology used in the current thesis is illustrated in **Figure 2.3**, and is further explained in the sections below. Briefly, the datasets collected included behavioural, functional and structural imaging data. The functional imaging data was processed using both a univariate approach (see 'Standard voxelwise GLM analysis' and 'Region of interest analysis' below) and also multivariate approaches (see 'Time course extraction for the PPI' and 'Psychophysiological interaction' sections below). Furthermore, a tractography mask

was applied to my patient group; the mask was generated in an independent group of healthy volunteers to define the rAI-preSMA/dACC pathway (see 'Structural White Matter Tractography Analysis' below) to my patient group. Taken together, this analysis pipeline allowed me to investigate how damage to the rAI-preSMA/dACC white matter tract can predict network dysfunction.
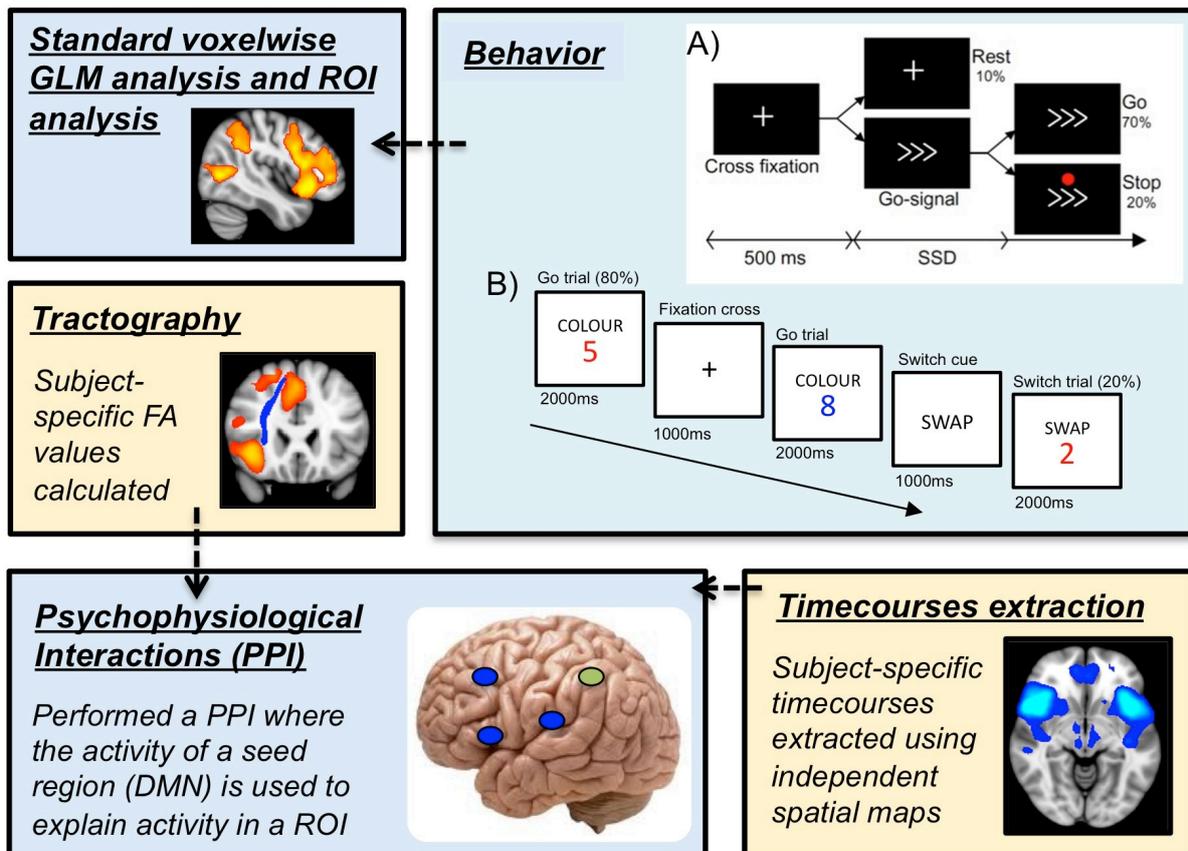
Figure 2.3: Methodology pipeline. *The initial fMRI data was analysed using a univariate approach to generate contrasts between key trial type regressors (such as stop > Go and switch > Go). I then implemented the first stage of dual regression to extract subject-specific timecourses for the DMN. The DMN spatial map came from an independent dataset defined by (Smith et al., 2009). These timecourses were then implemented in my PPI analysis, where I calculated general linear models (GLM) for each subject. This GLM included the DMN timecourse as my dependent variable. The independent variables (IVs) included a constant, the timecourse of our seed ROI (e.g. the rAI), task timecourses and interaction timecourses. The GLM generated parameter estimates for my IVs, where I contrasted the task interactions (e.g. stop x ROI interaction – Go x ROI interaction parameter estimates), to replicate my contrasts at the univariate level (e.g. stop > Go).*

2.4. Functional imaging paradigms

Two tasks with different levels of cognitive load were used to assess various aspects of cognitive dysfunctions after TBI: a SST and a task switching paradigm. The SST was used to investigate inhibitory control (chapters 3 and 5) and a task switching paradigm (chapters 4 and 6), which is broken down into two conditions, each with slightly different psychological parameters. Chapter 4 implements a motor task switching paradigm, whereas chapter 6 implements a cognitive task switch. The paradigms are described below.

2.4.1. The stop signal task

2.4.1.1. Principles of the stop signal task

The SST is based on a simple choice reaction time task, where participants are required to press left when the stimulus arrow is pointing to the left, and press right when the stimulus arrow is pointing to the right. These simple right or left arrows are the "Go" stimuli. Participants are required to make their response as quickly and as accurately as possible by pressing either left or right on a button response box. However, at irregular intervals and unpredictably for the participants, the Go stimulus is followed by a "stop" signal (e.g. a red dot above the arrow), which instructs subjects to withhold their response (Logan et al., 1984).

Participants are generally able to inhibit their response when the stop signal is presented close to the time of stimulus presentation, but fail to inhibit when it is presented closer to the moment of response execution. To account for these observations, Logan proposed a *'horse-race'* model. According to this model, 'Stop' and 'Go' processes are independent from one another, and a 'race' occurs between

the two processes for completion. The winner of this 'race' is whichever process finishes first - either the Stop response, or the Go response. If the Go process wins, the response is executed, resulting in an incorrect Stop trial; if the Stop process wins, the response is successfully inhibited (resulting in a correct Stop trial). The inhibition of a response thus depends on the relative finishing times of the Go and the Stop processes. The position of the stop signal during the Go process biases the race in favour of one process or the other. If the stop signal occurs early in the trial, the response will usually be inhibited. Conversely, if the signal occurs late enough, the response will rarely be inhibited (**Figure 2.4**).
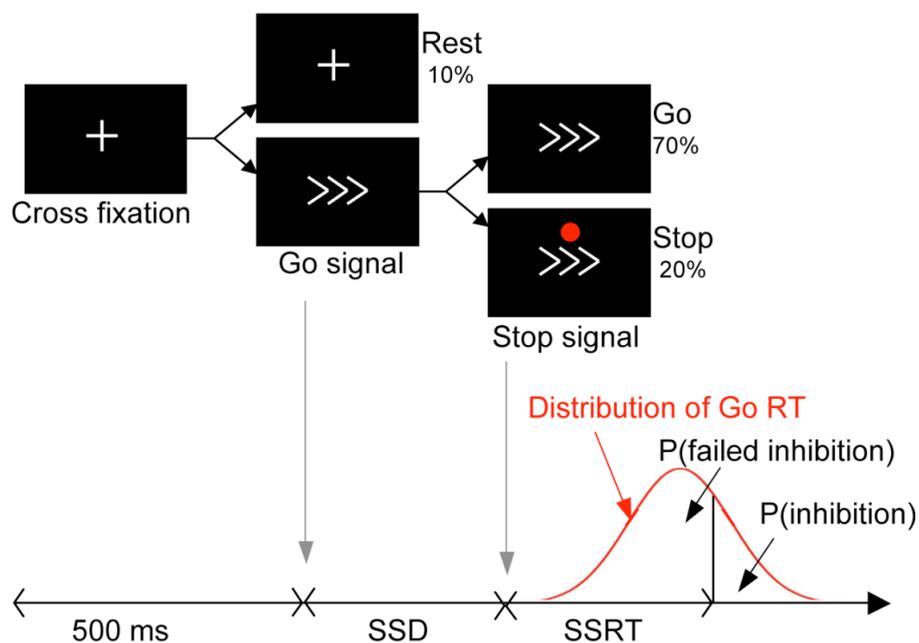
Figure 2.4: Stop Signal Task overview. *Trials started with a fixation cross, followed by a Go signal (right or left pointing arrow). 20% of the trials involved an unpredictable stop signal (red dot) presented at a variable delay following the Go signal (the stop signal delay; SSD). The time it takes for a participant to inhibit a response can be estimated by the stop signal reaction time (SSRT).*

2.4.1.2. Stop signal task description

Participants are presented with an initial fixation cross for 500ms, followed by a Go

signal in the form of a left or right pointing arrow. This arrow signals which response direction the participant needs to press. Button presses were made with the index finger of each hand. On 20% of the trials, a red circle appeared above the location of the Go stimulus (stop signal). This stop signal indicated that the participant should inhibit the button press (**Figure 2.4**).

Tracking procedure

The delay between the presentation of the Go and stop signals is termed the stop signal delay (SSD) (**Figure 2.4**). The ability to inhibit a response is a function of the length of the SSD, the longer the SSD, the more difficult it is to successfully inhibit a response. By varying the SSD according to participants' performances, it is possible to compute a 'critical' SSD, which represents the time delay required for the subject to succeed in withholding a response on 50% of the stop trials. Therefore, a staircase procedure can be used. Here, the SSD was initially set to correspond to the mean Go reaction time (RT) of a previously performed choice reaction time task, minus 200ms. Subsequently, the SSD was adaptively varied every two stop trials. If cumulative accuracy on previous stop trials was greater than 50%, the SSD was increased by 50ms, if less than 50%, the SSD was decreased by 50ms. A lower limit for SSD was set to 50ms. This tracking procedure has two principal advantages. Firstly, it allows the estimation of a 'stop signal reaction time' (SSRT). This measure is thought to reflect how well a participant can inhibit their response, with lower SSRT corresponding to better inhibition (see next paragraph for SSRT estimation). Secondly, it compensates for between participant differences in stopping success, by allowing us to equate Stop accuracy in both patients and control subjects to 50%. This is critical for the interpretation of results when comparing brain activation

between two groups (Price et al., 2006).

Estimation of the stop signal reaction time

The SSRT measures the speed of the inhibitory process and is most commonly used as a behavioural measure of response inhibition (Logan et al., 1984; Aron et al., 2007). The SSRT has been found to correlate with self-reported impulsivity (Logan et al., 1997) and also appears to be related to other measures of inhibition and executive control (Friedman and Miyake, 2004). SSRT corresponds to the time interval between the start and finish of the Stop process, at a defined level of Stop trial success, usually 50% (*Figure 2.4*). Therefore, it estimates how fast participants can cancel an already initiated response. The length of the response inhibition process cannot be measured directly, due to the absence of an overt response. However, it can be estimated using methods that are based on the assumptions of the horse-race model (Logan et al., 1984). The two main assumptions of this model are that the Go and Stop processes are independent, and that each participant's SSRT provides a reliable estimate of inhibitory control as a fixed ability. With these assumptions, and when using a staircase tracking procedure, SSRT can be estimated by subtracting the mean SSD from the mean or median Go RT (Aron and Poldrack, 2006).

Limitations with stop signal reaction time estimation

Although the horse-race model has been widely used to estimate the SSRT (Logan et al., 1997), it is not always valid. There are a number of situations where SSRT estimation may fail or be biased, because the Go and Stop processes are not fully independent, or because the SSRT might not be a fixed measure of inhibition ability

(Bonnelle et al., 2012).

Stop signal reaction time and strategic slowing down

In order for the race model to be applicable to behavioural data, participants must attempt to respond as quickly and as accurately as possible on Go trials. However, despite these explicit instructions, it is not uncommon that participants adopt a 'progressive slowing' strategy, where they increase their response-time in order to increase the probability of inhibiting a response when a stop signal is presented. Participants who exhibit such strategic slowing often produce shorter SSRT estimates independently of their real inhibitory capability (Leotti and Wager, 2010). This has been proposed as an explanation for the frequently observed negative correlation between task accuracy and SSRT, where slower responses results in better accuracy (speed-accuracy trade-off) and better SSRT (lower value) (Boehler et al., 2010). In the two SST versions used in this thesis, a negative feedback element was introduced to prevent subjects from slowing too much. This is described in more detail below.

Preventing slowing down

As the horse-race model assumes that the Go and Stop processes are independent, the RT for Go trials should thus not be influenced by the presentation of a stop signal in previous trials or by its anticipation in future trials (Alderson et al., 2008). Nevertheless, the presentation of Stop stimuli can affect processing of Go stimuli, which violates the assumptions of the horse-race model (Bekker et al., 2005). Moreover, SSRT has been found to correlate with the mean RT of Go trials (Boehler et al., 2010), indicating that the SSRT is a sensitive measure of response inhibition.

These findings imply that the use of different strategies may influence the SSRT, challenging the assumption of the horse-race model, and leading researchers to develop adaptations of the conventional SST.

One such modification of the SST was introduced to limit any strategic slowing on the task. The ability of individuals to slow down on Go trials was limited by providing feedback when participants actively slowed their responses, and passed a threshold for the speed of their Go response. Negative feedback in the form of the words "Speed up!" were presented on the screen in place of the subsequent trial, each time a response was made with a RT above the 95th percentile of the participant's current RT distribution.

2.4.1.3. The stop signal task and clinical studies

The SSRT has been found to be attention deficit and hyperactivity disorder (ADHD) (Schachar, 2000; Lijffijt et al., 2005), obsessive compulsive disorder (Chamberlain et al., 2006), schizophrenia (Nolan et al., 2011) as well as in TBI (Dimoska-Di Marco et al., 2011). However, most of these patient groups also have more general attentional deficits that could have resulted in an inflated estimation of the SSRT. For instance, a meta-analysis of SST studies in ADHD showed that higher SSRTs observed in ADHD reflected a more generalised deficit in attention processing rather than deficits of response inhibition (Alderson et al., 2008).

Taken together, these observations suggest that the degree to which the SSRT specifically indexes response inhibition might vary from one participant to another. This variation may be present particularly when investigating patients with other

cognitive deficits, as SSRT might not specifically index different degrees of inhibitory ability, but rather relate to more general factors, such as motivation and/or attention (Padmala and Pessoa, 2010).

2.4.1.4. Exclusion criteria for SSRT estimation

Abnormally low SSRTs can result from an inadequate performance of the task. This can manifest as an important slowing on Go trials (strategic slowing-down), poor Go trials accuracy, or a failure of the adaptive staircase procedure, resulting in Stop accuracies much lower or higher than 50%. However, only few studies have reported exclusion criteria for the estimation of SSRT. Rucklidge and colleagues reported the exclusion of 5 subjects out of 108 according to the following criteria: 1) percent inhibition less than 13% or greater than 85%, and 2) SSRT less than 50ms (Rucklidge and Tannock, 2002). Another study using a more stringent exclusion criteria reported the exclusion of 21 participants out of 67 based on: 1) a response rate on Go trials lower than 90%; 2) more than 10% incorrect trials on the Go task; 3) percentage inhibition on the Stop task less than 25% or greater than 75%; or 4) an SSRT of less than 80ms (Cohen et al., 2010). However, these criteria do not control for the strategic slowing-down that can also affect SSRT estimation, or include Stop accuracies that are too far from 50% for a critical SSD to be accurately estimated. Therefore, Bonnelle and colleagues developed the following exclusion criteria: 1) a Stop accuracy lower than 40% or higher than 60%; 2) a Go accuracy lower than 80%; 3) more than 30 'negative feedback' events (Bonnelle et al., 2012). Using these exclusion criteria, each SSRT measures included were in the typical range for both healthy participants and TBI patients. These criteria have been adopted in the work carried out in Chapters 3 and 5.

2.4.2. The task switching paradigm

To investigate mental processes involved in reconfiguring task-sets, a task switching paradigm was created using Matlab©, where participants were instructed to consistently switch between tasks. This allowed me to examine the behavioural and neural correlates of switching from task to task. The task switching paradigm is a two-choice, task switching paradigm, which requires reconfiguration of mental resources in order to execute an appropriate motor response (Monsell, 2003) based on a Switch cue (Sudevan and Taylor, 1987).

2.4.2.1. *Motor switch paradigm*

In the experiment described in Chapter 4, a motor switch was used as the switch cue. This paradigm required participants to classify target stimuli as either blue or red. Initially, participants were required to respond to blue targets with their left hand and red targets with their right hand (***Figure 2.5***). This part of the task was performed for a variable period of time before the switch. Trials that followed one another without change in this motor response mapping were classed as Go trials (stimulus duration = 2000ms). At various intervals participants were presented with a switch cue (1000ms), which preceded a switch trial (2000ms). This switch cue informed the participant to switch their motor response mapping on subsequent trials. Therefore, participants were subsequently required to respond to blue targets with their right hand and red targets with their left hand.
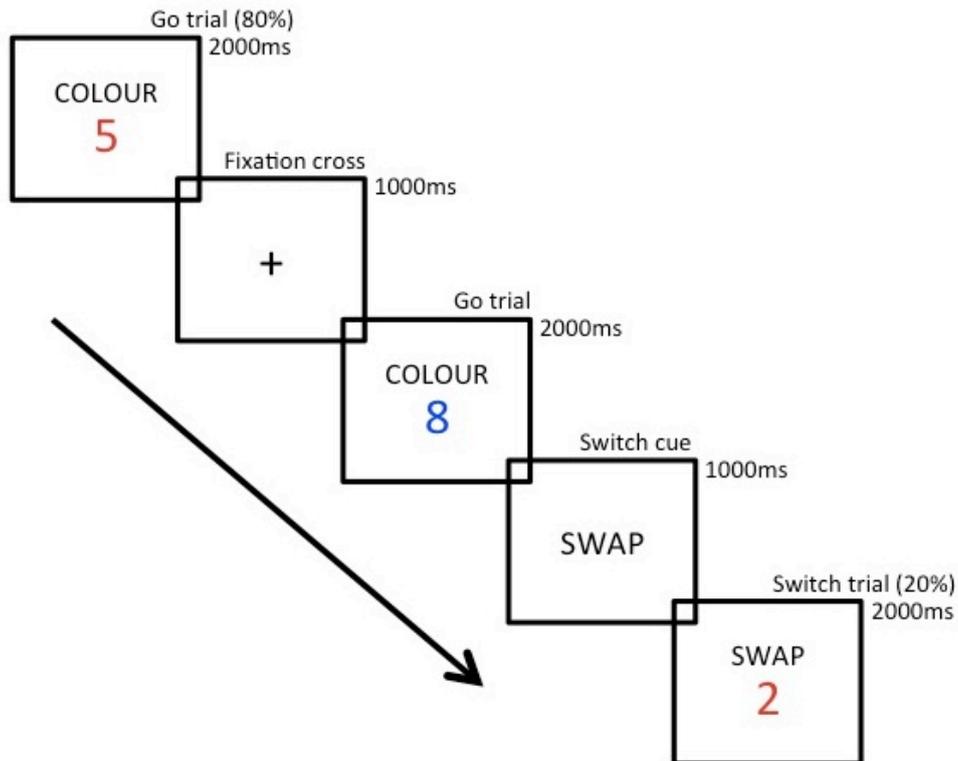
Figure 2.5: ***Schematic diagram of the motor task switching paradigm.*** *Eighty percent of trials are Go trials. These involved an initial fixation cross, followed by a colour stimulus signifying a left or right finger press (blue = left, red = right). Switch trials involve the presentation of a switch cue (e.g. the word 'SWAP') signifying the need to reverse the colour/response mapping (i.e. blue = right, red = left).*

2.4.2.2. Cognitive switch paradigm

In the experiments described in Chapter 6, a cognitive switch was used as the switch cue (***Figure 2.6***). This paradigm contained all the timing parameters as described above (motor switch paradigm) however, this time participants were required to classify target stimuli as either blue or red and then switch to classify targets as either odd or even numbers. Initially, participants were required to respond to blue targets with their left hand and red targets with their right hand, as in the motor switch paradigm. Again, at unpredictable and predictable intervals, participants were presented with a switch cue (1000ms), which preceded a switch trial (2000ms). This switch cue informed the participant to switch to the odd/even number rule on subsequent trials. Therefore, participants were required to respond to even number

targets (e.g. 2, 4, 6, 8) with their right hand and odd number targets (e.g. 1, 3, 5, 7, 9) with their left hand, whilst ignoring the colour of the stimuli.
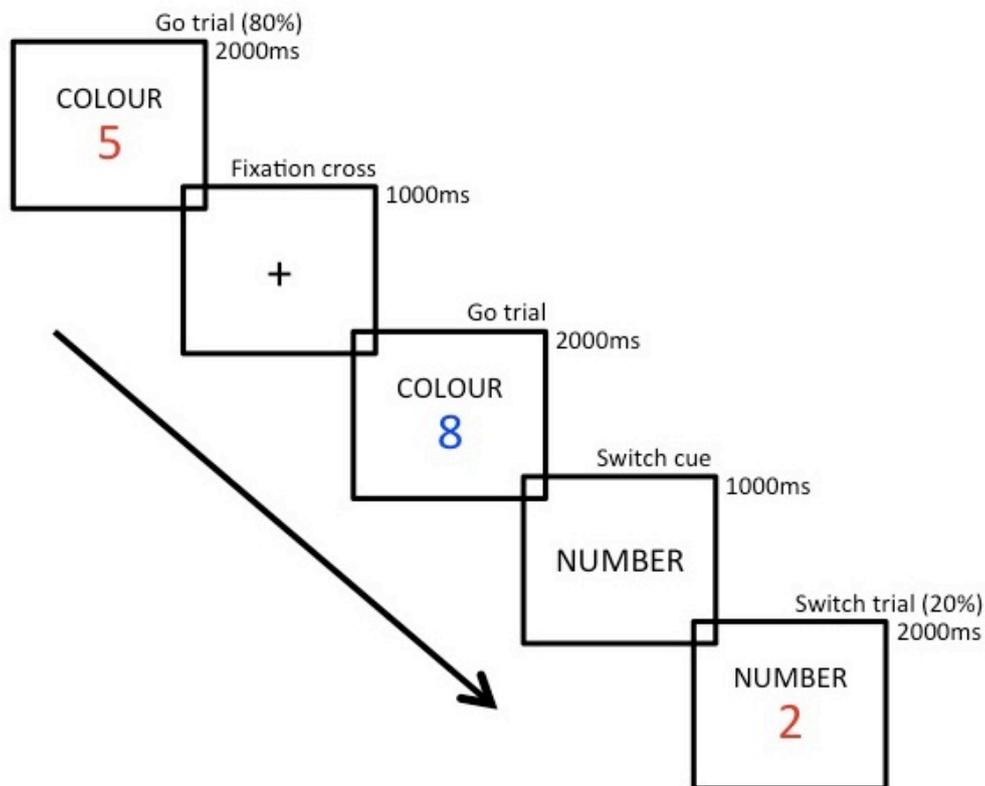
***Figure 2.6: Schematic diagram of the cognitive task switching paradigm.** Eighty percent of trials are Go trials. These involved an initial fixation cross, followed by a colour stimulus signifying a left or right finger press (blue = left, red = right). Switch trials involve the presentation of a switch cue (e.g. the word ''NUMBER') signifying the need to reverse the stimulus/response mapping (i.e. to even number = right, odd number = left).*

2.4.2.3.   Description of the paradigms

The paradigm began with instructions for the participants (e.g. "When you see the words ODD/EVEN, if the number is ODD, press left, if the number is EVEN, press right"). Each task switching condition contained 162 trials, with 20% of the trials constituting switch trials and 80% constituting Go trials. The interstimulus interval was 3000ms with each trial (2000ms) broken up by a fixation cross (1000ms). Participants were trained on the paradigm prior to scanning over a period of 62 trials.

Participants were also asked to recall the paradigm rules prior to entering the scanner. In order to reduce the memory load, participants were presented with the name of the current rule above the target stimuli. The paradigm recorded participants' accuracy and reaction times (RT) over the entire run. RT was calculated by subtracting the time to respond to the target stimuli from the onset of the target stimuli.

2.5. Introduction to magnetic resonance imaging

The neural mechanisms involved during performance of the SST and task switching paradigms were investigated using MRI. MRI has become one of the key tools in medical imaging, largely due to its sensitivity to different properties of tissue. MRI is also completely non-invasive. These properties, combined with the absence of any known biological hazard make it, in research and clinical environments, a very valuable tool. Below, I provide a background into the physics of how images are captured using an MRI machine, and how they are subsequently converted into images that can be processed to produce the results seen in this thesis.

2.5.1. A summary of MRI principles

MRI is an imaging technique that uses a strong magnetic field to produce images of tissue, based on the resonance of nuclei within a material when placed in a strong magnetic field and subjected to radiofrequency (RF) pulses as stimulation. These RF pulses result in absorption and subsequent release of energy by the nuclei. Depending on the type of sequence used, the MRI scanner can detect differences in tissue properties, through which images can be created, that differentiate low versus high proton density, grey matter versus white matter, or fluid versus tissue. It is from

these signals that the images are reconstructed.

2.5.2. Nuclear Magnetic Resonance

The basis of MRI is that of nuclear magnetic resonance (NMR). NMR was initially described in 1946, when two groups working independently using different substrates, specifically Felix Bloch et al (Bloch, 1946) looking at water in a liquid state and Edward Purcell (Purcell, 1946b) using solid paraffin, shared the 1952 Nobel Prize for physics for the discovery of NMR. The development of significantly more powerful magnets and magnetic field coils enabled this research tool to be implemented as a means of medical imaging in 1976.

The principal of NMR concerns the nucleus of an atom, as it consists of protons and neutrons, which both spin around their own axis. The spinning of the nuclear particles produces an angular momentum and if the atom has an odd number of protons and neutrons, this vector is different from zero. In addition, as a proton has mass, a positive charge and spins, it produces a small magnetic field that is referred to as the magnetic moment. The magnetic moment vector is oriented in the same direction as the angular momentum and the ratio between the angular momentum and the magnetic moment gives a constant known as the gyromagnetic ratio (γ), which is specific to each of the magnetically active nuclei.

Hydrogen is abundant in the human body, and has a significant magnetic moment. Therefore, MRI scanners are usually configured to detect it. The nucleus of the hydrogen atom contains a single proton that behaves like a tiny magnetic bar. Due to the spin characteristics of the proton, when it is placed in a large external magnetic

field (B0), it aligns (at a slight angle) either parallel or anti-parallel to the direction of the magnetic field. Protons aligned in the parallel orientation are said to be in a low energy state, while the others are in a high-energy state. The higher the B0 is, the more spins are aligned in the low-energy state. The magnetic moments of the spins in the low energy state that are in excess, compared to the number of spins in the high-energy state add to form the net magnetization vector (M), which is thus proportional to B0. In addition to aligning with B0, protons precess at a particular frequency that is equal to the strength of B0 multiplied by the gyromagnetic ratio. This is called the 'Larmor' frequency ($\omega 0$).

The varying amount of hydrogen in different tissues affects how the protons behave in the external magnetic field. For instance, because of the total amount of hydrogen in water relative to other brain tissues, it has one of the strongest net magnetization vectors. MRI experiments involve orienting this vector (M) away from the B0 axis (z-axis) toward a transverse 'xy plane' perpendicular to it and measuring the constants associated with its reorientation parallel to the z-axis. For that, a pulse of radio frequency (RF) energy is administered in the form of a RF wave that oscillates at the Larmor frequency. This produces a phenomenon known as resonance, where spins begin to precess in phase. As the RF pulse continues, some of the spins in the lower energy state absorb energy from the RF field and become 'excited' into the higher energy state. This has the effect of reorienting or 'flipping' M away from the z-axis towards the transverse xy plane. At this point, spins that had moved into the higher energy state return to the lower energy state, causing M to reorient along the z-axis. This 'relaxation' is described by constants known as T1 and T2. The longitudinal relaxation time T1 is the decay constant for the recovery of the z component of M

toward its thermal equilibrium, while the transverse relaxation T2 is the decay constant for the xy component of M. Compared to T1 relaxation, T2 decay process is very rapid. T2* is another relaxation constant that is related to T2, but also accounts for the combined effects of inhomogeneities in B0 and neighbouring molecules spin-spin interaction. This process is even shorter than T2 decay and is thus particularly useful to image rapid brain processes in functional MRI.

2.5.3. From NMR to MRI

The NMR signal is detected as a function of time, and demonstrates the presence of hydrogen atoms. However, the NMR signal does not provide any information to locate the Hydrogen atoms in space. Spatial information is recovered from the raw signal by using gradient coils that generate a magnetic field that increases in strength along one spatial direction. When a rotating field gradient is used, linear positioning information is collected along a number of different directions. That information can be combined to produce a two-dimensional map of hydrogen densities. Finally, shimming coils are also used to generate high-order compensatory magnetic fields that correct for the inhomogeneity of the magnetic field.

2.5.4. MRI parameters

There are two important factors that govern the time at which MR images are collected. One is the time interval between successive excitation pulses, known as repetition time (TR). The other is the time interval between excitation and relaxation, known as echo time (TE). Variations in these parameters will affect whether signal intensity is primarily due to T1, T2 or T2* relaxation.

2.5.4.1. T1-weighted images

T1-weighting is the most commonly used structural contrast for anatomical images of the brain. Images are T1-weighted when the relative signal intensity of voxels depends upon the T1 value of the tissue. This type of imaging typically requires an intermediate TR, to generate a contrast between the different type of tissues (those with high and low longitudinal magnetization), and a short TE, to minimize T2 contrast. T1-weighted images depict the spatial distribution of T1 values, so that voxels with short T1 values are bright and those with long T1 values are dark. Fluid appears as black, grey matter appears as dark grey and white matter appears as light grey.

2.5.4.2. T2-weighted images

To have an exclusive T2 contrast, TR must be long, so that the longitudinal recovery is almost complete in all tissues and T1 contrast is minimal. On these images, fluid appears bright, grey matter appears as light grey and white matter is dark. This type of images is particularly useful for many clinical considerations, as many pathological conditions (such as tumours) show up more readily under T2 contrast.

2.5.4.3. T2*-weighted images

Like the T2 contrast, T2* is provided by pulse sequences with long TR and medium TE. Also, the pulse sequence uses magnetic field gradients to generate the signal echo, as refocusing pulses would eliminate field inhomogeneity effects. T2*-weighted images are sensitive to the amount of deoxygenated haemoglobin present in the blood (see functional MRI section below).

2.5.5. Functional magnetic resonance imaging

2.5.5.1. *Principles*

Functional magnetic resonance imaging (fMRI) is a technique for measuring brain activity based on the differences in the magnetic properties of oxy- and deoxygenated haemoglobin, which run through our capillaries to carry oxygen around. The signal in fMRI, derived from the different oxygenation status of blood, is known as the blood-oxygen-level-dependant (BOLD) effect (Raichle, 2001) and is expanded on further below.

The basic principle of the BOLD signal is based at the point when a neuron fires, which results in an increase in 1) oxygen metabolism by approximately 5% and 2) cerebral blood flow to the local area by 20 - 40%. Immediately after neural activity, there is a momentary decrease in blood oxygenation, which is known as the initial dip in the haemodynamic response. Then, 4 to 6 seconds after this dip, blood flow to the active regions in the brain increases and oxygen rich blood displaces oxygen-depleted blood. The time course of this change in the local ratio of oxyhaemoglobin (HbO2) to haemoglobin (Hb) is known as the haemodynamic response function (HRF). This is followed by a period where the blood flow increases to above the level where oxygen demand is met, thereby overcompensating for the increase demand of oxygen. It is this difference between oxy- and deoxy- haemoglobin that is picked up by the MRI scanner.

Critically, Hb changes its magnetic properties depending or whether it is oxygenated (diamagnetic, same as tissue) or not (paramagnetic, different magnetic properties

from tissue). During neural activity, the change in proportion of Hb and HbO2 can be detected due to its difference in magnetic susceptibility, meaning that MRI is sensitive to changes in the BOLD response. The presence of Hb induces microscopic field inhomogeneities that lead to destructive interference from signal within the tissue voxel. This tends to shorten the T2* relaxation time, which is sensitive to field inhomogeneities. Thus, areas of the brain with enhanced local blood flow due to greater neuronal activity have longer T2* and can be visualised as areas of increased signal intensity relative to the baseline state (*Figure 2.7*).
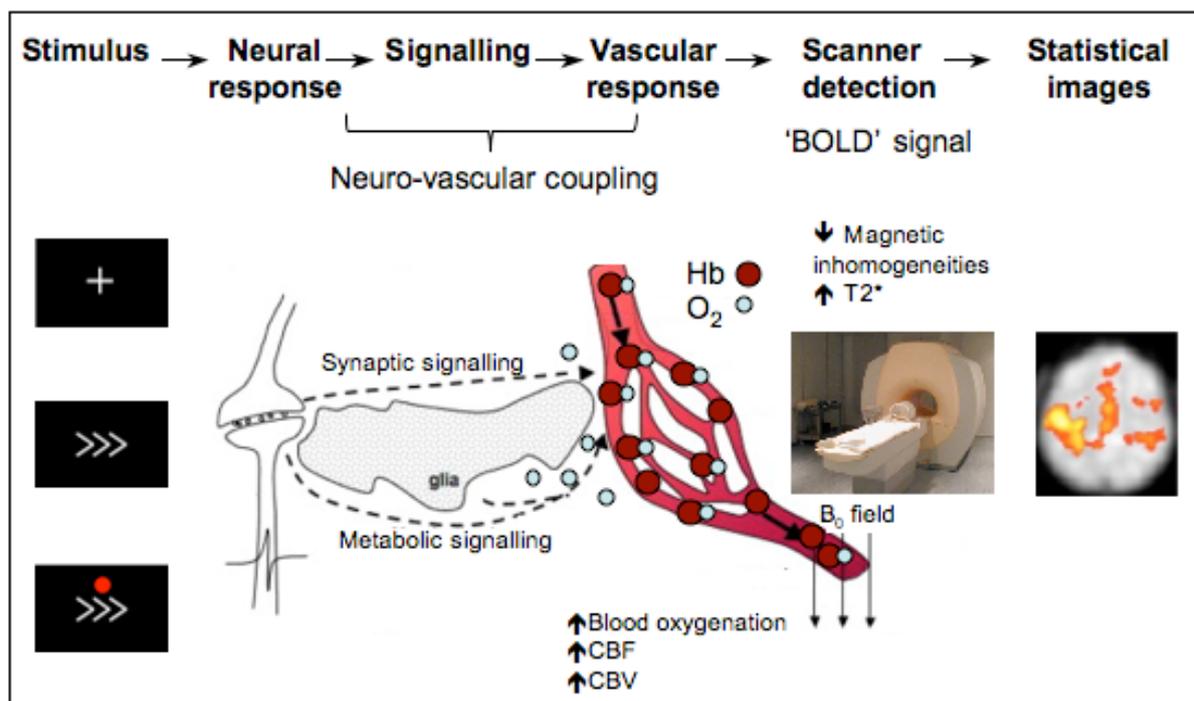
Figure 2.7: Basic principles of functional MRI. Schematic diagram of how the blood oxygen level-dependent (BOLD) signal is generated. Neuronal response to the task stimulus requires energy, which is provided by nearby glial cells. These cells need glucose and oxygen to produce energy. Neuronal activity is thus paralleled by an increase in oxyhaemoglobin (HbO2), which has different magnetic susceptibility than Hb. Hb magnetic properties disrupt the magnetic field B0, which results in T2 signal loss. Increase neural activity thus results in increase MRI signal (adapted from Iannetti and Wise, 2007).*

2.5.5.2. Echo-planar imaging for fast fMRI acquisition

One of the key differences between structural and functional imaging is that

functional data requires images to be acquired rapidly, in an attempt to be as close as possible to the rate of the physiological changes of interest. To achieve this rapid data acquisition, an imaging sequence called echo-planar imaging (EPI) is commonly used. This sequence is a T2*-weighted sequence that collects data from an entire image slice by slice, by sending one RF pulse from a transmitter coil and then introducing rapidly changing magnetic field gradients while recording the MR signal. This type of acquisition reduces the time needed to collect a single image from minutes to fractions of a second. However, due to the long readout time for each excitation, the spatial resolution is considerably lower (typically 4x4x4mm^3) than a conventional structural MRI scan. As a result, EPI images are more prone to artifacts and distortion and therefore need to be registered on images with better resolutions such as T1 images.

2.5.5.3. *Model based fMRI*

The basic principle of model-based fMRI experiments is to identify voxels that exhibit a statistical relationship with changes in the brain state of interest across the data acquisition. Model-based analyses typically compare brain 'activity' (i.e. BOLD signal) between two conditions that only differ in some specific ways. Providing the behavioural states of each condition are appropriately determined and the two conditions differ only in the precise process investigated, the contrast will reveal which brain regions are active during this particular process. For the model-based fMRI analyses presented in this thesis, I used FEAT (FMRI Expert Analysis Tool) version 5.98, which is a part of FSL software (FMRIB's Software Library; www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004).

2.5.5.4. Paradigm designs for fMRI

There are two main approaches for comparing brain responses in different states during fMRI experiments. One is the 'block' design, which consists in alternating periods with fixed stimuli, i.e. during which a given cognitive state is maintained. The simplest version of such design, which is also the most powerful in terms of producing a high signal-to-noise ratio, alternates between two different states throughout the experiment. However, this design is inappropriate when studying transient or infrequent processes. In such instances, an 'event-related' design in which data is acquired while various conditions are 'randomly' presented throughout the task is more suitable.

Prior to neuroimaging studies of task switching, and during the initial surge of the task switching literature, experimental designs contrasted single task blocks (trials in which a single task was repeated) against mixed task blocks (blocks in which multiple trials were intermixed (Braver et al., 2003). It was found through these designs (e.g. Pashler, 2000, in Braver et al., 2003) that response times were strikingly longer with an increased response latency of around 200-300ms per item (Pashler, 2000) and with more errors (error rates were higher in the mixed task blocks).

More recently, studies have opted to use a trial-by-trial design where researchers contrast task-repeat trials (trials in which the task has just been repeated) against task-switch trials (trials in which the task has just switched to another task). This type of design has proved popular because it allows for examination of within-trial effects, namely, the timing between different trial components (such as examining the difference between the interval and the previous response, and the occurrence of the

next task cue against the interval between the task cue and target stimulus (Braver et al., 2003) . Also, these trial-specific task switching paradigms allow for a more accurate linkage of switch costs with the processes associated with the internal reconfiguration of task-set representations (Braver et al, 2003) and are also more applicable with event-related fMRI based experiments. The cognitive processes of interest in the current thesis are transient (inhibitory control and task switching), therefore event-related designs were used.

2.5.5.5. *Standard voxelwise GLM analysis*

All the functional data was analysed using FEAT. The following pre-statistics processing was applied: motion correction using MCFLIRT (Jenkinson et al., 2002); non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 5mm; grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; and high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=50.0s). Mixed effects analyses of group effects were carried out using the FMRIB local analysis of Mixed Effects (FLAME). The final z statistic images were thresholded using a Gaussian random field–based cluster inference with a height determined by a threshold of Z > 2.3 and a cluster significance threshold of *P* = 0.05 corrected for the whole brain. Functional MRI data was analysed using voxel-wise time series analysis within the framework of the general linear model (Beckmann et al., 2003). A design matrix was generated with a synthetic haemodynamic response function and its first temporal derivative. Several types of events were distinguished for the SST data, these included: Go correct (Go), Stop correct (StC), Stop incorrect (StI) and Rest. Go incorrect trials were not included as there were too few to model accurately. To account for variation in the SSD

across runs, I modelled events using the timing of the SSD as the regressor for each trial. The following subject specific and run specific contrasts were generated: StC vs. Go and Go vs. Rest. For the motor switch paradigm, the following events were generated: Go correct (Go), switch correct (SwC), Errors (Er) and no response (NoR); and the following contrasts were generated: SwC > Go and Go > SwC.

Data preprocessing

The functional images must first be preprocessed before any statistical analysis can be carried out. This consists of a number of steps that are automated in FEAT, which are described below.

Brain extraction

This process removes the non-brain tissue from the T1 (structural) and the EPI (functional) images. Within FSL, it is performed using the Brain Extraction Tool (BET). This tool identifies the likely centre of gravity of the brain and initialises a tessellated spherical surface that expands gradually around these coordinates until an optimal solution is found to separate brain tissue from the rest (Smith, 2002) (**Figure 2.8**). These skull-extracted images are then visually inspected for each participant and re-processed if required.

Figure 2.8: Brain extraction in FSL

Temporal filtering

The purpose of applying a temporal filter is to remove noise from the EPI data in order to increase signal-to-noise ratio. High-pass filtering removes low frequency noise that can be caused by slow changes in the overall signal intensity due to minor instabilities in the scanning hardware. A temporal high-pass filter with a cut-off frequency of 1/50 Hz was used in the current work to correct for signal drift.

Motion correction

Motion correction is used to ensure that the anatomical location of a single voxel within the field of view is constant throughout the length of the scan. This is done in FSL by aligning all the images to a selected reference volume. The amount of movement in each direction required to align each volume is reported in the subject level analysis output. These motion parameters are also entered in the design matrix to identify and exclude any changes in signal intensity correlating with head motion. FEAT produces a summary of relative and absolute motion that is carefully checked for each subject (***Figure 2.9***). Participants were removed from the analysis if there were any absolute displacements greater than 2mm as calculated by MCFLIRT's estimated mean displacement. This was determined by the fMRI output produced by FEAT, which summarises the mean relative and mean absolute motion. The most problematic motion artifacts come from large jumps such as the one illustrated on ***Figure 2.9***.
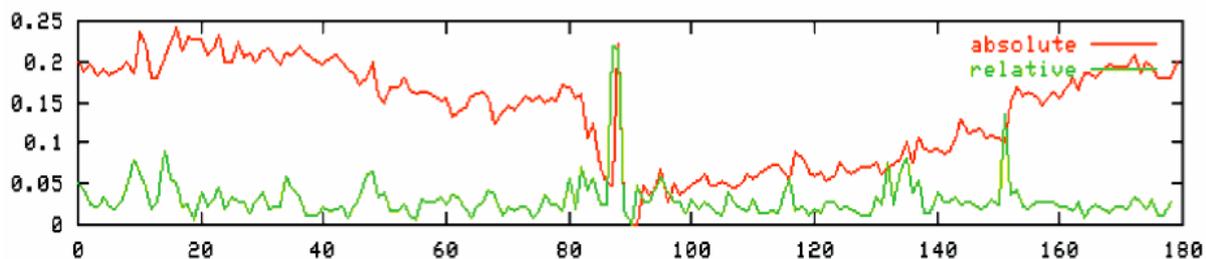
Figure 2.9: Motion correction from FSL output. *Summary of absolute (red) and relative (green) motion correction in mm, plotted against time course. A large motion artefact, likely caused by participant head movement, is evident between time points 80 and 100 along the x-axis.*

Spatial smoothing

Spatial smoothing improves the signal-to-noise ratio by filtering out the high spatial frequency components of the fMRI data, whilst enhancing areas of neighbouring activation. The justification for this step is that a signal coming from a biologically plausible source will typically take the form of spatially smooth area of activity (also called a 'cluster' of activity) of approximately 5 to 8 mm in diameter. Any areas of activity smaller than this are assumed to be noise. Therefore, spatial smoothing convolves the data with a Gaussian kernel with a full width at half maximum (FWHM) of the anticipated cluster size. In the studies presented here, I was mainly interested in cortical processes occurring in large areas of the brain and thus used a 5 mm FWHM Gaussian kernel.

Statistical analysis

To carry out statistical analysis on fMRI data, a multi-level approach is required. The General Linear Model (GLM) is used to produce summary statistics at each level, which are then passed on to the next level (Beckmann et al., 2003). Typically the levels include: the first level analysis, which involves each individual's sessions of data (often referred to as each 'run'); the intermediate fixed level, which combines

runs within subjects; and finally the higher level, which averages data across subjects or compares them between different groups.

First-level analysis

At the first level, each run is analysed separately using a voxelwise time series analysis within the framework of the GLM. To this end, a design matrix is generated with a synthetic HRF and its first temporal derivative. Adding this temporal derivative is equivalent to shifting the waveform slightly in time, in order to achieve a better fit to the data. The design matrix models all of the experimental conditions as 'explanatory variables' (EVs). For instance, for the SST 'Go' and 'Stop' trials are modelled as distinct EVs. The EVs describe the time course of each experimental condition within the run, convolved with a stereotypical HRF.

FSL uses a 3-column format for the EVs, which are generated in Matlab. These EV files are based on each subject's behavioural results matrices. The first number in each triplet is the onset of the event; the second number is the duration of the period (estimated to 0.2s); and the third number is the value of the input during that period (estimated to 1). Each EV in the design matrix results in a parameter estimate (PE) image. This estimate reflects how strongly the EV fits the data at each voxel. To convert a PE into a t-statistic image, the PE is divided by its standard error, which is derived from the residual noise after the complete model has been fitted. This t-statistic image is then transformed into a z-statistic image. To compare brain activation across two conditions, contrasts of parameter events (COPE) are generated, such as correct stop trials *vs.* Go trials. For that, one PE is subtracted

from another, a combined standard error is calculated and a new z-statistic image is created.

Intermediate level (Fixed-effects analysis)

In the studies presented in Chapters 3 and 5 (the SST studies), subjects performed more than one run of the same task. These runs were analysed separately at the first-level and then combined in a within-subject fixed-effects analysis. A fixed-effects model assumes that there is no difference between the variances of different sessions for a given participant and therefore the difference between them are not of interest.

Higher-level (Mixed-effects analysis)

Mixed-effects analysis takes the variance of each participant into consideration and the results reflect the likely group mean of the population from which the participants were drawn. It can also make comparisons between different groups (e.g. patients *vs.* controls). Such analysis is carried out using FLAME (FMRIB's Local Analysis of Mixed Effects).

Thresholding

After carrying out the initial statistical tests described above, the resulting z-statistic image is thresholded to show which voxels, or clusters of voxels, are activated at a particular significance level. If all the voxels were considered to be independent, then a Bonferroni correction would be applied. This states that for an image of N voxels, the overall probability of any false positive result is P if the individual voxel false positive probability is P/N. However, with ~20,000 voxels in an image, such a

technique is very stringent and the risk of falsely rejecting true activations is very high (type II error). An alternative and more realistic approach takes into account the fact that activation at each voxel is not truly independent. Instead of correcting for the number of voxels, the threshold can only be corrected according to the number of possible independent observations in the spatially smoothed data (i.e. plausible biological areas).

In FSL, the Gaussian Random Field Theory is used to implement cluster-based correction for multiple comparisons. The data analysis produces an image with a z-statistic at each voxel. A z-threshold (e.g. z > 2.3) is applied to define contiguous clusters, so that voxels with a z-statistic lower than 2.3 are set to 0. Significant clusters are then used to mask the original z-statistic image for later production of activation clusters.

FMRI results presented in this thesis are thresholded using Gaussian Random Field-based cluster inference with a standard height threshold of z > 2.3 and a cluster significance threshold of $P < 0.05$.

Registration

A key issue with fMRI is that, although it is optimised for good temporal resolution, the fMRI data has a very low spatial resolution. In addition, to compare or average brain activation between subjects, their images need to be in an identical space, so-called 'standard space'. In FSL, registration is performed using FMRIB's Linear Image Registration Tool (FLIRT) (Jenkinson et al., 2002). This proceeds in two steps, first, EPI functional data is registered to the high resolution anatomical skull extracted

images (T1), using transformations which require 6 degrees of freedom (translation and rotations in each of the three dimensions). Secondly, the high-resolution brain is registered to a brain template, using further transformations, which require 12 degrees of freedom. This brain template is based on the T1 MRI scans of 152 normal controls and is called the MNI-152 template (MNI = Montreal Neurological Institute). This second step requires a higher number of degrees of freedom as it uses 6 additional affine transformations to correct for the differences in brain shape between participants.

This automated registration method usually works well with healthy participants however, it can be less efficient when registering patients' images. This is generally due to increased distortion in the EPI images, possibly due to the presence of lesions or excessive movement. Registration in the patients can be improved manually using an FSL function called 'Nudge', which realigns the original image at a slight angle to improve registration. However, some patients ultimately have to be excluded from further analyses because their functional images could not be properly registered. In the current thesis, the numbers of patients removed are specified accordingly for each study in the relevant study chapter.

2.5.5.6. *Region of interest analysis*

A region of interest (ROI) analysis can be performed to increase statistical power when there is a clear hypothesis of where significant activity is expected. It can also be used to extract data upon which additional statistical analyses can be performed. In the studies presented here, I have used 10mm radius spheres as my ROIs, and performed ROI analyses using Featquery. Featquery is a FSL tool that allows the

interrogation of FEAT results, and extracts the mean percentage BOLD signal change within an ROI.

The ROIs utilised in the current thesis are consistent throughout all the results chapters and have been based upon the findings in previous work (Bonnelle et al., 2012). These ROIs were centered on peaks of activation for the contrasts of correct Stop with Go trials. 10mm radius spheres from the right anterior insula (rAI, x = 36, y = 24, z = -6) and the dorsal anterior cingulate cortex (dACC, x = 0, y = 22, z = 46) were used, corresponding to two major nodes of the SN. In Bonnelle et al, these ROIs were used as the seed points to define the tract connecting the rAI and dACC; this tract was the primary focus of my current analysis. I also defined a right inferior frontal gyrus (rIFG, x = 44, y = 18, z =16) ROI, to test if connectivity changes are specific to the salience network. This region acted as my control ROI, as the rIFG is spatially close to the rAI but is not strictly part of the SN. These three masks were applied to both the switching data presented in Chapters 4 and 6, and the stopping data presented in Chapter 5.

2.5.5.7. Functional connectivity

Most commonly, fMRI studies produce activation maps that depict the average level of activity of different regions in the brain in response to a specific stimulus. In addition, they can reveal how components of large-scale distributed neural systems are coupled together in performing specific functions (Rogers et al., 2007). The study of FC affords a fuller characterisation of brain networks supporting cognitive functions by investigating the correlations in fluctuations of the BOLD signal. Friston and colleagues describe FC as the "*temporal correlation between spatially remote*

neurophysiological events" (Friston et al., 1993). FC analysis can concern relationships between brain regions in a variety of contexts, such as when the brain is at 'rest' (Biswal et al., 1995), or during a task (Friston et a., 1997). Techniques for FC analysis include Dynamic Causal Modeling (Stephan et al., 2007); Granger causality (Granger, 1969); independent components analysis (Hyvarinen, 1999) and psychophysiological interaction (PPI) (the technique used in the current thesis) (Friston et al., 1997). In fMRI studies, temporal correlations can be observed in the activity of spatially remote brain regions, suggesting that these regions are forming functionally connected brain networks. To quantify the function of these networks, we measure how correlated the activity between spatially distinct areas are, with the assumption that this reflects neural interactions (Sporns et al., 2004). Therefore, FC describes the patterns of dynamic interactions that are extracted from neural time series data.

Psychophysiological interaction

The concept of PPI is explains neural responses in one brain region in terms of a statistical interaction between the influence of another region and a task-related parameter (Friston et al., 1997). Essentially, PPI has the ability to detect regions where BOLD activity significantly covaries with activity within a seed region of interest during performance of a task (Boksman et al., 2005). For example, one would find increased connectivity between motor regions during performance of a motor task. Regions which exhibit significant covariance with the activity of the seed region over the timecourse of the task, but not during the baseline condition scans, are said to be functionally connected to the seed region during task (Friston et al., 1993). A key principal of PPI is thus to investigate how the level of activity in two interacting

regions covaries over time, for example, if the neural response in two distinct brain regions increases and decreases over time together, then activity in one area may be driving activity in the other. It is important to emphasise here that in a PPI analysis, the directionality of this relationship cannot be inferred (O' Reilly et al., 2012).

PPI was originally described by Karl Friston in the 1990s (Friston et al., 1993) and recently gained popularity as a measure of FC (O' Reilly et al., 2012) and has also recently been applied to clinical populations (Boksman et al., 2005). The relationship between these co-active regions can be examined using a general linear model (GLM) to test whether activity in one region (the seed region) can explain activity in other voxels across the brain. Boksman and colleagues used PPI to examine FC patterns during word fluency in schizophrenic patients compared to healthy volunteers (Boksman et al., 2005). They scanned ten first-episode schizophrenia patients who had never been treated and ten age-matched controls using the right anterior cingulate as their seed region. This seed then determined which areas of commonly covarying BOLD response were elicited by task performance relative to baseline BOLD response. This seed region was selected for use in their PPI analysis as it was a region that was significantly active in the initial univariate subtraction analysis for both groups (which is necessary for the PPI procedure), and also for this region's importance in schizophrenia literature (Boksman et al., 2005).

Definition of the seed region is a key step in PPI analysis and this can be carried out in different ways. Firstly, a seed region can be defined by selecting the voxels with strongest task effect in a group analysis (e.g. the voxels most active during task, such as stopping or switching in the tasks used in this thesis). Secondly, the seed

region may be defined anatomically, given a strong *a priori* hypothesis about a particular region, and necessitates accurate identification of that region, often using an anatomical scan. Thirdly, the seed region may be defined individually for each participant as a region of interest by constraining the search to a volume of interest and then selecting the voxels in each participant with the strongest task effect. A possible limitation in the first and third case is the danger of biasing results due to the seed regions being defined from analysis within the same the data. However, we need not be concerned about circularity in this case, because the PPI analysis models the main effect of task and will only detect FC effects over and above (orthogonal to) the main effect of task (O' Reilly et al., 2012). Moreover, in the current thesis, regions were defined from spatial maps that were obtained from a completely independent sample of data which is publically available online (Smith et al., 2009) and from existing masks that have previously been used to define regions of interest (Bonnelle et al., 2012). Therefore, this further eliminates any issues of circularity.

In the current thesis, the focus of FC is around task-dependent changes in connectivity during stopping and switching. To do this, a GLM was used to perform the PPI analysis. The model examined the change of FC during stop vs. Go trials and switch vs. Go trials in a standard way (O' Reilly et al., 2012). A task-specific change in FC suggests a "change in the exchange of information" between regions (O' Reilly et al., 2012). This approach allows us to measure task related changes in FC and separate these from changes in regional brain activation. Following O' Reilly et al, the interaction time course is an element-by-element product of the mean-centered task time course and demeaned seed ROI time course. This GLM was calculated for each subject including the subject-specific DMN timecourse as the dependent variable.

The independent variables (IVs) were: (1) the timecourse of each frontal ROI (assessing FC unrelated to task); (2) the stop/switch, Go and error timecourses (modelling the main effects of task events); (3) confounding variables consisting of motion parameters and individualised timecourses of noise components from the dual regression, such as the subject-specific timecourses for motion components included in the dual regression (Smith et al., 2009); (4) the interaction timecourses between stop and the ROI (stop x ROI) and between Go and the ROI (Go x ROI); and (5) a constant. The GLM resulted in parameter estimates (PE) for each of the IVs, and the PEs for the interaction terms were contrasted (i.e. stop interaction – Go interaction). A positive contrast suggests that change in the relationship between DMN and the other ROI resulting from the task event is stronger during stop (or switch) events than during Go events.

Independent component analysis

Among the various existing approaches to analyse FC, Independent Component Analysis (ICA) is particularly useful and brain imaging software such as FSL make it straightforward to implement. The main advantage of this technique is that it is a model free, data-driven method that makes no assumptions about the underlying biology of the data. Furthermore, it does not require any knowledge about which regions are involved in a given task and/or what the underlying structural connectivity is. However, one complexity is that, depending on the settings used to generate FC maps, the FC maps can be further split into subcomponents, perhaps reflecting the complex structure of brain activity.

In FSL, ICA is performed using MELODIC (Multivariate Exploratory Linear Optimised

Decomposition into Independent Components) (Beckmann and Smith, 2004). Single or multiple subject data sets are decomposed into different components. For ICA group analyses, MELODIC uses either: a tensor ICA approach, where data is decomposed into spatial maps, time courses and subject/session modes; or a simpler temporal concatenation approach. The second temporal concatenation approach is preferred when looking for common spatial patterns when the associated temporal response is not necessarily consistent between sessions/subjects (e.g. randomized trials). This temporal concatenation approach requires preprocessing steps that are similar to those presented above for a FEAT analysis, and other additional automatic steps consisting of voxelwise variance normalization ('whitening') and data de-meaning. By default, MELODIC automatically estimates the number of components from the data. However, the number of components can also be explicitly specified. The number of ICs is set to 25 based on recommendations from previous work (Leech et al., 2011), which is also in keeping with the original description of the technique (Beckmann et al., 2005). This number is generally high enough to adequately distinguish between distinct functional networks such as the DMN and the SN, and low enough so that these networks are not further split into sub-systems.

Dual regression analysis

A technique called dual-regression can be used to compare participants' FC measures based on the ICs derived from a group ICA. This method reliably produces participant-specific approximations of the unthresholded spatial ICs in the group ICA output (Zuo et al., 2009).

Dual regression involves two main steps; first, ICs from the ICA output are linearly regressed against the preprocessed functional data from each individual (spatial regression). This produces a participant-specific timecourse corresponding to each group-level IC. Second, these timecourses are variance-normalized and then linearly regressed against individual subjects' fMRI data (temporal regression), resulting in a subject-specific spatial map of network coherence for each initial IC. These individual-level spatial maps can subsequently be used to evaluate individual FC measures.

Timecourse extraction

The current work uses the first stage of the dual regression analysis pipeline to extract timecourses from the DMN and the three frontal ROIs in individual subjects (Filippini et al., 2009; Zuo et al., 2009; Leech et al., 2011). These were then included in the PPI analysis (see below) to provide an unbiased estimate of DMN activity. As already noted, the map used for this was a network based on the independent component analysis of fMRI data from Smith and colleagues (Smith et al., 2009). The dual regression involves back-projecting (spatially regressing) each ICA component into individual subject's 4D functional data to derive a timecourse from each subject for the DMN. This timecourse is the subject specific signal fluctuation corresponding to each group-level independent component. In addition to the DMN component we also included fourteen noise components, also taken from the Smith analysis. These provide group level estimates of various sources of noise in the data, including motion, cerebro-spinal fluid and white matter signals. In summary, the dual regression approach provides a data-driven way of extracting time-series that best fit particular regions or networks. The procedure also controls for the potential

confounds, such as motion that may be present in the data. This procedure was used to define a timecourse from the DMN and frontal ROIs for each run of the stop Signal Task dataset for each subject, and the motor switch paradigm for each subject.

2.5.6. Magnetic resonance diffusion imaging

2.5.6.1. Principles

Diffusion-weighted imaging (DWI) has become an established means of providing brain images over the last 20 years. DWI is sensitive to the random microscopic movements of water molecules in tissue that are intimately related to the tissue structure surrounding the molecules. The phenomenon of MR signal attenuation in the presence of field gradients due to diffusion of molecules was initially described by Purcell (Purcell, 1946). The ability of DWI to reflect the movement of water molecules in tissue offered the possibility of a unique non-invasive means of probing the tissue architecture at a cellular level. In 1990, Moseley and colleagues (Moseley et al., 1990) used a cat brain stroke model to show that an area of ischaemia could be identified through a reduction in the apparent diffusion coefficient (of up to 50%) at thirty minutes of the induced 'pseudo'-stroke, whilst conventional imaging showed no appreciable change. The application was then used in the investigation of acute stroke patients (Baird and Warach, 1998) where regions of ischaemia could be visualised within minutes of the onset of a stroke or infarct (Cercignani and Horsfield, 2001; Dong et al., 2004).

2.5.6.2. Applications for DTI and tractography

The absence of a coherent arrangement of white matter fibres results in poor diffusion anisotropy, which can be demonstrated on diffusion tensor imaging (DTI).

The magnitude of the anisotropy is thought to depend on several factors including axonal density and degree of myelination (Beaulieu, 2002). From this it is inferred that diffusion anisotropy maps (Papadakis et al., 2000) may be useful in the investigation of the structure of white matter and the effect of disease on it. DTI and tractography has been shown to be a useful tool for several clinical groups however the current work is focused on TBI and healthy ageing.

2.5.6.3. *Diffusion Tensor Imaging measures*

It is possible to reconstruct a 3D ellipsoidal shape that best describes the pattern of water diffusion occurring in a given voxel by calculating the distance in which water diffuses in a given voxel in a given amount of time for several (at least six) non-collinear directions (***Figure 2.10***A). This ellipsoid can be mathematically described as a 3D tensor that can be characterised by 3 eigenvalues: $\lambda 1$ (major axis), $\lambda 2$ (median) and $\lambda 3$ (minor) (***Figure 2.10***B).
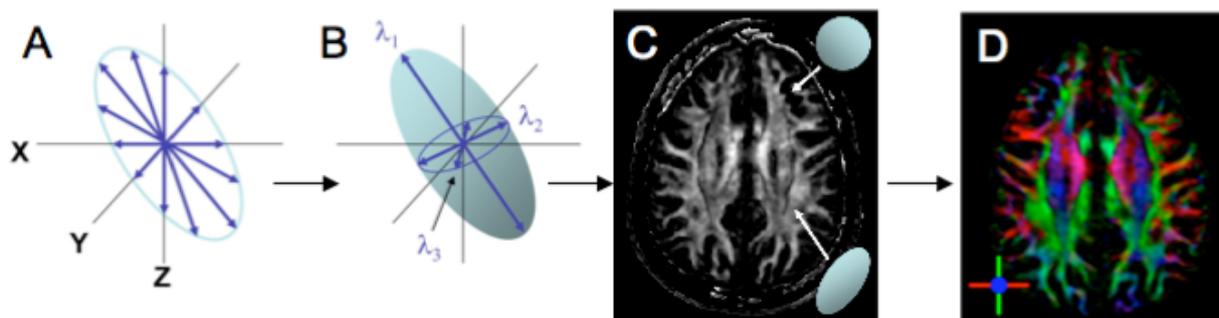
Figure 2.10: The principles of DTI image production*. (A) Diffusion is measured along multiple axes by applying various gradients. B) This allows the estimation of the shape of the diffusion ellipsoid that can be described by 3 eigenvalues. C) An anisotropic map can be created, in which regions with higher anisotropy are brighter. D) The principal orientations of each pixel can also be colour coded to produce a colour-coded orientation map. (Adapted from Mori and Zhang, 2006).*

By employing this diffusion tensor model, several diffusion parameters can be derived. The most frequently used is fractional anisotropy (FA), which estimates the

degree of diffusion directionality. FA is a function of the 3 eigenvalues characterising the diffusion tensor; an FA of 0 indicates a complete isotropic diffusion and values can increase from 0 to 1 with increasing diffusion anisotropy. FA provides important information about the composition of tissue within a voxel. In a white matter bundle, reduced FA is generally assumed to reflect damage to the axon membrane, reduced axonal myelination, reduced axonal packing density, and/or reduced axonal coherence (Arfanakis et al., 2002; Song et al., 2002). The display of tensor derived FA is illustrated in *Figure 2.11* below.
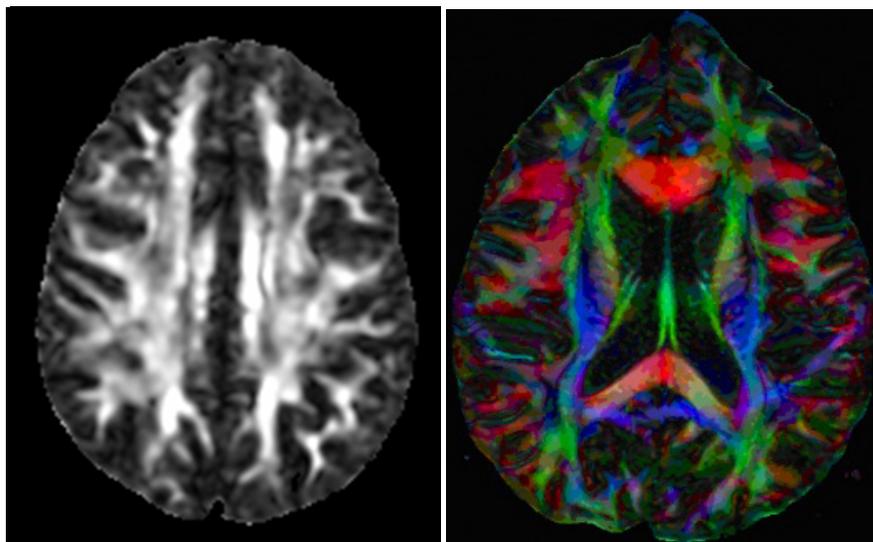
Figure 2.11: FA maps. *Left: FA map where bright pixels represent high anisotropy. Right: colour coded map indicate the direction of white matter fibre, where red = left–right direction; blue = superior–inferior direction; and, green = anterior-posterior direction.*

Directionally encoded colour maps have been used for the representation of the tensor in terms of orientation. The degree of anisotropy is reflected in the intensity of the colour and the principal eigenvector represented by the colour using the RGB (red, green and blue) spectrum. Pajevic and Pierpaoli developed this method and used it to show major white matter fibre tracts and their directions in the brain and brain stem (in terms of separating the vertically oriented sensory and motor fibres

and separating them from both the transverse pontine fibres and the cerebellar peduncles) (Pajevic and Pierpaoli, 1999).

2.5.6.4. *DTI data analysis*

Pre-processing

DTI analysis was performed using FMRIB's Diffusion Toolbox (FDT v2.0) as implemented in FSL. Each subject's diffusion weighted images were registered to their b=0 image and corrected for differences in spatial distortion due to eddy currents, induced by large diffusion gradients. Images were brain extracted using BET (as described above) and diffusion tensors calculated voxelwise, using a simple least squares fit of the tensor model to the diffusion data. From this, the tensor eigenvalues, describing the diffusion strength in the primary, secondary and tertiary diffusion directions, and FA maps were calculated.

Distinct approaches for DTI data analysis

Four basic approaches can be employed to analyse DTI data. These include: whole-brain histogram analysis; region of interest (ROI) analysis; diffusion tensor tractography and voxel-based analysis. Each of these forms of analysis have advantages and disadvantages depending on the question being addressed (for review, see (Niogi and Mukherjee, 2010). However, the work in this thesis is based on the tractography analyses, which I will discuss further below.

Tractography

Diffusion tensor imaging can produce images representing the principal direction of diffusion of water molecules in vivo. This principal eigenvector is thought to represent the underlying structure of the white matter tracts in a given voxel. Initially two-

dimensional representations of the white matter structures were reported using colour-coded maps to represent the fibre orientations (Pajevic and Pierpaoli, 1999). The encoded colour map provided an informative and easily interpretable summary of DTI features throughout the brain. The map utilised differences in hue to reflect tensor orientation, and the intensity of this hue reflected the FA. The demand was then created for a three-dimensional representation. This was achieved through the estimation of the orientation of white matter fibres by calculating the direction in which the diffusion is greatest. The ability to calculate fibre orientations at each white matter voxel has led to the proposal of several techniques to map the white matter pathways. Tractography follows the maximal diffusion direction from voxel to voxel, allowing an in vivo reconstruction of the connectivity of the brain (Conturo et al., 1999).

The means by which the tracts are reconstructed, the tractography method, has been described in several ways. In a DTI image, if two neighbouring voxels are located on the same white matter fibre, their diffusion orientations are also likely to be aligned. Diffusion tractography methods can infer *in vivo* continuity of fibres from voxel to voxel, and reconstruct an entire white matter pathway, or the trajectory of a fibre bundle connecting two ROIs (***Figure 2.12***A).

Different algorithms can be used to perform tractography such as deterministic tractography. This connects neighbouring voxels by propagating the ends of fibre tracts from seed to termination ROIs (***Figure 2.12***B) (Nucifora et al., 2007). Other termination criteria include excessive angular deviation of the fibre tracts or subthreshold voxel anisotropy. One limitation with a deterministic approach is that the

white matter fibres in the brain have a diameter of approximately 1μm; whereas the resolution of the DWI data acquired is of the order of magnitude of approximately 2mm. Therefore, it is possible that each voxel contains hundreds of thousands of white matter bundles, each going in different directions, and often "these large fibre bundles cross each other, split or merge with one another, or fan out as they approach   their   destinations" (https://humanconnectome.org/about/project/tractography.html). The problem with a deterministic approach is that it does not take this problem of distributed directionality into account. Of course, for large white matter bundles, such as the corticospinal tract, where the majority of fibres run in parallel, a deterministic approach would be satisfactory. However, as the work presented in this thesis is focused on the specific tract connecting two regions of the SN (described in Chapters 3 to 6 further), another algorithm, called probabilistic tractography, was utilised in this thesis.

Probabilistic tractography quantifies the probability of connectivity between two ROIs. For each voxel, it calculates a maximum likelihood solution for fibre direction. Indeed, some uncertainty is associated with the estimation of fibre direction due to the potential mix of crossing fibres within a voxel and image noise. This uncertainty can be represented as a probability density function. Probabilistic tractography incorporates the uncertainty in all local fibre directions derived from all relevant voxels to produce the best estimate of the probability density function on global connection between two points (Behrens et al., 2003). Therefore, it produces a global map where the value of each voxel corresponds to the likelihood that the voxel is included in the diffusion path between two ROIs (*Figure 2.12*C). Such an approach is particularly useful for tracking through regions of crossing fibres, or more generally, in

regions of lower anisotropy (Kinnunen et al., 2010).
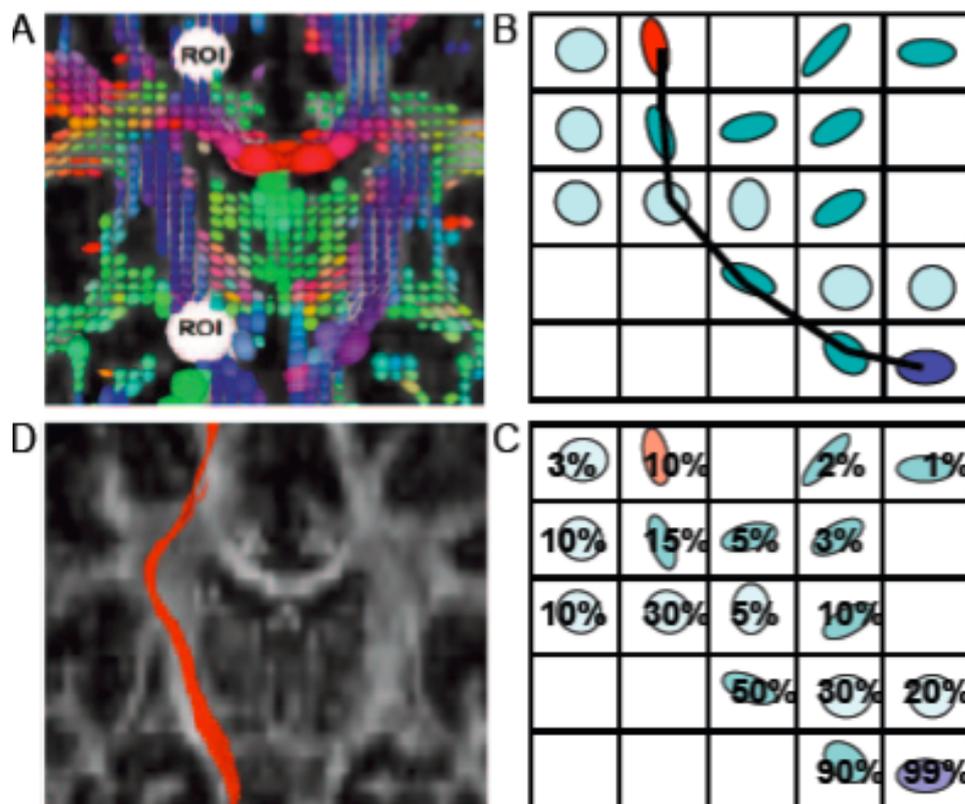
Figure 2.12: Principles of tractography. *A) Diffusion ellipsoid map with two regions of interest. B) Schematic representation of diffusion tensors in a 5x5 grid, with seed ROI in dark blue and termination ROI in red. The black line represents the propagation of the deterministic tractography streamline in the direction of principal eigenvector. C) Probabilistic tractography produces a likelihood map of the diffusion path between two ROIs. Rather than delineating a single best path, the likelihood map shows the probability that a particle diffusing between ROIs traverses each voxel. D) Resulting tract connecting the two ROIs. Adapted from Nucifora et al., 2007.*

Although tractography is more difficult to implement than ROI analysis, it can be more powerful and informative as it provides DTI measures over entire pathways linking two particular regions, as depicted by ***Figure 2.12***D. However, this technique can be problematic in clinical populations where the quality of the data is compromised, for instance, due to the presence of lesions (Hua et al., 2008) or due to more movement in the patient group.

The presence of white matter injury in TBI patients can cause failure of tractography algorithms and probabilistic tractography often fails to produce anatomically plausible tracts in TBI patients (Squarcina et al., 2012). In light of these problems, Squarcina et al report a method for measuring white matter connectivity in TBI, which bypasses the need for individual tractography in patients (Squarcina et al., 2012). The approach first generates a template for white matter connections using probabilistic tractography in a group of healthy controls. This template was validated by comparison with individual tractography in the same group, as well as with an independent control group and was used to sample DTI measures (e.g. FA) from a group of TBI patients. Importantly, sampling was constrained to the white matter skeleton produced by tract-based spatial statistics (TBSS). This skeleton defines the central points of large white matter tracts, and so provides a robust method of focusing the voxelwise analysis on locations where the risk of partial volume effects is low. In the studies presented in this thesis, the approach of Squarcina et al was used, allowing for a more accurate assessment of white matter damage after TBI in a way that is robust to the presence of varying amounts of traumatic axonal injury

In the current thesis, the mask connecting the right anterior insula to pre-supplementary motor area/dorsal anterior cingulate cortex mask (rAI-preSMA/dACC) that was defined by (Bonnelle et al., 2012) was used. This mask was generated by performing tractography on an independent group of 10 healthy young adults (6 males, mean age = 23 ± 2.5). Tracts were generated between 10mm radius spherical regions of interest placed on the peak activation or deactivation during the Stop vs. Go contrast. The tract generation method was by using probabilistic tractography in FSL.

To do this, the FA maps were nonlinearly warped and registered to the 1mm FMRIB MNI FA template, using FSL FNIRT, and the obtained transformations were used to bring the individual tractography outputs to the standard space. The projected tracts were then averaged across the 10 subjects. For the resulting map, a conservative threshold corresponding to 5% of voxels with highest connectivity values was used. For the tract connecting the right anterior insula to pre-supplementary motor area/dorsal anterior cingulate cortex (rAI-preSMA/dACC), tractography was performed from the rAI to preSMA/dACC and from preSMA/dACC to rAI. The two resulting thresholded tracts were then averaged and binarized.

The rAI to preSMA/dACC tract obtained with this procedure (Squarcina et al., 2012) was used as a mask for the ROI analysis of white matter integrity in TBI patients and in a group of 30 age matched controls distinct from the one used to generate the tracts. This tract was projected into each individual's DTI space by using the inverse of the nonlinear transformation used to align the subject-space FA maps to the MNI template. To reduce the possibility of sampling non-white matter regions the transformed tracts were constrained within a white matter tract mask derived from TBSS (Smith et al., 2006). A mean FA image was created using the FA maps aligned to the MNI template, and then thinned to generate a "skeleton" representing the centre of the tracts. The aim was to include only the core of the tract, while excluding peripheral parts of the fibre tract that show pronounced inter-individual variability. The resulting FA skeleton outlines the centre of large white matter tracts and so allows for the calculation of DTI metrics to avoid sampling the edges of these tracts, which are more prone to artifacts, such as partial volume effects due the edge of the ventricles.

The maps obtained following the above procedures were binarized and applied to the FA maps to obtain one mean FA value per tract and per subject. Mean FA values were therefore calculated from the area of overlap between the whole white matter skeleton and the mask of the particular tract in individual space. Linear regression was then used to derive FA values corrected for any effects of age in the analyses reported. This shows that the back-projection of the skeleton and the rAI–preSMA/dACC tract are well constrained to the white matter in each subject's individual DTI space.

Having now completed the description of the methodological frameworks being deployed in this thesis, the following chapter is the first results chapter of the current thesis.

3. The Salience Network and Default Mode Network interactions involved during response inhibition

3.1. Introduction

Efficient behaviour requires the coordinated activity of large-scale brain networks. Tight coupling between activity in two networks, the SN and the DMN, appears important for attentional control (Kelly et al., 2008; Bonnelle et al., 2012). The SN responds to external events that are behaviourally salient (Seeley et al., 2007), whereas the DMN shows high activity when participants have an internal focus of attention (Buckner et al., 2008), for example when retrieving memories, or planning for future events. Changing from relatively automatic behaviour, where attention is often focused internally, to behaviour guided by external events is accompanied by increased activation within the SN and deactivation of the DMN (Sharp et al., 2011). Bonnelle and colleagues have previously studied how the dynamics of the SN and the DMN change using the SST (Sharp et al., 2010; Bonnelle et al., 2012). In the current study, participants made relatively automatic motor responses when responding to left or right arrows, but occasionally had to inhibit their responses after a 'Stop' signal unexpectedly appeared. This paradigm is described in depth in Chapter 2.

Stopping is associated with activation within a right lateralized part of the SN and deactivation within the DMN (Sharp et al., 2011; Chen et al., 2013). Furthermore, the whole process of stopping, activated similar brain regions found in previous studies (Rubia et al., 2003). These regions included activation within the rAI cortex and middle frontal gyrus, as well as bilaterally within the inferior, middle, and superior frontal gyri. However, how the activations involved in stopping affected the dynamic interactions between the SN and DMN was not investigated, which is the scope of the current chapter.

The effect of damage to the SN and DMN can be studied after TBI, where impairments of executive function and attention are common (Stuss and Alexander, 2007; Bonnelle 2012). TBI often produces traumatic axonal injury to large white matter tracts, which disconnects nodes within large-scale brain networks e.g. (Bonnelle et al., 2011). Problems with efficiently stopping after a TBI are accompanied by a failure to deactivate their DMN; and the locations for traumatic axonal injury are important for explaining the abnormalities in network function (Bonnelle et al., 2012). Our lab has previously shown that structural damage within one particular SN tract, connecting the right anterior insula to the midline pre-supplementary motor area/dorsal anterior cingulate cortex (referred to as the rAI-preSMA/dACC tract), was a strong predictor of failure to appropriately deactivate the DMN (Bonnelle et al., 2012). This result provides support for a model of cognitive control where activity in the rAI, in response to behaviourally salient events triggers, changes in large-scale network function, including deactivation of the DMN (Sridharan et al., 2008; Chiong et al., 2013).

Here, investigating whether damage to the rAI-preSMA/dACC tract impairs dynamic interactions between the DMN and SN after TBI extends this previous work. This chapter uses FC measured with functional MRI to infer interactions between the networks (Friston et al., 1997). A task-specific change in FC suggests a "change in the exchange of information" between regions (O' Reilly et al., 2012). I investigate whether stopping is associated with increased FC between the rAI and the DMN, and whether damage to the structural integrity of the SN leads to a change in its FC with the DMN, using the technique of PPI (Friston et al., 1997). This approach allows one

to measure task related changes in FC, and separate these from changes in regional brain activation.

The specific hypotheses tested were that: (1) stopping in healthy controls would be accompanied by increased FC between the rAI and the DMN; (2) patients with impairments of response inhibition would fail to show this change in FC during stopping; and (3) the amount of damage to the rAI-preSMA/dACC tract would inversely correlate with FC between the rAI and DMN during stopping.

3.2. Methods and materials

3.2.1. Patient demographics and clinical details

Sixty-five TBI patients with on-going neurological problems were initially recruited. Seven patients were removed after initial analysis due to: (1) poor task performance during fMRI scanning; or (2) distortion on the imaging files. In addition, one patient had an unexpected neurological abnormality and was therefore removed. In total, fifty-seven TBI patients were included in the analyses (11 females, mean age = 36.7 years ± 11.5, range 18-62 years). All the patients were in the post-acute/chronic phase post TBI (mean = 20 months, range 2-96 months). Most patients had injuries secondary to either road traffic accidents (35%), assaults (24%), falls (21%) or sports injury (12%). A further 8% of patients suffered a TBI from an unknown cause. Based on the Mayo classification system for TBI severity (Malec et al., 2007), there were 42 moderate/severe and 15 mild cases of TBI. The Mayo classification integrates the duration of loss of consciousness; length of posttraumatic amnesia; lowest recorded Glasgow Coma Scale score in the first 24 hours; and initial neuroimaging results. The exclusion criteria were as follows: neurosurgery, except for invasive intracranial

pressure monitoring (one patient); history of psychiatric or neurological illness before head injury; history of significant previous TBI; antiepileptic medication; current or previous drug or alcohol abuse; or contraindication to MRI.

3.2.2. Clinical imaging

Patients were assessed using standard T1 MRI to assess evidence of focal brain injury and gradient echo imaging to identify any evidence of microbleeds, a marker of DAI (Scheid et al., 2003). A senior consultant neuroradiologist reviewed all study MRI scans. At the time of the study, the scans showed the following: 11 patients had residual evidence of contusions; 12 had microbleeds (as demonstrated on gradient echo imaging); and 10 had evidence of both. Contusions were mainly situated in the inferior parts of the frontal lobes, including the orbitofrontal cortex and the temporal poles, in a typical lesion distribution for TBI patients (Gentry et al., 1988). Clinical and imaging details of this patient group can be found in **Table 3.1**.

Table 3.1: Clinical details for TBI group 1.

Age at first visit	Sex	Mechanism	Medication at first visit	GCS	LOC	PTA (days)	Time since TBI (mo.)	Initial CT
21	M	RTA	Gabapentin 400mg bd, Amitriptyline 25mg od, Omeprazole 20mg od, Etoricoxib 90mg od	NK	Intubated	17	16	NK
37	M	Assault	Phenytoin 200mg mane and 300mg nocte, Levetiracetam 250mg	NK	NK	0.3	11	Bilateral haemorrhagic contusions, SAH, L temporal zygomatic fractures

			mane and 500mg nocte					
62	M	RTA	Atorvastatin 80mg, Lamotrigine 50mg bd, Aspirin 75mg od	NK	NK	0.5	34	NK
40	M	Assault	Nil	NK	NK	0.08	28	NK
60	M	Incidental blow	Nil	NK	NK	0.002	6	NAD
47	M	RTA	Fluoxetine 20mg od, Nortriptyline 20mg nocte, Tramadol 100mg qds, Fentinyl patch, Paracetamol 1g qds, Simvastatin 20mg od	NK	NK	NK	42	Small petechial haemorrhages throughout
33	M	RTA	Nil	NK	<1 min	0.06	1	NAD
21	M	Sport injury	Nil	NK	<5min	0.04	3	R temporal lobe contusion
46	F	RTA	Gabapentin tds	NK	<1min	0.003	11	NAD
36	M	Fall	Glargine 30u bd, Humalog 16u tds	NK	NK	28	4	Basal skull fracture, bifrontal contusions and R SDH
18	M	Fall	Nil	15	<1 min	<0.003	14	L frontal EDH, skull fracture
23	M	Assault	Nil	15	NK	12	20	L fronto-parietal SDH and skull fracture
54	M	Fall	Nil	NK	<5min	Nil	9	L parietal EDH, R frontal contusion, and skull fracture
37	M	Fall	Nil	4	Intubated	52	38	Oedema and contusion
56	M	Fall	Telmisartan 80 mg od	3	10 min	NK	27	L frontal EDH, R temporal

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								contusion, mastoid and orbital fracture
50	M	RTA	Ramipril 10mg od, Amlodipine 10mg od	4	Intubated	42	19	SAH, skull fractures (L petrous temp, R sphenoid, bilat orbits), R frontal contusion and oedema
41	M	RTA	Nil	6	Intubated	30	56	Oedema and L haemorrhagic frontal contusions
39	F	RTA	Nil	6	Intubated	30	48	Bifrontal contusions
33	F	Fall	Nil	NK	NK	NK	22	SAH and oedema
33	M	RTA	Nil	3	Intubated	42	47	NAD
49	M	Assault	Nil	NK	NK	NK	33	SAH, bifrontal contusions, SDH and skull fracture
48	M	Assault	Anti TNF alpha, Co-codamol PRN	NK	NK	5	27	NK
47	F	RTA	Salbutamol PRN	5	Intubated	42	20	SAH and general oedema
36	M	RTA	Nil	NK	Intubated	10	10	L sided ICH, SAH and L ganglionic and mid-brain haematoma
23	M	Sport injury	Nil	NK	0	0.02	6	NAD
53	M	Fall	Nil	15	0	0	25	NAD
66	F	RTA	Amitriptyline nocte, Tramadol PRN	NK	NK	77	65	NK
29	F	NK	NK	NK	NK	NK	24	NK
42	F	RTA	Co-codamol qds	12	30 min	56	68	L frontal EDH
34	M	Assault	Nil	14	NK	42	3	Bifrontal contusions,

								skull fracture, SAH and L sided SDH
53	F	Sport injury	Nil	15	Nil	Nil	2	NK
24	M	Assault	Nil	NK	>1h	2	3	Bifrontal contusions, skull fracture, SDH and SAH
45	M	Assault	Thamine 100mg od	8	NK	30	13	Global sulcal effacement
24	M	Assault	Nil	NK	NK	0.25	2	SAH, oedema and skull fracture
26	M	Fall	Nil	15	<5 min	0.02	2	Skull fracture, bifrontal contusions, SDH
50	M	Assault	Nil	NK	Intubated	5	37	NK
33	M	Assault	Ciprofloxacin 250mg od	NK	<5min	0.5	3	R frontal contusion, L occipital EDH and skull fracture
49	M	Assault	Nil	NK	NK	1	14	NK
44	M	Fall	Nil	9	<5min	1	9	NK
22	F	RTA	Propranolol 40mg bd	15	<5min	0.33	5	R frontal SDH, R hemisphere swelling, SAH, and L temporal fracture
25	M	Assault	Tramadol, Codeine, Paracetamol	NK	NK	NK	1	Bifrontal contusions, SDH, SAH and basal skull fracture
48	M	RTA	Nil	NK	1min	0.04	13	Not performed
34	F	RTA	Thyroxine	15	<5min	0.003	5	R temporal EDH
39	M	RTA	Citalopram 40mg, Omeprazole 20mg	NK	Nil	Nil	101	Not performed
29	M	RTA	Nil	NK	NK	2	2	EDH
43	M	Assault		12	NK	0.5	8	R basal skull fracture, L fronto-parietal extraaxial

								haemorrhage with subarachnoid extension
23	M	Fall	Levetiracetam 250mg bd	NK	NK	0.04	1	R frontal haemorrhagic contusion with subarachnoid extension
34	M	Assault	Nil	14	<15min	0.5	3	L parietal and possible R temporal skull fracture, SAH, bifrontal and bitemporal contusions
23	M	Assault	Mesalazine 1g bd, Calcium supplements	NK	10 minutes	4	3	NAD
24	M	RTA	Codeine 20-60mg qds, Zopiclone 7.5mg nocte, Omeprazole 40mg od	6			8	Midbrain haemorrhage, and intraventricular haemorrhage with associated hydrocephalus
55	M	RTA	Salbutamol PRN	3	12h	1	8	NK
21	M	Sport injury	Amitryptiline 20 mg nocte, Tramadol PRN, Diclofenac PRN, Paracetamol PRN	15	10 minutes	3	5	NAD
35	F	RTA	Thyroxine 100mcg, Levothyroxine 50mcg	NK	<5min	1	3	SAH and temporal skull fracture
33	M	Assault	Nil	7	NK	1	4	Occipital EDH, R parietal SDH and R occipital skull fracture

22	M	Fall	NK	6	Intubated	16	48	NK
37	F	Sport injury	Nil	15	Nil	Nil	4	NK
21	M	Assault	Nil	3	Intubated	35	3	L fronto-parietal EDH and haemorrhagic contusion

Abbreviations: bd = twice a day, EDH = extradural haematoma, GCS = Glasgow Coma Scale, ICH = intracranial haemorrhage, LOC = Loss of consciousness, NAD = no abnormality detected, NK = Not known, od = once a day, PRN = as required, PTA = Post-traumatic amnesia, qds = four times a day, SAH = subarachnoid haemorrhage, SDH = subdural haematoma, RTA = road traffic accident, R = Right, L = Left.

3.2.3. Control groups

Three age-matched control groups were used for different parts of the analysis. A control group of 25 participants were used for the fMRI experiment (17 males, mean age = 34.2 years ± 9.6). The second control group consisted of 30 participants (14 males, mean age = 37.2 years ± 8.9) were used as controls for the diffusion tensor imaging. The third control group consisted of 26 participants (12 males, mean age 35.4 ± 11.1) who performed the neuropsychology battery outlined in chapter 2. The control subjects had no history of neurological or psychiatric disorders. The Hammersmith and Queen Charlotte's and Chelsea Research ethics committee approved the study, and all the participants gave written informed consent.

3.2.4. Neuropsychological assessment

A neuropsychological assessment was administered on the participants to assess cognitive function. The battery used is described in detail in Chapter 2.

3.2.5. Stop signal task procedure

The SST was used to study response inhibition in the scanner. The paradigm is explained in depth in Chapter 2.

3.2.6. MRI image acquisition and analysis

The data collection and analysis pipeline are described in Chapter 2.

3.2.7. Scanning protocol

3.2.7.1.   Description of scanning sessions

Patients had two MRI sessions which were separated by a short break; one session consisted of structural brain imaging sequences which included T1, a variety of different T2 sequences (T2 FLAIR, T2 FFE, T2-SWI), and 4 x 16 directions DTI scans of 5mins each and a resting state fMRI sequence.

A second session consisted of task fMRI. For the SST, all subjects performed two runs of a choice reaction time task (CRT; not presented in this thesis) and two runs of the SST. This data were collected by other lab members and made available to the group for analysis. One age and gender-matched control group had the same functional session as patients, and another control group had a similar 'structural' session, comprising resting state and DTI. Before the functional session, all subjects completed an initial training session consisting of one full run of the CRT, and one full run of the SST.

3.2.7.2. Scanner parameters

MRI data were obtained using a Philips (Best, The Netherlands) Intera 3.0 Tesla MRI scanner using Nova Dual gradients, a phased array head coil, and sensitivity encoding (SENSE) with an under-sampling factor of 2.

Structural MRI

High-resolution images (T1-weighted) were acquired with the following acquisition parameters: matrix size 208 × 208; slice thickness=1.2 mm; 0.94 mm × 0.94 mm in plane resolution; 150 slices; TR=9.6 ms; TE=4.5 ms; flip angle 8°. Diffusion-weighted volumes with gradients applied in 64 non-collinear directions were collected. The following parameters were used: 73 contiguous slices, slice thickness = 2 mm, field of view 224 mm, matrix 128 x 128 (voxel size = 1.75 x 1.75 x 2 mm3), *b* value = 1000 and four images with no diffusion weighting (b=0).

Functional MRI

Functional MRI images were obtained using a T2*-weighted EPI sequence with whole-brain coverage (TR/TE = 2000/30; 31 ascending slices with thickness 3.25 mm, gap 0.75 mm, voxel size 2.5×2.5×5 mm, flip angle 90°, field of view 280×220×123 mm, matrix 112×87). Quadratic shim gradients were used to correct for magnetic field inhomogeneities within the brain. Paradigms were programmed using Matlab® Psychophysics toolbox (Psychtoolbox-3 www.psychtoolbox.org) and stimuli presented through an IFIS-SA system (In Vivo Corporation). Responses were recorded through a fibre optic response box (Nordicneurolab, Norway), interfaced with the stimulus presentation PC running Matlab.

3.3. Results

3.3.1. Neuropsychological assessment

A subset of 52 patients (mean age 38 ± 12) and 26 age-matched controls (mean age 35.4 years ± 11.1) underwent neuropsychological assessment. As a group, TBI patients demonstrated impairments during the Verbal Fluency Letter Fluency and the Colour-Word (Stroop) test, which tap inhibitory control and cognitive flexibility. Patients were slower than controls on the Colour-Word test on trials requiring the ability to inhibit a prepotent response and/or to flexibly switch between alternating tasks. The TBI patients showed an expected pattern of neuropsychological impairment, with evidence of slow information processing speed, impaired inhibition, and reduced cognitive flexibility compared with an age-matched control group. They were also slower on the Trail Making Test A, which reflects impaired information processing speed. These were specific impairments limited to a subset of the behavioural measures, rather than a global impairment that spanned many domains of cognition. The patients were well matched with controls on most cognitive variables. Indeed, the patients showed better performance on a test of verbal abstract reasoning (**Table 3.2**).

Table 3.2: Neuropsychological results for TBI group 1 and control group 1

Cognitive Variable	Control Group 1 Mean ± SD	TBI Group 1 Mean ± SD
Similarities	35.1 ± 6.2	38.7 ± 3.8*
Matrix Reasoning	26.5 ± 4.2	27.4 ± 4.8
Verbal Fluency Letter Fluency	48.5 ± 12.0	44.1 ± 11.2
Stroop Colour Naming (s)	32.2 ± 14.1	34.0 ± 8.9
Stroop Word Reading (s)	29.6 ± 5.1	23.4 ± 4.8
Stroop Inhibition (s)	22.4 ± 4.2	58.3 ± 20.9**
Stroop Inhibition-Switching (s)	51.5 ± 18.7	68.4 ± 21.2**
Trail Making Test A (s)	21.5 ± 5.7	27.4 ± 10.4*
Trail Making Test B (s)	53.7 ± 38.5	64.7 ± 35.1
Trail Making Test Switch Cost	29.3 ± 31.3	33.2 ± 6.6
Digit Span forward	11.2 ± 2.0	10.6 ± 2.2
Digit Span backward	7.6 ± 1.7	7.4 ± 2.3
Logical Memory I 1st recall total	28.1 ± 8.4	27.9 ± 6.5
Logical Memory I recall total	45.1 ± 12.8	45.5 ± 8.7
Logical Memory II recall total	26.6 ± 8.5	29.4 ± 7.0
People Test immediate total	27.5 ± 6.2	24.1 ± 5.6
People Test delayed total	9.2 ± 3.6	8.8 ± 2.3

*Neuropsychological results for TBI patients compared with an age-matched control group. Significant differences between patients and controls shown by *P < 0.05 and **P < 0.01. Stroop test refers to the D-KEFS Colour-Word Interference Test*

3.3.2. Behaviour

Fifty-seven TBI patients (11 females, mean age 36.7 years ± 11.5) and 25 healthy volunteers performed two runs of the SST. Here, sudden demands for motor control are studied on 20% of the trials where subjects attempt to stop a motor action in response to an unexpected stop signal (*Figure 2.4*). Both patients and controls were able to perform the SST to the desired level of accuracy (~50% accuracy on stop trials and >95% correct on Go trials). The SSRT, a measure of inhibitory processing, was significantly higher in patients than age matched controls, indicating an impairment of response inhibition in the patient group as a whole (t = 2.01, df = 66, P = 0.014). The SSRT was negatively correlated with accuracy on Go trials in both controls (r = −0.481, p = 0.023) and patients (r = −0.455, P = 0.002). Furthermore, patients' SSRT also correlated with intra-individual variability (IIV) in Go RT (r = 0.458, P = 0.002) and mean Go RT (r = 0.395, P = 0.007). This provides evidence that performance on stop trials is related to attentional processes that influence both Go and Stop trial performance. Although accuracy on Go trials was high for both groups (>95%), patients were slightly less accurate than controls (t = 2.81, df = 80, P = 0.006). Except for the SSRT, and accuracy on Go trials, there were no behavioural differences on other measures of SST performance. This included mean RT for correct Go trials, accuracy on Go and stop trials, the number of negative feedbacks the participants received, as well as the IIV of Go RT (*Table 3.3*).

Table 3.3: Behavioural results for TBI group 1 and control group 1 on the stop signal task.

	Control Group 1 (n = 25)	TBI Group 1 (n = 57)
Median RT (ms)	443 ± 106	483 ± 116
Go % Accuracy	98.4 ± 1.5	95.5 ± 4.8*
Stop % Accuracy	49.5 ± 2.2	49.6 ± 2.6
Negative Feedback	13 ± 8	12 ± 9
IIV	0.181 ± 0.037	0.188 ± 0.054
SSRT (ms)	238 ± 32	268 ± 67*

Behavioural results for the SST. Reaction times (RT), accuracy (%), negative feedback, intra-individual variability (IIV) and stop signal reaction time (SSRT), with standard deviations (± SD) for both patients and controls are reported. Significant differences between patients and controls shown by $*P < 0.05$.

3.3.3. Region of interest analysis

Prior to conducting the FC analysis pipeline, a standard GLM and region of interest analysis was carried out to define active regions during stop trials and Go trials. Regions of interests (ROIs) were defined on the basis of patterns of activity observed during stopping and has been described previous in Chapter 2. Bonnelle and colleagues have previously reported: (1) that the rAI and dACC show increased activity during stopping; (2) that the DMN normally shows reduced activity during stopping; (3) that TBI results in a failure of DMN deactivation, which is significantly lower than controls; and (4) this is predicted by the amount of structural damage to the white matter tract connecting the rAI and the dACC (Bonnelle et al., 2012) (**Figure 3.1** for illustration). The nodes (shown in **Figure 3.2**) used for the PPI analysis in this chapter showed regional activity changes during stopping consistent with this overall pattern.
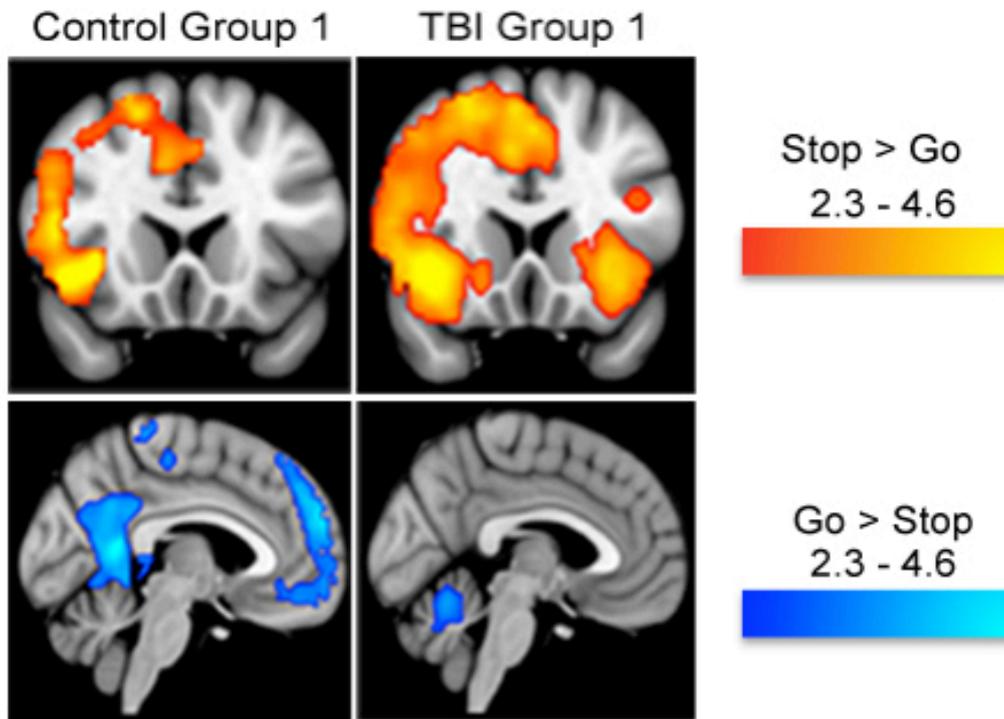
Figure 3.1: Overlay of stopping brain activation. *Brain activity associated with correct stop (StC) vs. Go trials for controls and patients, reanalysed from (Bonnelle et al., 2012). Results are superimposed on the MNI-152 T1 1-mm brain template. Cluster corrected z = 2.3, P < 0.05.*

A) Stopping
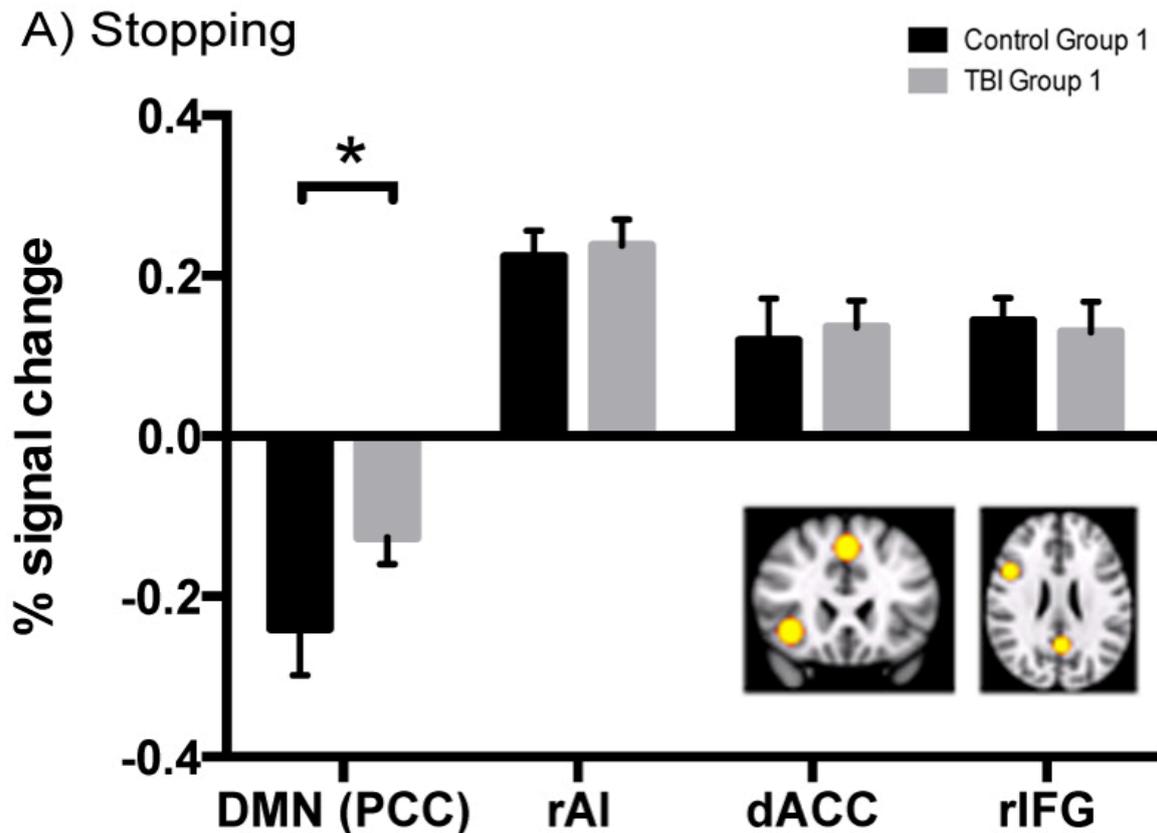
*Figure 3.2: Region of interest (ROI) analysis. ROI analysis showing percentage BOLD signal change during correct stop trials vs. Go trials in the posterior cingulate cortex (PCC), the right anterior insula (rAI), the dorsal anterior cingulate cortex (dACC) and the right inferior frontal gyrus. (Inset) Spatial maps of each ROI superimposed on the MNI 152 1mm-brain template. *P < 0.05.*

3.3.4. Functional connectivity analysis

To investigate the interaction between the SN and DMN, the FC analyses focused on two core nodes of the SN, the rAI and the dACC, together with the right inferior frontal gyrus (rIFG), a region adjacent to the rAI. The analysis focused on the rAI and the dACC nodes of the SN, as these two regions are connected by the tract where damage predicts DMN (dys)function (Bonnelle et al., 2012). The rIFG was selected as a control node for the FC analyses, as the rIFG is spatially close to the rAI and often shows a similar pattern of functional activity (Bonnelle et al., 2012; Sharp et al., 2010), but is not strictly a part of the SN.

3.3.4.1. *Hypothesis 1: Stopping is accompanied by increased functional connectivity between the rAI and the DMN (Figure* 3.3*)*

The change of FC (O'Reilly et al., 2012) was examined between the DMN and the three task-positive ROIs during stop vs. Go trials (Friston et al., 1997; O'Reilly et al., 2012). A task specific change in the relationship between the DMN and the ROIs (a PPI effect) would suggest "a task specific change in the exchange of information" during stop vs. Go trials (O'Reilly et al., 2012). FC between the DMN and the SN changed during stopping. In healthy subjects, a one-way ANOVA of the PPI between the three frontal ROIs and the DMN showed a main effect of region (F = 5.5 df = 1.5, 39, P < 0.02; Huyn-Feldt correction applied). Pairwise planned contrasts between the rAI PPI and each of the other two ROIs showed that the FC with the DMN during stopping was significantly higher for the rAI than either the dACC or rIFG (F > 6, df = 1, 24, P < 0.02 in each case). One-sample t-tests showed that the increase in FC during stopping between the DMN and the rAI was significantly greater than zero (t = 4.2, df = 24, P < 0.001), but was not significantly above zero for the dACC or rIFG. It is noteworthy that the increase in FC between the SN and DMN occurred in the context of distinct patterns of relative activation change; an increase in the rAI, but a decrease in the DMN.

3.3.4.2. *Hypothesis 2: Patients with impairments of response inhibition fail to show increased functional connectivity during stopping (Figure 3.3)*

Cognitive impairment on the SST in TBI patients was associated with abnormalities of FC. A 2 x 3 Group by Region ANOVA, adding in the patient group, showed a significant region x group interaction (F = 5.95, df = 2, 160, P = 0.003). Planned contrasts comparing FC of the DMN with the rAI and each of the other two ROIs in interaction with the Group factor, showed that the increase in FC for the rAI compared with either of the other ROIs, was significantly greater in the controls than in the patients (F > 7.8, df = 1, 80, P < 0.006 in each case). Pairwise t-tests (comparing controls and patients) revealed a significant group difference in the PPI between the rAI and DMN (t = 3.72, df = 28, P = 0.001; corrected for inhomogeneity of variance between groups), but there were no group differences in the other regions (t < 0.91, P > 0.35 in each case) (**Figure 3.3**). In the patients, there was no significant PPI in any of the three regions tested, and no regional differences in PPI magnitude.
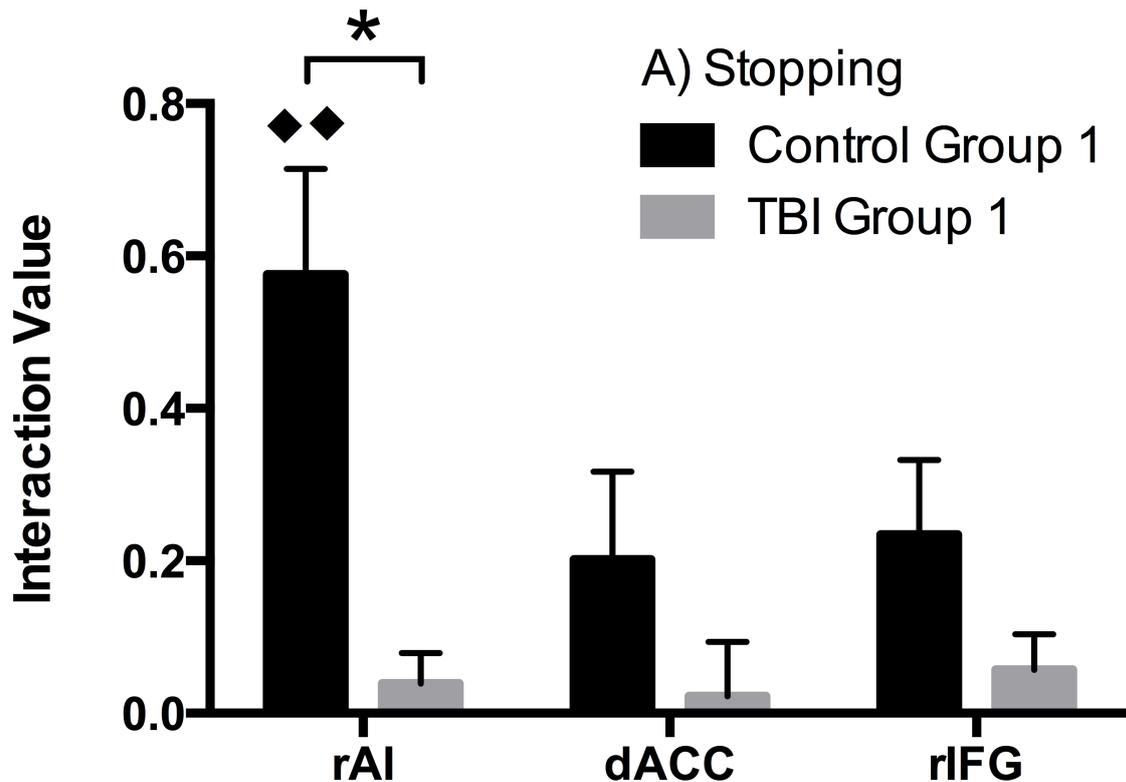
Figure 3.3: PPI analysis. *The bar chart represents the strength of FC during stopping from the PPI analysis, with the DMN and our three ROIs, in controls (black) and patients (grey).* ◆◆*P < 0.005, *P < 0.005 between groups.*

3.3.4.3. Hypothesis 3: The amount of damage to the rAI-preSMA/dACC tract inversely correlates with the extent of reduced functional connectivity between the rAI and DMN during stopping (Figure 3.4)

Next, the hypothesis that the integrity of the structural connection between the rAI and the preSMA/dACC predicted the breakdown of FC between the two networks was tested. Fractional anisotropy (FA) provides a validated marker of white matter integrity post TBI (MacDonald et al., 2007). In the patients, there was a significant positive correlation between tract integrity and the strength of PPI between the DMN

and rAI (r = 0.4, *P* = 0.003). Patients with more damage to this tract (lower FA values) showed less change in the functional interaction (a more negative value) between the networks (***Figure 3.4***A). There was no significant correlation between the same white matter tract and the FC between the DMN and dACC (r = 0.1, *P* = 0.51) (***Figure 3.4***B), nor the DMN and the rIFG (r = 0.05, P = 0.69) (***Figure 3.4***C). The analysis was repeated for the DMN and dACC after excluding outliers; following exploratory data analysis using boxplots, outlier scores $\geq$ 1.5 x interquartile range outside the middle half of the sample were excluded variable-wise. Again, there was no significant relationship between the white matter tract and FC between the DMN and dACC (r = -0.07, *P* = 0.61).

Furthermore, in order to test the specificity in the correlation between white matter FA and FC between the DMN and rAI against the other correlations, pairwise comparisons of the correlations (using FA as the common variable) were computed. There was a significant difference in the strength of the correlation between the white matter tract and the FC between the DMN and the rAI (i.e., ***Figure 3.4***A) and (1) the white matter tract and the FC between the DMN and the dACC (i.e., ***Figure 3.4***B) (z = 1.8, P = 0.03); and (2) the white matter tract and the FC between the DMN and the rIFG (i.e., ***Figure 3.4***C) (z = 1.6, P = 0.02). There was no difference between the white matter tract and the FC between the DMN and the dACC and the white matter tract and the FC between the DMN and the rIFG (z = 0.3, P = 0.36).
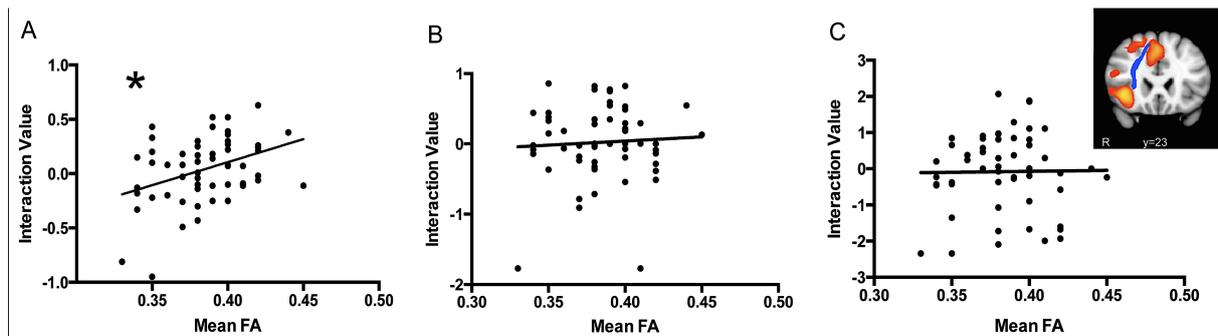
Figure 3.4: Mean fractional anisotropy (FA) predicts FC. *Mean FA of the rAI-preSMA/dACC tract in patients plotted against the FC of the DMN with (A) the right anterior insula, and (B) the dorsal ACC, and (C) the right inferior frontal gyrus, on correct stop trials vs. Go trials. (Inset) Coronal view of the white matter connection between the rAI and preSMA/dACC (blue) overlaid on the activation map for the contrast correct stop trials > Go in patients (orange). *P < 0.05.*

3.3.5. White matter integrity predicts rAI BOLD activity in TBI patients

The relationship between the integrity of the rAI-preSMA/dACC white matter tract and percentage BOLD signal change during stopping was investigated next. Bonnelle and colleagues have previously demonstrated that white matter structural integrity is closely related to the brain activity during task (Bonnelle et al., 2012). The current ROI analysis was extended by investigating whether the relationship between the structural integrity of the rAI-preSMA/dACC tract in the TBI group predicts BOLD activation change during stopping in our ROIs. A significant positive correlation between the percentage BOLD signal change during stopping in the rAI and the structural integrity of the rAI-preSMA/dACC tract (r = 0.25, P = 0.02) (**Figure 3.5**A). No significant correlations between dACC (**Figure 3.5**B) and rIFG (**Figure 3.5**C) activation and the integrity of the white matter tract were found (r = -0.17, P = 0.21; r = -0.99, P = 0.5 respectively). The analysis was repeated for the rIFG after excluding outliers, again, following exploratory data analysis using boxplots, outlier scores ≥ 1.5 x interquartile range outside the middle half of the sample were excluded variable-wise. Again, there was no significant relationship between the white matter tract and percent signal change in the rIFG after outlier removal (r = -0.14, P = 0.32).

Furthermore, in order to test the specificity in the correlation between white matter FA and regional signal change in the rAI against the other correlations, pairwise comparisons of the correlations (using FA as the common variable) were computed as above. There were no significant differences in the strengths of the correlations between the white matter tract and any of the regional signal change during stopping.
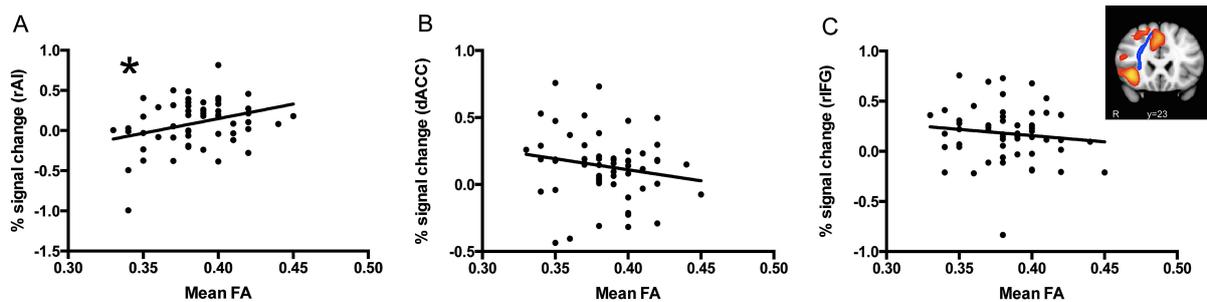
Figure 3.5: Mean fractional anisotrophy (FA) and regional signal change during stopping. *Mean FA of the rAI-preSMA/dACC tract in patients plotted against the regional activation changes in (A) the right anterior insula, and (B) the dorsal ACC, and (C) the right inferior frontal gyrus, on correct stop trials (StC) vs. Go trials. (Inset) Coronal view of the white matter connection between the rAI and preSMA/dACC (blue) overlaid on the activation map for the contrast StC > Go in patients (orange). *P < 0.05.*

3.3.6. Regional activation changes predict SSRT in TBI patients.

The next analysis further investigated whether the imaging parameters had a relationship with the SSRT, a behavioural measure, from the scanner performance. Within the TBI group, greater rAI activity during stopping was associated with more efficient response inhibition (lower SSRT) (r = -0.28, *P* = 0.016) (***Figure 3.6***A). This relationship was not observed in the dACC (r = -0.23, P = 0.08) (***Figure 3.6***B) and the rIFG (r = -0.78, P = 0.57) (***Figure 3.6***C). This was also true after removing an outlier in the rIFG (as described above) (r = 0.3, P = 0.81). There was no difference

between the strength of these correlations. However, there were no significant

differences between the strength of these correlations.
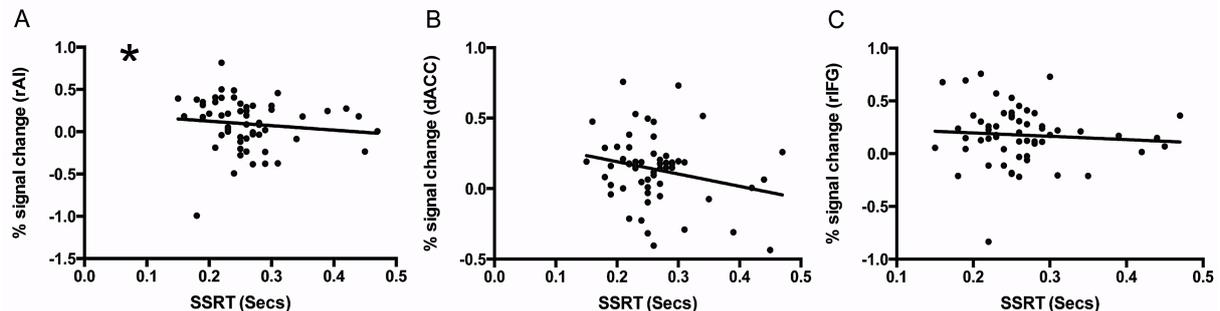
Figure 3.6. Stop signal reaction time (SSRT) and regional activity during stopping. *A measure of response inhibition (SSRT), is shown to significantly correlate with regional activation changes within the right anterior insula (A), but not with the dorsal anterior cingulate cortex (B), nor the inferior frontal gyrus (C), during stopping. *P < 0.05.*

3.3.7. Interaction between the rAI and DMN remains significant independent of focal lesion

To exclude any artefactual effect of focal lesions in my main findings, the PPI analysis was repeated excluding patients with focal cortical lesions. After removing those 21 patients with focal lesions, there remained a significant difference between patients and controls in their PPI with the rAI (t = 3.4, df = 59, *P* = 0.001). Furthermore, the relationship with the rAI-preSMA/dACC tract also remained significant (r = 0.4, *P* = 0.02).

3.3.8. Accounting for possible effects of Motion

The next analysis investigated the possibility that differences in the FC between patients and controls could be driven by any changes in motion parameters. To test this, average motion parameters from each subject's lower level FEAT directory were

carried out and compared using an independent sample's t-test between the two groups. No difference in these motion parameters between patients and controls were found. Furthermore, to test any differences at the PPI level, motion parameters were added into the multiple regression model (alongside the task variables). This provided a subject-specific 6-dimension motion parameter, which was averaged and carried out an independent samples t-test. Again, no motion differences between the two groups were observed.

3.4. Discussion

3.4.1. Results overview

In the current study, a significant interaction is observed between the right anterior insula (rAI), a key node in the SN, and the DMN during stop trials in the SST in healthy controls. In this task, participants are required to attend to an infrequent stop stimulus, which is associated with right inferior frontal cortex function, and inhibit an on-going motor response. This is compatible with a model of cognitive control that suggests tight coupling of networks is required to produce efficient behaviour (Menon and Uddin, 2010). This interaction was then tested in traumatic brain injured patients, who showed that the interaction was significantly reduced in this patient group. Furthermore, in this patient group, the structural disconnection within the SN predicted a failure of the networks to interact efficiently, resulting in poor behavioural performance. Taken together, these results show that the structural integrity of the tract connecting the rAI and the dACC cortex predicts the interaction between the DMN and SN during stopping, as well as a behavioural measure of inhibition.

The results in this chapter tested the strength of FC between the DMN and key nodes of the SN, namely the rAI and the dorsal anterior cingulate cortex (dACC). The

regulation of DMN activity is important for cognitive control (Leech and Sharp, 2013). Regions within the DMN show highly correlated activity during rest, as well as most tasks where attention is directed internally, such as autobiographical memory retrieval or planning for future event (Chiong et al., 2013; Spreng, 2012). However, the DMN is often referred to as a 'task-negative' network, as it shows rapid deactivation when attention is directed externally (Shulman et al., 1997). In tasks where attention must be directed towards external stimuli, activity increases in 'task-positive' networks, notably the SN. These increases are synchronised with deactivation in the DMN in a tightly coupled way (Leech and Sharp, 2013). This anticorrelated pattern of activity between the SN and DMN allows for efficient behaviour, with increases in the magnitude of anticorrelation associated with improved behavioural performance (Kelly et al., 2008).

The second hypothesis concerned the strength of (FC) in a group of fifty-seven TBI patients. The DMN shows aberrant activity across a variety of neurological and psychiatric disorders, which include schizophrenia (Kubicki et al., 2003; 2005; Liang et al., 2006), autistic spectrum disorder (Chiu et al., 2008; Kennedy, Redcay, and Courchesne, 2006), Alzheimer's disease (Buckner et al., 2005; Greicius, Srivastava, Reiss, and Menon, 2004) and depression (Berman et al., 2011; Zhu et al., 2012). This manifests in part as a failure of PCC deactivation at appropriate moments. The PCC is a key node of the DMN (Buckner et al., 2008), which is highly anatomically connected (Hagmann et al., 2008) and has a high baseline metabolic rate (Raichle et al., 2001). In the healthy brain, a failure to supress the PCC is associated with impaired cognitive control (Kelly et al., 2008). Bonnelle and colleagues have previously shown abnormalities in DMN activity after TBI (Bonnelle et al., 2012;

Bonnelle, Leech, Kinnunen, Ham, Beckmann, De Boissezon, Greenwood, and Sharp, 2011a; Sharp et al., 2011), and the current work extends that previous finding by directly showing that the strength of FC between the DMN and rAI is significantly reduced in the TBI group, who as a group, show impairments of executive function.

Thirdly, the relationship between the underlying white matter structure that connects the rAI to the preSMA/dACC and the strength of FC between the DMN and rAI was investigated. This relationship demonstrated that damage to this white matter tract predicted impairment in the strength of FC between the DMN and the rAI. TBI frequently produces DAI, which damages the connections between large scale brain regions and produces cognitive impairment (Kinnunen et al., 2010). More specifically, using a simple two choice reaction time task, our group demonstrated that TBI patients have sustained attention deficits (Bonnelle et al., 2011). The behavioural performance of patients was normal in the first third of the task, however in the final third patients' performance became significantly slower and more variable compared to the controls (Bonnelle et al., 2011). Importantly, this decline in performance was predicted by the pattern of FC from the PCC to the rest of the DMN, and this predictive information was present at the beginning of the task when behaviour was normal. In addition, a structural analysis was carried out, which measured damage to the cingulum bundle that connects the PCC to the anterior part of the DMN and found a strong negative correlation between integrity in these tracts and performance in the sustained attention task. These results suggest that disruption of structural and FC within the DMN contribute to impairments of sustained attention (Leech and Sharp, 2013).

3.4.2. Activity in task positive regions preserved

It is interesting to note that no abnormal brain activity was observed in regions positively activated by the SST, that is on the stop correct > Go contrast. It is particularly noteworthy that activation within the SN was normal, despite the presence of structural damage to white matter connecting the SN's nodes. It is possible that current imaging methods are not able to pick up the temporally transient changes in the SN, perhaps as a consequence of the limitations of fMRI in resolving rapid activity fluctuations.

Furthermore, there was no evidence that the white matter tract (rAI-preSMA/dACC) correlated with activity within 'task-positive' regions. These regions included the nodes of the SN and the Executive Network (EN). One possible explanation may be that the effects of subtle regional dysfunction within the SN may be amplified within the DMN, possibly due to inter-connected organisation of brain regions. Based on the proposal that the SN is involved in switching between DMN and the EN, changes in the overarching EN should have been seen in patients with damage to their rAI-preSMA/dACC tract. However, previous work carried out (Bonnelle et al., 2012) has shown no evidence for such an effect. A possible explanation is that while the rAI exerts control over the DMN via the dACC (Sridharan et al., 2008), the rAI might be connected to regions of the EN via more direct pathways. However, work carried out at our lab has shown that there is no relationship between the structural integrity of the white matter that connects the rAI to other regions of the EN. By virtue of the fact that TBI patients showed a relatively normal activation of task positive regions, it might be more difficult to establish a clear relationship between white matter structure and activation within those regions.

3.4.3. White matter integrity vs. lesion study

Neuropsychological studies have demonstrated that damage to parts of the right inferior frontal cortex (rIFC) produces impairments in task monitoring and the inhibition of inappropriate behaviour (Aron et al., 2003; Floden and Stuss, 2006). Behaviourally, the amount of damage in this rIFC area has been shown to correlate with the SSRT (Aron et al., 2003). Work of this type has tended to focus on the relationship between cortical damage and behaviour. However, the lesions studied almost always result in a degree of damage to large white matter tracts and the contribution of this damage to cognitive impairment has been difficult to differentiate from that of damage to the overlying cortex (Corbetta and Shullman, 2011). Previous work has shown that frontal white matter damage influences SN function (Hogan et al., 2006). Hogan and colleagues studied a group of sickle-cell disease patients. These patients show discrete lesions in the frontal white matter, notably between the dorsolateral prefrontal cortex (DLPFC) and the posterior medial frontal cortex (pMFC), which involves the ACC. They found that performance monitoring depends on the connectivity between these frontal regions, based on diminished event related potential amplitude between errors and correct responses (Hogan et al., 2006). Their study provided evidence that frontal lobe lesions that do not directly involve the cortex of either the DLFC or pMFC (ACC) also impact on performance-monitoring pathways. The results from this chapter show that connections between the rAI and the dACC relate to the functional interaction between networks and behaviour. These relationships are present in a subgroup of patients without clear cortical damage, thus demonstrating the importance of studying the contribution of structural connections within large-scale brain networks to cognitive control.

4. The Salience Network and Default Mode Network interactions involved in motor task switching

4.1. Introduction

To test whether the network interaction between the DMN and SN was not an isolated phenomenon during stopping, I tested the hypotheses that FC between the rAI and the DMN is (1) accompanied by an increase in FC in healthy controls during motor task switching; (2) but this increase in FC between the rAI and the DMN is not seen in TBI patients; and (3) the amount of damage to the tract connecting the rAI to the preSMA/dACC after TBI predicts this strength of FC. Here, a different group of TBI patients performing a different cognitive task were investigated. These patients performed a motor task switching paradigm (as described in Chapter 2) which in addition to the inhibition of motor responses that is required during performance of the SST, the participants were also required to switch to a new type of motor response.

The ability to switch from one task to another (task switching) is a key part of cognitive control, as flexibility in our daily routines frequently requires us to switch between tasks. This switching requires mental resources to be reconfigured in order to successfully execute this new task. Switching as a form of cognitive control is integral for behavioural flexibility, as it allows us to adapt to changing events in the world (Hayden et al., 2010). However, network interactions in motor switching after TBI has not been investigated in as much depth as regional activation changes.

Previous work has investigated the changes in brain function and structure involved in motor task switching after TBI (e.g., Leunissen et al., 2014); and recent work has shown switching leads to similar activity changes as those observed stopping a response. These similar activation changes were seen in right lateralized brain regions such as the inferior frontal gyrus and insula cortex (e.g., MacDonald et al.,

2000). In Leunissen and colleagues' study, twenty-three moderate-severe TBI patients and twenty-six healthy controls performed a motor task switching paradigm. Patients made synchronised circular movements with both hands, before a visual cue informed them to either switch or continue their right hand movement in terms of the right hand's circling direction. They found a network of switching activation that included the bilateral insular cortex and anterior cingulate cortex (both key nodes of the SN), as well as other regions such as the supplementary motor area and dorsolateral prefrontal cortex. Although their study adds to the understanding of structure-function post TBI, the work does not directly investigate how network interactions are affected post TBI.

The work described in this chapter builds on the work carried out in the previous chapter. This chapter aims to demonstrate whether an increase in FC, as described in the previous chapter using the SST, is also seen during another motor response condition. In the present chapter the action required is not specific to stopping, but rather is a type of action that requires a reconfiguration of motor control and is also not specific to a particular group of TBI patients.

4.2. Methods

4.2.1. Patient demographics and clinical details

Thirty-four patients with a history of TBI were recruited. There was no overlap in the patients with those investigated in the SST work. Three patients were not included in the imaging analyses because: (1) two were unable to perform the task accurately; and (2) one was removed due to distortion on the imaging files, this was likely to be due to movement artefact. As a result, 30 patients with a history of TBI were included

in the analysis (10 women; ages 20–62 years, mean age = 37 years, S.D = 11.9 years). They were all in the postacute/chronic phase post TBI (with an average of 15 months since injury, ranging from 2-88 months). Exclusion criteria included previous neurosurgery, a history of significant previous TBI or psychiatric or neurologic illness, antiepileptic medication, previous drug or alcohol abuse, or contraindication to MRI. All patients were assessed for structural damage and abnormalities using initial CT imaging and follow-up MRI (standard T1 and gradient echo). Pathologies present on initial CT imaging included cerebral contusions (20%), diffuse brain swelling (oedema) (5%), skull fractures (30%), subdural or extradural haemorrhage (29%), and intraventricular or subarachnoid haemorrhage (16%). MRI at the time of the study showed residual evidence of contusions (40%) and diffuse axonal injury (33%).

4.2.2. Clinical imaging

Most patients had injuries secondary to road traffic accidents (48%), falls (25%), assaults (10%) or an incidental blow (3%). A further 14% of patients suffered a TBI from an unknown cause. Based on the Mayo classification system for TBI severity (Malec et al., 2007), there were 24 moderate/severe and 2 mild cases of TBI, with 5 patients unknown. The Mayo classification integrates the duration of loss of consciousness, length of posttraumatic amnesia, lowest recorded Glasgow Coma Scale score in the first 24 hours, and initial neuroimaging results. The exclusion criterion was the same as patients group 1. Clinical details about the patients, including injury cause, severity and presence of contusions or microbleeds are given in **Table 4.1**.

Patients were assessed using standard T1 MRI to assess evidence of focal brain injury, and gradient echo imaging to identify any evidence of microbleeds, a marker

of diffuse axonal injury (Scheid et al., 2003). A senior consultant neuroradiologist reviewed all study MRI scans. At the time of the study, the scans for the patient group 2 showed the following: 9 patients had residual evidence of contusions, 10 patients had microbleeds (as demonstrated on gradient echo imaging), and 5 had evidence of both. Contusions were mainly situated in the inferior parts of the frontal lobes, including the orbitofrontal cortex and the temporal poles, in a typical lesion distribution for TBI patients (Gentry et al., 1988).

Table 4.1: Clinical details for TBI group 2.

Age at first visit	Sex	Mechanism	Medication at first visit	GCS	LOC	PTA (days)	Time since TBI (mo)	Initial CT
47	M	Fall	Nil	NK	NK	0.5	3	Bifrontal contusions and L frontal EDH
50	M	Fall	Fluticasone nasal spray	NK	2 min	Nil	10	L frontal SDH
41	M	RTA	Diclofenac 75mg bd, Co-dydramol 500mg bd	NK	NK	7	3	L frontal contusion
36	M	Fall	Glargine 30u bd, Humalog 16u tds	NK	NK	28	4	Basal skull fracture, bifrontal contusions and R SDH
33	M	Assault	Nil	7	NK	1	4	Occipital EDH, R parietal SDH and R occipital skull fracture
22	M	Fall	Salbutamol inhaler	6	Intubated	16	48	R temporal EDH, R fronto-temporal haemorrhage
35	M	Assault	Nil	NK	NK	2	12	R temporal haematoma and skull fracture
62	M	RTA	Atorvastatin 80mg, Lamotrigine 50mg bd, Aspirin 75mg od	NK	NK	0.5	34	NK

35	F	RTA	Thyroxine 100mcg, Levothyroxine 50mcg	NK	<5min	1	3	SAH and temporal skull fracture
20	F	RTA	OCP (Yasmin)	NK	Intubated	28	12	NK
34	F	RTA	Nil	NK	Nil	Nil	6	NAD
43	M	RTA	Nil	13	Few minutes	3	4	Bifrontal SAH, fronto-parietal SDH, and complex R temporal skull fracture
39	M	Fall	Paracetamol 1g qds, Amitriptyline 10mg nocte	14	NK	2	4	Displaced frontal skull fracture and associated frontal lobe swelling
21	F	Incidental blow	Oral contraceptive pill	15	Nil	Nil	2	Not performed
29	M	RTA	Nil	NK	Intubated	90	16	NK
39	F	RTA	Nil	NK	NK	3	9	SAH and L frontal haemorrhage
50	F	RTA	Atenolol 50mg od	NK	NK	30	88	NK
42	M	RTA	Co-codamol 6-8 tablets/day	3	NK	90	15	NK
45	M	RTA	Bupropion, Ecitalopram 20mg od, Carbamazepine 200mg bd	NK	<1hr	0.04	30	Bifrontal contusions and maxillofacial fractures
21	M	RTA	Nil	NK	Intubated	NK	34	NK
26	M	Assault	Nil	NK	Nil	Nil	7	L temporal skull fracture with adjacent SAH, SDH and contusion
50	F	Fall	Lansoprazole 15mg od	NK	<5 mins	2	11	SAH and R temporal lobe contusion
43	F	RTA	Nil	15	NK	0.003	12	Not performed
38	M	RTA	NK	NK	NK	NK	18	NK
61	F	NK	Nil	NK	NK	NK	NK	NK
26	F	NK	NK	NK	NK	NK	11	NK
56	M	NK	NK	NK	NK	NK	31	NK
20	M	NK	NK	NK	NK	NK	8	NK
30	M	Fall	Nil	NK	1 hr	NK	14	Possible

								contusion in temporal lobe
46	M	RTA	Nil	7	1-2 weeks	NK	4	L occipital and bilateral frontal contusions, SAH bilaterally, diffuse cerebral swelling, small EDH, venous sinus thrombosis
21	M	Fall	Nil	NK	NK	Nil	3	Bifrontal and L anterior temporal cortical contusions, regional oedema, maybe a thin SDH. Suspected minor subarachnoid component

Abbreviations: GCS = Glasgow Coma Scale, LOC = Loss of consciousness, PTA = Post-traumatic amnesia, NK = Not known, EDH = extradural haematoma, SDH = subdural hematoma, SAH = subarachnoid haemorrhage, NAD = no abnormality detected, RTA = road traffic accident, R = Right, L = Left.

4.2.3. Control group 2

Twenty control participants (10 females, mean age 28.5 ± 8.7 years) were included in the motor switch analysis. There was no overlap in the control participants with those investigated in the SST work. The Hammersmith and Queen Charlotte's and Chelsea Research ethics committee approved the study, and all the participants gave written informed consent.

4.2.4. Neuropsychological assessment

A detailed neuropsychological battery was used to assess cognitive function, which can be found in Chapter 2 (section 2.2).

4.2.5. Motor switch paradigm

The motor switch paradigm is a two-choice task switching paradigm as described in Chapter 2 (2.4.2.1). Briefly, subjects responded to a visual colour cue with either a right or left button press. The side of the response required is determined by the colour of the cue. On switch trials subjects are instructed prior to the appearance of the visual cue to reverse the mapping between colour and motor response so, for example, a red stimulus would switch from signalling a right hand button press to signalling a left hand press (***Figure 2.5***).

4.2.6. MRI data acquisition and analysis

The data collection and analysis pipeline are explained in Chapter 2.

4.2.7. Scanning protocol

The scanning protocol was identical to that described in chapter 3 in terms the scanner parameters, and both structural and functional MRI parameters. The description of the motor task switching paradigm session is below.

4.2.7.1. Description of scanning sessions

During the task switching fMRI session, all the participants performed both task switching conditions; the order of performance was counterbalanced across the participants. An age and gender-matched control group had the same functional session as patients and these data were used to compare across the groups. Before the functional session, all participants completed a shorter training session on both versions of the task switching paradigms. Participants were also asked to recall the rules of the paradigm conditions prior to entering the scanner.

4.3. Results

4.3.1. Neuropsychological assessment

As with the patient group one who performed the stop signal task, TBI patients in this study (TBI group 2), who performed the motor switch paradigm, showed a predictable pattern of neuropsychological impairment with evidence of slow information processing speed, impaired inhibition, reduced executive functions, and working memory capacity. Compared with the age-matched control group, the second group of TBI patients also showed a similar and expected pattern of neuropsychological impairment to that of our patient group 1. All 31 patients and 26 age-matched controls (14 females, mean age 35.4 ± 11.1) underwent neuropsychological assessment. As a group, the TBI patients demonstrated significant impairments during the Verbal Fluency Letter Fluency and the Colour-Word (Stroop) test, which taps inhibitory control and cognitive flexibility. Patients were slower than controls on the Colour-Word test on trials requiring the ability to inhibit a prepotent response and/or to flexibly switch between alternating tasks. They were also slower on the Trail Making Test A, which reflects impaired information processing speed. Furthermore, patient group 2 were significantly more impaired in their working memory capacity, as measured by the digit span test. Again, these were specific impairments limited to a subset of the behavioural measures, rather than a global impairment that spanned many/most domains of cognition (*Table 4.2*).

Table 4.2: Neuropsychological results for patients and controls

Cognitive Variable	Control Group Mean ± SD	TBI Group 2 Mean ± SD
Similarities	35.1 ± 6.2	34.8 ± 5.2
Matrix Reasoning	26.5 ± 4.2	24.9 ± 6.2
Verbal Fluency Letter Fluency	48.5 ± 12.0	35.9 ± 14.3*
Stroop Colour Naming (s)	32.2 ± 14.1	35.6 ± 8.5
Stroop Word Reading (s)	29.6 ± 5.1	24.6 ± 6.5
Stroop Inhibition (s)	22.4 ± 4.2	56.9 ± 18.1**
Stroop Inhibition-Switching (s)	51.5 ±18.7	66.8 ± 19.5**
Trail making Test A (s)	21.5 ± 5.7	30.3 ± 14.1**
Trail making Test B (s)	53.7 ± 38.5	67.4 ± 44
Trail making Test Switch Cost	29.3 ± 31.3	35.9 ± 8.2
Digit Span forward	11.2 ± 2.0	9.6 ± 2.2**
Digit Span backward	7.6 ± 1.7	7.3 ± 2.5
Logical Memory I 1st recall total	28.1 ± 8.4	25.7 ± 7.9
Logical Memory I recall total	45.1 ± 12.8	41.6 ± 11.5
Logical Memory II recall total	26.6 ± 8.5	25.2 ± 9.6
People Test immediate total	27.5 ± 6.2	21.6 ± 7.5**
People Test delayed total	9.2 ± 3.6	7.6 ± 4

*Neuropsychological results for TBI patients compared with an age-matched control group. Significant differences between patients and controls shown by *P < 0.05 and **P < 0.01. Stroop test refers to the D-KEFS Colour-Word Interference Test.*

4.3.2. Behaviour

The TBI patients showed impairments on task performance in the scanner. Although accuracy on Go trials for both groups was generally high (> 90%), patients were slightly less accurate than controls on both Go (t = 2.08, df = 50, *P* = 0.02), and switch trials (t = 2.03, df = 50, P = 0.02). Patients were also slower to respond to switch trials than controls (t = -4.17, df = 50, *P* < 0.005), as well as Go trials (t = -5.41, df = 50, *P* < 0.005) (**Table 4.3**).

Table 4.3: Behavioural results for TBI group 2 and control group 2 on the motor switch paradigm

	Control Group 2	TBI Group 2
Switch Trial RT (ms)	745±100	898±100**
Go Trial RT (ms)	619±100	807±100**
Switch Cost (ms)	126±100	91±100
Switch Trial % Accuracy	92.3 ± 7.8	84.9±14.4*
Go Trial % Accuracy	97±2.9	90.8±13.5*

*Behavioural results for the motor switch paradigm. Reaction times (RT) for switch and Go trials, switch cost, accuracy (%) for switch and Go trials with standard deviations (± SD) for both patients and controls are reported. Significant differences between patients and controls shown by *P < 0.05, **P < 0.005.*

4.3.3. Standard voxelwise GLM analysis

Prior to conducting the FC analysis pipeline, a standard GLM analysis was carried out to define active brain regions during switch trials and Go trials. Brain activity during switching was similar to previous studies in both patients and controls e.g.

(Dosenbach et al., 2006; Kim et al., 2011; Leunissen et al., 2012). Switch compared to Go trials (i.e. switch > Go) showed increased activity in the anterior cingulate cortex/preSMA, bilateral inferior and middle frontal gyri, frontal operculum cortex and insular cortex. More posteriorly, activation was observed within the precuneus cortex, lingual gyrus, supramarginal gyrus, and intraparietal sulcus and the lateral occipital cortices (IPS). Decreased activity was observed in the ventromedial prefrontal cortex (vmPFC), superior frontal gyrus, and the posterior cingulate cortex (PCC). The direct contrast of control and patient groups showed reduced activity in the TBI group within the rAI, frontal operculum cortex, precentral gyrus, frontal orbital cortex and paracingulate gyrus (***Figure 4.1***) (***Table 4.4***).
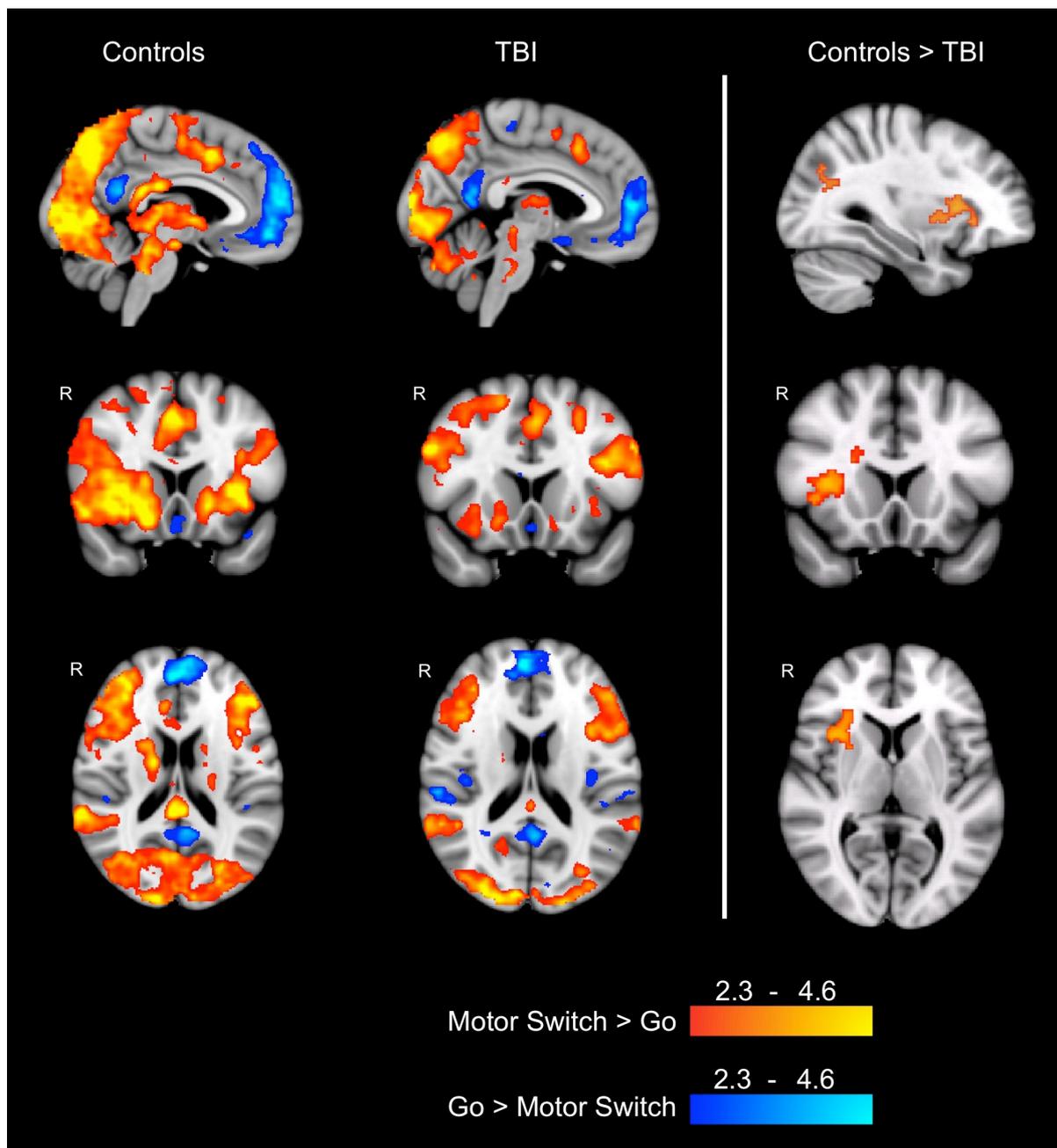
Figure 4.1: Overlay of brain activation in the motor switch paradigm. *Overlay of brain activation associated with correct switch (SwC) vs. Go trials (yellow-red) and Go trials vs. correct switch (blue), in control group 2 (left) and patient group 2 (centre). Right: Brain regions where control group 2 shows a greater activation on switch trials vs. Go trials than patient group 2. Results are superimposed on the MNI 152 T1 1-mm brain template. Cluster corrected Z = 2.3, P < 0.05.*

Table 4.4: Local maxima of brain activation differences between controls and TBI patients for the contrast switch correct vs. Go.

Controls>Patients		MNI Coordinates		
SwC > Go	Z-score	x	y	z
R Insular cortex	3.75	32	26	-2
Frontal operculum cortex	3.6	36	16	8
Precentral gyrus	2.98	58	4	22
Frontal orbital cortex	2.81	44	28	-8
Frontal pole	2.71	32	44	18
Paracingulate gyrus	2.36	12	50	8

4.3.4. Region of interest analysis

In addition to the whole brain analysis, a region of interest analysis was performed to quantify active brain regions during switching. To allow comparisons across the studies, ROIs were defined on the basis of patterns of activity observed during stopping (as described in Chapter 3). It has previously been found that TBI results in a failure of DMN deactivation during stopping, which is significantly lower than controls (t = 2.46, df = 80 P = 0.02) (**Figure 3.1**). In contrast during motor switching, I found a significantly reduced amount of rAI activation in the TBI patients during switching compared to controls (t = 2.4, df = 48, P < 0.05) (**Figure 4.2**). Other regions, including the DMN (PCC), showed no difference in switch trial minus Go trial activation levels between the groups.
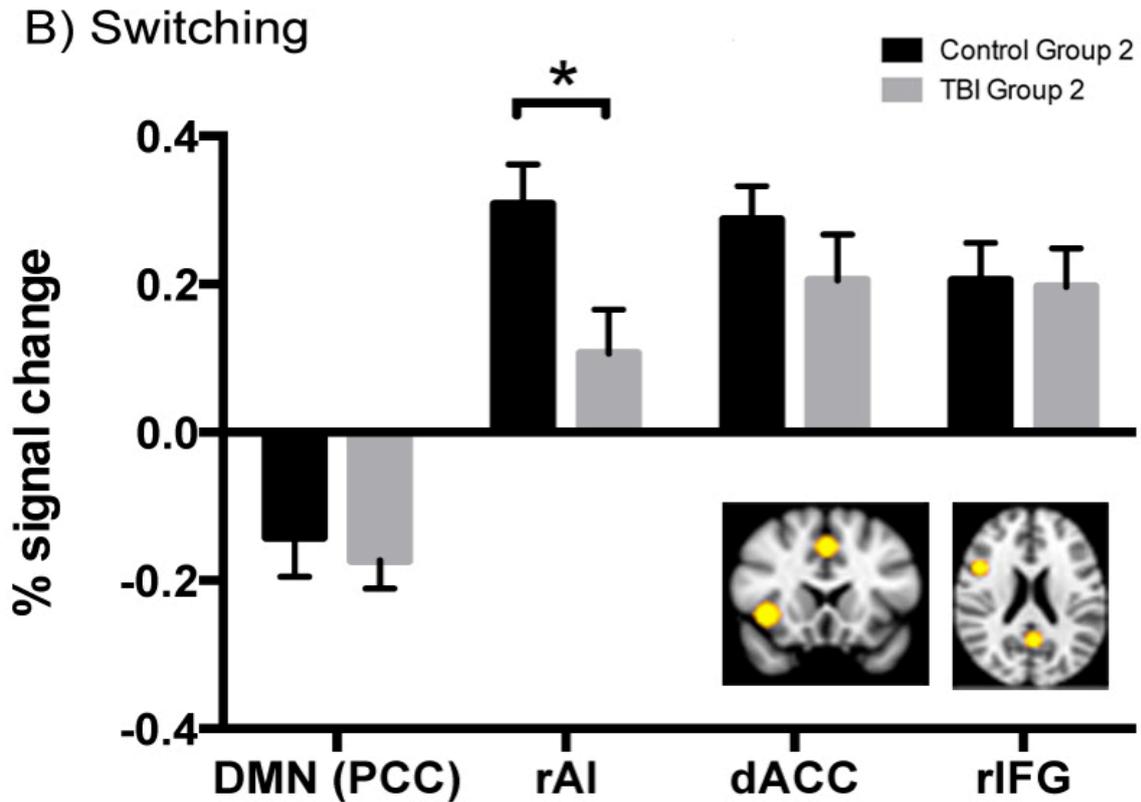
Figure 4.2: Region of interest (ROI) analysis. *Region of interest analysis of regional activation change during switching compared with Go trials in the posterior cingulate cortex (PCC), the right anterior insula (rAI), the dorsal anterior cingulate cortex (dACC) and the right inferior frontal gyrus (rIFG). *P < 0.05.*

4.3.5. Functional connectivity analysis

To investigate whether the interaction between the SN and DMN found during stopping can be generalised to another form of motor control, a FC analysis on the univariate motor switching data was carried out. Again, I focused on the rAI and the dACC, as well as the rIFG, and investigated interaction of these nodes with the DMN.

4.3.5.1. Hypothesis 1: Motor switching is accompanied by increased functional connectivity between the rAI and the DMN in healthy controls (Figure 4.3).

Despite distinct group differences in regional brain activation within the rAI, the same pattern of PPI abnormality was observed in switching, as observed in stopping (Chapter 3). A one-way ANOVA of the PPI between the three frontal ROIs and the DMN showed a main effect of region (F = 13,5 df = 1.3, 26, P = 0.001; Huyn-Feldt correction applied). Planned contrasts between the rAI PPI and each of the other two ROIs showed that the FC with the DMN during switching was significantly higher for the rAI than either the dACC or rIFG (F > 13.8, df = 1, 19, P < 0.001 in each case). One-sample t-tests showed that the increase in FC during motor switching between the DMN and the rAI was significantly greater than zero (t = 4.52, df = 19, P < 0.001), but was not significantly above zero for the dACC or rIFG (t < 0.4, P > 0.21 in each case) (**Figure 4.3**).

4.3.5.2. Hypothesis 2: Patients with impairments of switching fail to show increased functional connectivity during task switching (Figure 4.3).

Similar to stopping, the normal PPI between the rAI and DMN was not significant in the TBI group and task switching impairments on the motor switching paradigm was associated with a breakdown in FC in the patient group. A 2 x 3 Group by Region ANOVA, adding in the patient group, showed a significant region x group interaction (F = 4.85, df = 2, 96, P = 0.01). Planned contrasts comparing FC of the DMN with the rAI and each of the other two ROIs in interaction with the Group factor, showed that the increase in FC for the rAI compared with either of the other ROIs, was significantly greater in the controls than in the patients (F > 7.7, df = 1, 48, P < 0.007

in each case). Pairwise t-tests (comparing controls and patients) revealed a significant group difference in the PPI between the rAI and DMN (t = 3.13, df = 48, P = 0.003; corrected for inhomogeneity of variance between groups), but there were no group differences in the other regions ($t < 0.2$, $P > 0.36$ in each case). In the patients, there was no significant PPI in any of the three regions tested, and no regional differences in PPI magnitude (**Figure 4.3**).
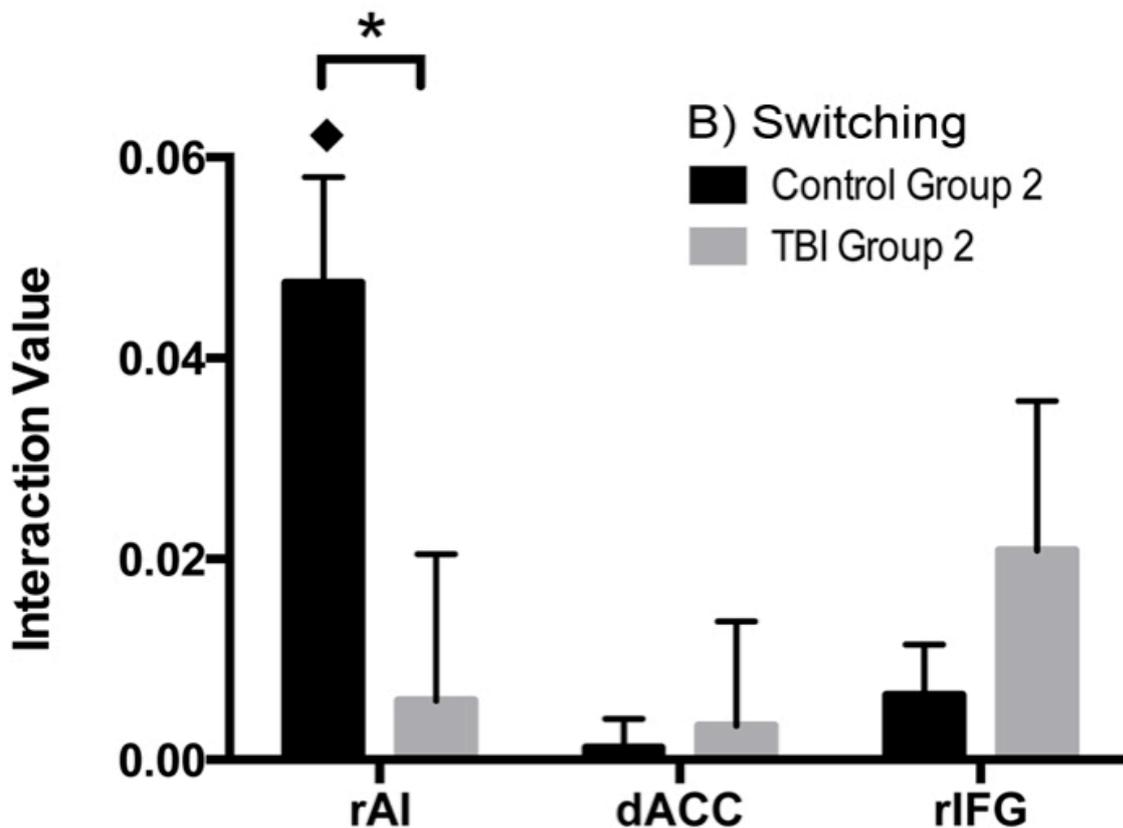
Figure 4.3: Psychophysiological (PPI) interaction. *The bar chart represents the strength of FC during switching from our PPI analysis with the DMN and our three ROIs in controls (black) and patients (grey).* ◆*P < 0.05*

4.3.5.3. Hypothesis 3: The amount of damage to the rAI-preSMA/dACC tract inversely correlates with the extent of reduced functional connectivity between the rAI and DMN during motor switching (Figure 4.4).

As with stopping, the integrity of the rAI-preSMA/dACC tract in the TBI group was positively correlated with the strength of PPI during switching between the rAI and the PCC (r = 0.4, *P* = 0.03) (**Figure 4.4**A). Greater white matter damage to this tract was associated with reduced strength of PPI. No significant relationship was observed with the other PPIs studied (dACC; r = 0.1, P = 0.3, and rIFG; r = 0.04, P = 0.4, **Figure 4.4**B and **Figure 4.4**C, respectively).

Comparisons between the strengths of these correlations showed significant borderline differences between: (1) the integrity of the white matter tract and the FC between the DMN and rAI (**Figure 4.4**A) and the integrity of the white matter tract and the FC between the DMN and dACC (**Figure 4.4**B) (z = 1.5, P = 0.06); and (2) the integrity of the white matter tract and the FC between the DMN and rAI (**Figure 4.4**A) and the integrity of the white matter tract and the FC between the DMN and rIFG (**Figure 4.4**C) (z = 1.6, P = 0.06). There was no significant difference between the strengths of correlations between the integrity of the white matter tract and the FC between the DMN and dACC (**Figure 4.4**B) and the integrity of the white matter tract and the FC between the DMN and rIFG (**Figure 4.4**C) (z = 0.2, P = 0.4).

There was no other significant relationship between the integrity of the rAI-preSMA/dACC tract and the amount of rAI activation in either participant group.
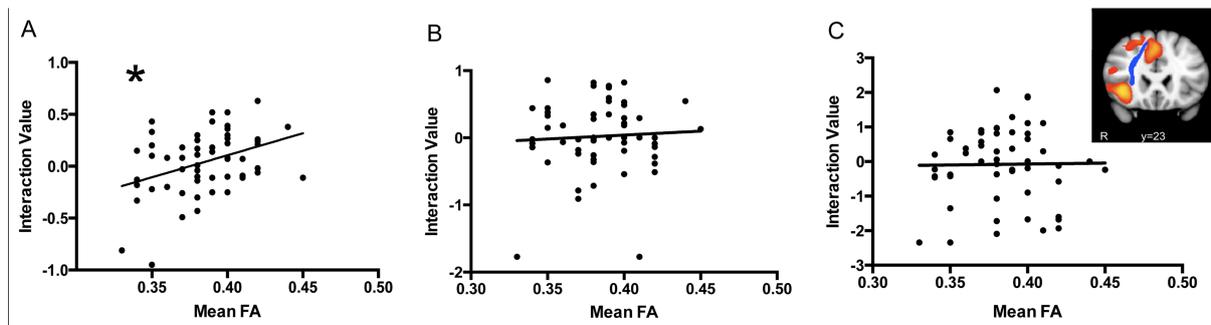
Figure 4.4: *Mean fractional anisotrophy (FA) predicts FC. Mean FA of the rAI-preSMA/dACC tract in patients plotted against the FC of the DMN with (A) the right anterior insula, (B) the dorsal ACC, and (C) the right inferior frontal gyrus, on correct stop trials (StC) vs. Go trials. (Inset) Coronal view of the white matter connection between the rAI and preSMA/dACC (blue) overlaid on the activation map for the contrast StC > Go in patients (orange). *P < 0.05.*

4.3.6. Salience network disconnection, activation and behaviour on the motor switch paradigm.

In contrast to the results for stopping in chapter 3, there was no relationship between the integrity of the rAI-preSMA/dACC tract and the amount of rAI activation in either participant group, or any relationship between rAI activation and task switching behaviour in the scanner.

4.3.7. Interaction between the rAI and DMN, and relationship with white matter remains significant independent of focal lesion.

A further analysis was carried out to see if the FC result was being driven by focal lesions that a proportion of the patients had. However, the PPI between the rAI and DMN remained significant even after I removed patients with focal cortical lesions, as reported on their MRI scans ($t = 3.08$, df $= 32$, $P = 0.004$). Furthermore, the relationship between the mean FA of the rAI-preSMA/dACC tract and PPI was stronger without patients with focal cortical lesions (r $= 0.6$, $P = 0.02$).

4.3.8. Regional rAI activation during switching predicts executive function performance

The relationship between the amount of BOLD activity in the rAI during switching, and a cognitive variable of switching that was performed outside of the scanner was next tested. Patients performed parts A and B of the trail making test (TMT), which records a measure of information processing speed. However, the switch cost component from the TMT was of particular interest in this patient group. The switch cost associated with the TMT performance by subtracting the time taken to complete part B by the time taken to complete part A was calculated. This sensitive measure of switching was negatively predicted by the patients' regional activity in the rAI during switching in the scanner (r = -0.3, *P* = 0.03). Therefore, patients who activate their rAI less during switch trials in the scanner were significantly slower when performing a task designed to measure switches, outside of the scanner (***Figure 4.5***). No other cognitive variable assessed during the neuropsychological battery showed a significant relationship with rAI signal change during switching.
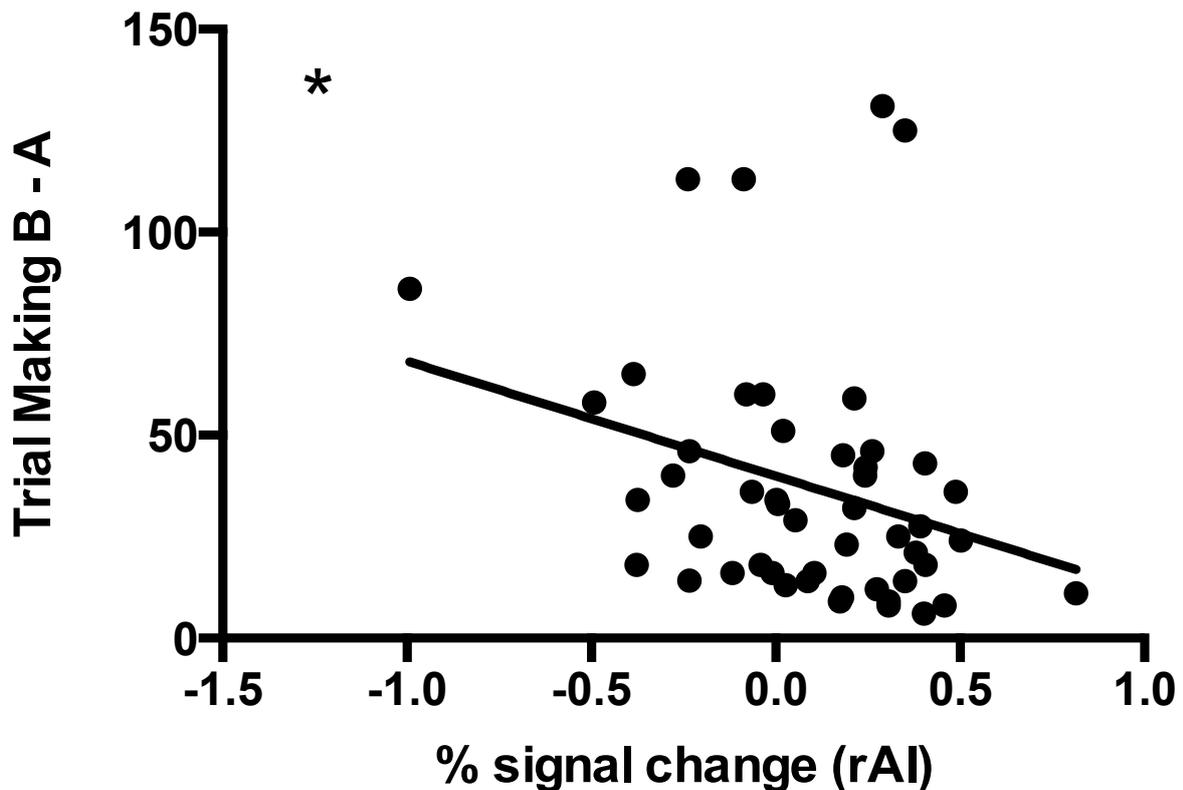
Figure 4.5: Regional activity and switching. *Percent BOLD signal change correlates with the switch component of Trail Making Test (TMT). Percent signal change within the right anterior insula (rAI) plotted against a standard neuropsychological measure of switch cost (taken from the trail making test B-A). *P < 0.05.*

1.9.3 Mean FA predicts executive function performance

A further analysis investigated cognitive variables, measuring executive functions outside of the scanner and found that the damage on the rAI-preSMA/dACC tract in the patient, predicted performance on the switching component of the stroop test ($r = -0.240$, $P = 0.04$). This switching component provides a sensitive measure of cognitive flexibility outside of the scanner and the current analysis showed greater damage to the rAI-preSMA/dACC tract predicted a slower (better) switching time on this test (***Figure 4.6***). Alongside the Stroop switching component, there was also a

significant relationship between the mean FA of the rAI-preSMA/dACC tract and a working memory variable, notably the digit span forward test (r = 0.5, *P* = 0.003).
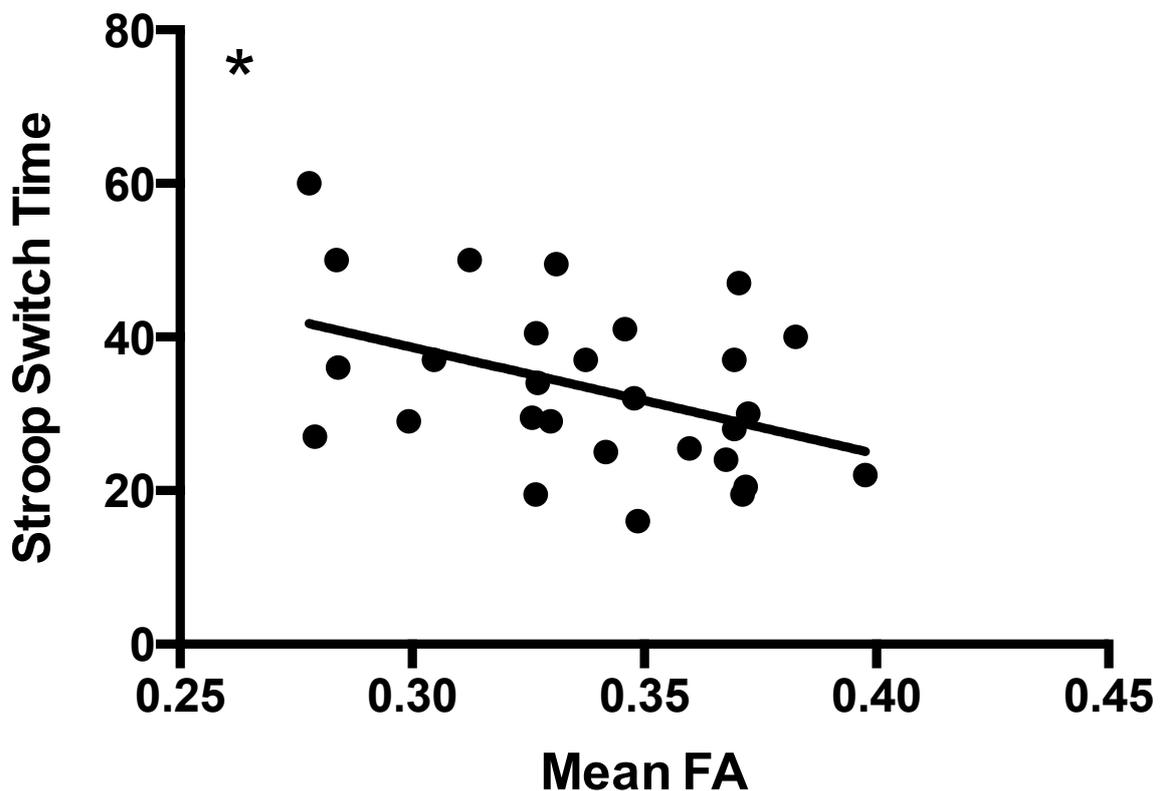
Figure 4.6: Mean fractional anisotropy and switching on the Stroop test (in seconds). *Integrity of the rAI-preSMA/dACC tract predicts better performance on the switching component of the Stroop test. *P < 0.05.*

4.4. Discussion

Here, a pattern of network interaction between the rAI and DMN was found that was similar to that found in Chapter 3 (using a stop signal task), during a motor task switching paradigm. In the current task, participants performed a series of Go trials before being required to switch their response mapping based on a visual cue. This switching was associated with a similar pattern of activity to stopping, whereby activity in the right inferior frontal cortex and predominantly in the key nodes of the SN was found. However, patients deactivated their DMN during switching. This initial

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result is compatible with Menon's model of SN function whereby the SN signals the need for behavioural change (Menon et al., 2010). Another TBI group was also investigated in this motor task switching paradigm, who failed to show normal activation, on switch trials compared with Go trials, in the right insular cortex compared to controls. This rAI activation also predicted performance on a neuropsychological test aimed at investigating switching deficits, such as the switching between numbers and letters in the trail making test. This reduced insula activity was related to a breakdown in the FC between the rAI and DMN in the patient group. Furthermore, in this second patient group, it was also found that the degree of structural disconnection within the SN predicted a failure of the networks to interact efficiently (a pattern similar to that found in the previous chapter). Taken together, the result in the current chapter show that the structural integrity of the tract connecting the rAI and the dACC predicts the interaction between the DMN and SN during motor task switching, as well as correlating with neuropsychological measures, notably associated with task switching.

4.4.1. Summary

The results presented in this chapter show that the structural integrity of the white matter tract connecting the rAI to the preSMA/dACC predicts the strength of FC between nodes of the SN and the DMN during motor task switching. TBI patients were found to have significantly reduced FC, during switch trials compared with Go trials, between the rAI and the DMN. This reduction in FC was when compared to healthy control subjects. The degree of the patient's loss of FC was predicted by the structural connectivity of this white matter tract. The FC of the DMN with the same three brain regions as used in the previous chapter (rAI, dACC, rIFG) was tested,

and it was found that this change of FC on switch trials to be affected in patients only for the connection between the rAI and the DMN. Patients who failed to generate a change of FC between the SN and DMN were also more likely to show evidence of cognitive deficits related to task switching. In addition, a lower degree of structural integrity in the rAI-preSMA/dACC tract was associated amongst TBI patients with a poorer ability to cope with the demands of switching between two task rules on the Stroop test. These findings, taken together, provide insight into how damage to the SN influences behaviour.

5. The effects of healthy ageing on network connectivity

5.1. Introduction

The current chapter investigates interactions between the SN and DMN within a healthy ageing group of participants who also performed the SST. This work investigated whether the impairments in FC and white matter damage after TBI are seen in a completely independent group of participants, who have not suffered a TBI, but who demonstrate similar patterns of cognitive dysfunction to those seen in TBI patients.

Age-related cognitive impairment is an important cause of disability in older adults. Cognitive control declines with age, and impairments of inhibitory processing are one important component (Zacks, 1989). As described previously, response inhibition can be studied using the SST (described in Chapter 2 and with data in TBI participants previously presented in Chapter 3). The neural systems involved in the attentional and inhibitory parts of this change in behaviour have been clearly defined in healthy younger adults (Sharp et al., 2010). However, the neurological mechanisms of age-related inhibitory deficits in older adults remain unclear (Eyler et al., 2011).

Efficient behaviour requires the coordinated activity of the DMN and SN. The work in this thesis has so far shown that interaction between these networks is abnormal after TBI. In Chapter 3, data acquired from the SST was analysed to demonstrate an impairment of FC between these two networks in TBI patients. Successful stopping during the SST was associated with activation in a predominantly right lateralized area of the SN, including the rAI and dACC/preSMA. These structures comprise the main nodes in the SN, which is involved in processing unexpected behaviourally salient information (Seeley et al., 2007). In addition, stopping was associated with a

rapid deactivation within the precu/PCC and ventro-medial prefrontal cortex (vmPFC), which are parts of the DMN. The work presented so far has also shown that following TBI, a failure to deactivate the precu/PCC (a key node of the DMN), and an impairment of the FC between the SN and DMN was strongly predicted by the disruption of white matter connections within the SN. In particular, damage to the tract connecting the rAI to the preSMA/dACC predicted these functional failures, as well as behavioural measures of response inhibition.

Abnormalities of DMN function have been a consistent finding in previous studies of age-related cognitive impairment (Sambataro et al., 2010; Prakash et al., 2012). For example, when attention is directed externally, the failure to deactivate the DMN is associated with slower and less successful cognitive control and with lapses of attention (Spreng and Schacter, 2012). This failure of DMN control has been observed in a range of disease states (Kennedy et al., 2006; Harrison et al., 2007) as described in previous chapters. Age-related damage to the white matter connections of the SN might explain uncontrolled DMN activity in an ageing population, if damage to the connections within the SN has the same effect whether the white matter damage was caused by TBI or ageing.

The current chapter therefore investigates whether the relationship between white matter structure in the SN and network connectivity between the DMN and SN are similar to those observed post TBI during response inhibition (O'Sullivan et al., 2001; Madden et al., 2009). Since impairment of inhibitory function can be observed in both TBI and elderly groups, we tested the hypothesis that age-related damage to the

white matter tract connecting the rAI to the preSMA/dACC, results in a breakdown in FC between the DMN and SN, and executive function impairment.

5.2. Methods and materials

5.2.1. Participant demographics

Sixty-two volunteers, whose results have not been previously reported in this thesis, were recruited from the community, of which 33 were young (age range 20-33 years, mean = 28, males=19), and 29 were old (age range 64-81 years, mean = 69.5 years, males = 12). All participants performed the SST and structural parts of the scanning protocol (as described in Chapters 2 and 3). Seventeen young volunteers (age range 20-30 years, median = 25, males = 9) and all members in the older group had additional DTI. Exclusion criteria were left-handedness; history of head trauma; depression; neuropsychological illness; gross pathology on structural MRI; and a score of <28 on the Mini Mental State Examination (MMSE). There were no significant differences between the groups for years of education. Three members of the older group were on medication for hyperlipidaemia, four for hypertension and four for both hyperlipidaemia and hypertension. Ethical approval was granted by the Imperial College Ethics Committee London (ICREC) and the Hammersmith and Queen Charlotte's and Chelsea Research Ethics Committee). Written informed consent was obtained prior to scanning.

5.2.2. Neuropsychological assessment

The same battery of cognitive tests as described in Chapter 2 (section 2.2) was administered on the participants in this study.

5.2.3. Stop signal task

The SST was performed by all the participants in this study. This paradigm is described in detail in Chapter 2 (***Figure 2.4***).

5.2.4. MRI image acquisition and scanning protocol

The same image acquisition, analysis pipeline and scanning protocol used was described in Chapter 3 (sections 3.2.6 and 3.2.7).

5.3. Results

5.3.1. Neuropsychological assessment

The older group showed a pattern of neuropsychological impairment similar to the TBI groups, with evidence of slow information processing speed and impaired inhibition compared with the younger group. As a group, the older participants demonstrated impairments during the Colour-Word (Stroop) test, which taps inhibitory control and cognitive flexibility. Interestingly, they were slower than the younger participants on trials requiring the ability to inhibit a prepotent response. They were also globally slower on the Trail Making Test, which reflects impaired information processing speed. These were specific impairments limited to a subset of the behavioural measures, rather than a global impairment that spanned many domains of cognition (**Table 5.1**).

Table 5.1: Neuropsychological results for older and younger groups

Cognitive Variable	Young Group Mean ± SD	Old Group 1 Mean ± SD
Similarities	28.65 ± 4.3	29.9 ± 5
Matrix Reasoning	24.28 ± 5.3	18.21 ± 4
Verbal Fluency Letter Fluency	51.2 ± 12	54.4 ± 21
Stroop Colour Naming (s)	25.5 ± 4.4	31.2. ± 5.5**
Stroop Word Reading (s)	18.2 ± 2.9	20.9 ± 3.5**
Stroop Inhibition (s)	21.8 ± 3.3	26.1 ± 4.2**
Stroop Inhibition-Switching (s)	43.4 ± 10.6	58.4 ± 13.3**
Trail making Test A (s)	16.6 ± 4	29.9 ± 6.4**
Trail making Test B (s)	41.5 ± 11.6	55 ± 22.4*
Trail making Test Switch Cost	25 ± 10.5	85 ± 25.6**
Digit Span forward	12.8 ± 1.8	11.9 ± 2.5
Digit Span backward	8.8 ± 2.6	8.6 ± 3.4
Logical Memory I 1st recall total	25.1 ± 8.3	25.8 ± 8.2
Logical Memory I recall total	41.1 ± 12.9	40.8 ± 11.7
Logical Memory II recall total	28.5 ± 8.6	24.9 ± 8.4
People Test immediate total	21.7 ± 4.6	19.6 ± 5.5
People Test delayed total	10.5 ± 1.7	8.2 ± 3.3

*Neuropsychological results for older group compared with a young group. Significant differences between young and old groups shown by *P < 0.05 and **P < 0.01. Stroop test refers to the D-KEFS Colour-Word Interference Test.*

5.3.2. Behaviour

Age-related changes in behaviour on the SST were in keeping with findings from Chapters 3. The adaptive staircase procedure employed produced similar stop trial accuracy in both young and old groups (**Table 5.2**). However, the older group had slower inhibitory reaction times (SSRT) (t = -2.742, df = 41, P = 0.037). Furthermore, during simple Go trials, the older group had longer mean reaction times (t = -8.24, df = 41, P < 0.001) and were less accurate (t = 2.23, df = 41, P = 0.023). Subjects were instructed to speed up if reaction times were too slow, and the older group also had significantly larger number of this type of negative feedback (t = -3.22, df = 41, P = 0.0015).   There were no other behavioural differences between the two groups (**Table 5.2**).

*Table 5.2: **Behavioural results for the younger and older group for the stop signal task.***

	Old Group Mean ± SD	Young Group Mean ± SD
Mean RT (s)	0.62 ± 0.14	0.42 ± 0.06**
Go accuracy %	0.95 ± 0.07	0.984 ± 0.02*
Stop accuracy %	0.503 ± 0.04	0.50 ± 0.02
Negative feedback	19.7 +/- 10.1	12.5 ± 7.5*
IIV	0.179 ± 0.04	0.18 ± 0.04
SSRT (s)	0.25 ± 0.03	0.23 ± 0.03

*Behavioural results for the SST. Reaction times (RT), accuracy (%), negative feedback, interindividual variability (IIV) and stop signal reaction times (SSRT), with standard deviations (± SD) for both the old and young groups are reported. *P = 0.05, **P < 0.001.*

5.3.3. Standard voxelwise GLM analysis

Contrasting correct stop trials with correct Go trials elicited a similar pattern of activity described in Chapter 2 for both the older and younger groups. Both groups recruited a right lateralized network of region, with activity in the rIFG, the rAI, the middle and superior frontal gyri, and within the dACC and preSMA. More posteriorly, activation was observed within the right supramarginal gyrus, the right temporo-parietal junction (rTPJ), the right intraparietal sulcus (rIPS), and the lateral occipital cortices. In addition, older people demonstrated activation in the left frontal lobe, with prominent activation in the left insula.

The reverse contrast of correct Go vs. correct stop trials (Go vs. StC) showed regions with more activity during Go trials, i.e. regions relatively deactivated during stopping. Extensive parts of the DMN were deactivated during stopping in the young group, replicating the observations found in the participant group in Chapter 3. In contrast, there was no significant DMN deactivation in the older group.

5.3.4. Region of interest analysis

To further test the specific hypothesis that ageing is associated with less deactivation of the DMN, brain areas showing activation or deactivation during successful stop trials were investigated. These ROIs were defined from the results of the participants used in Chapter 3, therefore providing an independent method for defining the ROIs and not biasing the findings for either age group (i.e. old or young).

The older group showed greater activity in the precuneus/PCC (i.e. DMN) during

successful stopping compared to the younger group (**Figure 5.1**). The increased

precu/PCC activity in the older participants is interpreted as reflecting an inability to

sufficiently deactivate the DMN during stopping. Activity within the SN did not show

any significant group differences.
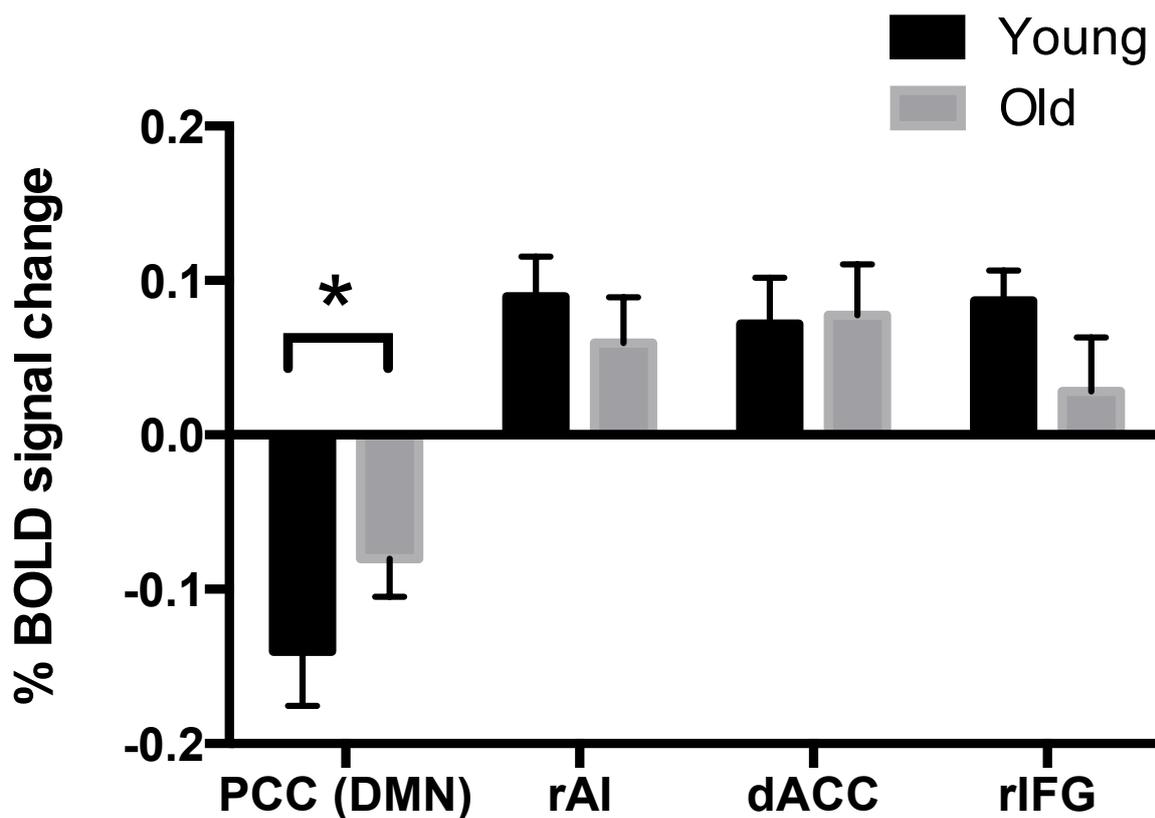
Figure 5.1: Region of interest (ROI) analysis. *ROI analysis of percentage BOLD signal change during correct stop trials vs. Go trials in the posterior cingulate cortex (PCC), the right anterior insula (rAI), the dorsal anterior cingulate cortex (dACC) and the right inferior frontal gyrus (rIFG) for young (black) and old (grey) groups. *P < 0.05.*

5.3.5. Functional connectivity analysis

As per the previous chapters, the change of FC (O'Reilly et al., 2012) was examined

between the DMN and the three task-positive ROIs during stop vs. Go trials (Friston

et al., 1997; O'Reilly et al., 2012) to investigate whether the interaction between these networks was impaired as a result of ageing. In keeping with the previous chapters, the focus of the analysis was on the rAI and the dACC, as well as the rIFG, to investigate how these ROIs interact with the DMN.

5.3.5.1. Hypothesis 1: Stopping is accompanied by increased functional connectivity between the rAI and the DMN in younger participants (Figure 5.2).

FC between the DMN and the SN changed during stopping. In healthy younger subjects, a one-way ANOVA of the PPI between the three frontal ROIs and the DMN showed a main effect of region (F = 3.9 df = 1.5, 43, P = 0.03; Huynh-Feldt correction applied). Planned contrasts between the rAI PPI and each of the other two ROIs showed that the FC with the DMN during stopping was significantly higher for the rAI than either the dACC or rIFG (F > 3, df = 1, 32, P < 0.04 in each case). One-sample t-tests showed that the increase in FC during stopping between the DMN and the rAI was significantly greater than zero (t = 7.7, df = 32, P < 0.001), but was not significantly different from zero for the dACC or rIFG. As with the TBI group 1 (from Chapter 3), it is noteworthy that the increase in FC between the SN and DMN occurred in the context of distinct patterns of relative activation change; an increase in the rAI, but a decrease in the DMN.

5.3.5.2. *Hypothesis 2: Older participants with impairments of response inhibition fail to show increased functional connectivity during stopping (Figure 5.2).*

Cognitive impairment on the SST in the ageing group was associated with abnormalities of FC. A 2 x 3 Group by Region ANOVA, adding in the patient group, showed a significant region x group interaction (F = 6.5, df = 2, 120, P = 0.02). Planned contrasts comparing FC of the DMN with the rAI and each of the other two ROIs in interaction with the Group factor, showed that the increase in FC for the rAI compared with either of the other ROIs, was significantly greater in the controls than in the patients (F > 4.2, df = 1, 60, P < 0.043 in each case). Pairwise t-tests (comparing controls and patients) revealed a significant group difference in the PPI between the rAI and DMN (t = 2.18, df = 43, P = 0.03; corrected for inhomogeneity of variance between groups), but there were no group differences in the other regions (t < 0.5, P > 0.62 in each case) (**Figure 5.2**). In the patients, there was no significant PPI in any of the three regions tested and no regional differences in PPI magnitude.
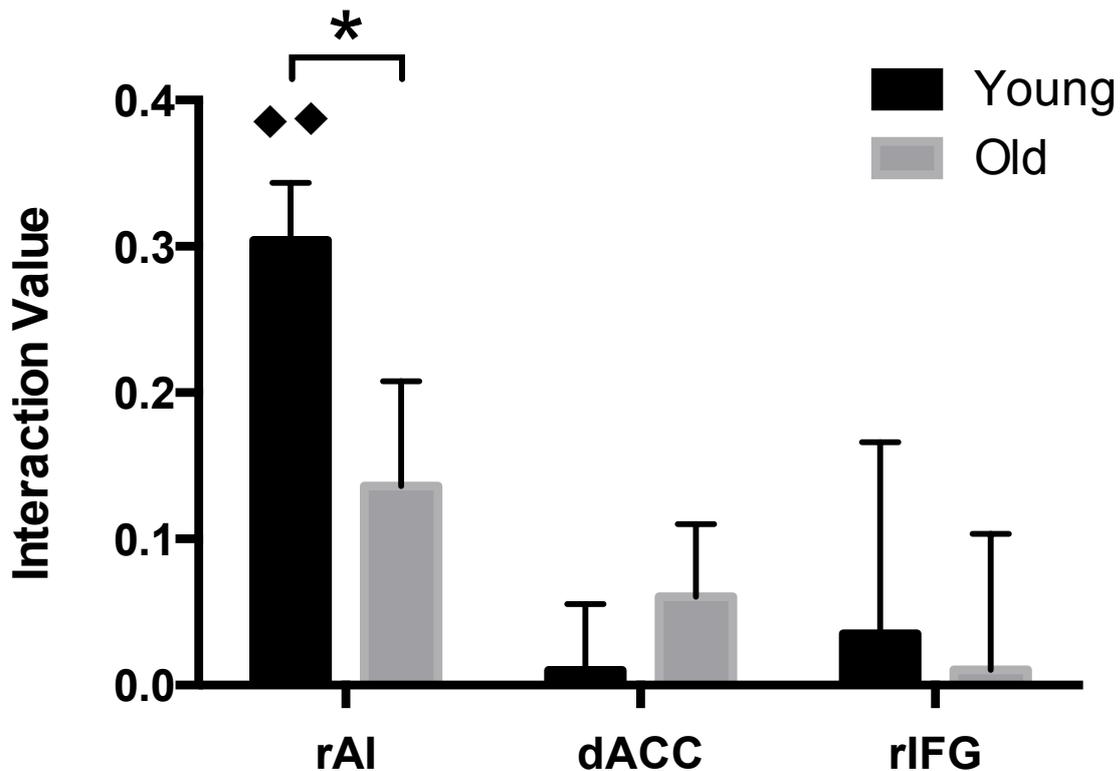
Figure 5.2: PPI analysis. *The bar chart represents the strength of FC during stopping from the PPI analysis, with the DMN and our three ROIs, in young (black) and old (grey) groups.* ◆◆P < 0.001, *P < 0.05.

5.3.5.3. Hypothesis 3: The amount of damage to the rAI-preSMA/dACC tract inversely correlates with the extent of reduced functional connectivity between the rAI and DMN during stopping (Figure 5.3).

The next hypothesis tested was that the integrity of the structural connection between the rAI and the preSMA/dACC predicted the breakdown of FC between the two networks. In the older group, a significant positive correlation between tract integrity and the strength of PPI between the DMN and rAI ($r = 0.5$, $P = 0.003$) was found. Patients with more damage to this tract showed less functional interaction between the networks (**Figure 5.3**A). There was no significant correlation between the same

white matter tract and the FC between the DMN and dACC (**Figure 5.3**B), nor the DMN and the rIFG (**Figure 5.3**C).

Comparisons between the strengths of these correlations showed significant differences between: (1) the integrity of the white matter tract and the FC between the DMN and rAI (**Figure 5.3**A) and the integrity of the white matter tract and the FC between the DMN and dACC (**Figure 5.3**B) (z = 1.8, P = 0.03); and (2) the integrity of the white matter tract and the FC between the DMN and rAI (**Figure 5.3**A) and the integrity of the white matter tract and the FC between the DMN and rIFG (**Figure 5.3**C) (z = 2.8, P = 0.002). There was no significant difference between the strengths of correlations between the integrity of the white matter tract and the FC between the DMN and dACC (**Figure 5.3**B) and the integrity of the white matter tract and the FC between the DMN and rIFG (**Figure 5.3**C) (z = -1.6, P = 0.9).
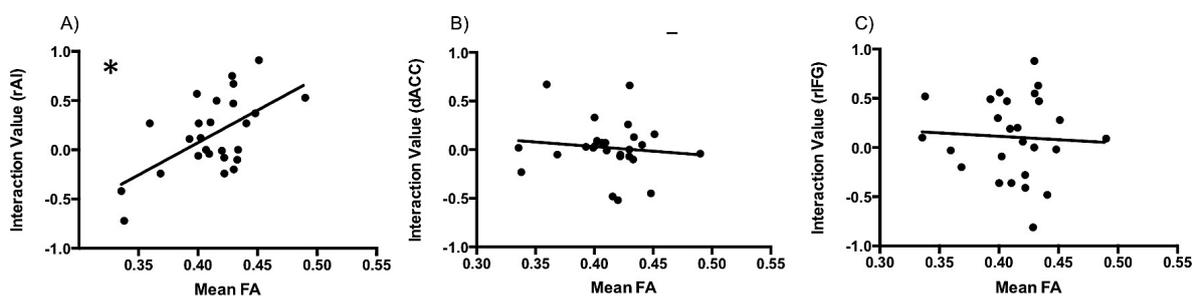
*Figure 5.3: Mean fractional anisotropy (FA) predicts FC. Mean FA of the rAI-preSMA/dACC tract in older participants plotted against the FC of the DMN with (A) the right anterior insula, and (B) the dorsal ACC, and (C) the right inferior frontal gyrus, on correct stop trials (StC) vs. Go trials. *P < 0.05.*

5.3.6. Regional activation changes in the rAI predict inhibition (SSRT)

The next analysis further investigated whether the imaging parameters had a relationship with a behavioural measure from the task performance in the scanner. Across both groups, greater rAI activity during stopping was associated with more efficient response inhibition (lower SSRT) (r = -0.23, P = 0.03) (***Figure 5.4***A). This relationship was not observed in the dACC (Figure 4B), the rIFG (***Figure 5.4***C) or the PCC (***Figure 5.4***D), nor did this relationship exist within groups.

Comparisons between the strengths of these correlations showed a significant difference between the amount of activation during stopping in the rAI and SSRT (***Figure 5.4***A) and the amount of activation during stopping in the rIFG and SSRT (***Figure 5.4***C) (z = -7.5, P < 0.001) but no differences between the amount of activation during stopping in the rAI and SSRT (***Figure 5.4***A) and the amount of activation during stopping in the dACC and SSRT (***Figure 5.4***B) (z = 1.4, P = 0.07). There was also no significant difference between the amount of activation during stopping in the rAI and SSRT (***Figure 5.4***A) and the amount of activation during stopping in the PCC and SSRT (***Figure 5.4***D) (z = 0.8, P = 0.19).

There was also a significant difference between the amount of activation during stopping in the dACC and SSRT (***Figure 5.4***B) and the amount of activation during stopping in the rIFG and SSRT (***Figure 5.4***C) (z = -9.3, P <0.001).
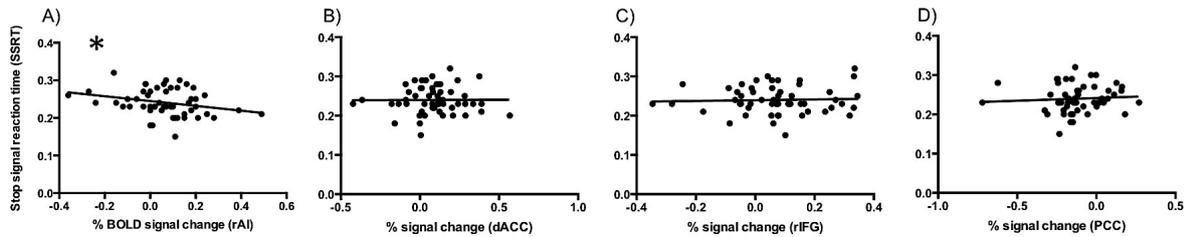
Figure 5.4: Regional activity and stop signal reaction time (SSRT). Slower stop signal reaction time (SSRT), a measure of response inhibition, is shown to significantly correlate with regional activation changes within the (A) right anterior insula, but not with (B) the dorsal anterior cingulate cortex, the (C) inferior frontal gyrus, nor the (D) posterior cingulate cortex, during stopping. *P < 0.05.

5.3.7. Regional PCC activation predicts inhibition performance

A further analysis tested the relationship between the amount of BOLD activity in the four ROIs during stopping (stop > Go) and a cognitive variable of inhibition that was performed outside of the scanner. Both groups performed the Stroop test, which records a measure of inhibition where the participant is required to inhibit a highly practiced behaviour of reading aloud the word by instead saying the colour of the ink. This sensitive measure of inhibition was predicted, across both groups, by the regional activity in the PCC during stopping in the scanner (r = 0.32, *P* = 0.01) (**Figure 5.5**A). Participants who deactivated their PCC more during stop trials in the scanner, were significantly better when performing the Stroop task designed to measure inhibition outside of the scanner (**Figure 5.5**A). This result did not exist within either group when analysed separately, but only across both groups combined. Moreover, the relationship was non-significant for the other three regions analysed (**Figure 5.5**B-D).

Comparisons between the strengths of these correlations showed no significant differences between the amount of activation during stopping in the PCC and

inhibition on the Stroop (**Figure 5.5**A) and (1) the amount of activation during stopping in the rAI and inhibition on the Stroop (**Figure 5.5**B); (2) the amount of activation during stopping in the dACC and inhibition on the Stroop; and (3) the amount of activation during stopping in the rIFG and inhibition on the Stroop (z > 1, P > 0.1 in all cases).
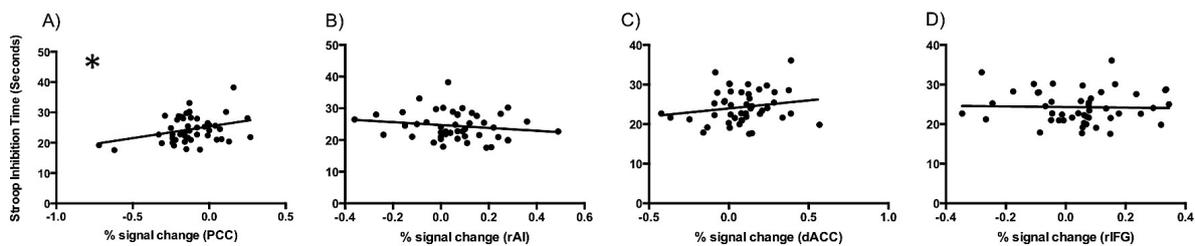
*Figure 5.5: Regional activation predicts inhibition. Percentage BOLD signal change during stopping within the (A) posterior cingulate cortex (B) right anterior insula C) dorsal anterior cingulate cortex D) right inferior frontal gyrus, plotted against a standard neuropsychological measure of inhibition taken from the Stroop test. *P < 0.05.*

5.4. Discussion

5.4.1. Results overview

The experimental design described in Chapter 3 was replicated in the current chapter and applied to an elderly group of participants. This chapter provides evidence that abnormal interactions between the SN and DMN provides a general explanation for cognitive control impairments across different populations, regardless of the specific mechanism of SN disruption.

Activation of SN and simultaneous deactivation of the DMN is seen when attention is focused on external events (Menon and Uddin, 2010). The failure of task-dependent deactivation is seen in many disease states (Greicius et al., 2004; Kennedy et al.,

2006; Harrison et al., 2007). The current thesis has demonstrated that damage to the structural connections of the SN following TBI results in a FC failure between the DMN and SN and an accompanying impairment of executive function.

This chapter shows that this phenomenon is not specific to TBI and extends these findings to the study of age-related cognitive impairment. Here, I demonstrate that structural disconnection of the SN in older individuals is associated with a remarkably similar pattern of functional and behavioural consequences. Damage to the white matter connection between the rAI and the medial prefrontal cortex (dACC/preSMA) predicts a failure of the DMN and SN to 'communicate' during stopping. This provides evidence that this particular white matter connection within the SN is important for the moment-to-moment control of DMN activity, and that damage to this tract, regardless of disease mechanism, can disrupt network interactions.

5.4.2. Ageing

Previous work (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Sambataro et al., 2010; Prakash et al., 2012), has shown that decoupling of activity across the DMN was associated with age-related cognitive impairment. DMN activity during cognitively demanding tasks where attention is directed externally is usually anticorrelated with activity within the SN (Kelly et al., 2008; Spreng and Schacter, 2012), and efficient attention to external stimuli requires rapid and reactive deactivation of the DMN (Lustig et al., 2007). In many disease states, increased DMN activity during cognitively demanding tasks has been associated with inefficient cognitive control (Kennedy et al., 2006; Harrison et al., 2007; Lustig et al., 2007). These results suggest that uncontrolled DMN activity during cognitively demanding

tasks may be a core mechanism for cognitive impairment. It is likely that high coupling between nodes of the DMN is necessary for the rapid and co-ordinated changes of activity levels within the DMN, and that age-related disruption of this coupling results in relatively uncontrolled DMN activity with consequent behavioural impairments.

5.4.3. Summary

These results provide further evidence that the SN plays a pivotal role in goal-directed cognition by influencing activity in the DMN (Sridharan et al., 2008). Age-related damage to the structural integrity of the tract connecting the rAI to the dACC/preSMA of the SN predicts FC between DMN and SN, as well as inhibitory task performance. The mechanism of structure-function-behaviour-cognition is shown to be very similar in the TBI population and that an older group of volunteers, who both exhibit the same failure to modulate SN and DMN activity through this pathway, leading to poor cognitive control.

6. The neural basis of cognitive switching: Switching between task rules

6.1. Introduction

The work presented so far in this thesis has focused on motor control. In the current chapter, previous work investigating motor control is extended by using a task switching paradigm that requires participants to switch between task sets rather than switching motor responses (Monsell et al., 2003). This chapter investigates whether interactions between nodes of the SN and DMN change during performance of this type of cognitive switch. Furthermore, comparisons are made between the activation associated with both cognitive and motor switches in order to investigate regions of the brain that subserve the processing of these distinct types of motor control.

The previous studies reported have focused on paradigms that predominantly involve motor control (i.e. stopping and motor switching). The current chapter focuses on network interactions between the SN and DMN in the context of cognitive switches, that is, switching between task rules as well as delineating the regional neural changes found during cognitive switching in and between healthy controls and TBI patients. Furthermore, this chapter also investigates differences between the neural responses of cognitive and motor task switching in both healthy controls and TBI patients and discusses these results later in the chapter.

6.2. Methods and materials

6.2.1. Patient demographics and clinical details.

The patient group who participated in the cognitive switch paradigm was the same as the patient group who participated in the motor switch paradigm. This has been previously described in Chapter 4 (section 4.2.1).

6.2.2. Control Group

Twenty control participants (10 females, mean age 28.5 ± 8.7 years) were included in the cognitive switch analysis. The Hammersmith and Queen Charlotte's and Chelsea Research ethics committee approved the study, and all the participants gave written informed consent.

6.2.3. Neuropsychological Assessment

The same detailed neuropsychological battery as described in Chapters 2-4 was used to assess cognitive function. Briefly, this battery consisted of a subset of assessments that tested verbal and non-verbal reasoning ability, verbal fluency, cognitive flexibility, executive functions, information processing speed, working memory, immediate and delayed verbal recall and associative learning and recall.

6.2.4. Cognitive Switch Paradigm

The cognitive switch paradigm is a two-choice task switching paradigm as described in Chapter 2. In summary, subjects responded to a visual cue with either a right or left button press. The response required is determined by either the colour (red or blue) or the number (odd or even) of the cue. On switch trials subjects are instructed by the appearance of the visual cue to switch their cognitive set between colour and number response, so a right hand button press would switch from a red number to an even number (*Figure 2.6*). Further details can be found in Chapter 2.

6.2.5. MRI data Acquisition and Analysis

The data collection and analysis method has been previously described in detail in Chapter 2.

6.3. Results

6.3.1. Behaviour

Patients showed impairment on task performance in the scanner. Accuracy for both groups on Go trials was generally high (~ 90%), although patients were slower than controls in responding to Go trials (t = -3.69, df = 48, *P* = 0.001) (**Table 6.1**). There was no difference in accuracy between the groups on switch trials or switch trial reaction time, nor any differences in the other behavioural measures listed in **Table 6.1**. Furthermore, as the paradigm contains between two and five Go trials prior to the switch trial, the next analysis tested for differences between the RT and accuracy of these Go trials that appear at different positions prior to the switch trial. Again, there were no significant differences in RTs between Go trial positions for controls (F = 7.25, *P* = 0.29) or patients (F = 5.89, *P* = 0.47).

The participants respond with a right button press to even and red numbers (in the number and colour rules respectively) and with a left button press to odd and blue numbers (in the number and colour rules respectively). This meant that on some trials the participant was presented with a Go trial that required a right button press prior to a switch trial that also required a right button press, which is referred to here as a congruent switch trial. There were also trials in which the participant is presented with a Go trial that required a left button press but a right button press on the corresponding switch trial, which is referred to as an incongruent switch trial. The

next analysis tested for differences between congruent and incongruent switch trial types and again found no differences in RT between congruent and incongruent switch trial types in controls (t = 0.86, *P* = 0.28) or patients (t = 0.77, *P* = 0.74).

Table 6.1: Behavioural results for patient group 2 and control group 2 on the cognitive switch paradigm.

	Control Group 2	TBI Group 2
Switch Trial RT (ms)	793±140	853±117
Go Trial RT (ms)	720 ± 72	845±132**
Switch Cost (ms)	73 ± 85	8 ± 129
Switch Trial % Accuracy	91 ± 7	87 ± 148
Go Trial % Accuracy	95 ± 3	92 ± 126

*Reaction times (RT) for switch and Go trials, switch cost, accuracy (%) for switch and Go trials with standard deviations (± SD) for both patients and controls are reported. Significant differences between patients and controls shown by **P < 0.001.*

6.3.2. Neuropsychological assessment

Performance on the neuropsychological testing was the same as described in Chapter 4 and the performance measures can be seen in Table 4.2.

6.3.3. Standard voxelwise GLM analysis

Correct cognitive switch trials compared to correct Go trials showed increased activity in the anterior cingulate cortex/preSMA, frontal operculum cortex, bilateral inferior and middle frontal gyri, stretching back to the left pre and post central and supramarginal gyri. There was also activity in the insular cortex bilaterally. More posteriorly, activation was observed within the precuneus, lingual gyrus,

supramarginal gyrus, and intraparietal sulcus and the lateral occipital cortices (*Figure 6.1*). Decreased activity was observed in the ventromedial prefrontal cortex (vmPFC), superior frontal gyrus, left lateral occipital cortex, and the PCC (*Figure 6.1*). The direct contrast of control and patient groups showed no areas where activity was significantly different for either the correct cognitive switch > Go contrast, or the Go > correct cognitive switch contrast.
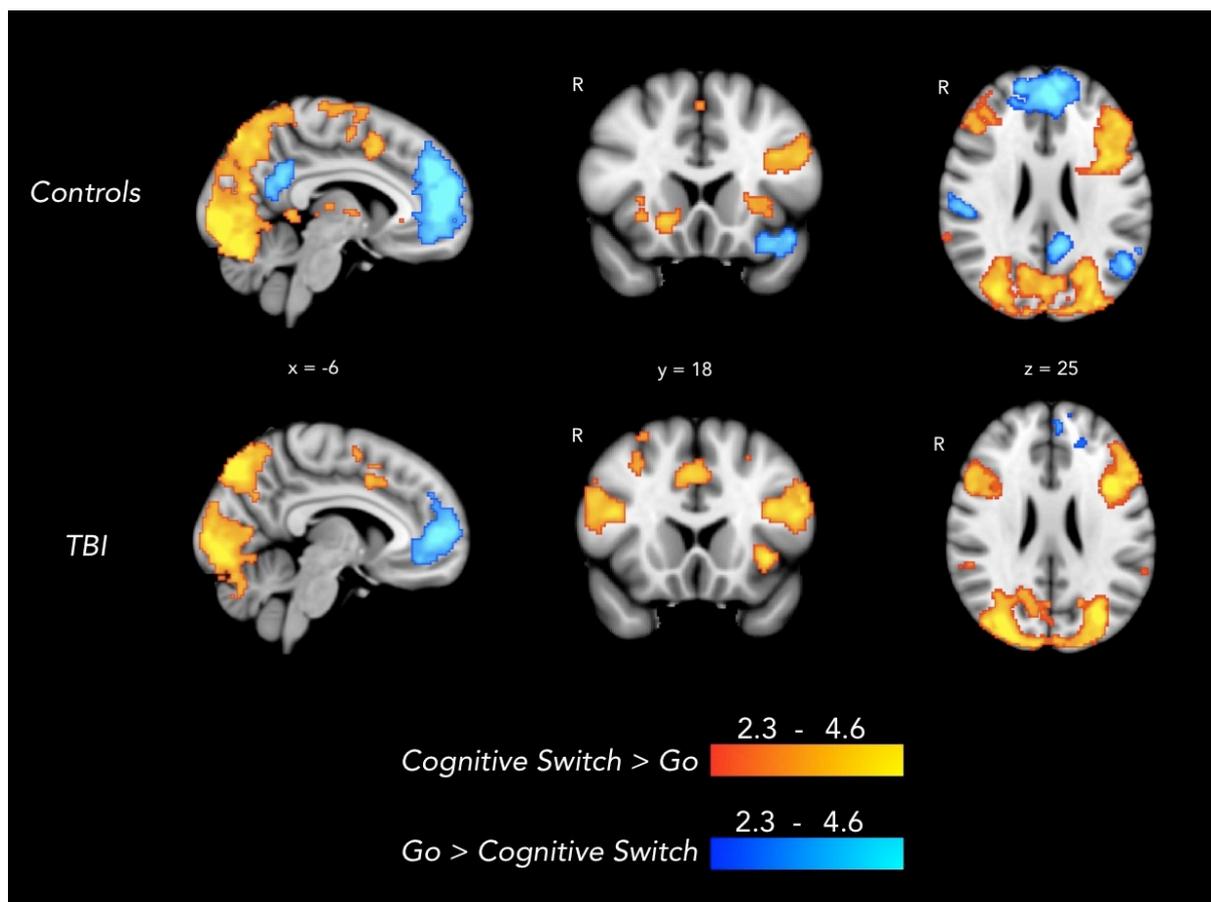
Figure 6.1: Overlay of brain activation during the cognitive switch paradigm. *Overlay of brain activation associated with correct switch (SwC) vs. Go trials (yellow-red) and Go trials vs. correct switch (blue), in control group 2 (left) and patient group 2 (centre). Results are superimposed on the MNI 152 T1 1-mm brain template. Cluster corrected Z = 2.3, P < 0.05.*

Table 6.2: Local maxima of brain activation during the cognitive switch condition in the cognitive switch > Go contrast for A) control group 2, B) TBI patient group 2, C) the group mean; and for the inverse contrast of Go > cognitive switch for D) for control group 2, and E) patient group 2.

SwC > Go		MNI Coordinates		
A) Control Group 2	Z-score	x	y	z
Occipital fusiform gyrus	5.97	-42	-68	-22
Insular cortex	3.62	20	32	-2
Frontal pole/middle frontal gyrus	3.77	38	40	34
Middle temporal gyrus	3.65	-48	-46	8
Angular gyrus	3.8	50	-44	23
B) TBI Group 2				
Occipital fusiform gyrus	5.78	36	-72	-18
Inferior frontal gyrus	4.86	-40	12	24
Middle frontal gyrus	4.52	28	4	50
Paracingulate gyrus	3.71	-2	8	50
Supramarginal gyrus	3.63	54	-44	16
C) Groups combined				
Occipital fusiform gyrus	6.18	24	-76	-20
Frontal pole/Middle frontal gyrus	4.53	34	2	52
Supramarginal gyrus	3.97	50	-44	14
Insular cortex	4.09	36	18	-4
Go>SwC				
D) Control Group 2				
Paracingulate gyrus	5.12	-4	56	10
Parietal operculum cortex	4.13	48	-28	20
Frontal orbital cortex	4.2	-38	22	-20
Posterior cingulate cortex	3.95	-10	-50	26
Lateral occipital cortex	3.95	-52	-62	26

E) TBI Group 2				
Paracingulate gyrus	4.69	-8	54	8
F) Groups combined				
Paracingulate gyrus	5.97	-12	48	7

6.3.4. Region of interest analysis

A ROI analysis was also carried out to quantify active brain regions during cognitive switching in brain regions where there were a priori hypotheses. These ROIs were defined on the basis of the functional activity observed during stopping in the SST, as reported in chapter 2. This ROI analysis extended the previous analyses carried out in the subsequent chapters to investigate if there are common mechanisms across different types of switching. During cognitive switching, there was significant activity (switch > Go) in the rAI ($t = 2.92$, df = 28, $P = 0.007$), the dACC ($t = 4.17$, df = 28, $P < 0.001$) and rIFG ($t = 4.99$, df = 28, $P < 0.001$) in the patient group, and significant activity in the dACC in the control group ($t = 3.35$, df = 19, $P = 0.003$). However, there were no significant differences in the three frontal ROIs and the PCC between patients and controls for the cognitive switch > Go contrast (***Figure 6.2***).
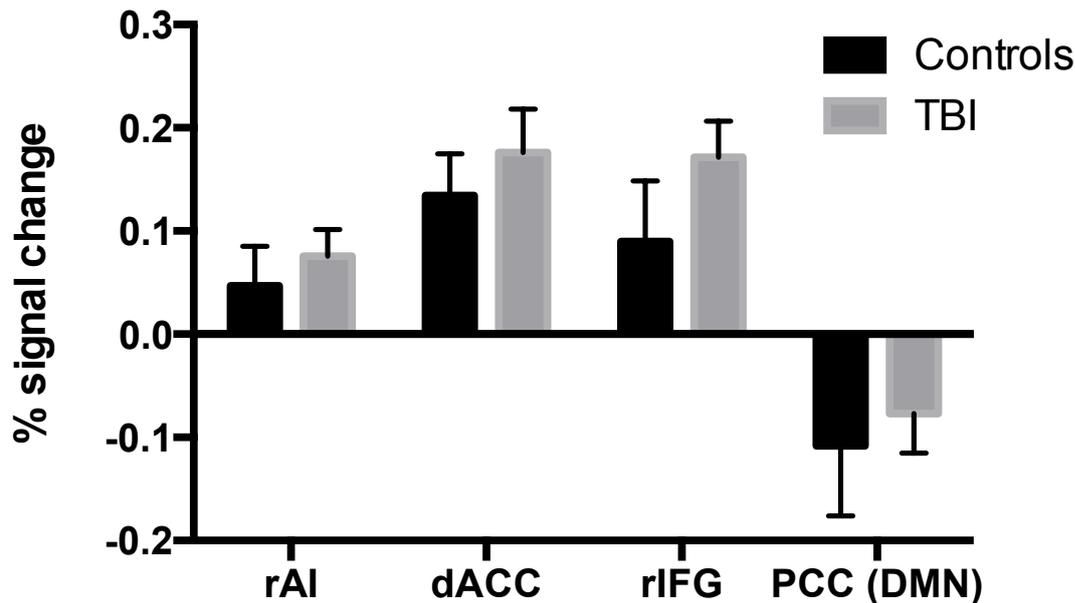
Figure 6.2: Region of interest (ROI) analysis. *Region of interest analysis of regional activation change during cognitive switching (switch > Go), in the posterior cingulate cortex (PCC), the right anterior insula (rAI), the dorsal anterior cingulate cortex (dACC) and the right inferior frontal gyrus (rIFG).*

6.3.5. Functional connectivity analysis

6.3.5.1. *Hypothesis 1: Cognitive switching is accompanied by increased functional connectivity between the rAI and the DMN (Figure* 6.3*)*

FC between the DMN and the SN did not change during cognitive switching. In healthy subjects, a one-way ANOVA of the PPI between the three frontal ROIs and the DMN did not show a main effect of region (F = 3.1, P = 0.06). One-sample t-tests showed that the increase in FC during cognitive switching between the DMN and the rAI, DMN and the dACC, DMN and the rIFG, were not significantly different from zero (t < 1.5, P > 0.13 in all cases). A further FC analysis was conducted in order to test for changes in FC in regions were specifically activated during cognitive switching. This was carried out by defining other regions of interest masks based on the peak of the mean activity of cognitive switching from both groups. These regions included the

frontal pole/middle frontal gyrus (MFG) (coordinates; x = 34, y = 2, z = 52) and also another rAI mask (coordinates; x = 36, y = 18, z = -4). There was no significant change in FC between either of these newly defined regions and the DMN during cognitive switching in the healthy control group (t < -1.8, *P* > 0.09 in both cases) (**Table 4.4**).

6.3.5.2. *Hypothesis 2: Patients fail to show increased functional connectivity during cognitive switching (Figure* 6.3*)*

TBI patients showed a similar pattern of FC as controls during performance of the cognitive switch task. A 2 x 3 Group by Region ANOVA, adding in the patient group, did not show a significant region x group interaction (F = 0.96, *P* = 0.39). Pairwise t-tests (comparing controls and patients) revealed no significant group differences in any of the PPIs (t < -0.13, *P* > 0.32 in all cases). In the patients, there was no significant PPI in any of the original three regions tested, and no regional differences in PPI magnitude. A further analysis of the patient group included applying the newly generated MFG and rAI masks in the patient group. Again, there was no significant change in FC between these regions and the DMN during cognitive switching in the patient group (t < 0.27, *P* > 0.79 in both cases) and no difference in this change in FC between these regions and DMN between patients and controls (t < -0.36, *P* > 0.27 in each case).
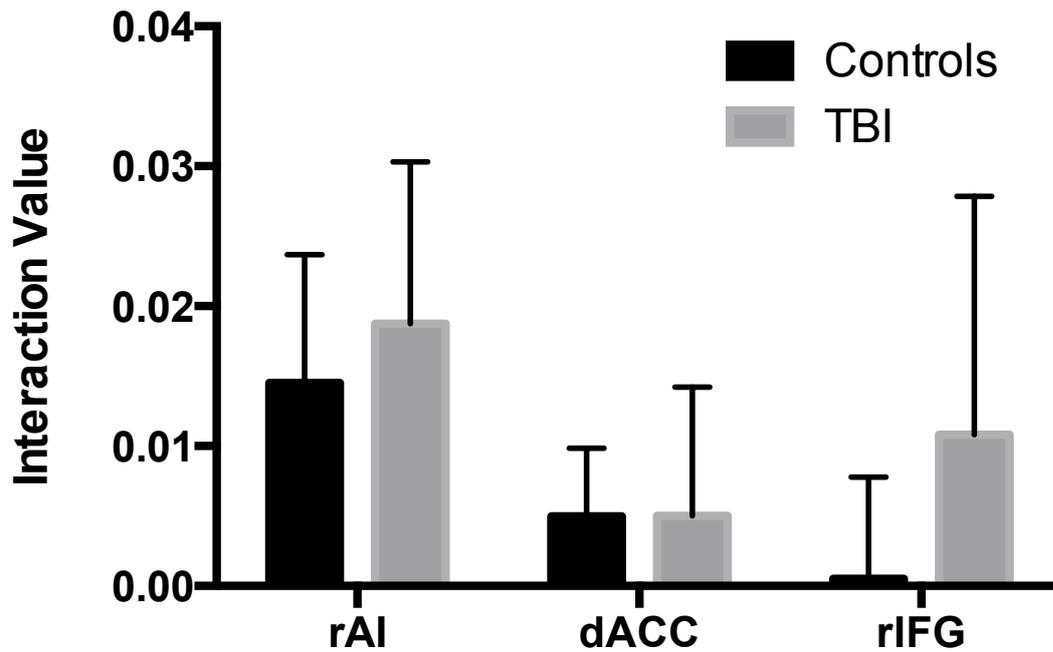
Figure 6.3: PPI analysis. *The bar chart represents the strength of FC during cognitive switching from my PPI analysis of the DMN and the three original ROIs in controls (black) and patients (grey).*

6.3.5.3. *Hypothesis 3: The amount of damage to the rAI-preSMA/dACC tract in the TBI patients correlates with the extent of functional connectivity (Figure 6.4)*

The next analysis tested the hypothesis that the integrity of the structural connection between the rAI and the preSMA/dACC predicted the degree of FC between the two networks, despite having found no significant differences in the connectivity of each region with the DMN. In the patients considered separately, the correlation between tract integrity and the strength of PPI between the DMN and the rAI was non significant (r = 0.25, *P* = 0.24) (**Figure 6.4**A). However, there was a significant relationship between the integrity of the white matter tract connecting the rAI to the preSMA/dACC and the strength of FC between the rIFG and DMN (r = 0.43, P = 0.04) (**Figure 6.4**C). There was no significant correlation between the integrity of the same white matter tract and the FC between the DMN and dACC (r = 0.4, P = 0.06)

(**Figure 6.4**B). A further analysis involving the new rAI region's (which was defined from within the cognitive switch condition) connectivity with the DMN revealed a significant relationship with the integrity of the rAI-preSMA/dACC tract (r = 0.48, P = 0.03) and the MFG (r = 0.45, P = 0.03).
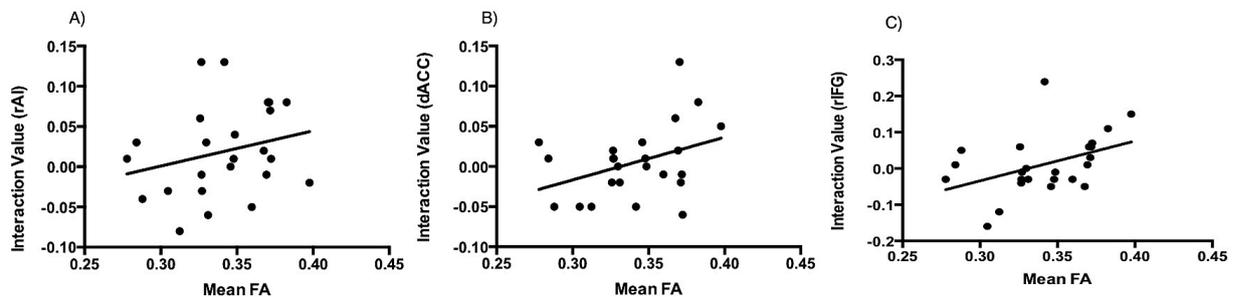
Figure 6.4: Mean fractional anisotropy (FA) and FC relationship. Mean FA of the rAI-preSMA/dACC tract in patients plotted against the FC of the DMN with (A) the right anterior insula, (B) the dorsal ACC, and (C) the right inferior frontal gyrus, on correct cognitive switch trials vs. Go trials.

6.3.6. Differences between cognitive and motor switches

6.3.6.1. Behaviour

Direct comparisons between the motor switch and cognitive switch behaviour in healthy controls revealed significantly slower RTs on Go trials in the cognitive switch condition than for Go trials in the motor switch condition (t = -2.9, df = 19, *P* = 0.008). There were no other differences in behaviour, including RTs for switch trials, switch cost as well as differences in accuracy on both switch and Go trials in patients and controls between the cognitive and motor switch paradigms.

6.3.6.2. *Functional imaging*

The next analysis investigated the neural differences between the cognitive and motor switches in both patients and controls. Cognitive and motor switches showed many similar regions of activity for both patients and controls (**Figure 6.5**) including the middle and inferior frontal gyri, encapsulating pars triangularis and opercularis and the precentral gyrus. In the control participants, a pattern of activity within the SN, which included the bilateral insular cortex and anterior cingulate cortex was found. However, TBI patients showed no significant activity (switch > Go) in the right insular cortex/inferior frontal gyrus regions. More posteriorly, significant activity (switch > Go) was found in the post central and angular gyri, precuneus and cuneal cortices and the lingual gyrus in both groups, for both switch types.
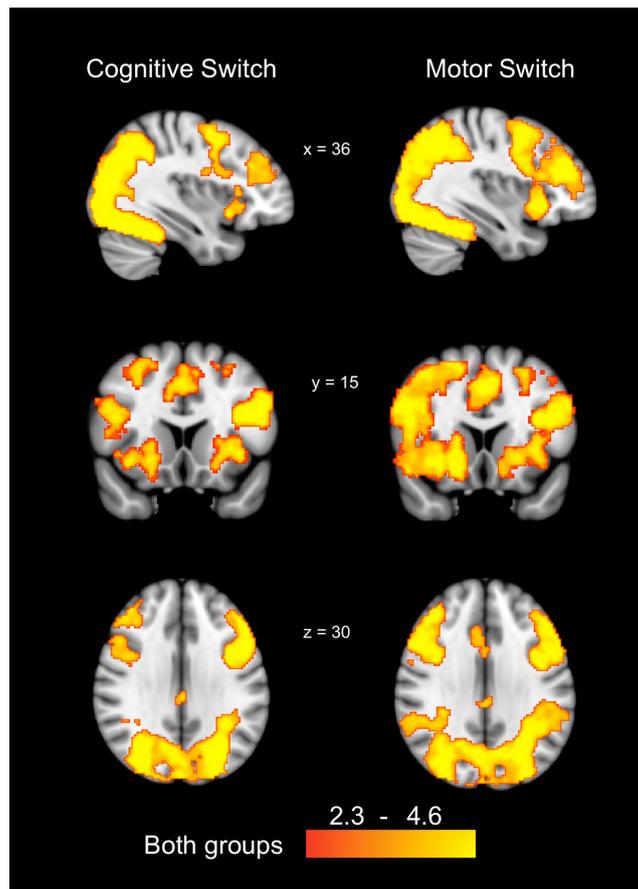
Figure 6.5. Overall BOLD response in Cognitive (left) and Motor (right) switching (irrespective of group). Results are superimposed on the MNI 152 T1 1-mm brain template. Cluster corrected Z = 2.3, P < 0.05.

Contrasting motor and cognitive switch conditions showed areas where increased activity relative to the Go baseline was higher for motor switches. In the motor switch > cognitive switch contrast for healthy control participants, there was significantly greater activity in the frontal cortex with right lateralized activity in the middle and inferior frontal gyri, frontal orbital cortex and the insular cortex. Posteriorly, significant activity was seen bilaterally in the supramarginal and angular gyri, middle temporal gyrus, precuneus and bilateral occipital cortex. In the TBI patient group, no differential anterior activity was seen between the switch conditions, although activity was greater for motor switches in the left supramarginal and angular gyri posteriorly

(*Figure 6.6*). The direct contrast of motor switch > cognitive switch across both groups revealed activity in supramarginal gyrus and precuneus, and also the right insular cortex (*Figure 6.6*) (*Table 6.3*). There were no significant regions of activity in the direct contrast between healthy controls > TBI patients in the motor > cognitive switch condition.
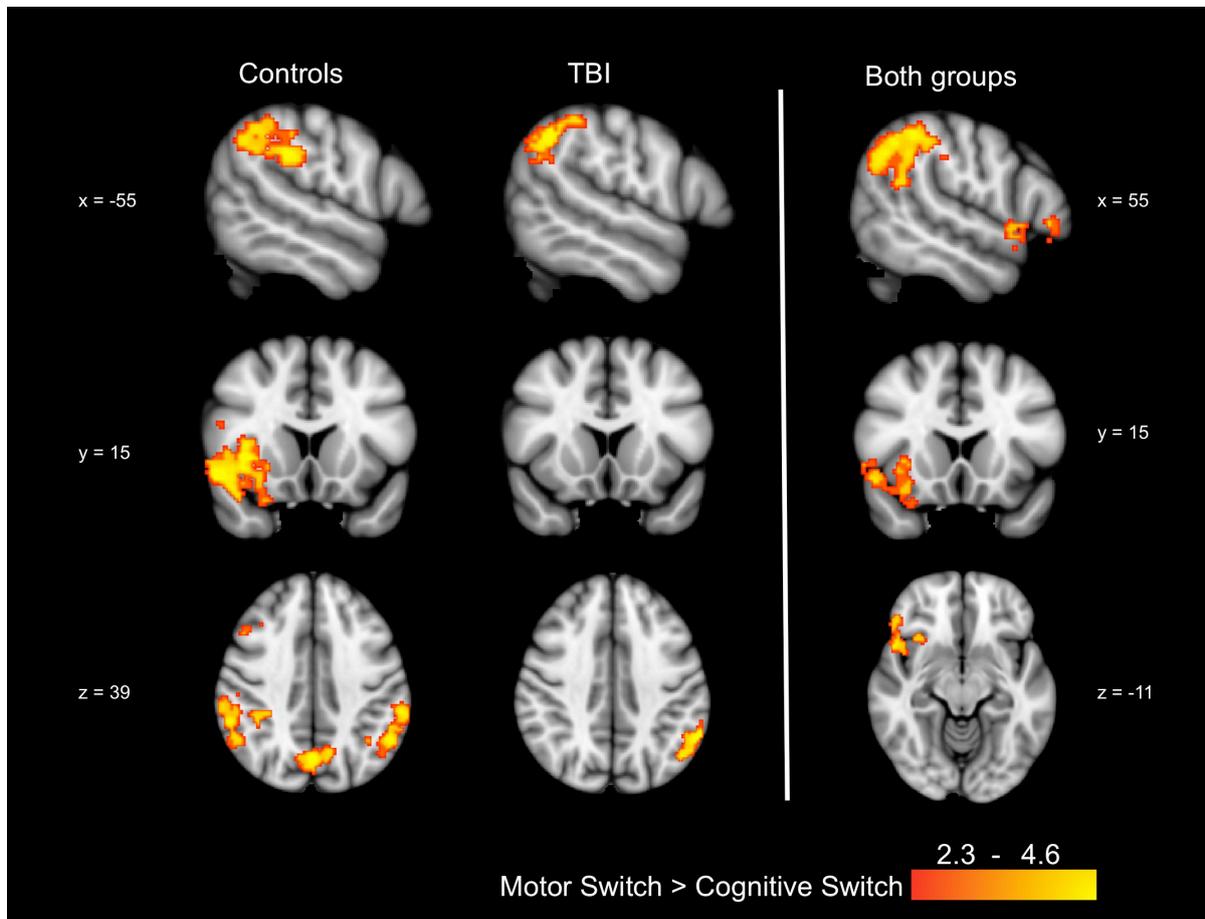
Figure 6.6. Differences in neural response between motor > cognitive switch trials in controls (left) and TBI (middle) patients and overall difference (right). Results are superimposed on the MNI 152 T1 1-mm brain template. Cluster corrected Z = 2.3, P < 0.05.

Table 6.3. Local maxima of brain activation differences between motor switching and cognitive switching across both controls and TBI patients.

Motor switch > cognitive switch		MNI Coordinates		
Both groups	Z-score	x	y	z
Supramarginal gyrus	3.63	58	-40	44
Insular cortex / temporal pole	3.95	50	14	-12
Precuneus	3.37	-8	-70	56

6.4. Discussion

6.4.1. Overall summary

Although patients were slower than healthy controls on Go trials and showed a trend of abnormal DMN function similar to the stopping groups (in Chapters 3 and 5), there was no significant change in FC between nodes of the SN with the DMN during cognitive switching in either healthy controls or patients. Furthermore, there was no significant relationship between the underlying white matter connecting two key nodes of the SN and the strength of FC between any of the original SN nodes and the DMN. However, when the rAI was defined from within the cognitive switch, a significant positive relationship between the changes in FC with the integrity of the white matter was detected.

6.4.2. No difference between patients and controls during Cognitive task switching.

The cognitive switch task performed in the current chapter was behaviourally more difficult than the motor switch task based on the participant's performance on the Go

trials. Therefore the neural responses, although mainly similar, are slightly different to those observed in the motor control paradigms (both the motor switch paradigm and the SST). The switch performed in the cognitive switch condition possibly reflected the heightened demand on executive control due to the requirement to configure the system for one task in the context of interference elicited by the second task. Therefore, the lack of differences between active brain regions between patients and controls could be because TBI patients and control participants found the task similarly difficult. As a result, the contrast of cognitive switch > Go must be investigated and interpreted with caution, as this baseline difficulty in control participants makes interpretation of the cognitive switch difficult. Go trials were more difficult, and as a result, more cognitive control was engaged during performance of the Go trials. Therefore, the difference between switch and Go trials is smaller. The impact of this baseline difficulty affects the analysis and interpretation of the results, as the neural activity of the task (in this case the cognitive switch) is determined by subtracting the baseline activity from the task activity. To overcome this issue, future studies should be designed that have 'rest' trials embedded within the paradigm. These rest trials would provide a non-task variable that can be used to compare the switch and Go trials to, thus providing a baseline that is not modulated by task performance, which can be compared to by any other variable.

7. Discussion

7.1. Results overview

The work presented in this thesis investigated interactions between the SN and DMN during cognitive control by studying the impact of damage to the SN following TBI and in healthy ageing. The current thesis presents evidence that links together the structural and functional relationship of the brain, in that damage to the underlying white matter structure in the brain impairs the interactions of large-scale functional brain networks. These results provide novel insights into brain network interactions, showing how damage to white matter in one network can affect the function of remote brain regions.

Bonnelle and colleagues have previously shown that damage produced by TBI to the white matter tract connecting the rAI and dACC/preSMA predicts a failure to suppress DMN activity normally during stopping (Sridharan et al., 2008; Bonnelle et al., 2012). The current work extends this finding by showing that: (1) FC between the SN and the DMN normally increases when motor responses are rapidly inhibited or changed; (2) a transient increase in FC is reduced in patients with impairments of motor control following TBI; and (3) the amount of post-traumatic damage to structural connections within the SN correlates with the extent of breakdown of this functional network interaction.

Furthermore, (4) these findings are replicated across an independent group of TBI patients performing a different task, showing a similar relationship when actions are switched to an alternative response, rather than being stopped altogether; and (5) the findings are not unique to TBI by demonstrating similar findings in an elderly group of participants. An overview of the model of cognitive control suggested by these

findings is shown in **Figure 7.1**.

7.2. Network interactions

The anticorrelation of activity between the SN and DMN reflects their distinct but coupled cognitive functions. The DMN shows high activity when attention is directed internally, such as during memory retrieval or when subjects thoughts are not relatively unconstrained e.g. during 'resting' state scanning (Raichle et al., 2001). When attention is focused externally, activity within the DMN normally shows a load-dependent reduction as cognitive demands increase (Singh et al., 2011). Failures of DMN deactivation are associated with lapses of attention in healthy adults (Weissman et al., 2006), and are observed across many diseases (Leech and Sharp, 2013) (discussed further below). When attention is externally focused, DMN activity is usually anticorrelated with that of the SN, and greater anticorrelation between the SN and DMN is associated with more efficient cognitive control (Kelly et al., 2008).

This suggests that the coupling of the two networks influences attentional focus, and that controlling the balance of activity in the two networks is an important mechanism for cognitive control. The SN typically shows increased activity in situations where attention needs to be directed externally, for example when actions need to be unexpectedly cancelled or changed (Menon and Uddin, 2010; Bonnelle et al., 2012). These situations often require a rapid response, and are characterised by increased autonomic and emotional activity, in addition to changes in motor control.
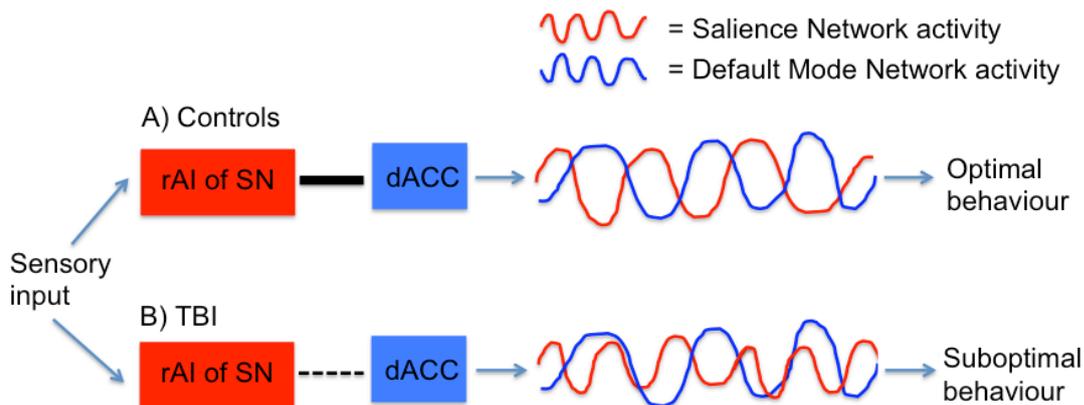
Figure 7.1: A network model of structural and functional connectivity between the SN and DMN. *Salient sensory input is processed by the right anterior insula of the Salience Network (rAI of SN on left). A) In healthy controls, the integrity of the rAI-preSMA/dACC tract within the Salience Network (solid black line) is correlated with tightly coupled and anticorrelated interactions between the SN and DMN. This allows efficient attention to the salient input leading to optimal behaviour. B) In the TBI patient group, reduced structural integrity in the Salience Network (dashed black line) which leads to decoupling of activity between the SN and DMN, which in turn leads to inefficient attention to the salient input and sub-optimal behaviour.*

7.3. Location of the Salience Network tract

The key tract of studied in the current work connects the rAI to a region around the boundary of the dorsal part of the rAI-preSMA/dACC (***Figure 7.2***). The existence of FC between brain regions suggests that the existence of anatomical pathways between the SN and DMN facilitate this high level of on-going interregional communication must exist to support information transfer (van den Heuval et al., 2009).
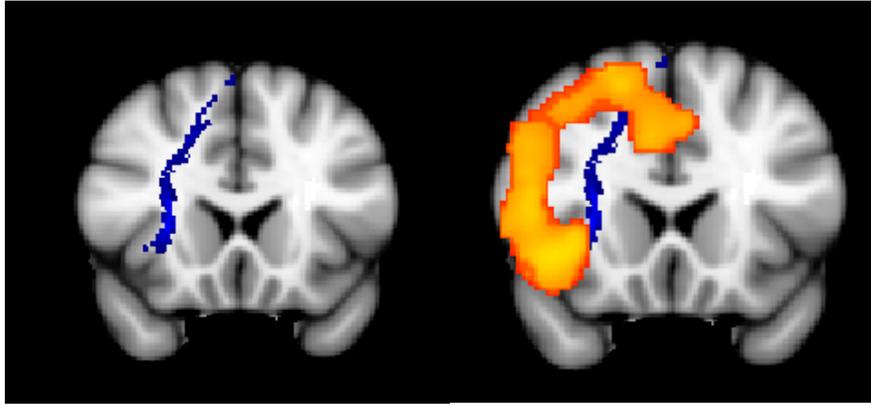
Figure 7.2: White matter tracts connecting the Salience Network. *The current thesis used diffusion tensor imaging to carry out tractography (left) in functionally active brain regions (right) and found a similar white matter tract to that in van den Heuval et al., 2009).*

7.4. The role of the Salience Network

Activity across brain networks must be coordinated during rapid changes in behaviour. The SN comprises of paralimbic structures, most prominently bilateral anterior insula cortices and medial prefrontal areas such as the dACC stretching out to the preSMA, which are anatomically and functionally interconnected (Seeley et al., 2007; van den Heuvel et al., 2009). It is proposed that the SN plays a key role in co-ordinating activity by causally influencing the DMN (Menon and Uddin, 2010; Chiong et al., 2013). If this causal influence occurs, damage to the SN should disrupt this interaction, particularly when cognitive control needs to be engaged. The findings from the current work provide evidence that the SN is required for efficient control of DMN activity when external events require rapid behavioural response. In particular, the current work supports a role for the rAI in switching activity in other networks including the DMN (Sridharan et al., 2008; Menon and Uddin, 2010; Chen et al., 2013).

Previous work has suggested that the SN may causally influence activity in the DMN; however, the clearest evidence for this is based on Granger causality analysis (GCA) (Sridharan et al., 2008; Chiong et al., 2013). Briefly, the concept of GCA is that a variable X is said to 'Granger-cause' a variable Y if the past of X contains information useful for predicting the future of Y, over and above that information already available in the past of Y (Seth et al., 2013). Although GCA is a useful technique when applied to certain types of data, there remain a number of issues that raises doubt about the accuracy of GCA when applied to fMRI data (Smith et al., 2011). Firstly, GCA relies on predictions based on the fMRI BOLD signal (which is captured as the haemodynamic response function), which at its core is already an indirect variable from which one infers neural activity. Secondly, the constraint that fMRI protocols involve severe down sampling, with sample intervals (repetition times, TRs) that typically range from 1–3s (Seth et al., 2013), means that this time is substantially longer than typical inter-neuron delays. Therefore this may disturb the information of precedence and predictability that GCA depends upon. Therefore, convergent evidence for the causal influence of the SN over the DMN remains important.

The above doubts raised over GCA are consistent with recent work using transcranial magnetic stimulation (TMS) to stimulate or inhibit an anterior node of the SN. This study failed to show evidence of causal influence of the network on the DMN, despite stimulation of an adjacent region within the central executive network modulating activity within the DMN (Chen et al., 2013).

The current work contributes to the above debate by demonstrating, for the first time, that there is an interaction between the nodes of the SN and DMN during a variety of

cognitive control mechanisms in both control and TBI groups. Damage to the white matter that connects nodes within the SN is shown to predict impaired FC between the rAI and the DMN, which as a result, relate to impaired cognitive control. The current results broadly corroborate the proposed functions for the SN, which include initiation of cognitive control (Menon et al., 2010). Menon's model proposes that the core function of the proposed SN (and in particular the rAI) is to first identify salient stimuli from the vast and continuous stream of sensory stimuli that impact the senses (Menon and Uddin, 2010). Once such a salient stimulus is detected, the rAI facilitates task-related information processing by initiating appropriate transient control signals, to engage brain areas mediating higher order cognitive processes, while disengaging the DMN. Critically, these switching mechanisms help focus attention on external stimuli, as a result of which they take on added further significance or saliency (Menon and Uddin, 2010).

In the current work, by demonstrating the link between structural damage to the rAI and dACC white matter connections and network interactions, the results provide converging evidence that structural integrity of the SN is important for the efficient interaction of the DMN and SN during cognitively demanding behaviour. The results were similar whether the task was to stop a prepotent action or switching to a new action. Coordinated activity between the SN and DMN is important to ensure optimal behaviour, as during cognitively demanding tasks such as the SST or the motor switch task (where attention is directed to external information), activity increases in nodes of the SN, whilst at the same time decreases within the DMN. This produces an anticorrelated pattern over time. Furthermore, increases in the magnitude of this anticorrelation is associated with improved behavioural responses (Kelly et al., 2008)

The current work utilised the standard SST, which involves the attentional capture of the stimuli. The participant must attend to a cue, appreciate its significance, and engage response inhibition. On stop trials, there is a significant increase in FC between the rAI and the DMN, but not the rIFG and the DMN. These results might suggest a model whereby the brain regions involved during stopping are activated as a result of the attentional processing of an external stimulus, in this case the stop cue. This model is corroborated by the work presented in chapter 4, whereby a similar right lateralized network is active alongside increased FC between the rAI and DMN during motor task switching.

7.4.1. Other models of salience network function

An alternative role for the rAI has been also been argued by Adam Aron and colleagues who propose that the rAI is simply part of the larger right inferior frontal cortex, which acts as a module that subserves response inhibition only (Adam et al., 2014). Aron and colleagues thus make an argument about Sharp et al's finding that the rIFG/rAI is important for attentional detection rather than for outright inhibition (Sharp et al., 2010), based on Sharp et al's use of 'continue' trials in the SST.

Sharp et al modified the standard version of the SST (as described in Chapter 2) to separate attentional processing of the cue to stop, from response inhibition that actually stops an initiated response. They did this by adding a control condition that involves the presentation of an unexpected continue cue, which is attentionally processed as an unexpected event, but requires no change in output behavior (Sharp et al., 2010). They identified regions that are specifically activated by the

outright stopping of a motor response by contrasting correct stop trials with correct continue trials, as this continue trial controlled for the attentional capture of an unexpected event. This contrast demonstrated medial frontal activation, with peaks of activation within the preSMA and no significant activity in the rAI or rIFG, suggesting that these regions (rAI/rIFG) are not specifically supporting outright response inhibition.

Aron and colleagues argues that this conclusion is likely to be flawed because the 'continue' trials induce a 'braking' effect where many subjects stop at the continue signal before they restart, therefore still engaging an inhibitory process (Aron et al., 2014). Although Aron is correct in that participants did slow their responses during continue trials (by approximately 40ms), Sharp et al address the possibility that incomplete inhibition may have occurred without the response actually being stopped (Sharp et al., 2010). Slowing on continue trials could result from an inhibitory process that is triggered by the observation of an unexpected event, in this case, the continue cue. Therefore, if the preSMA, which was found to be activated during outright stopping, influences response slowing arising from partial inhibition, then there would also be increased preSMA activity during slowing. Sharp et al (2010) compared participants who demonstrated a lot of slowing against those participants who demonstrated little slowing on continue trials. They found activity in the preSMA was observed only for participants in the high slowing group. This was corroborated with a region of interest analysis, which also showed that high slowing during continue trials was associated with a significant increase in preSMA activity, but no such activation was seen for the rIFG. This direct comparison of high and low slowing in participants allowed Sharp and colleagues to demonstrate that the preSMA was more active

when subjects slowed their responses. Therefore, inhibitory processing that is supported by the preSMA may result in outright stopping, if it is sufficient to overcome excitatory motor processing, or may slow a produced response by interacting with ongoing excitatory processing (Sharp et al., 2010).

In addition to the foregoing evidence, Aron et al's argument that the rIFC implements a brake over response tendencies seems somewhat at odds with other evidence. For example, if the rIFG were involved in inhibitory control specifically, then brain activity should increase specifically during the inhibition of a pre-potent response (Hampshire et al., 2010). Instead, the counting of cues; the initiation of responses and the inhibition of responses activated the rIFG. Therefore, it is logical to infer that the rIFG responds whenever salient cues that have a bearing on the current task plan, are detected (Hampshire et al., 2010); this would be the case with Sharp et al's continue trials (Sharp et al., 2010).

Furthermore, in Hampshire et al, the inhibitory processes during the SST recruited a network of brain regions including the IFG bilaterally and the preSMA. Importantly, these brain regions were also recruited during other conditions in the SST, such as when participants where required to count the number of stop signals, or even when participants were required to respond to the stop cue with a left or right button press according to the immediately preceding lateral arrow. This condition was intended to examine whether brain activity in the rIFG increased when cue detection was associated with the generation of a motor response (as opposed to the cancellation of a motor response in the classical SST design). In conclusion, there was no

evidence from Hampshire et al's study to support the notion that "inhibition is localized to the rIFG alone" as proposed by Aron et al (Aron et al., 2004).

The results in the current thesis contribute further to this debate. Here, the use of a region of interest approach to fractionate the regions, which Aron describes as the right inferior frontal cortex, is applied in a FC analysis. These sub-regions, separated out in the current work, include the rAI and the rIFG. The findings presented in this thesis argue for a specific role for the rAI, as the rAI but not the rIFG, showed a significant functional interaction with the DMN during both stopping and switching. The results in this thesis demonstrate clear differences between the rAI and the overlying rIFG, which would *not* have been predicted by Aron's model of the inferior frontal cortex. By fractionating regions of the right inferior frontal cortex, the current work suggests that the rAI facilitates task-related information processing by initiating appropriate transient control signals to engage brain areas mediating higher order cognitive processes while disengaging the DMN. Critically, these switching mechanisms may help focus attention on external stimuli, as a result of which they take on added significance or saliency (Menon and Uddin, 2010).

7.5. Disease and abnormal DMN control

The results presented in the current thesis directly link structural damage to a specific white matter tract within the SN to abnormalities in network interactions, and are thus in keeping with work demonstrating that disruption of SN function in patients with fronto-temporal dementia is associated with abnormalities in DMN function (Zhou et al., 2010). Efficient cognitive control appears to be associated with (reduced) activity

within the DMN (Sonuga-Barke and Castellanos, 2007; Kelly et al., 2008; Leech et al., 2011), in that the DMN usually shows deactivation as task difficulty increases (Singh et al., 2008). Failure of the DMN to deactivate has been associated with poorer cognitive function in various disease states. This has been observed in individuals who suffer from attention deficit hyperactivity disorder (ADHD) (Fassbender et al., 2009; Peterson et al., 2009; Liddle et al., 2010), and this change has been associated with increased distractibility (Fassbender et al., 2009). A failure of task-related DMN deactivation has also been observed in Parkinson's disease (van Eimeren et al., 2009; Delaveau et al., 2010), Alzheimer's disease and mild cognitive impairment (Rombouts et al., 2005), and finally in autism, when it was associated with greater social impairment (Kennedy et al., 2006).

The precuneus/posterior cingulate cortex (Precu/PCC) region is a central node of the DMN (Fransson and Marrelec, 2008) and forms part of what has been termed the structural core of the brain (Hagmann et al., 2008). Activity within this region appears very sensitive to changes elsewhere in the brain and a failure to deactivate this region during task performance is, as noted above, associated with cognitive impairment (Fassbender et al., 2009; Frings et al., 2010). The current thesis demonstrates that impairments of response inhibition deficits following TBI are associated with an inability to deactivate within the DMN over time, which in turn is linked to impairment in the FC between the DMN and SN. This impairment in FC between the DMN and SN maybe a general feature of cognitive impairment across different types of disease. However, the disruption to the structural-functional system discussed in this thesis could arise from different pathophysiological mechanisms,

including for example DAI in TBI, amyloid deposition in Alzheimer's Disease, neurochemical imbalances in schizophrenia and altered metabolism in depression.

7.5.1. Ageing

Reduction of DMN activity during cognitive tasks is also abnormal in older adults relative to younger adults (Lustig et al., 2003; Persson et al., 2007; Miller et al., 2008). This failure to reduce activity, especially within the Precu/PCC, was most prominent in older adults who performed poorly on a subsequent memory test (Miller et al., 2008), and we have also seen this pattern of activity in Chapter 5. As humans get older, there is a natural decline in cognitive performance (Salthouse et al., 1998; Salthouse, 2000). The work presented in the current thesis now allows us to add to the structural-functional model of cognitive control by demonstrating across two groups (TBI and the elderly) that the structural integrity of the white matter tract connecting the right insula to the preSMA/dACC within the SN determines the down regulation of the DMN during high levels of cognitive control. This provides a mechanism by which frontal white matter damage produces deficits in the executive control required when making responses to salient stimuli.

This finding in the ageing work suggests that it would be informative to look at functional system across various diseases, to investigate whether the model presented in this thesis subserves other disease forms. It can be hypothesised that: 1) abnormal task-dependent DMN deactivations; and 2) reduced anticorrelated activity between the DMN and the SN during either task or resting-state fMRI, would be impaired in disease states (e.g. in a schizophrenic population), which might be expected to have 3) damage to the underlying white matter structure that connects

key nodes within the SN. These functional and structural impairments would then predict impairments in cognitive and behavioural domains (e.g. working memory performance).

7.5.2. Behavioural correlates of DMN dysfunction

7.5.2.1.   The interference hypothesis

Aberrant DMN function may represent a mechanism underlying impaired top-down control (Mason et al., 2007; Sonuga-Barke and Castellanos, 2007). This is in keeping with the suggestion that spontaneous low frequency DMN activity may interfere with task goals and focused attention and contribute to impaired task performance (Fox et al., 2005). Sonuga-Barke and Castellanos hypothesised that "altered modulation of DMN coherence" may lead to intrusive DMN activity and lapses of attention, and give rise to sustained attention deficits (Sonuga-Barke and Castellanos, 2007).

The DMN interference hypothesis argues that DMN activity is normally attenuated during goal-directed action. This attenuation can be affected by cognitive load, under sustained or focused attention requirements, and during tasks that involve functions subserved by the DMN, but is otherwise independent of task content. It is argued that when the magnitude of DMN activity exceeds a certain threshold, lapses in attention occur due to intrusions of task unrelated thought.

7.5.2.2.   DMN dysfunction and self-regulatory disorder following TBI

Early research postulated that the DMN maybe involved in autobiographical, self-referential mental activity (Raichle et al., 2001; Buckner et al., 2008). Interestingly,

impairments in behavioural self-regulation, i.e. the ability to exert control over thoughts and action, have often been observed in TBI. Levine and colleagues proposed that these symptoms correspond to a 'self-regulatory disorder' (Levine et al., 2002). They proposed that such disorder would give rise to deficits in sustained attention, inhibition, and self-awareness. Previous lesion studies have proposed that self-regulatory disorder was typically associated with ventral prefrontal damage (Shallice and Burgess, 1991). One recent study, performed by Ham and colleagues tested the hypothesis that impaired self-awareness is associated with abnormal brain network function (Ham et al., 2013). They studied a group of 63 TBI patients who performed both resting state and task fMRI. The TBI group was split into high and low performance-monitoring groups, based on their ability to recognise and correct their own errors on the fMRI task. They found that low self-awareness is associated with abnormal network function within the key nodes of the SN. These nodes include the dACC and the bilateral insulae. This abnormal pattern of FC within the SN was accompanied by an abnormal response to errors within the anterior insulae, which are normally tightly linked to the dACC. These results suggest that interactions between the anterior insulae and dACC subserve the internal monitoring for self-awareness (Ham et al., 2013).

7.5.3. The DMN and previous TBI studies

7.5.3.1. DMN deactivation

The studies presented in this thesis are the first to report impaired FC using PPI between the SN and DMN in TBI patients and in healthy ageing. The concept of the DMN, as well as studies investigating network function in patients, have both been

around for more than ten years. In the absence of notions such as 'task-negative network' and brain 'deactivation', a *decrease* in DMN *deactivation* could have been previously reported as an *increase in activation* of additional brain regions (Rasmussen et al., 2008; Caeyenberghs et al., 2009; Newsome et al., 2009). For instance, Scheibel and colleagues found that TBI patients had greater task-related *activation* within a midline region that included the posterior cingulate gyrus and the thalamus. They proposed that it might reflect the allocation of more extensive neural resources to allow patients with the most severe injuries to maintain adequate task performance (Scheibel et al., 2009). In another study, more precuneus *activation* has also been observed in TBI patients during dual tasking as compared to controls (Rasmussen et al., 2008). In the current thesis, the importance of the terminology is most key in respect to the DMN, as the context of the DMN is not 'activation' but a failure of deactivation as attention is directed externally.

7.6. Von Economo neurons

The microscopic structure of the SN may be specialised for generating a rapid 'circuit breaking' signal. The right lateralized insular cortex and the dACC contain von Economo neurons (VENs) (Economo and Koskinas, 1925). As a result of these VENs, these brain regions have histological properties that are potentially relevant to their role in cognitive control (Allman et al., 2005; Allman et al., 2010). Post-mortem studies show that layer 5 of the right lateralized insular cortex and the dACC contain VENs. VENs are large bipolar projection neurons that are predominantly found in the right hemisphere, and are a phylogenetically recent specialisation in hominoid evolution. They are found in humans, great apes, cetaceans (Nimchinsky et al., 1999) but not other primates (Allman et al., 2010). Their large size and simple

dendritic structure spanning cortical layers suggests a specialisation for integrating cortical signals and rapidly communicating with remote brain regions.

The structural-functional model presented in this thesis can be applied to real life situations where one is required to 'fight or flee.' This could be an evolutionarily preserved system that is fundamental for re-orienting attention in situations of threat made, where the sensory process to act quickly is coming from the rAI. The 'flight or fight' response involves rapid allocation of resources towards potential external threats and puts a premium on the capacity to respond quickly to a rapidly changing environment. Although there is some uncertainty about the termination of VEN projections, it is likely that the rAI-preSMA/dACC tract studied in the current thesis contains von Economo axonal projections (Allman et al., 2010). As the SN response to salient behavioural events is characterised by very short latencies, these von Economo projection neurons may provide the histological basis for these fast control signals (Menon et al., 2010). This could explain why damage to the connectivity of the SN might be particularly disruptive to the rapid changes in network activity that accompany the response to unexpected but behaviourally relevant events. Taken together, the SN may have evolved to rapidly integrate information from a variety of sources to signal potentially relevant changes in the environment critical for initiating fast adaptive behavioural responses.

7.7. Functional connectivity and regional activation differences

In the current results, it is notable that an increase in FC between the rAI and DMN is accompanied by distinct patterns of local changes in brain activity i.e. a relative increase in the SN and a decrease in the DMN. This is not unexpected, and

illustrates how increased 'communication' between brain regions can occur at the same time as a relative reduction in the activity in one or both of the connected regions. In the case of the PCC, we have previously shown how sub-regions can show distinct patterns of FC change during an attentionally demanding task, whilst at the same time the whole region shows a reduction in activity relative to baseline (Leech et al., 2012). The pattern of results we report in this thesis is in keeping with a model where increased cognitive control is accompanied by increased FC between the rAI and the PCC, which through interactions between the dorsal and ventral PCC produces an overall reduction of activity and FC within the core nodes of the DMN.

7.8. Is white matter damage a better predictor of cognitive deficits than lesions in TBI patients?

TBI frequently produces focal brain injury. The presence and location of these focal lesions do not always explain clinical outcome (Lee et al., 2008; Niogi et al., 2008). Furthermore, many symptomatic patients do not have any evidence of focal damage (Belanger et al., 2007). For these patients, cognitive deficits are therefore likely to be due to structural changes in the white matter, which can go easily undetected with conventional imaging. Recent MRI techniques (T2*, SWI) demonstrated DAI pathology in 75% of moderate to severe TBI (Skandsen et al., 2010), and are thought to be more sensitive than traditional T1 MRI. However, these imaging techniques are still likely to underestimate the extent of white matter damage. In contrast DTI provides a validated and sensitive way to investigate the impact of DAI.

The results presented in the current work confirm the relevance of this imaging technique in TBI research. Both inhibitory control and task switching deficits were

associated with white matter damage within the SN's white matter connections, and the relationships observed were still present, and often became stronger, when excluding patients with lesions. These results thus support the general hypothesis that some cognitive deficits after TBI arise from structural disconnection within brain networks (such as the SN) that mediate cognitive functions. In addition, this thesis again confirms the utility and relevance of DTI as a tool to investigate white matter damage and the impact it has on brain function.

7.9. Limitations

The studies presented in this thesis have a number of potential limitations. The method implements a focused analysis of FC to test a specific hypothesis, which was motivated by previous work (Bonnelle et al., 2012). Future work could usefully expand the analysis in various ways. Other brain regions are undoubtedly involved in cognitive control, and so additional nodes in the networks assessed should be investigated in more complex models of network interactions. The current work uses a simple analysis of FC in order to maximise power in order to detect relationships between brain structure and function that can be subtle. However, multivariate approaches to FC analysis could provide important additional information. Additionally the current work does not provide a mean to comment on the causality of interactions between the SN and the DMN using the PPI technique, and this limitation might be addressed using techniques such as dynamic causal modelling (Friston et al., 1997).

The DTI analyses in this thesis are focused on a specific white matter tract connecting two nodes of the salience network. It could be the case that other tracts

are likely to be important for cognitive control. For example, tracts that connect the subthalamic nucleus to the dACC have been shown to predict SSRT in older populations (Coxon et al., 2009) and there are a number of other pathways connecting the anterior insula to the medial frontal lobe, including parts of the uncinate fasciculus and external capsule (Schmahmann and Pandya, 2006; Petrides and Pandya, 2007; Schmahmann et al., 2007; Uddin et al., 2011). However, the work presented in this thesis was hypothesis driven, and the tract generated (rAI-preSMA/dACC) was defined based on peaks of activation observed during stop signal task performance. Furthermore, Bonnelle and colleagues have previously reported that this specific tract is correlated with the amount of regional DMN (de)activation seen during the stop signal task (Bonnelle et al., 2012).

Taken together, more work is necessary to define the mechanism(s) by which the SN influences the DMN, both in terms of regional brain activity changes and altered connectivity of activity during task. Further studies will be required to provide a comprehensive description of the organisation of these tracts and the effects of their damage on behaviour.

7.10. Summary

The main goal of the current research was to clarify the relationship between brain function, structure, behaviour and cognition following TBI, with the general hypothesis that cognitive impairments after TBI would arise from brain network dysfunction, due to structural disconnection resulting from DAI. The work presented in this thesis confirms this hypothesis, and brings a new understanding to the cognitive deficits observed following TBI. Here, the work shows that coupling

between the rAI and DMN increases with task demands for cognitive control, and that damage within the SN impairs this dynamic network interaction. This provides compelling evidence for a model of cognitive control where the rAI signals the attentional capture of salient stimuli, and interacts with the DMN to produce a reduction of its activity when attention is externally focused. Hence, white matter damage within the SN predicts failure of DMN control in two populations with different mechanisms of white matter damage. This work proposes that this provides a general mechanism by which damage to a specific frontal white matter tract leads to executive dysfunction, in part through a failure of DMN control.

8. References

Adams JH, Doyle D, Ford I, Gennarelli TA, Graham DI, McLellan DR (1989) Diffuse axonal injury in head injury: definition, diagnosis and grading. *Histopathology,* 15:49–59.

Akiyama Y, Miyata K, Harada K, Minamida Y, Nonaka T, Koyanagi I, Asai Y, Houkin K (2009) Susceptibility-weighted magnetic resonance imaging for the detection of cerebral microhemorrhage in patients with traumatic brain injury. *Neurol Med Chir (Tokyo)*, 49:97–9–discussion99.

Alderson RM, Rapport MD, Sarver DE, Kofler MJ (2008) ADHD and behavioral inhibition: a re-examination of the stop-signal task. *Journal of abnormal child psychology*, 36:989–998.

Allman J. M., Watson K. K., Tetreault N. A., Hakeem A. Y. (2005) Intuition and autism: a possible role for Von Economo neurons. *Trends Cogn Sci,* 9 (8), 367-373.

Allman J. M., Tetreault N. A., Hakeem A. Y., Manaye K. F., Semendeferi K., Erwin J. M., Park S., Goubert V., Hof P. R. (2010) The von Economo neurons in frontoinsular and anterior cingulate cortex in great apes and humans. *Brain Struct Funct,* 214 (5-6), 495-517.

Allport DA (1994) Shifting intentional set: Exploring the dynamic control of tasks. *Available at: http://psycnet.apa.org/psycinfo/1994-98352-017.*

Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, Buckner RL (2007) Disruption of large-scale brain systems in advanced aging. *Neuron* 56:924–935.

Arfanakis K, Haughton VM, Carew JD, Rogers BP, Dempsey RJ, Meyerand ME (2002) Diffusion tensor MR imaging in diffuse axonal injury. *AJNR,* 23:794–802.

Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA (2007) Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. *J Neurosci*, 27:3743–3752.

Aron AR, Fletcher, P. C., Bullmore ET, Sahakian BJ, Robbins TW (2003) Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience,* 6:115–116.

Aron AR, Fletcher, P. C., Bullmore ET, Sahakian BJ, Robbins TW (2003b) Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience,* 6:115–116.

Aron AR, Monsell S, Sahakian BJ and Robbins TW (2004) A componential analysis of task switching deficits associated with lesions of left and right frontal cortex. *Brain*, 127:1561–1573.

Aron AR, Poldrack RA (2006) Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. *J Neurosci,* 26:2424–2433.

Aron AR, Robbins TW, Poldrack RA (2014) Inhibition and the right inferior frontal cortex: one decade on. *Trends in cognitive sciences*, 18:177-185.

Azouvi P (2000) Neuroimaging correlates of cognitive and functional outcome after traumatic brain injury. *Curr Opin Neurol,* 13:665–669.

Azouvi P, Couillet J, Leclercq M, Martin Y, Asloun S and Rousseaux M (2004) Divided attention and mental effort after severe traumatic brain injury, *Neuropsychologia*, 42:1260–1268.

Babikian T, Freier MC, Tong KA, Nickerson JP, Wall CJ, Holshouser BA, Burley T, Riggs ML and Ashwal S (2005) Susceptibility weighted imaging: neuropsychologic outcome and pediatric head injury. *Pediatr Neurol*, 33:184–194.

Baddeley AD, Emslie H, Nimmo-Smith I (1994) Doors and People Test: A Test of Visual and Verbal Recall and Recognition. Bury-St-Edmunds: Thames Valley Test Company.

Baird AE and Warach S (1998) Magnetic resonance imaging of acute stroke. *J Cereb Blood Flow Metab*, 18:583–609.

Bate AJ, Mathias JL and Crawford JR (2001) Performance on the Test of Everyday Attention and standard tests of attention following severe traumatic brain injury. *Clin Neuropsychol*, 15:405–422.

Beaulieu C (2002) The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed*, 15:435–455.

Beckmann CF and Smith SM (2004) Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Trans Med Imaging*, 23:137–152.

Beckmann CF, DeLuca M, Devlin JT, Smith SM (2005) Investigations into resting-state connectivity using independent component analysis. *Philos Trans R Soc Lond B Biol Sci*, 360:1001–1013.

Beckmann CF, Jenkinson M, Smith SM (2003) General multilevel linear modelling for group analysis in FMRI. *NeuroImage,* 20:1052–1063.

Behrens TE, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, Matthews PM, Brady JM and Smith SM (2003) Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magn Reson Med*, 50:1077–1088.

Bekker EM, Overtoom CC, Kenemans JL, Kooij JJ, De Noord I, Buitelaar JK, and Verbaten MN (2005) Stopping and changing in adults with ADHD. *Psychol Med*, 35:807-816.

Belanger H. G., Vanderploeg R. D., Curtiss G., Warden D. L. (2007) Recent neuroimaging techniques in mild traumatic brain injury. *J Neuropsychiatry Clin Neurosci,* 19 (1), 5-20.

Berg EA (1948) A simple objective technique for measuring flexibility in thinking. *The Journal of general psychology,* 39:15-22.

Binder JR, Frost JA, Hammeke TA, Bellgowan PS, Rao SM, Cox RW (1999) Conceptual processing during the conscious resting state. A functional MRI study. *J Cogn Neurosci*, 11:80–95.

Binder S, Corrigan JD, Langlois JA (2005) The public health approach to traumatic brain injury: an overview of CDC's research and programs. *J Head Trauma Rehabil*, 20:189–195

Biswal B, Yetkin FZ, Haughton VM and Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, 34:537–541

Biswal BB *et al*. (2010) Toward discovery science of human brain function. *Proc Natl Acad Sci USA,* 107:4734–4739.

Bloch (1946) Nuclear induction. *Phys Rev*, 70:460.

Blood AJ and Zatorre RJ (2001) Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proc Natl Acad Sci USA*, 98:11818–11823.

Boehler CN, Appelbaum LG, Krebs RM, Hopf JM and Woldorff MG (2010) Pinning down response inhibition in the brain--conjunction analyses of the Stop-signal task. *Neuroimage*, 52:1621–1632.

Boksman K, Théberge J, Williamson P, Drost DJ, Malla A, Densmore M, Takhar J, Pavlosky W, Menon RS and Neufeld RW (2005) A 4.0-T fMRI study of brain connectivity during word fluency in first-episode schizophrenia. *Schizophr Res*, 75:247–263.

Boly M, Moran R, Murphy M, Boveroux P, Bruno MA, Noirhomme Q, Ledoux D, Bonhomme V, Brichant JF, Tononi G, Laureys S, Friston K (2012) Connectivity changes underlying spectral EEG changes during propofol-induced loss of consciousness. *J Neurosci,* 32:7082–7090.

Boly M, Tshibanda L, Vanhaudenhuyse A, Noirhomme Q, Schnakers C, Ledoux D, Boveroux P, Garweg C, Lambermont B, Phillips C, Luxen A, Moonen G, Bassetti C, Maquet P, Laureys S (2009a) Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. *Hum Brain Mapp*, 30:2393–2400.

Bonnelle V, Ham TE, Leech R, Kinnunen KM, Mehta MA, Greenwood RJ, Sharp DJ (2012) Salience network integrity predicts default mode network function after traumatic brain injury. *Proc Natl Acad Sci U S A,* 109:4690–4695.

Bonnelle V, Leech R, Kinnunen KM, Ham TE, Beckmann CF, De Boissezon X, Greenwood RJ, Sharp DJ (2011) Default Mode Network Connectivity Predicts Sustained Attention Deficits after Traumatic Brain Injury. *J Neurosci,* 31:13442–13451.

Brass M and Haggard P (2010) The hidden side of intentional action: the role of the anterior insular cortex. *Brain Struct Funct*, 214:603–610.

Brass M, Derrfuss J, Forstmann B and von Cramon DY (2005) The role of the inferior frontal junction area in cognitive control. *Trends Cogn Sci*, 9:314–316.

Braver TS, Reynolds JR and Donaldson DI (2003) Neural mechanisms of transient and sustained cognitive control during task switching. *Neuron*, 39:713–726.

Bressler SL, Menon V (2010) Large-scale brain networks in cognition: emerging methods and principles. *Trends in cognitive sciences*, 14:277-290.

Broca P. (1863) Localization of cerebral function. Siege of the language articulates. *Bulletins de la Societe d'Anthropologie (Paris),* 4, 200-203.

Brodmann K. (1960) On the comparative localization of the cortex. *In: Some papers on the cerebral cortex Springfield, IL: Charles C Tomas,* 201-230.

Brouwer WH, Withaar FK, Tant ML and van Zomeren AH (2002) Attention and driving in traumatic brain injury: a question of coping with time-pressure. *J Head Trauma Rehabil*, 17:1–15.

Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The Brain's Default Network. *Ann N Y Acad Sci*, 1124:1–38.

Caeyenberghs K., Wenderoth N., Smits-Engelsman B. C., Sunaert S., Swinnen S. P. (2009) Neural correlates of motor dysfunction in children with traumatic brain injury: exploration of compensatory recruitment patterns. *Brain,* 132(Pt 3):684-694.

Caeyenberghs K, Leemans A (2014) Hemispheric lateralization of topological organisation in structural brain networks. *Hum Brain Mapp,* 35(9):4944-4957.

Cantor JB, Ashman T, Gordon W, Ginsberg A, Engmann C, Egan M, Spielman L, Dijkers M and Flanagan S (2008) Fatigue after traumatic brain injury and its impact on participation and quality of life. *J Head Trauma Rehabil*, 23:41–51.

Castellanos Np Fau Paul N, Paul N Fau Ordonez VE, Ordonez Ve Fau Demuynck O, Demuynck O Fau Bajo R, Bajo R Fau Campo P, Campo P Fau Bilbao A, Bilbao A Fau Ortiz T, Ortiz T Fau del-Pozo F, del-Pozo F Fau Maestu F, Maestu F (2010)

Reorganisation of functional connectivity as a correlate of cognitive recovery in acquired brain injury. *Brain*, 133:2365-2381.

Cauda F, Micon BM, Sacco K, Duca S, D'Agata F, Geminiani G, Canavero S (2009) Disrupted intrinsic functional connectivity in the vegetative state. *J Neurology, Neurosurgery, and Psychiatry,* 80:429–431.

CDC (2004) Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths. Available at: http://stacks.cdc.gov/view/cdc/13379/.

Cercignani M and Horsfield MA (2001) The physical basis of diffusion-weighted MRI. *J Neurol Sci,* 186 Suppl 1:S11–S14.

Chamberlain SR, Fineberg NA, Blackwell AD, Robbins TW, Sahakian BJ (2006) Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. *Am J Psychiatry,* 163:1282–1284.

Chen JJ, Salat DH, Rosas HD (2012) Complex relationships between cerebral blood flow and brain atrophy in early Huntington's disease. *NeuroImage*, 59:1043-1051.

Chevrier AD, Noseworthy MD and Schachar R (2007) Dissociation of response inhibition and performance monitoring in the stop signal task using event-related fMRI. *Hum Brain Mapp*, 28:1347-1358.

Chiong W, Wilson SM, D'Esposito M, Kayser AS, Grossman SN, Poorzand P, Seeley WW, Miller BL, Rankin KP (2013) The salience network causally influences default mode network activity during moral reasoning. *Brain,* 136:1929–1941.

Christodoulou C, Deluca J, Ricker JH, Madigan NK, Bly BM, Lange G, Kalnin AJ, Liu WC, Steffener J, Diamond BJ, Ni AC (2001) Functional magnetic resonance imaging of working memory impairment after traumatic brain injury. *Journal of Neurology, Neurosurgery, and Psychiatry,* 71:161–168.

Cicerone K, Levin H, Malec J, Stuss D, Whyte J (2006) Cognitive rehabilitation interventions for executive function: moving from bench to bedside in patients with traumatic brain injury. *J Cogn Neurosci,* 18:1212–1222.

Cocchi L, Zalesky A, Fornito A and Mattingley JB (2013) Dynamic cooperation and competition between brain systems during cognitive control. *Trends in Cog Neurosci,* 17:493–501.

Coetzer R, Carroll R, Ruddle JA (2011) "Depression, anxiety and employment status after traumatic brain injury", *Social Care and Neurodisability,* 2:200-207

Cohen JR, Asarnow RF, Sabb FW, Bilder RM, Bookheimer SY, Knowlton BJ and Poldrack RA (2010) Decoding developmental differences and individual variability in response inhibition through predictive analyses across individuals. *Front Hum Neurosci*, 4:47–47.

Conturo TE, Lori NF, Cull TS, Akbudak E, Snyder AZ, Shimony JS, McKinstry RC, Burton H and Raichle ME (1999) Tracking neuronal fiber pathways in the living human brain. *Proc Natl Acad Sci U S A*, 96:10422–10427.

Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews,* 3:201–215.

Coull JT, Frackowiak RS and Frith CD (1998) Monitoring for target objects: activation of right frontal and parietal cortices with increasing time on task. *Neuropsychologia*, 36:1325–1334.

Coxon J. P., Stinear C. M., Byblow W. D. (2009) Stop and go: the neural basis of selective movement prevention. *J Cogn Neurosci,* 21(6):1193-1203.

Craig AD (2002) How do you feel? Interoception: the sense of the physiological condition of the body. *Nature reviews*, 3:655–666.

Craig AD (2003) Interoception: the sense of the physiological condition of the body. *Current Opinion in Neurobiology,* 13:500–505.

Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ (2004) Neural systems supporting interoceptive awareness. *Nature Neuroscience,* 7:189–195.

Damoiseaux JS and Greicius MD (2009) Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity.

Brain Struct Funct, 213:525–533.

Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF (2006) Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci U S A,* 103:13848–13853.

De Luca M, Beckmann CF, De Stefano N, Matthews PM and Smith SM (2006) fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *Neuroimage*, 29:1359-1367.

Debener S, Ullsperger M, Siegel M, Fiehler K, Cramon von DY, Engel AK (2005) Trial-by-trial coupling of concurrent electroencephalogram and functional magnetic resonance imaging identifies the dynamics of performance monitoring. *J Neurosci,* 25:11730–11737.

Delis DC, Kaplan E, Kramer JH (2001) Delis-Kaplan Executive Function System.

Derrfuss J, Brass M, Neumann J and von Cramon DY (2005) Involvement of the inferior frontal junction in cognitive control: meta-analyses of switching and Stroop studies. *Hum Brain Mapp*, 25:22–34.

DiGirolamo GJ, Kramer AF, Barad V, Cepeda NJ, Weissman DH, Milham MP, Wszalek TM, Cohen NJ, Banich MT, Webb A, Belopolsky AV and McAuley E (2001) General and task-specific frontal lobe recruitment in older adults during executive processes: A fMRI investigation of task switching. *Neuroreport*, 12:2065.

DiMaio D, Vincent JM (2001) Forensic Pathology, Second Edition. CRC Press.

Dimitrov M, Nakic M, Elpern-Waxman J, Granetz J, O'Grady J, Phipps M, Milne E, Logan GD, Hasher L and Grafman J (2003). Inhibitory attentional control in patients with frontal lobe damage. *Brain Cogn*, 52:258-270.

Dimoska-Di Marco A, McDonald S, Kelly M, Tate R and Johnstone S (2011) A meta-analysis of response inhibition and Stroop interference control deficits in adults with traumatic brain injury (TBI). *J Clin Exp Neuropsychol*, 33:471–485.

Dockree PM, Bellgrove MA, O'Keeffe FM, Moloney P, Aimola L, Carton S, Robertson IH (2006) Sustained attention in traumatic brain injury (TBI) and healthy controls: enhanced sensitivity with dual-task load. *Exp Brain Res* 168:218–229.

Dockree PM, Kelly SP, Roche RA, Hogan MJ, Reilly RB, Robertson IH (2004) Behavioural and physiological impairments of sustained attention after traumatic brain injury. *Brain Res* 20:403–414.

Dong Q, Welsh RC, Chenevert TL, Carlos RC, Maly-Sundgren P, Gomez-Hassan DM and Mukherji SK (2004) Clinical applications of diffusion tensor imaging. *J Magn Reson Imaging*, 19:6-18.

Dosenbach NU, Visscher KM, Palmer ED, Miezin FM, Wenger KK, Kang HC, Burgund ED, Grimes AL, Schlaggar BL, Petersen SE (2006) A core system for the implementation of task sets. *Neuron,* 50:799–812.

Dove A, Pollmann S, Schubert T, Wiggins CJ (2000) Prefrontal cortex activation in task switching: an event-related fMRI study. *Brain Res Cogn Brain Res,* 9:103-109.

Dreisbach G and Goschke T (2004) How positive affect modulates cognitive control: reduced perseveration at the cost of increased distractibility. *J Exp Psychol Learn Mem Cogn*, 30:343-353.

Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith SM, Matthews PM, Beckmann CF, Mackay CE (2009) Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proc Natl Acad Sci U S A,* 106:7209–7214.

Fiset P, Paus T, Daloze T, Plourde G (1999) Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study. *J Neuroscience,* 19:5506-5513.

Floden D, Stuss DT (2006) Inhibitory control is slowed in patients with right superior medial frontal damage. *J Cogn Neurosci*, 18:1843–1849.

Fox MD, Corbetta M, Snyder AZ, Vincent JL, Raichle ME (2006) Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proc Natl Acad Sci U S A,* 103:10046–10051.

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A,* 102:9673–9678.

Fransson P (2005) Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. *Hum Brain Mapp*, 26:15–29.

Fransson P, Marrelec G (2008) The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. *NeuroImage,* 42:1178–1184.

Friedman NP and Miyake A (2004) The relations among inhibition and interference control functions: a latent-variable analysis. *J Exp Psychol Gen*, 133:101-135.

Friston KJ, Frith CD, Liddle PF, Frackowiak RS (1993) Functional connectivity: the principal-component analysis of large (PET) data sets. *J Cereb Blood Flow Metab,* 13:5–14.

Friston KJ, C. Buchel, G.R. Fink, J. Morris, E. Rolls, and R. Dolan (1997) Psychophysiological and modulatory interactions in Neuroimaging. *NeuroImage*, 6:218-229,

Fukunaga M, Horovitz SG, van Gelderen P, de Zwart JA, Jansma JM, Ikonomidou VN, Chu R, Deckers RH, Leopold DA and Duyn JH (2006) Large-amplitude, spatially correlated fluctuations in BOLD fMRI signals during extended rest and early sleep stages. *Magn Reson Imaging*, 24:979–992.

Gennarelli TA and Graham DI (1998) Neuropathology of the Head Injuries. *Semin Clin Neuropsychiatry*, 3:160–175.

Gentry LR (1994) Imaging of closed head injury. *Radiology*, 191:1–17.

Gentry LRL, Godersky JCJ, Thompson BB (1988) MR imaging of head trauma: review of the distribution and radiopathologic features of traumatic lesions. *AJR Am R Roentgenol,* 150:663–672.

Geschwind N (1965) Disconnexion syndromes in animals and man. *Brain,* 88:237-294.

Grady MS, McLaughlin MR, Christman CW, Valadka AB, Flinger CL and Povlishock JT (1993) The use of antibodies targeted against the neurofilament subunits for the detection of diffuse axonal injury in humans. *J Neuropathol Exp Neurol*, 52:143–152.

Granacher RP Jr (2007) Traumatic brain injury: Methods for clinical and forensic neuropsychiatric assessment. CRC Press.

Granger CWJ (1969) Investigating causal relations by econometric models and cross-spectral methods. *Econometrica*, 37(3):424-438.

Greicius MD, Srivastava G, Reiss AL, Menon V (2004) Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci U S A,* 101:4637–4642.

Greicius MD, Supekar K, Menon V, Dougherty RF (2009) Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cereb Cortex,* 19:72–78.

Gusnard DA, Akbudak E, Shulman GL, Raichle ME (2001) Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci U S A*, 98:4259–4264.

Gusnard DA, Raichle ME (2001) Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews,* 2:685–694.

Gustavsson A et al. (2011) Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol*, 21:718–779.

Guye M, Bartolomei F and Ranjeva JP (2008) Imaging structural and functional connectivity: towards a unified definition of human brain organisation? *Curr Opin Neurol*, 21:393–403.

Haacke EM, Xu Y, Cheng YC and Reichenbach JR (2004) Susceptibility weighted imaging (SWI). *Magn Reson Med*, 52:612–618.

Habas C, Kamdar N, Nguyen D, Prater K, Beckmann CF, Menon V and Greicius MD (2009) Distinct cerebellar contributions to intrinsic connectivity networks. *J Neurosci*, 29:8586–8594.

Hagmann CF, Robertson NJ, Sams VR, Brookes JA (2007) Postmortem magnetic resonance imaging as an adjunct to perinatal autopsy for renal-tract abnormalities. *Arch Dis Child Fetal Neonatal Ed,* 92:F215–F218.

Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, Sporns O (2008) Mapping the structural core of human cerebral cortex. *PLoS Biol,* 6:e159.

Hahn B, Ross TJ, Stein EA (2007) Cingulate activation increases dynamically with response speed under stimulus unpredictability. *Cereb Cortex,* 17:1664–1671.

Ham T, Leff A, De Boissezon X, Joffe A (2013a) Cognitive control and the salience network: an investigation of error processing and effective connectivity. *J Neuroscience,* 33:7091-7098.

Ham TE, Bonnelle V, Hellyer P, Jilka S, Robertson IH (2014) The neural basis of impaired self-awareness after traumatic brain injury. *Brain*.

Ham TE, de Boissezon X, Leff A, Beckmann C, Hughes E, Kinnunen KM, Leech R, Sharp DJ (2013b) Distinct Frontal Networks Are Involved in Adapting to Internally and Externally Signaled Errors. *Cereb Cortex,* 23:703–713.

Ham TE, Sharp DJ (2012) How can investigation of network function inform rehabilitation after traumatic brain injury? *Current opinion in neurology,* 25:662–669.

Hampshire A, Chamberlain SR, Monti MM, Duncan J (2010) The role of the right inferior frontal gyrus: inhibition and attentional control. *NeuroImage*, 50: 1313:1319.

Hampshire A, Owen AM (2006) Fractionating attentional control using event-related fMRI. *Cerebral cortex*, 16:1679-1689.

Hampson M, Driesen NR, Skudlarski P, Gore JC, Constable RT (2006) Brain connectivity related to working memory performance. *J Neurosci,* 26:13338–13343.

Harrison BJ, Pujol J, Lopez-Sola M, Hernandez-Riba R, Deus J, Ortiz H, Soriano-Mas C, Yucel M, Pantelis C and Cardoner N (2008) Consistency and functional specialization in the default mode brain network. *Proc Natl Acad Sci U S A*, 105:9781–9786.

Hayden BY, Smith DV, Platt ML (2010) Cognitive control signals in posterior cingulate cortex. *Front Hum Neurosci,* 4:223.

He BJ, Shulman GL, Snyder AZ and Corbetta M (2007) The role of impaired neuronal communication in neurological disorders. *Curr Opin Neurol*, 20:655-660.

Hebert LE, Scherr PA, Bienias JL (2003) Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch Neurol,* 60:1119-1122.

Heine L, Soddu A, Gómez F (2012) Resting state networks and consciousness: alterations of multiple resting state network connectivity in physiological, pharmacological, and pathological consciousness states. *Front Psychol,* 3:295.

Hester RL, Murphy K, Foxe JJ, Foxe DM, Javitt DC and Garavan H (2004) Predicting success: patterns of cortical activation and deactivation prior to response inhibition. *J Cogn Neurosci*, 16:776-785.

Hillary FG, Slocomb J, Hills EC, Fitzpatrick NM, Medaglia JD, Wang J, Good DC, Wylie GR (2011) Changes in resting connectivity during recovery from severe traumatic brain injury. *Int J Psychophysiol,* 82:115–123.

Hogan A. M., Vargha-Khadem F., Saunders D. E., Kirkham F. J., Baldeweg T. (2006) Impact of frontal white matter lesions on performance monitoring: ERP evidence for cortical disconnection. *Brain,* 129: 2177-2188.

Holroyd CB, Nieuwenhuis S, Yeung N, Nystrom L, Mars RB, Coles MG, Cohen JD (2004) Dorsal anterior cingulate cortex shows fMRI response to internal and external error signals. *Nature Neuroscience,* 7:497–498.

Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, Hagmann P (2009) Predicting human resting-state functional connectivity from structural connectivity. *Proc Natl Acad Sci U S A,* 106:2035–2040.

Hua K, Zhang J, Wakana S, Jiang H, Li X, Reich DS, Calabresi PA, Pekar JJ, van Zijl, P. C., Mori S (2008) Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. *NeuroImage,* 39:336–347.

Hunter JV, Wilde EA, Tong KA and Holshouser BA (2012) Emerging imaging tools for use with traumatic brain injury research. *J Neurotrauma*, 29:654–671.

Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G and Kobusingye OC (2007) The impact of traumatic brain injuries: a global perspective. *NeuroRehabilitation*, 22:341–353.

Hyvarinen A (1999) Fast and robust fixed-point algorithms for independent component analysis. *Neural Networks*, 10:626–634.

Iannetti GD and Wise RG (2007) BOLD functional MRI in disease and pharmacological studies: room for improvement? *Magn Reson Imaging*, 25:978–988.

Ibañez A, Gleichgerrcht E, Manes F (2010) Clinical effects of insular damage in humans. *Brain Struct Funct,* 214:397-410.

Jenkinson M, Bannister P, Brady M, Smith S (2002) Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*, 17:825–841.

Jersild, AT (1927) Mental Set and Shift. *Archives Psychol*, p.89.

Jersild, AT (2011) Mental Set and Shift. Nabu Press.

Johnston JM, Vaishnavi SN, Smyth MD (2008) Loss of resting interhemispheric functional connectivity after complete section of the corpus callosum. *J Neuroscience,* 28:6453-6458.

Kahneman D (1973) Attention and effort. Prentice Hall.

Kasahara M, Menon DK, Salmond CH, Outtrim JG, Tavares JV, Carpenter TA, Pickard JD, Sahakian BJ, Stamatakis EA (2011) Traumatic brain injury alters the functional brain network mediating working memory. *Brain injury*, 25:1170–1187.

Kasahara M, Menon DK, Salmond CH, Outtrim JG, Taylor Tavares JV, Carpenter TA, Pickard JD, Sahakian BJ, Stamatakis EA (2010) Altered functional connectivity in the motor network after traumatic brain injury. *Neurology*, 75:168–176.

Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP (2008) Competition between functional brain networks mediates behavioral variability. *NeuroImage,* 39:527–537.

Kim C, Johnson NF, Cilles SE, Gold BT (2011) Common and distinct mechanisms of cognitive flexibility in prefrontal cortex. *J Neurosci,* 31:4771–4779.

Kim J, Whyte J, Patel S, Avants B, Europa E, Wang J, Slattery J, Gee JC, Coslett HB, Detre JA (2010) Resting cerebral blood flow alterations in chronic traumatic brain injury: an arterial spin labeling perfusion FMRI study. *Journal of Neurotrauma,* 27:1399–1411.

Kinnunen KM, Greenwood R, Powell JH, Leech R, Hawkins, P. C., Bonnelle V, Patel MC, Counsell SJ, Sharp DJ (2010) White matter damage and cognitive impairment after traumatic brain injury. *Brain* 134:449–463.

Koch MA, Norris DG, Hund-Georgiadis M (2002) An investigation of functional and anatomical connectivity using magnetic resonance imaging. *NeuroImage,* 16:241-250.

Kraus JF, Morgenstern H, Fife D, Conroy C and Nourjah P (1989) Blood alcohol tests, prevalence of involvement, and outcomes following brain injury. *Am J Public Health*, 79:294–299.

Kraus MF, Susmaras T, Caughlin BP, Walker CJ, Sweeney JA, Little DM (2007) White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain,* 130:2508–2519.

Langlois JA, Rutland-Brown W, Wald MM (2006) The epidemiology and impact of traumatic brain injury: a brief overview. *The Journal of head trauma rehabilitation,* 21:375–378.

Laureys S, Goldman S, Phillips C, Van Bogaert P, Aerts J, Luxen A, Franck G, Maquet P (1999) Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. *NeuroImage,* 9:377–382.

Lawes I, Barrick TR, Murugam V, Spierings N (2008) Atlas-based segmentation of white matter tracts of the human brain using diffusion tensor tractography and comparison with classical dissection. *NeuroImage,*39:62-79.

Lawrence NS, Ross TJ, Hoffmann R, Garavan H and Stein EA (2003) Multiple neuronal networks mediate sustained attention. *J Cogn Neurosci*, 15:1028–1038.

Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N and Chabriat H (2001) Diffusion tensor imaging: concepts and applications. *J Magn Reson Imaging*, 13:534–546.

Lee H, Wintermark M, Gean AD, Ghajar J, Manley GT and Mukherjee P (2008) Focal lesions in acute mild traumatic brain injury and neurocognitive outcome: CT versus 3T MRI. *J Neurotrauma*, 25:1049–1056.

Leech R, Braga R, Sharp DJ (2012a) Echoes of the brain within the posterior cingulate cortex. *J Neurosci,* 32:215–222.

Leech R, Kamourieh S, Beckmann CF, Sharp DJ (2011) Fractionating the default mode network: distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. *J Neurosci,* 31:3217–3224.

Leotti LA and Wager TD (2010) Motivational influences on response inhibition measures*. J Exp Psychol Hum Precept Perform*, 36:430–447.

Leunissen I, Coxon JP, Caeyenberghs K, Michiels K, Sunaert S, Swinnen SP (2014) Task switching in traumatic brain injury relates to cortico-subcortical integrity. *Human Brain Mapp,* 35:2459-2469.

Levin HS and Goldstein FC (1986) Organisation of verbal memory after severe closed-head injury. *J Clin Exp Neuropsychol*, 8:643–656.

Levin HS, Wilde E, Troyanskaya M, Petersen NJ, Scheibel R, Newsome M, Radaideh M, Wu T, Yallampalli R, Chu Z and Li X (2010) Diffusion tensor imaging of mild to moderate blast-related traumatic brain injury and its sequelae. *J Neurotrauma*, 27:683-694.

Lezak MD (2004) Neuropsychological assessment. Oxford University Press.

Li CS, Huang C, Constable RT, Sinha R (2006) Imaging response inhibition in a stop-signal task: neural correlates independent of signal monitoring and post-response processing. *J Neurosci,* 26:186–192.

Li CS, Yan P, Bergquist KL and Sinha R (2007) Greater activation of the "default" brain regions predicts stop signal errors. *Neuroimage*, 38:640–648.

Lijffijt M, Kenemans JL, Verbaten MN and van Engeland H (2005) A meta-analytic review of stopping performance in attention-deficit/hyperactivity disorder: deficient inhibitory motor control? *J Abnorm Psychol*, 114:216–222.

Lipton ML, Gulko E, Zimmerman ME, Friedman BW, Kim M, Gellella E, Gold T, Shifteh K, Ardekani BA and Branch CA (2009) Diffusion-tensor imaging implicates prefrontal axonal injury in executive function impairment following very mild traumatic brain injury. *Radiology*, 252:816-824.

Little DM, Kraus MF, Joseph J, Geary EK, Susmaras T, Zhou XJ, Pliskin N and Gorelick PB (2010) Thalamic integrity underlies executive dysfunction in traumatic brain injury. *Neurology*, 74:558-564.

Lo C, Shifteh K, Gold T, Bello JA and Lipton ML (2009) Diffusion tensor imaging abnormalities in patients with mild traumatic brain injury and neurocognitive impairment. *J Comput Assist Tomogr*, 33:293–297.

Logan GD (1994) On the ability to inhibit thought and action: A users' guide to the stop signal paradigm. Academic Press.

Logan GD, Cowan WB, Davis KA (1984) On the ability to inhibit simple and choice reaction time responses: a model and a method. *Journal of experimental psychology,* 10:276–291.

Logan GD, Russell JS and Tannock R (1997) Impulsivity and Inhibitory Control. *Psychological Science*, 8:60–64.

Luck SJ, Hillyard SA, Mouloua M and Hawkins HL (1996) Mechanisms of visual-spatial attention: resource allocation or uncertainty reduction? *J Exp Psychol Hum Percept Perform*, 22:725–737.

MacDonald AW 3rd, Cohen JD, Stenger VA, Carter CS (2000) Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science, 288:1835-1838.

MacDonald CL, Dikranian K, Bayly P, Holtzman D, Brody D (2007) Diffusion tensor imaging reliably detects experimental traumatic axonal injury and indicates approximate time of injury. *J Neurosci,* 27:11869–11876.

Mackworth (1948) The breakdown of vigilance durning prolonged visual search. *The Quarterly Journal of Experimental Psychology*, 1:6-21

Maegele M, Engel D, Bouillon B, Lefering R, Fach H, Raum M, Buchheister B, Schaefer U, Klug N and Neugebauer E (2007) Incidence and outcome of traumatic brain injury in an urban area in Western Europe over 10 years. *Eur Surg Res,* 39:372–379.

Malec JF, Brown AW, Leibson CL, Flaada JT, Mandrekar JN, Diehl NN, Perkins PK (2007) The mayo classification system for traumatic brain injury severity. *Journal of Neurotrauma,* 24:1417–1424.

Margulies DS, Vincent JL, Kelly C, Lohmann G, Uddin LQ, Biswal BB, Villringer A, Castellanos FX, Milham MP, Petrides M (2009) Precuneus shares intrinsic functional architecture in humans and monkeys. *Proc Natl Acad Sci U S A,* 106:20069–20074.

Marsh NV, Kersel DA, Havill JH and Sleigh JW (1998) Caregiver burden at 1 year following severe traumatic brain injury. *Brain Inj*, 12:1045–1059.

Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN (2007) Wandering minds: the default network and stimulus-independent thought. *Science,* 315:393–395.

Mayer AR, Mannell MV, Ling J, Gasparovic C, Yeo RA (2011) Functional connectivity in mild traumatic brain injury. *Hum Brain Mapp,* 32:1825–1835.

McAllister (1992) Neuropsychiatric sequelae of head injuries. *Psychiatr Clin North Am,* 15:395–413.

McAvinue L, O'Keeffe F, McMackin D, Robertson IH (2005) Impaired sustained attention and error awareness in traumatic brain injury: implications for insight. *Neuropsychological rehabilitation,* 15:569–587.

McDonald BC, Flashman LA and Saykin AJ (2002) Executive dysfunction following traumatic brain injury: neural substrates and treatment strategies. *NeuroRehabilitation*, 17:333–344.

McKiernan KA, Kaufman JN, Kucera-Thompson J and Binder JR (2003) A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *J Cogn Neurosci*, 15:394–408.

McKinlay WW, Brooks DN, Bond MR, Martinage DP and Marshall MM (1981) The short-term outcome of severe blunt head injury as reported by relatives of the injured persons. *J Neurol Neurosurg Psychiatry*, 44:527–533.

Menon DK, Schwab K, Wright DW and Maas AI (2010) Position statement: definition of traumatic brain injury. *Arch Phys Med Rehabil*, 91:1637–1640.

Menon V, Uddin LQ (2010) Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct,* 214:655–667.

Mesulam M, Mufson EJ (1982) Insula of the old world monkey. III: Efferent cortical output and comments on function. *Journal of Comparative Neurology*, 212:38-52.

Mesulam MM (1981) A cortical network for directed attention and unilateral neglect. *Ann Neurol*, 10:309–325.

Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience,* 24:167–202.

Millis SR, Rosenthal M, Novack TA, Sherer M, Nick TG, Kreutzer JS, High WM Jr and Ricker JH (2001) Long-term neuropsychological outcome after traumatic brain injury. *J Head Trauma Rehabil*, 16:343–355.

Miyake A, Friedman NP, Emerson MJ, Witzki AH (2000) The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cogn Psychol,* 41:49-100.

Moll J, Oliveira-Souza R, Moll FT, Bramati IE (2002) The cerebral correlates of set-shifting: an fMRI study of the trail making test. *Arq Neuropsiquiatr*, 60(4):900-5.

Monsell S (2003) Task switching. *Trends in Cognitive Sciences*, 7:134–140.

Mori S, Zhang J (2006) Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron,* 51:527–539.

Moseley ME, Cohen Y, Kucharczyk J, Mintorovitch J, Asgari HS, Wendland MF, Tsuruda J, Norman D (1990) Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. *Radiology,* 176:439–445.

Mouraux A, Diukova A, Lee MC, Wise RG and Iannetti GD (2011) A multisensory investigation of the functional significance of the "pain matrix." *Neuroimage*, 54:2237-2249.

Mufson EJ, Mesulam M (1982) Insula of the old world monkey. II: Afferent cortical input and comments on the claustrum. *Journal of Comparative Neurology,* 212:23-37.

Murray CJ and Lopez AD (1997) Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet*, 349:1436–1442.

Nachev P, Kennard, C and Husain M (2008) Functional role of the supplementary and pre-supplementary motor areas. *Nature*, 9:856–869.

Nakashima T, Nakayama N, Miwa K, Okumura A, Soeda A, Iwama T (2007) Focal brain glucose hypometabolism in patients with neuropsychologic deficits after diffuse axonal injury. *AJNR,* 28:236–242.

Nakayama N, Okumura A, Shinoda J, Yasokawa YT, Miwa K, Yoshimura SI and Iwama T (2006) Evidence for white matter disruption in traumatic brain injury without macroscopic lesions. *J Neurol Neurosurg Psychiatry,* 77:850–855.

Nanetti L, Cerliani L, Gazzola V, Renken R, Keysers C (2009) Group analyses of connectivity-based cortical parcellation using repeated k-means clustering. *NeuroImage,* 47:1666–1677.

NCCAC (2007) (National Collaborating Centre for Acute Care) Head Injury: triage, assessment, investigation and early management of head injury in infants, children and adults, http://www.nice.org.uk/CG56.

Niemann H, Ruff RM and Kramer JH (1996) An attempt towards differentiating attentional deficits in traumatic brain injury. *Neuropsychol Rev*, 6:11–46.

Nimchinsky EA, Gilissen E, Allman JA, Perl DP, Erwinǁ JM, Hof PR (1999) A neuronal morphologic type unique to humans and great apes. *Proc Natl Acad Sci U S A*, 96:5268-5273.

Niogi NN and Mukerjee P (2010) Diffusion Tensor imaging of Mild Traumatic brain injury. *J Head Trauma Rehabil*, 25:241-255.

Niogi SN, Mukherjee P, Ghajar J, Johnson C, Kolster RA, Sarkar R, Lee H, Meeker M, Zimmerman RD, Manley GT and McCandliss BD (2008) Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive

reaction time: a 3T diffusion tensor imaging study of mild traumatic brain injury. *AJNR Am J Neuroradiol*, 29:967–973.

Nolan KA, D'Angelo D and Hoptman MJ (2011) Self-report and laboratory measures of impulsivity in patients with schizophrenia or schizoaffective disorder and healthy controls. *Psychiatry Res*, 187:301–303.

Norton L, Hutchison RM, Young GB, Lee DH, Sharpe MD, Mirsattari SM (2012) Disruptions of functional connectivity in the default mode network of comatose patients. *Neurology,* 78:175–181.

Nucifora PG, Verma R, Lee SK and Melhem ER (2007) Diffusion-tensor MR imaging and tractography: exploring brain microstructure and connectivity. *Radiology*, 245:367–384.

O'Keeffe FM, Dockree PM, Moloney P, Carton S, Robertson IH (2007) Characterising error-awareness of attentional lapses and inhibitory control failures in patients with traumatic brain injury. *Exp Brain Res,* 180:59-67.

O'Keeffe FM, Dockree PM, Robertson IH (2004) Poor insight in traumatic brain injury mediated by impaired error processing? Evidence from electrodermal activity. B*rain Res*, 22:101–112.

O'Reilly JX, Woolrich MW, Behrens TE, Smith SM and Johansen-Berg H (2012) Tools of the trade: psychophysiological interactions and functional connectivity. *Soc Cogn Affect Neurosci,* 7:604–609.

O'Sullivan M, Jones DK, Summers PE, Morris RG, Williams SC, Markus HS (2001) Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology,* 57:632–638.

Ommaya AK and Gennarelli TA (1974) Cerebral concussion and traumatic unconsciousness. Correlation of experimental and clinical observations of blunt head injuries. *Brain*, 97:633–654.

Onmaya AK and Hirsch AE (1971) Tolerances for cerebral concussion from head impact and whiplash in primates. *J Biomechanics*, 4:13–21.

Padmala S and Pessoa L (2010) Interactions between cognition and motivation during response inhibition. *Neuropsychologia*, 48:558–565.

Pajevic S and Pierpaoli C (1999) Color schemes to represent the orientation of anisotropic tissues from diffusion tensor data: application to white matter fiber tract mapping in the human brain. *Magn Reson Med*, 42:526–540.

Papadakis NG, Murrills CD, Hall LD, Huang CL, Adrian Carpenter T (2000) Minimal gradient encoding for robust estimation of diffusion anisotropy. *Magn Reson Imaging*, 18:671–679.

Parasuraman R (2000) The Attentive Brain. MIT Press.

Park NW, Moscovitch M and Robertson IH (1999) Divided attention impairments after traumatic brain injury. *Neuropsychologia*, 37:1119–1133.

Parvizi J, van Hoesen GW, Buckwalter J, Damasio A (2006) Neural connections of the posteromedial cortex in the macaque. *Proc Natl Acad Sci U S A,*103:1563–1568.

Patel HC, Bouamra O, Woodford M, King AT, Yates DW, Lecky FE (2005) Trends in head injury outcome from 1989 to 2003 and the effect of neurosurgical care: an observational study. *Lancet,* 366:1538–1544.

Paterakis K, Karantanas AH, Komnos A and Volikas Z (2000) Outcome of patients with diffuse axonal injury: the significance and prognostic value of MRI in the acute phase. *J Trauma*, 49:1071–1075.

Paus T, Zatorre RJ, Hofle N, Caramanos Z, Gotman J, Petrides M and Evans AC (1997) Time-related changes in neural systems underlying attention and arousal during the performance of an auditory vigilance task. *J Cogn Neurosci*, 9:392–408.

Perlstein WM, Larson MJ, Dotson VM and Kelly KG (2006) Temporal dissociation of components of cognitive control dysfunction in severe TBI: ERPs and the cued-Stroop task. *Neuropsychologia*, 44:260–274.

Petrides M (2000) The role of the mid-dorsolateral prefrontal cortex in working memory. *Exp Brain Res*, 133:44-54.

Peyron R, García-Larrea L, Grégoire MC, Convers P, Richard A, Lavenne F, Barral FG, Mauguière F, Michel D and Laurent B (2000) Parietal and cingulate processes in central pain. A combined positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) study of an unusual case. *Pain*, 84:77–87.

Pfefferbaum A, Chanraud S, Pitel AL, Muller-Oehring E, Shankaranarayanan A, Alsop DC, Rohlfing T, Sullivan EV (2011) Cerebral blood flow in posterior cortical nodes of the default mode network decreases with task engagement but remains higher than in most brain regions. *Cereb Cortex,* 21:233–244.

Pinsk MA and Kasnter S (2007) Neuroscience: unconscious networking. *Nature*, 447:46-47.

Posner MI and Petersen SE (1989) The Attention System of the Human Brain. *Annu Rev Neuroscience*, 13:25-42.

Posner MI, Rothbart MK, Sheese BE and Tang Y (2007) The anterior cingulate gyrus and the mechanism of self-regulation. *Cogn Affect Behav Neurosci*, 7:391–395.

Povlishock JT (1993) Pathobiology of traumatically induced axonal injury in animals and man. *Ann Emerg Med*, 22:980–986.

Povlishock JT, Katz DI (2005) Update of neuropathology and neurological recovery after traumatic brain injury. *The Journal of head trauma rehabilitation,* 20:76–94.

Price CJ, Crinion J, Friston KJ (2006) Design and analysis of fMRI studies with neurologically impaired patients. *J Magn Reson Imaging,* 23:816–826.

Purcell (1946) Resonance absorption by nuclear magnetic moments in a solid. *Phys Rev*, 69:37.

Robertson, I.H. and Garavan, H. (2004) Vigilant attention. In Gazzaniga, M.S., (Eds), The Cognitive Neurosciences. Cambridge, MIT Press (3rd Ed.), pp. 631–640.

Raichle ME (2001) Cognitive neuroscience. Bold insights. *Nature*, 412:128-130.

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA and Shulman GL (2001) A default mode of brain function. *Proc Natl Acad Sci U S A,* 98:676-682.

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. *Proc Natl Acad Sci U S A,* 98:676–682.

Rasmussen IA, Xu J, Antonsen IK, Brunner J, Skandsen T, Axelson DE, Berntsen EM, Lydersen S, Haberg A (2008) Simple dual tasking recruits prefrontal cortices in chronic severe traumatic brain injury patients, but not in controls. *Journal of Neurotrauma*, 25:1057–1070.

Reitan RM, Wolfson D (2004) The Trail Making Test as an initial screening procedure for neuropsychological impairment in older children. *Archives of Clinical Neuropsychology,* 19:281–288.

Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S (2004) The role of the medial frontal cortex in cognitive control. *Science,* 306:443–447.

Robertson IH, Manly T, Andrade J, Baddeley BT, Yiend J (1997) "Oops!": performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia,* 35:747–758.

Roelofs A, van Turennout M and Coles MGH (2006) Anterior cingulate cortex activity can be independent of response conflict in Stroop-like tasks. *Proc Natl Acad Sci U S A*, 103:13884–13889.

Rogers BP, Morgan VL, Newton AT and Gore JC (2007) Assessing functional connectivity in the human brain by fMRI. *Magn Reson Imaging*, 25:1347–1357.

Rogers RD and Monsell S (1995) Costs of a predictable switch between simple cognitive tasks. *J Experimental Psych*, 124:207-231.

Rubia K, Russell T, Overmeyer S, Brammer MJ, Bullmore ET, Sharma T, Simmons A, Williams SC, Giampietro V, Andrew CM, Taylor E (2001) Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. *NeuroImage* 13:250–261.

Rubia K, Smith AB, Brammer MJ, Taylor E (2003) Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *NeuroImage,* 20:351–358.

Rucklidge JJ and Tannock R (2002) Neuropsychological profiles of adolescents with ADHD: effects of reading difficulties and gender. *J Child Psychol Psychiatry*, 43:988–1003.

Rueckert L, Grafman J (1998) Sustained attention deficits in patients with lesions of posterior cortex. *Neuropsychologia,* 36:653–660.

Ruge H, Brass M, Koch I, Rubin O, Meiran N and von Cramon DY (2005) Advance preparation and stimulus-induced interference in cued task switching: further insights from BOLD fMRI. *Neuropsychologia*, 43:340–355.

Rushworth MFS (2008) Intention, choice, and the medial frontal cortex. *Annals of the New York Academy of Sciences*, 1124:181–207.

Rutland-Brown W, Langlois JA, Thomas KE and Xi YL (2006) Incidence of traumatic brain injury in the United States, 2003. *J Head Trauma Rehabil*, 21:544–548.

Ruttan L, Martin K, Liu A, Colella B and Green RE (2008) Long-term cognitive outcome in moderate to severe traumatic brain injury: a meta-analysis examining

timed and untimed tests at 1 and 4.5 or more years after injury. *Arch Phys Med Rehabil*, 89(12 Suppl):S69-76.

Sakai K (2008) Task set and prefrontal cortex. *Ann Rev Neurosci*, 31:219–245.

Salmond CH, Menon DK, Chatfield DA, Williams GB, Pena A, Sahakian BJ, Pickard JD (2006) Diffusion tensor imaging in chronic head injury survivors: correlations with learning and memory indices. *NeuroImage,* 29:117–124.

Salthouse TA (2000) Aging and measures of processing speed. *Biol Psychol*, 54:35-54.

Salthouse TA, Fristoe N, McGuthry KE and Hambrick DZ (1998) Relation of task switching to speed, age, and fluid intelligence. *Psychol Aging*, 13(3):445-461.

Samann PG, Wehrle R, Hoehn D, Spoormaker VI, Peters H, Tully C, Holsboer F, Czisch M (2011) Development of the Brain's Default Mode Network from Wakefulness to Slow Wave Sleep. *Cereb Cortex,* 21:2082–2093.

Sanchez-Cubillo I, Perianez JA (2009) Construct validity of the Trail Making Test: role of task switching, working memory, inhibition/interference control, and visuomotor abilities. *J Int Neuropsychol Soc*, 15(3):438-50.

Sarter M, Givens B and Bruno JP (2001) The cognitive neuroscience of sustained attention: where top-down meets bottom-up. *Brain Research Reviews*, 35:146-160.

Schachar R, Mota VL, Logan GD, Tannock R, Klim P (2000) Confirmation of an inhibitory control deficit in attention-deficit/hyperactivity disorder. *J Abnorm Child Psychol,* 28:227–235.

Scheibel R. S., Newsome M. R., Troyanskaya M., Steinberg J. L., Goldstein F. C., Mao H., Levin H. S. (2009) Effects of severity of traumatic brain injury and brain reserve on cognitive-control related brain activation. *J Neurotrauma,* 26(9):1447-1461.

Scheid R., Preul C., Gruber O., Wiggins C., von Cramon D. Y. (2003) Diffuse axonal injury associated with chronic traumatic brain injury: evidence from T2*- weighted gradient-echo imaging at 3 T. *AJNR Am J Neuroradiol,* 24(6):1049-1056.

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007) Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci,* 27:2349–2356.

Shallice T, Stuss DT, Alexander MP, Picton TW, Derkzen D (2008) The multiple dimensions of sustained attention. *Cortex,* 44:794–805.

Shallice T, Stuss DT, Picton TW, Alexander MP, Gillingham S (2007) Multiple effects of prefrontal lesions on task switching. *Frontiers in human neuroscience,* 1:2.

Sharp DJ, Beckmann CF, Greenwood R, Kinnunen KM, Bonnelle V, De Boissezon X, Powell JH, Counsell SJ, Patel MC, Leech R (2011) Default mode network functional and structural connectivity after traumatic brain injury. *Brain,* 134:2233–2247.

Sharp DJ, Bonnelle V, De Boissezon X, Beckmann CF, James SG, Patel MC, Mehta MA (2010) Distinct frontal systems for response inhibition, attentional capture, and error processing. *Proc Natl Acad Sci U S A,* 107:6106–6111.

Sharp DJ, Bonnelle V, De Boissezon X, Beckmann CF, James SG, Patel MC, Mehta MA (n.d.) Distinct frontal systems for response inhibition, attentional capture, and error processing. *Proc Natl Acad Sci U S A,* 107:6106–6111.

Sharp DJ, Ham TE (2011) Investigating white matter injury after mild traumatic brain injury*. Current Opinion in Neurology*, 24:558–563.

Sharp DJ, Scott G, Leech R (2014) Network dysfunction after traumatic brain injury. *Nature Reviews Neurology*. 10:156-166.

Shmueli K, van Gelderen P, de Zwart JA, Horovitz SG, Fukunaga M, Jansma JM, Duyn JH (2007) Low-frequency fluctuations in the cardiac rate as a source of variance in the resting-state fMRI BOLD signal. *NeuroImage* 38:306–320.

Sidaros A, Engberg AW, Sidaros K, Liptrot MG, Herning M, Petersen P, Paulson OB, Jernigan TL, Rostrup E (2008) Diffusion tensor imaging during recovery from severe

traumatic brain injury and relation to clinical outcome: a longitudinal study. *Brain* 131:559–572.

Silver JM, McAllister TW and Yudofsky, SC (2005) Textbook of Traumatic Brain Injury. American Psychiatric Pub.

Simon JR (1969) Reactions toward the source of stimulation. *Journal of Experimental Psychology,* 81:174-176.

Simon JR, Small AM Jr (1969) Processing auditory information: interference from an irrelevant cue. *Journal of Applied Psychology,* 53:433-435.

Skandsen T., Kvistad K. A., Solheim O., Strand I. H., Folvik M., Vik A. (2010) Prevalence and impact of diffuse axonal injury in patients with moderate and severe head injury: a cohort study of early magnetic resonance imaging findings and 1-year outcome. *J Neurosurg,* 113(3):556-563.

Smith DH and Meaney DF (2000) Axonal damage in traumatic brain injury. *The Neuroscientist*, 6: 483-495.

Smith SM (2002) Fast robust automated brain extraction. *Hum Brain Mapp,* 17:143–155.

Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, Filippini N, Watkins KE, Toro R, Laird AR, Beckmann CF (2009) Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci U S A* 106:13040–13045.

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE (2006) Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *NeuroImage* 31:1487–1505.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM (2004) Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage, 23* Suppl 1:S208–S219.

Smith SM, Miller KL, Salimi-Khorshidi G, Webster M, Beckmann CF, Nichols TE, Ramsey JD, Woolrich MW (2011) Network modelling methods for FMRI. *NeuroImage* 54:875–891.

Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J and Cross AH (2002) Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage*, 17:1429-1436.

Sonuga-Barke EJ, Castellanos FX (2007) Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. *Neurosci*

Biobehav Rev, 31:977–986.

Sosin DM, Sniezek JE and Thurman DJ (1996) Incidence of mild and moderate brain injury in the United States, 1991. *Brain Inj*, 10:47–54.

Sporns O, Chialvo DR, Kaiser M and Hilgetag CC (2004) Organisation, development and function of complex brain networks*. Trends Cogn Sci*, 8:418-425.

Squarcina L, Bertoldo A, Ham TE, Heckemann R, Sharp DJ (2012) A robust method for investigating thalamic white matter tracts after traumatic brain injury. *NeuroImage* 63:779–788.

Sridharan D, Levitin DJ, Menon V (2008) A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc Natl Acad Sci U S A*, 105:12569–12574.

Stephan KE, Harrison LM, Kiebel SJ, David O, Penny WD and Friston KJ (2007) Dynamic causal models of neural system dynamics: current state and future extensions. J Biosci, 32:129-144.

Stevens M, Lovejoy D, Kim J, Oakes H, Kureshi I, Witt S (2012a) Multiple resting state network functional connectivity abnormalities in mild traumatic brain injury. *Brain Imaging and Behavior,* 6:293–318.

Stevens MC, Lovejoy D, Kim J, Oakes H, Kureshi I, Witt ST (2012b) Multiple resting state network functional connectivity abnormalities in mild traumatic brain injury. *Brain Imaging and Behavior,* 6:293–318.

Strangman G, O'Neil-Pirozzi TM, Burke D, Cristina D, Goldstein R, Rauch SL, Savage CR, Glenn MB (2005) Functional neuroimaging and cognitive rehabilitation for people with traumatic brain injury. *American journal of physical medicine and rehabilitation / Association of Academic Physiatrists,* 84:62–75.

Strangman GE, Goldstein R, O'Neil-Pirozzi TM, Kelkar K, Supelana C, Burke D, Katz DI, Rauch SL, Savage CR and Glenn MB (2009) Neurophysiological alterations during strategy-based verbal learning in traumatic brain injury. *Neurorehabil Neural Repair,* 23:226–236.

Strich, S (1956) Diffuse degeneration of the cerebral white matter in severe dementia following head injury. *J Neurol Neurosurg Psychiatry*, 19(3):163–185.

Stroop JR (1935) Studies of interference in serial verbal reactions. *Journal of experimental psychology,* 18:643-662.

Stuss DT (2011) Traumatic brain injury: relation to executive dysfunction and the frontal lobes. *Curr Opin Neurol*, 24:584–589.

Stuss DT, Alexander MP (2007) Is there a dysexecutive syndrome? *Philos Trans R Soc Lond B Biol Sci*, 362:901–915.

Stuss DT, Stethem LL, Hugenholtz H, Picton T, Pivik J, Richard MT (1989) Reaction time after head injury: fatigue, divided and focused attention, and consistency of performance. *Journal of Neurology, Neurosurgery, and Psychiatry,* 52:742–748.

Sudevan P and Taylor DA (1987) The cuing and priming of cognitive operations. *J Exp Psychol Hum Percept Perform,* 13:89–103.

Sugiyama K Kondo T, Oouchida Y, Suzukamo Y, Higano S, Endo M, Watanabe H, Shindo K and Izumi S (2009) Clinical utility of diffusion tensor imaging for evaluating patients with diffuse axonal injury and cognitive disorders in the chronic stage. *J Neurotrauma*, 26:1879–1890.

Tagliaferri F, Compagnone C, Korsic M, Servadei F and Kraus J (2006) A systematic review of brain injury epidemiology in Europe. *Acta Neurochir (Wien)*, 148:255–68–discussion268.

Thornhill S, Teasdale GM, Murray GD, McEwen J, Roy CW, Penny KI (2000) Disability in young people and adults one year after head injury: prospective cohort study. *BMJ,* 320:1631–1635.

Thurmann DJ, Branche CM and Sniezek JE (1998) The epidemiology of sports-related traumatic brain injuries in the United States: recent developments. *J Head Trauma Rehabil*, 13:1–8.

Tisserand DJ, Stanisz G, Lobaugh N, Gibson E, Li T, Black SE and Levine B (2006) Diffusion tensor imaging for the evaluation of white matter pathology in traumatic brain injury. *Brain Cogn*, 60:216–217.

Tombaugh TN (2004) Trail Making Test A and B: normative data stratified by age and education. *Archives of Clinical Neuropsychology*, 19:203-214.

Tong KA, Ashwal S, Holshouser BA, Nickerson JP, Wall CJ, Shutter LA, Osterdock RJ, Haacke EM, Kido D (2004) Diffuse axonal injury in children: clinical correlation with hemorrhagic lesions. *Ann Neurol,* 56:36–50.

Uddin LQ, Kelly AM, Biswal BB, Xavier Castellanos F, Milham MP (2009) Functional connectivity of default mode network components: correlation, anticorrelation, and causality. *Hum Brain Mapp,* 30:625–637.

Ullsperger M, Cramon von DY (2001) Subprocesses of performance monitoring: A dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *NeuroImage,* 14:1387–1401.

Vakil E (2005) The effect of moderate to severe traumatic brain injury (TBI) on different aspects of memory: a selective review. *J Clin Exp Neuropsychol*, 27:977–1021.

van den Heuvel MP, Mandl RC, Kahn RS, Hulshoff Pol HE (2009) Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Hum Brain Mapp,* 30:3127–3141.

Vanhaudenhuyse A, Noirhomme Q, Tshibanda LJF, Bruno M-A, Boveroux P, Schnakers C, Soddu A, Perlbarg V, Ledoux D, Brichant J-F, Moonen G, Maquet P, Greicius MD, Laureys S, Boly M (2010) Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. *Brain,* 133:161–171.

Vincent JL, Patel GH, Fox MD, Snyder AZ, Baker JT, Van Essen DC, Zempel JM, Snyder LH, Corbetta M, Raichle ME (2007) Intrinsic functional architecture in the anaesthetized monkey brain. *Nature,* 447:83–86.

Vincent JL, Snyder AZ, Fox MD, Shannon BJ, Andrews JR, Raichle ME, Buckner RL (2006) Coherent spontaneous activity identifies a hippocampal-parietal memory network. *J Neurophysiol,* 96:3517–3531.

Vogt B (2009a) Cingulate Neurobiology and Disease. Oxford University Press.

Vogt BA (1993) Structural organisation of the cingulate cortex: Areas, neurons, and somatodendritic transmitter receptors. In: Neurobiology of Cingulate Cortex and Limbic Thalamus (Vogt BA, Gaybriel M, eds), pp 19–70. Boston: Birkhauser.

Vogt BA (2009b) Cingulate Neurobiology and Disease. Oxford: Oxford University Press.

Vogt BA, Laureys S (2005) Posterior cingulate, precuneal and retrosplenial cortices: cytology and components of the neural network correlates of consciousness. *Progress in brain research,* 150:205–217.

Wechsler D (1997) Wechsler Memory Scale- Third Edition: Administration and Scoring Manual. San Antonio: TX: Psychological Corporation.

Wechsler D (1999) Wechsler Abbreviated Scale of Intelligence.

Wedeen VJ, Wang RP, Schmahmann JD, Benner T, Tseng WY, Dai G, Pandya DN, Hagmann P, D'Arceuil H, de Crespigny AJ (2008) Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. *NeuroImage,* 41:1267–1277.

Weissman DH, Roberts KC, Visscher KM, Woldorff MG (2006) The neural bases of momentary lapses in attention. *Nature Neuroscience,* 9:971–978.

Wen X, Rangarajan G, Ding M (2013) Is Granger causality a viable technique for analyzing fMRI data? *PLoS One,* 8(7):e67428.

Whitnall L, McMillan TM, Murray GD, Teasdale GM (2006) Disability in young people and adults after head injury: 5-7 year follow up of a prospective cohort study. *Journal of Neurology, Neurosurgery, and Psychiatry*, 77:640–645.

Whyte J, Polansky M, Fleming M, Coslett HB and Cavallucci C (1995) Sustained arousal and attention after traumatic brain injury. *Neuropsychologia*, 33(7):797-813.

Wilberger JE Jr, Rothfus WE, Tabas J, Goldberg AL and Deeb ZL (1990) Acute tissue tear hemorrhages of the brain: computed tomography and clinicopathological correlations. *Neurosurgery*, 27:208–213.

Wilde EA, McCauley SR, Hunter JV, Bigler ED, Chu Z, Wang ZJ, Hanten GR, Troyanskaya M, Yallampalli R, Li X, Chia J, Levin HS (2008) Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. *Neurology,* 70:948–955.

Wilde EA, Ramos MA, Yallampalli R, Bigler ED, McCauley SR, Chu Z, Wu TC, Hanten G, Scheibel RS, Li X, Vásquez AC, Hunter JV and Levin HS (2010) Diffusion tensor imaging of the cingulum bundle in children after traumatic brain injury. *Dev Neuropsychol*, 35:333–351.

Wilkins AJ, Shallice T and McCarthy R (1987) Frontal lesions and sustained attention. *Neuropsychologia*, 25(2):359-365.

Xiong J, Parsons LM, Gao JH and Fox PT (1999) Interregional connectivity to primary motor cortex revealed using MRI resting state images. *Hum Brain Mapp*, 8:151–156.

Yaghmai A and Povlishock J (1992) Traumatically induced reactive change as visualized through the use of monoclonal antibodies targeted to neurofilament subunits. *J Neuropathol Exp Neurol*, 51:158–176.

Yantis S (2008) The Neural Basis of Selective Attention: Cortical Sources and Targets of Attentional Modulation. *Current Directions in Psychological Science,* 17:86–90.

Yeung N, Nystrom LE, Aronson JA and Cohen JD (2006) Between-task competition and cognitive control in task switching. *J Neurosci*, 26:1429–1438.

Zappalà G, Thiebaut de Schotten M and Eslinger PJ (2012) Traumatic brain injury and the frontal lobes: what can we gain with diffusion tensor imaging? *Cortex*, 48:156–165.

Zhang S and Li CS (2010) A neural measure of behavioral engagement: task-residual low-frequency blood oxygenation level-dependent activity in the precuneus. *Neuroimage*, 49:1911–1918.

Zuo XN, Kelly C, Adelstein JS, Klein DF, Castellanos FX, Milham MP (2009) Reliable Intrinsic Connectivity Networks: Test-Retest Evaluation Using ICA and Dual Regression Approach. *NeuroImage*, 49:2163-2177.