ANOSOGNOSIA FOR MEMORY LOSS

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To my family,

My parents, amazing sister, and the love of my life Olaf,

thank you for that everlasting and never wavering support.

“In examining disease, we gain wisdom about anatomy and physiology and biology. In examining the person with disease, we gain wisdom about life.”

— *Oliver Sacks (1985), The Man Who Mistook His Wife for a Hat*

DECLARATION

This dissertation is the result of my own work and includes nothing, which is the outcome of work done in collaboration except where specifically indicated in the text. It has not been previously submitted, in part or whole, to any university or institution for any degree, diploma, or other qualification.

Parts of the research included in this thesis form part of manuscripts that have been published or are in preparation during my enrollment in this PhD program, including the following:

- Chapman, S., Beschin, N., Cosentino, S., Elkind, M. S. V., Della Sala, S., & Cocchini, G. (in press). The Visual Analogue Test for Anosognosia for Memory Impairment (VATAmem). *Neuropsychology.*

- Chapman, S., Cosentino, S., Abdurahman, A., Igwe, K., Brickman, A., Elkind, M. S. V. & Cocchini, G. (in prep). Reality monitoring and filtering in anosognosia for memory loss.

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Related articles conducted during the PhD not included in this thesis include:

DeFeis, B., Chapman, S., Zhu, C, Azar, M., Sunderaraman, P., Ornstein, K., Gu, Y., & Cosentino, S. (*in press*). Reduced awareness of deficit is associated with increased Medicare home health care use in dementia. *Journal of Alzheimer's Disease and Associated Disorders.*

In accordance with the University of London guidelines, this thesis does not exceed 100,000 words.

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Date MAY 20th 2019

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ABSTRACT

Anosognosia for memory loss is a common feature of degenerative disorders and acquired brain injuries that manifests as the lack of awareness of memory difficulties following injury to the brain. Patients who are unaware of their memory loss, might engage in riskier behaviours, have increased difficulties managing their medication and making appropriate medical decisions. Although many studies have investigated this disorder of awareness, the underlying mechanisms of anosognosia for memory loss remain unclear. Though methodological biases in measurement have been proposed for the variable findings across studies, it has become increasingly accepted that anosognosia is a multifaceted phenomenon.

The main aims of this thesis are (i) to provide a new measure for anosognosia for memory loss: a measure that attempts to improve on existing biases in current assessments; and (ii) to provide a comprehensive examination of anosognosia from a multifaceted framework. Specifically, this thesis provides an examination of psychological (personality and mood), cognitive and metacognitive (monitoring factors) and neuroanatomical factors (lesion mapping). Results from this thesis support (i) the new measure of anosognosia presented in this thesis as a valid and reliable tool that overcomes some of the common pitfalls of existing measures and that there are (ii) underlying multifactorial factors for anosognosia for memory loss. Indeed, psychological factors such as personality traits (decreased neuroticism trait); memory monitoring abilities (memory performance and source monitoring); and neuroanatomical factors (cerebellar lesions) were found to be associated with unawareness of memory loss. Findings are discussed with regard to their relevance on current theoretical models of anosognosia for memory loss.

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Chapter 1

General Introduction & Background Information

1.1. Overview of thesis

Awareness also referred to as insight, self-consciousness or self-knowledge, refers to one broad, elusive and complex construct explored in many disciplines including philosophy, sociology, psychology, neuroscience and neuropsychology. Awareness is a key construct, one that is intrinsic to our own understanding of ourselves and the world that surrounds us. In this thesis, the concept of awareness is presented from a neuropsychological perspective, from the standpoint of deficits following brain injury, and their impact on awareness (Mograbi & Morris, 2018). Awareness will be used throughout the text as the ability to reflect upon one's own physical and/or sensory or cognitive abilities or as Clare, Markova, Roth, and Morris (2011) define it, "the reasonable or realistic perception or appraisal of a given aspect of one's situation, functioning or performance, or of the resulting implications, which may be expressed explicitly or implicitly", (p. 936).

The focus of this thesis is on the degradation of such awareness. Specifically, on the lack of awareness in the context of memory deficits following brain damage, also known as anosognosia for memory loss (Agnew & Morris, 1998; Mograbi & Morris, 2018; Schacter, 1991). Structurally, this thesis includes 7 chapters. An introductory and a methods chapters (Chapter 1 and 2) introduce the background and design of the main research questions included in this thesis (described in Chapter 3 – 6). Chapter 3 aims to describe the development of a new tool to measure anosognosia for memory loss in an attempt to overcome some of the most common pitfalls in commonly used tasks used to assess anosognosia. Chapters 4 to 6 aim at using different tasks and measures to

understand what factors can affect the expression of anosognosia for memory loss. Within these chapters, three main factors are explored: (i) psychological factors (Chapter 4); (ii) self-monitoring factors (Chapter 5); and (iii) neuroanatomical factors (Chapter 6) (see also Chapter 2 for a summary of main research questions included in this thesis). Finally, a conclusion chapter (Chapter 7), includes a general discussion of main findings, their implications, limitations and future research.

The aim of this introductory chapter is to provide the reader with the context of the study of anosognosia for memory loss. In order to do so, a broad review of memory, memory loss and etiologies that lead to its deterioration is provided. This broad review will be followed by the definition of anosognosia and a summary of the current theoretical landscape for anosognosia of memory loss.

1.2. Definition & contextualization of memory

One of the fundamental domains of cognition is that of memory. Memory can be defined as the ability to encode, store and retrieve information, or the maintenance of learning that can be revealed at a later time (Squire, 1987). Learning different types of information and being able to both consciously and unconsciously retrieve it, is at the core of many of our everyday abilities that define who we are, and what we do (Conway, 2005). The beginnings of memory research are attributed to Ebbinghaus (1913, 1985) whose work established the founding seeds of careful experimental methodology in the study of memory. Ebbinghaus' experiments showed a linear relationship between time elapsed from learning, and the amount of information recalled. He realized that the longer the time lapse since he first learned a list of nonsense syllables, the less he was able to

remember. This forgetting though, could be undone through rehearsing or relearning the information. James (1980), echoed these seemingly different properties of memory processes and differentiated between *primary memory* (concerning the present), and *secondary memory* (concerning past learned information) (Cowan, 2008).

The beginnings of what is considered modern memory research, and more generally the beginning of modern neuropsychology, was defined by one individual case study, widely known as H. M. (Henry Molaison). H. M. was a 27 year old man who had a bilateral medial temporal lobectomy to treat uncontrollable seizures. Following this procedure, he developed a specific deficit in his ability to form new memories (Scoville & Milner, 1957; Squire, 2009). H.M.'s lesion and deficits suggested the involvement of the Medial Temporal Lobe (MTL) in the formation of new memories (Broadbent, Clark, Zola, & Squire, 2002). This groundbreaking discovery led to a large increase of studies, most of which included clinical cases of memory loss (i.e., amnesia) and animal models of memory functioning. Through the study of both brain injured individuals and animals, we now know that structures such as the hippocampus, entorhinal cortex, perirhinal cortex, parahipocampal cortex and cortical areas (spanning frontal, temporal and parietal) are critical for the formation of new memories and related processes (Kopelman & Stanhope, 2002; Mishkin, 1978; Mishkin, Spiegler, Saunders, & Malamut, 1982; Nadel & Moscovitch, 1997; Salmon, Zola-Morgan, & Squire, 1987; Zola-Morgan & Squire, 1990). Further, these studies also helped formulate the way that we define and conceptualize different memory processes.

1.2.1. Terms of memory

Over 250 terms have been used to refer to different types of memory, many of

which overlap and can refer to similar underlying processes (Tulving, 1982, 2007). In the following sections some of the most commonly used terms that are relevant to this thesis will be summarized.

1.2.1.1. Explicit/Declarative vs. Implicit/Non-declarative

The terms explicit (declarative) memory versus implicit memory (non-declarative) are commonly used to distinguish memories that can be consciously retrieved, as opposed to those that remain unconscious and/or automatic (Cohen & Squire, 1980; Squire, 1992, 2009). Explicit memories are formed of previously learned information that can be subjectively recalled at a later time. Implicit memories on the other hand, are formed of previously learned information that can operate without conscious experience or recall (Squire, 2009). Within this broad characterization, different types of memory processes can be identified. For example, implicit memories have been proposed to vary in their typology to encompass different types of learning that require no subjective recall: classic conditioning (e.g., learning an association between two stimuli, such as association of the ice cream truck jingle with a cone of refreshing ice cream); skill learning (e.g., learning patterns of behaviour through repetitive practice such as driving); priming (e.g., unconscious influence of a stimulus on the response of another stimulus, such as responding to the word elephant is easier after seeing the word giraffe than after seeing the word hospital); etc. (Mondragón, Alonso, & Kokkola, 2017; Ploog, 2012; Schendan, 2017). Similarly, within explicit memory different typologies have been defined. Following Tulving (1972, 1993, 2002), underlying properties of explicit memories are suggestive of two main memory systems: *semantic memory* and *episodic memory*. These terms were originally coined to refer to

those memories pertaining to facts and events respectively (Tulving, 1972).

Semantic memory is conceptualized as a 'storage' where information about ourselves and the world is held (Tulving, 1972, 1982; Warrington, 2017). It thus includes knowledge of words, names and categories (Shayna Rosenbaum, Kim, & Baker, 2017). The way semantic memory operates remains a matter of debate, and different conceptualizations have been proposed (Balota & Coane, 2008). For instance, some researchers have proposed that concepts stored in semantic memory are represented by a combination of relevant features. These features are hypothesized to combine with others at retrieval to give rise to a determined concept such as the concept of a plane (e.g., motorized, wings, flies, and transports people). These features can also be part of different concepts (e.g., wings can be part of the concept airplane and the concept bird), allowing a fluid and efficient storage of information (McRae, De Sa, & Seidenberg, 1997; Smith, Shoben, & Rips, 1974). Other researchers have argued that all individual concepts are stored in semantic memory (i.e., bird, airplane) as individual entities embedded within complex networks (Loftus & Collins, 1975; Quillian, 1968). The location of each concept in relation to others is determined by learned associations (e.g., dog, cat…), leading to small world structures. These in turn connect with other small world structures creating larger sets of networks (Balota & Coane, 2008). Although the operationalization of semantic memory remains a matter of debate, there is a general agreement over its underlying neural structures. Indeed, studies with patients with deficits in semantic memory due to a degenerative disease, namely Semantic Dementia, have shown that regions such as the anterior temporal lobe, the perirhinal cortex (PRC) and Brodmann areas 35 and 36 appear to be key in supporting semantic memory (Davies, Graham,

Xuereb, Williams, & Hodges, 2004; Davies, Halliday, Xuereb, Kril, & Hodges, 2009; Suzuki & Amaral, 2003).

Episodic memory was initially hypothesized as the ability to remember and re-experience information pertaining to one's own past (Tulving, 1982). Rooted in this early formulation, the conceptualization of episodic memory has developed over the years to encompass distinct properties that make this memory system unique to humans (Tulving, 2002). For example, episodic memory allows individuals to remember aspects of the past by consciously travelling to the time at which the event was experienced. Therefore, episodic memory does not only hold information about the world (such as semantic memory), but establishes a conscious connection with both the self, who experienced the event, and subjective time, when it happened (Moscovitch, 1995b; Tulving, 1972, 1993, 2002, 2005). This 'conscious experience' is referred to as *autonoetic consciousness*, one that allows awareness of when and how the memory was acquired in relation to one's self (Metcalfe & Son, 2012). Further, recent examinations of episodic memory, including neuroimaging and clinical population studies, appear to support its role in future thinking and imagination of future events, also referred to as *episodic simulation* (Schacter et al., 2012). Indeed, many studies have observed common underlying neural regions for both remembering past events and imagining the future. These shared structures include the medial temporal, parietal and frontal cortices, the angular gyrus, the posterior cingulate and the retrosplenial cortex (see Andrews-Hanna, 2012; Buckner, Andrews-Hanna, & Schacter, 2008; Schacter et al., 2012; Thakral, Madore, & Schacter, 2017). Studies with clinical populations (e.g., patients with memory loss due to Alzheimer's Disease (AD), Mild Cognitive Impairment (MCI), amnesic syndrome, depression, or schizophrenia),

have also shown decreases of the richness of episodic detail in both remembering and imagining future information supporting the idea that these processes might indeed rely on similar neural networks (Addis, Sacchetti, Ally, Budson, & Schacter, 2009; Andelman, Hoofien, Goldberg, Aizenstein, & Neufeld, 2010; D'Argembeau, Raffard, & Van der Linden, 2008; Gamboz, Brandimonte, & De Vito, 2010; Hassabis, Kumaran, Vann, & Maguire, 2007; Williams et al., 1996).

1.2.1.2. Prospective vs. Retrospective memory

The distinction between prospective and retrospective memory draws upon the qualitative differences in the temporal use of memory in everyday life. For example, the previous paragraph has highlighted the difference between those memories considered implicit (e.g., classical conditioning, priming, skill learning) versus explicit (e.g., semantic and episodic memory), both of which pertain to past learned information. Memories that are reflective of a past event, irrespective of their explicit or implicit nature, can also be referred to as retrospective memories (Roediger Iii, Zaromb, & Goode, 2008). Though past experience is embedded in the definition of memory, certain types of memories, namely prospective memories, are anchored in the future experience (Einstein & McDaniel, 1996; Harris, 1984; McDaniel & Einstein, 2007). Prospective memory is the process by which one remembers to perform self-initiated actions in the future (Ellis & Nimmo-smith, 1993). Such intentions to act can be seen in most of our everyday activities. For example, trying to remember to call someone that was out, trying to remember to take a pill every day, trying to remember your appointment next week, etc. This use of memory, though rooted in retrospective memory (i.e., a past intention), has its own distinct nature defined by the future intent and the time constraint for that

memory to affect our actions (e.g., you need to remember that you have an appointment before it's due) (Balota & Coane, 2008).

Though historically, the majority of research has focused on retrospective memory, there has been an increased interest in prospective memory processes over the past few decades (Einstein, McDaniel, Marsh, & West, 2008). Further, some of these more recent studies have supported, through factor analytic approaches, the distinction between awareness of prospective and retrospective memories (Crawford, Smith, Maylor, Della Sala, & Logie, 2003; Maylor, Smith, Della Sala, & Logie, 2002). Intuitively, being able to remember to take future actions is crucial for a successful and independent life, and awareness of these deficits thus should also be examined conjointly with awareness of retrospective memories (Smith, Della Sala, Logie, & Maylor, 2000).

Different types of prospective memory have been defined based on the type of cue that is used to elicit the action that was intended and can include (i) event based and (ii) time based prospective memory (McDaniel & Einstein, 2007; Shum, Valentine, & Cutmore, 1999). Event cued prospective memory involves remembering to do something in a given context, (e.g., remembering that is triggered by an external cue). Time cued prospective memory involves remembering to perform an intended action at a specific time. Although this is a commonly used distinction, some authors have argued that the observed differences between these subtypes of memory (event versus time cued prospective memories) across clinical populations might be due to methodological pitfalls in the way these prospective memories are measured. For example, while event cued prospective memories are usually assessed in terms of success/failure, time cued prospective memory is usually assessed in terms of response time (see Cuttler & Graf,

2009). Further research is needed to understand whether these subtypes of prospective memories relying on shared and or unique mechanisms. With regard to the underlying mechanisms hypothesized to support overall prospective memory, these have been hypothesized to be very similar to those of episodic simulation, described above (Brewer & Marsh, 2010). Indeed, several studies have found an association between performance in tasks assessing event cued prospective memory and imagining of future events (Altgassen et al., 2015; Neroni, Gamboz, & Brandimonte, 2014). These studies have also found support for shared neural regions such as the Medial Temporal Lobe (MTL) and the frontal lobe known to be involved in memory and executive functions (monitoring and control), processes proposed to be also key for episodic simulation (Kopp & Thöne-Otto, 2003; Spreng, Madore, & Schacter, 2018).

1.2.1.3. Long term, short term, and working memory

As noted earlier, one of the earliest forms of categorizing memories has been between how much information the mind can hold within a present moment versus what is held after a longer delay (Cowan, 2008). Therefore, a way of distinguishing memories has been defined by the temporal access of the information that each memory system or process can hold. Though terms might vary, two main memory subtypes can be defined: *short-term memory and long-term memory.* In its original conceptualization, short term memory was defined as having a lifespan of seconds and long term memory from minutes to days and years (Gazzaniga, Ivry, & Mangun, 1998). The differentiation between short and long term memory, though originally questioned by some (e.g., Melton, 1963), has received support from several studies with amnesic patients (Squire, 2009). These studies have shown that patients with damage specific to the Medial Temporal Lobe (MTL) are

impaired in long, but not short-term memory (Baddeley & Warrington, 1970; Squire, 2009). Similarly, the reverse has been observed where patients show specific impairments of short but not long term memory processes (Shallice, 1988). Although this model has been widely accepted, recently different authors have argued against the dichotomization or dissociation of these types of memories and suggested a reliance of STM functioning on LTM (see Jonides et al., 2008 for review). Indeed some case studies of patients with hippocampal amnesia have shown impairments in both STM and LTM, suggesting that these memories rely on similar networks and thus are dependent on each other (Jonides et al., 2008). These seemingly contradicting results are hard to reconcile and thus increased examination of both STM and LTM is necessary to elucidate the relation that these might hold.

Other classifications of LTM and STM have expanded to include rehearsal of recently learned information as part of their conceptualization of memory (e.g., Atkinson & Shiffrin, 1968). The ability to rehearse and manipulate information in the short term is now widely known as *Working Memory* (WM) (Baddeley & Hitch, 1974; Miller, Galanter, & Pribram, 1960). One of the most influential models of WM proposes a dichotomous underlying structure. This structure is defined by two main processes, one of storage and one in charge of controlling and manipulating information. The storage processes are proposed to be supported by specific short term buffers across various domains (e.g., *visuospatial sketchpad, episodic buffer and phonological loop*). These hold the information of each domain in the short term. This information is then used by a *central executive*, responsible for controlling and manipulating the information stored (Baddeley, 2001). These short term memory buffers have been hypothesized to rely on

the Prefrontal Cortex (PFC), as disruption to this region impairs performance across various WM tasks (e.g., Funahashi, Bruce, & Goldman-Rakic, 1993; Ptito, Crane, Leonard, Amsel, & Caramanos, 1995) (see Postle, 2015 for review). Although Baddeley & Hitch's original proposal in 1974 has received extensive support, other theories have suggested various mechanisms for WM. For example, Cowan's embedded process theory (Cowan, 1999) suggests that the information, which WM manipulates, is hierarchically derived from (i) LTM, (ii) the 'subset of LTM that is activated, and (iii) the attentional processes that operate these 'activated' memories. These attentional processes are deemed crucial for the manipulation of information in WM and determines how much information individuals can hold in WM (Cowan, 1999). Other theories such as that proposed by Engle and colleagues (Engle et al., 1999; Engle & Kane, 2004) suggest that other cognitive processes, such as inhibition are needed to allow the manipulation of specific information without the contamination of irrelevant information in LTM. More recently, alternative conceptualizations have proposed WM as an 'emergent process', a process that does not rely on domain specific buffers of the PFC (e.g., Postle, 2006). This proposal suggests that WM represents a combination of different processes specific to the information manipulated (Postle, 2006). For example, if WM is manipulating visual information, perceptual processing will be recruited, in addition to previously learned associations regarding the visual information processed (e.g., what the information means, where it was learned etc.) (Postle, 2006). To this date, there is no clear agreement on which theory best defines WM. As the different aspects of these various theories have received empirical support, it is important that future research attempts to reconcile these findings and attempts to build a cohesive conceptualization of WM.

1.2.2. Memory loss

Following the previous sections, different types of memories can be described, and selective degradation of these can also be observed across healthy ageing adults and clinical populations (see Squire, 2009). Within older adults, the ageing process has been found to be associated with a progressive decline across several cognitive functions (Wilson, Gallagher, Eichenbaum, & Tanila, 2006). This deterioration can include an increased difficulty in the ability to retain new long term episodic memories and learn new complex associations (Gallagher & Rapp, 1997; Hedden & Gabrieli, 2004). Within clinical populations, different profiles of memory deficits can be observed. For example, patients who suffer from Alzheimer's disease (AD) (described below) typically exhibit episodic memory deficits during earlier stages of the disease, as AD pathology tends to target regions in the MTL such as the hippocampus and the entorhinal cortex (Dore et al., 2013; Mormino et al., 2009). Due to the progressive nature of the disease, these deficits will continue to progress. Further, as AD pathology and neuronal death spreads across larger regions of the brain, other cognitive deficits will manifest (e.g., impairments in executive functions, language, attention and visuospatial abilities) (see Weintraub, Wicklund, & Salmon, 2012 for review). Following a non-degenerative brain injury, patients can also develop an array of specific memory deficits which may or may not be accompanied by other deficits (depending on the regions affected by the injury) (Wilson, 2013). As described in the previous sections, different types of memories have been hypothesized to rely on different regions thus different types of brain injuries can affect memory differently. For example, if a brain injury affects the anterior temporal pole of the MTL patients may exhibit deficits in semantic memory (see section 1.2.1.1. above).

If structures of the MTL such as the hippocampus, entorhinal cortex and angular gyrus are affected, patients may exhibit episodic memory deficits which can also span to prospective memory deficits (see section 1.2.1.1. and 1.2.1.2. above). If these regions are selectively affected, specific deficits in forming new memories are commonly described as an *amnesic syndrome* (e.g., patient H.M.) (Fradera & Kopelman, 2009). Patients suffering amnesic syndrome typically have their intellectual abilities and other cognitive abilities spared, but have a specific and isolated deficit in forming new memories (De Renzi, 2000). Pure amnesic syndromes occur with rarity, and more commonly patients will present with other concomitant cognitive difficulties such as language, executive function or attentional difficulties (Wilson, 2013).

Besides other concomitant cognitive deficits, memory loss can also manifest with associated symptoms or phenomena. One such phenomena is known as *confabulation* (Bonhoeffer, 1904). This term has received many different conceptualizations, but following its conventional definition, confabulation is defined as false memory remarks made by amnesic patients who are not intending to deceive, and have full conviction of the veracity of their claims (Dalla Barba, 1993; Moscovitch, 1995a). Recent research has supported a delineation between confabulations that are *provoked* by an examiner or interviewer, from those that are *spontaneous* for which different mechanisms have been proposed (Fradera & Kopelman, 2009; Kopelman, 1987; Schnider, von Däniken, & Gutbrod, 1996). Interestingly, an intrinsic characteristic of confabulators is their profound anosognosia for their memory loss suggesting possible overlapping mechanisms (Feinberg, Roane, Kwan, Schindler, & Haber, 1994; McGlynn & Schacter, 1989; Schacter, 1991).

1.2.2.1. Etiologies of memory loss

1.2.2.1.1. Acquired Brain injury

Different etiologies can give rise to pathological memory loss, many of which are considered under the umbrella term Acquired Brain Injury (ABI). This term encompasses any injury to the brain due to external injury (e.g., concussion) or internal injury (e.g., vascular pathology, tumors etc.), intoxication (e.g., alcohol or drug abuse), deficiencies (e.g., thiamine deficiency), infections (e.g., meningitis) and deprivation of oxygen to the brain (e.g., hypoxia due to asphyxiation). The most commonly observed ABI are those cause by external force (e.g., traumatic brain injuries), considered the leading cause of death and disability among children and younger adults, and those caused by a vascular internal injury (e.g., Stroke), considered the 3rd most common cause of death in most industrialized countries in older adults (World Health Organiztion [WHO], 2006).

1.2.2.1.1.1. Traumatic brain injury

Traumatic Brain Injury (TBI) refers to the event by which the brain receives an injury by a blunt force. This force can be due to an external blow against the skull or from the brain moving within the skull due to strong, and sudden acceleration or deceleration. The latter is commonly observed in road vehicle accidents (Baddeley, Eysenck & Anderson, 2015). The leading cause of brain injury depends on the age range observed. For example, younger adults will be more likely to have TBI resulting from a road vehicle accident and assault; Meanwhile older adults will be more likely to suffer a TBI following a fall (Centers for Disease Control [CDC], 2006-2010; World Health Organization [WHO], 2006).

Consequences of brain injury are varied and dependent on the extent and location of the injury. Commonly though, patients that suffer moderate to severe brain injury will lose consciousness (Cartlidge & Shaw, 1981). The length of the loss of consciousness depends on the degree of the injury and can range from minutes or hours, to what is known as *vegetative state* where the likelihood of regaining consciousness is lost due to the degree of brain damage (Bender, Jox, Grill, Straube, & Lule, 2015). In the case of moderate and some severe brain injuries, individuals will eventually regain consciousness (Baddeley et al., 2015). Different cognitive and behavioural problems can arise once consciousness is regained including memory impairment (Wilson, 2013). Difficulties with memory following a TBI is also known as *post-traumatic amnesia* where patients with brain injuries experience difficulties remembering or forming new memories (*anterograde amnesia)* and remembering past learned information (*retrograde amnesia*) (Kopelman & Stanhope, 2002). As noted in section 1.2.2. above, isolated impairment in memory is not very common and patients with TBI's and patients with other ABI's will have other concomitant deficits. Other salient and common features of brain injured patients are behavioural disturbances due to frontal injury. Such behavioural disturbances are characterized by inappropriate social interactions, impulsiveness, inability to plan or execute complex plans, etc. (Prigatano, 1999; Wilson, 2013). Unawareness of deficits is also common in these patients, who appear unaware of the array of deficits including motor, cognitive, and behavioural deficits (Prigatano, 1996; 2010).

1.2.1.1.2. Vascular Brain Injury: Stroke and White Matter Hyperintensities

Strokes affect 15 million people yearly, of the 10 million individuals that survive,

5 million will suffer from permanent disability (MacKay & Mensah, 2013). The economic burden of stroke has been estimated to be very high. For example, the estimated cost of stroke in the U.K. is of approximately 7 billion pounds per year (Markus, Pereira, & Cloud, 2010), and approximately 34 billion dollars in direct and indirect costs during the 2012-2013 period in the U.S. (Benjamin et al., 2017). Elderly individuals are at higher risk of developing a stroke (World Health Organization [WHO], 2004). Although prevention and medication management strategies have reduced the overall incidence of strokes, with the growing ageing population this disease will remain one of the leading causes of death and disability in our current and future society (World Health Organization [WHO], 2004). The concept of stroke is used to refer to the event by which the blood supply to the brain stops due to a focal interruption (i.e., ischeamic stroke) or a haemorrhage (i.e., haemorrhagic stroke) in the blood vessels supplying the brain (National Health Service [NHS], 2017; World Health Organization [WHO], 2006). Ischeamic strokes tend to be more prevalent (75-80%) than haemorrhagic strokes (10-15%) (World Health Organization [WHO], 2006). Classic acute symptoms of stroke include facial muscle droopiness, slurred speech and motor deficits. These can resolve soon after the event or can remain for days or months. If the acute stroke symptoms resolve within minutes the syndrome is classified as a Transient Ischeamic Attack (TIA) (American Stroke Association, 2017).

Strokes are also commonly classified depending on the affected blood supplying circulation system that is affected. For example, a broad distinction can be found between strokes affecting large cortical vessels as opposed to those affecting deep penetrating vessels (Markus et al., 2010). Conventionally, circulation within the brain is split into

anterior circulation supplied by the carotid artery distribution, and *posterior circulation*, supplied by the vertebral and basilar distribution. The carotid artery distribution includes the internal carotid arteries (ICAs) and their branches (i.e., middle cerebral arteries (MCA), anterior cerebral arteries (ACAs) and intracranial vessels) (Rea, 2015; Traystman, 2017). The regions to which they supply expand to most of the brain except the medial temporal lobes and the occipital lobes (Fuller & Manford, 2010). The vertebral and basilar distributions include the vertebral branches (i.e., anterior spinal artery, posterior spinal artery and posterior inferior cerebellar artery (PICA), the basilar artery, perforating arteries and posterior cerebral arteries (Michael-Titus, Revest, & Shortland, 2010). These supply inferior parts of the cortex including temporal and occipital lobes, and structures known to support memory functioning such as the thalamus and the hippocampus (Michael-Titus et al., 2010).

Within the anterior circulatory system, two distinct clinical syndromes can been delineated: (i) MCA syndrome and (ii) ACA syndrome (Chung, 2017). An MCA syndrome can typically involve contralateral hemiplegia (i.e., paralysis of contralateral limbs), anosognosia or unawareness, hemianopsia (i.e., partial visual loss) or hemianaesthesia (i.e., loss of tactile sensibility), eye deviation, neglect (i.e., attentional deficit disorder in which patients ignore parts of themselves or the environment), dyspraxia (i.e., disorder of movement organization), aphasia (i.e., language comprehension or expression disorders) and motor disorders (i.e., chorea). An ACA syndrome can involve limb and trunk weakness, sensory disturbances, decreased speech and activity, excessive crying or laughing, callosal disconnection (i.e., disconnection of the two hemispheres due to damage to the corpus callosum) and perseveration. Posterior

circulatory strokes or syndromes are more commonly defined by the regions they affect. These regions can include the medial temporal lobes, occipital lobes, cerebellum and brain stem (Michael-Titus et al., 2010). Medial and occipital lobes affect abilities such as vision and produce disorders such as hemianopsia, prosopagnosia (i.e., inability to recognize faces), and agnosia (i.e., inability to recognize objects). Cerebellar strokes can cause dizziness, nausea, vertigo, vomiting, impaired level of consciousness, and localizing signs such as ataxia (i.e., difficulty coordinating movements), nystagmus (i.e., uncontrolled repetitive eye movements) and dysarthria (i.e., difficulty with the articulation of speech) (Lee et al., 2006; Wityk, 2017; Wright, Huang, Strbian, & Sundararajan, 2014). Strokes affecting the brain stem can have an array of symptoms specific to the region affected, including sensory or motor disturbances such as hemiparesis (i.e., weakness of one side of the body), ataxia, loss of pain or temperature sensation between others (Bassetti, Bogousslavsky, Barth, & Regli, 1996; Kameda et al., 2004; Ortiz de Mendivil, Alcalá-Galiano, Ochoa, Salvador, & Millán, 2013)

Strokes occurring in small penetrating vessels that affect deep subcortical structures are known as Lacunar infarcts or Lacunar syndrome which can affect both anterior and posterior circulation territories (Lindgren, Norrving, Rudling, & Johansson, 1994). Lacunar syndromes or infarcts are the most common type of subcortical strokes affecting white matter, and deep grey matter nuclei. Lacunar strokes can manifest with varied symptoms such as sensory disturbances, sleep disturbances, hemiataxia (i.e., loss of muscle control) and cognitive deficits such as memory impairment as they can affect key structures such as the thalamus or the basal ganglia (Lopes et al., 2012; Su, Chen, Kwan, Lin, & Guo, 2007; Tatemichi et al., 1994; Wityk, 2017).

White Matter Hyperintensities (WMHs) are disruptions to white matter integrity also known as Leukoaraiosis (LA). WMHs have been proposed to reflect small vessel cerebrovascular disease and can be commonly observed in stroke and AD patients (Brickman et al., 2010; Brickman et al., 2008; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Thomas et al., 2002). However, WMHs can be observed in healthy ageing adults and have been associated with a range of vascular risk factors and cognitive difficulties such as executive functions, processing speed and attention (Debette & Markus, 2010; Dufouil et al., 2009; Poggesi, 2011; Inzitari et al., 2009; Smith, 2010; van Gijn, 1998) and thus should be included when examining the relation of vascular pathology and different outcomes such as unawareness.

1.2.1.2. Dementia

The term dementia is an umbrella term used to describe a group of disorders that affect cognition in a progressive fashion. Though they are more common in the ageing population, early onset dementias can also occur (Knopman, Petersen, Cha, Edland, & Rocca, 2006). The differentiation of different types of dementia is based on the combination of symptoms and different pathological mechanisms within the brain (see Table 1.1. for a summary of most prevalent dementias as described in Robinson, Tang, and Taylor (2015)). Following the National Institute on Ageing 2011 guidelines, an 'all cause dementia' can be diagnosed when an individual shows cognitive (involving two or more domains) or/and neuropsychiatric symptoms (not explained by delirium or other psychiatric disorders), that interfere with their social and occupational life. A component of progressive deterioration should also be present (McKhann et al., 2011).

Table 1.1. Summary of main types of dementias adapted from Robinson et al. (2015)

Type of Dementia	Main characteristics
Alzheimer's disease	• Most prevalent cause for dementia • Memory loss as early indicator of the disease • At least one other cognitive domain impaired, can include language, executive function, visuospatial deficits for example.
Frontotemporal Dementia	• More common in younger age groups (50-60 years) • The most common clinical type is behavioural variant frontotemporal dementia, with changes in personality and behaviour. • Disinhibition and impulsiveness can be features. • Memory function can be intact early on
Vascular dementia	• Wide range of signs and symptoms depending on extent, location, and severity of the cerebrovascular disease • Symptoms can develop abruptly after a stroke or more insidiously with small vessel disease • Memory loss can be a feature but typically is less noticeable than in Alzheimer's disease. Language, information processing, decision making, and visuospatial deficits can also be found • Mood changes and apathy are common symptoms; can co-occur with Alzheimer's disease and this is termed mixed dementia
Dementia with Lewy Bodies	• Complex visual hallucinations are a key feature. In the early stages they may only occur during periods of physical stress (for example, infections) or at night time and may be followed by more subtle visuoperceptual symptoms—for example, illusions • Parkinsonism (tremor, slowed movements, postural instability, shuffling gait) is also a feature. Tremor may be less evident, but people with early dementia with Lewy bodies may be slower in movements and more prone to falls • Fluctuations or noticeable variations in cognitive function can occur and can be difficult to separate from delirium • Autonomic symptoms may occur—for example, postural hypotension • Sleep disturbances such as rapid eye movement sleep behaviour disorder (shouting out or moving while asleep) can occur many years before the onset of dementia
Parkinson's disease with dementia	• As many as 80% of patients with Parkinson's develop dementia • Symptoms are similar to those of dementia with Lewy bodies, although motor Parkinson's symptoms typically predate cognitive and psychiatric symptoms by more than a year
Posterior cortical atrophy	• A less common form of Alzheimer's disease, which tends to affect younger people (50s and 60s) • Visual agnosias (difficulties with recognizing faces, objects, or perceiving more than one object at a time), apraxias (motor planning difficulties), acalculia (difficulty with calculation), and alexia (difficulty reading) are symptoms • Memory can be preserved early on
Other uncommon causes to dementia	• Alcohol related dementia, Creutzfeldt-Jakob disease, HIV related cognitive impairment, Huntington's chorea, corticobasal syndrome,movement related dementias (for example, progressive supranuclear palsy), multiple sclerosis, Niemann-Pick disease type C, pressure hydrocephalus

1.2.1.2.2. Alzheimer's disease (AD)

The most common type of dementia and the type of dementia examined in this thesis is that of AD, encompassing over 50 % of dementia cases and an approximate 24 million cases a year worldwide, and increasing (Mayeux & Stern, 2012). In order to meet criteria for a clinical diagnosis of *probable AD*, the criterion for 'all cause dementia' must be met and existing symptoms must not be caused by vascular disease or other types of dementia. Though progressive deficits in episodic memory are characteristic of typical AD (see Table 1.1.), non-amnesic presentations (where language, executive functions and or visuospatial abilities are deteriorating) can also form part of this diagnosis (McKhann et al., 1984; McKhann et al., 2011). As AD progresses an array of different impairments can manifest across various cognitive abilities affecting executive functions, attention, language etc. (see also section 1.1.2.). Finally, in order to establish a *definite* diagnosis of AD, in addition to the progressive cognitive and behaviour decline, post mortem analysis of the pathological brain process should confirm the presence of extracellular amyloid plaques, intracellular neurofibrillary tangles and neuronal death (Serrano-Pozo, Frosch, Masliah, & Hyman, 2011).

1.3. Definition & contextualization of anosognosia

Historically, the syndrome of anosognosia was described for the first time over 100 years by von Monakov in 1885 and neurologists Anton and Pick in 1898, before the term was first coined (Prigatano & Schacter, 1991). It was not until 1914, that Babinski described unawareness for motor impairment (i.e., hemiplegia) under the term of anosognosia. The etymology roots of its origins are ascribed to ancient Greek.

Anosognosia thus translates to ἀ- *a*-, "without", νόσος *nosos*, "disease" and γνῶσις *gnōsis*, "knowledge". This term is now widely used to describe unawareness or lack of insight of motor impairments (Jenkinson, Preston, & Ellis, 2011); cognitive deficits (Adair, Schwartz, & Barrett, 2003; Agnew & Morris, 1998; Rubens & Garrett, 1991); and behavioural disturbances (i.e., socially inappropriate behaviours) following brain damage and psychiatric disorders (Gilleen, Greenwood, & David, 2010; Prigatano, 1991) (see also Mograbi & Morris, 2018 for a recent definition of anosognosia).

Studying disordered awareness in clinical populations has critical implications for patients' treatment and care plans. Decreased awareness of deficits or symptoms in patients with motor or cognitive loss, has been associated with a variety of societal and clinical consequences. For example, patients suffering from anosognosia, tend to engage and benefit less from clinical management, and be less independent when making treatment decisions (Appelros, Karlsson, Seiger, & Nydevik, 2002; Cosentino, Metcalfe, Cary, De Leon, & Karlawish, 2011; Cosentino & Stern, 2005; Giallanella & Mattioli, 1992; Koltai, Welsh-Bohmer, & Schmechel, 2001; McGlynn & Schacter, 1989; Prigatano, 2008). Studies have also observed a higher likelihood of riskier behaviours in those patients unaware of their difficulties (Cotrell & Wild, 1999; D'Imperio, Bulgarelli, Bertagnoli, Avesani, & Moro, 2017; Kaszniak, Keyl, & Albert, 1991; Starkstein, Jorge, Mizrahi, Adrian, & Robinson, 2007; Wild & Cotrell, 2003). Further, those responsible for patients' care report higher degrees of stress and burden (DeBettignies, Mahurin, & Pirozzolo, 1990; Prigatano, 2005; Rymer et al., 2002; Seltzer, Vasterling, Yoder, & Thompson, 1997). These examples alone, provide some insight as to how crucial it is to forward our understanding, continuing our efforts in understanding the underlying

mechanisms and associated phenomena of anosognosia. Further, the study of patients who suffer from deficits and their associations observed between unawareness and cognitive, psychological, neural aspects may provide an important basis towards clearer understanding of how intact self-reflective processes function in healthy adults.

Though it has been over 100 years since it was first described, and much has advanced in the field since, anosognosia or unawareness is a construct that remains largely unknown. Many different underlying cognitive, emotional, and social factors have been related to it, but no unified theory has succeeded in embracing the complex array of manifestations of this disorder (see Table 1.2. for summary of major theories for anosognosia). More recently, a movement towards a multifactorial representation of anosognosia has gained wider acceptance, acknowledging the unlikelihood of one single factor underlying this complex disorder (Cocchini, Beschin, & Della Sala, 2012; Cocchini, Beschin, & Sala, 2002; Davies, Davies, & Coltheart, 2005; Fotopoulou, 2014; Gainotti, 2018; Marcel, Tegnér, & Nimmo-Smith, 2004; Orfei et al., 2007; Vuilleumier, 2004).

Table 1.2. Summary of hypotheses on anosognosia following acquired brain injury adapted from Vocat & Vuilleumier (2010)

Study	Theories and mechanisms proposed
Babinski (1914); Critchley (1940)	Sensory and/or proprioceptive feedback deficits prevent patients from realising they have a deficit
Weinstein and Kahn (1955)	Denial and personality traits: Psychological mechanisms protect the ego from hurtful or painful information regarding the self (e.g., deficits).
Geschwind, (1956)	An underlying language impairment prevents patients from appropriately expressing awareness.
Bisiach et al. (1986)	Spatial or personal neglect/dyschiria prevent patients from becoming aware of motor deficits due to a lack of attention to the deficit and or lack of ability to know which side of the body has been touched.
McGlynn & Schachter (1989)	*CAS model*: Patients fail to become aware of their deficits due to an impairment in a general conscious awareness system that supervises information regarding one's abilities.
Levine (1990)	*Discovery theory:* Proprioceptive deficits exacerbate an impairment in inference preventing patients from becoming aware of their motor difficulties.
Heilman et al. (1992)	*Feedforward theory*: Deficits in the forward component (e.g., intentions and predictions of motor movement) of a motor comparator system.
Starkstein et al. (1992)	Deficits in mental flexibility and memory abilities prevent patients from becoming aware of their deficits
Feinberg (1997)	Deficits in attention to the side of the lesion (Neglect) and memory disturbances (confabulation) lead to unawareness of deficits.
Agnew & Morris (1998);Morris & Mograbi (2013)	*CAM model*: Three different types of unawareness based on their underlying mechanisms (e.g., mnemonic (memory), executive (executive functions) and global anosognosia (conscious awareness system).
Clare (2004); Ownsworth et al. (2006)	Biopsychosocial model of anosognosia: Unawareness should be explained through different aspects relating to social, biological and psychological factors (e.g., personality).
Marcel et al. (2004)	Overestimation of self-performance and lack of mental flexibility.
Vuilleumier (2004)	*ABC model* (deficits in appreciation, beliefs, and checks).
M. Davies et al. (2005)	*Two-factor theory:* anosognosia for hemiplegia can be understood under the two-factor theory of delusions arising from a neuropsychological deficiency
Berti & Pia (2006); Fotopoloulou (2012)	Impairment of monitoring between predicted and desired motor outcomes and the sensory feedback from the actual motor outcome.
Rosen (2011)	Self-Monitoring deficits affected by negative mood states.

Clinical manifestations of this syndrome have portrayed a disorder with a large range of variability in its presentation and associated phenomena. For example, anosognosia is a graded syndrome that can manifest with different degrees of severity (Prigatano, 1991). A patient suffering from memory loss can be mildly aware that they are having difficulties, meanwhile another might show a profound denial of a deficit (Prigatano, 1991, 2010). As highlighted earlier, this disorder has very important clinical implications with those more unaware of their deficits suffering from less independence, more risk and overall more difficult management than those aware (Fleming, Strong, & Ashton, 1998; Kelleher, Tolea, & Galvin, 2016; Rymer et al., 2002; Seltzer et al., 1997; Sherer, Oden, Bergloff, Levin, & High, 1998; Wild & Cotrell, 2003).

In patients with ABI and/or dementia, different deficits can coexist, and awareness for these deficits has also been shown to dissociate. For example, a patient with two coexisting deficits, might be unaware of one deficit and have an adequate awareness for the other (Breier et al., 1995; Cocchini, Crosta, Allen, Zaro, & Beschin, 2013; Kinsbourne & Warrington, 1963). Even within a deficit that they show unawareness for, they might be aware of part of the deficit, but not the other (e.g., dissociations of awareness between upper and lower limbs in anosognosia for motor impairment - Berti, Ladavas, & Della Corte, 1996; Della Sala, Cocchini, Beschin, & Cameron, 2009; Ramachandran, 1995). Even more puzzling is the differentiation between what a patient says about his or her deficits (i.e., *explicit awareness*) and how they behave (i.e., *implicit awareness*). Several studies have shown that these two can also differ. For instance, a patient might be able to explicitly acknowledge that they have a motor deficit such as hemiplegia, but attempt to pick up things with both hands or try to

stand up and walk (Cocchini, Beschin, Fotopoulou, & Della Sala, 2010; D'Imperio et al., 2017; Fotopoulou, Pernigo, Maeda, Rudd, & Kopelman, 2010).

Unawareness of deficits can also manifest with accompanying symptoms or syndromes. Some of the most salient psychiatric or positive phenomena are observed in anosognosia for motor deficits. One of these psychiatric phenomena is known as *somatoparaphrenia* (Gerstmann, 1942). Following Gerstmann's 1942 definition, for this syndrome to occur, a patient must be experiencing (i) acquired contralateral motor deficits, (ii) unawareness of such deficits and (iii) delusional beliefs of the limbs affected by these deficits (Feinberg & Venneri, 2014). These delusional beliefs are specific to body ownership defined by Jenkinson, Moro, and Fotopoulou (2018) as the "sense, feeling or judgement that body belongs to me and is ever present" (p.1). Body ownership delusions are not specific to somatoparaphrenia and can also be observed in other delusions accompanying anosognosia such as *asomatognosia.* While somatoparaphrenia typically includes delusions of *disownership* or *misidentification*, asomatognosia typically entails delusions of *existence, visual self-reflection and sense of belonging* of the contralateral limb (Jenkinson et al., 2018). Other positive syndromes associated with anosognosia for motor deficits include *misoplegia* and *anosodiaphoria* (Critchley, 1953, 1974). Misoplegia is observed when a patient in addition to being unaware of their motor deficit, manifests hatred and abuse against their paralyzed limb. Anosodiaphoria on the other hand manifests when a patient shows a lack of caring or indifference towards the paralyzed limb (Babinski, 1914). Delusions that are not specific to motor deficits (e.g., confabulations) have also been observed. Confabulations can present with any deficit but more commonly do so concomitant to impaired memory processes (Kopelman, 1987;

Kopelman, 2010). Patients who confabulate express no awareness of their memory deficits and make implausible claims about their abilities and their past memories with a full conviction of telling the truth (Dalla Barba, 1993; Moscovitch, 1995a). Confabulation is not necessary to be unaware of one's deficits but those that confabulate have been systematically shown to be unaware of their memory deficits (Schacter, 1991).

1.3.1. Challenges in the study of anosognosia

The field of the study of anosognosia faces multiple challenges. As described in the previous sections this disorder presents with an intrinsic complexity that makes its underlying structure hard to tease apart. The variability of deficits accompanying awareness and the variable degrees of awareness observed across different samples has highlighted the unlikelihood of a single factor explaining anosognosia. Further studies that examine patients with unawareness from a multifaceted framework are necessary, that is from a framework that approaches the patient from a multidimensional perspective (Clare et al., 2011; Cocchini et al., 2012; Davies et al., 2005; Fotopoulou, 2014; Gainotti, 2018). Another challenge that the study of anosognosia and its future faces, is that there is no gold standard in assessing patients' awareness of their deficits. Many different approaches, scales and assessments have been used from study to study. Thus, the translation of each finding into a cohesive advancement of the field has been clouded by methodological issues (see Chapter 3 for extensive review of assessment methods and pitfalls). Though there is a growing understanding of this disorder, it is of key importance to develop a standardized measuring instrument across different deficits that could shed some needed light on the common yet unknown anosognosic disorder.

1.3.2. Anosognosia for memory loss

Earlier descriptions of unawareness for memory deficits, date back to 1889 when Korsakoff first described patients suffering from a thiamine deficiency disorder, now bearing his name, who seemed unconcerned about the mnemonic difficulties consequential of their deficiency (Prigatano & Schacter, 1991). Other amnesic patients from different etiologies, such as ruptured aneurysm of the anterior communicating artery or frontal tumors, have also been found to underestimate their memory deficits (Luria, 1976; McGlynn & Schacter, 1989; Vilkki, 1985). Unawareness though, does not consistently accompany memory loss, and some patients with dense amnesia have been reported as acutely aware of their deficits (Milner, Corkin, & Teuber, 1968; Rose & Symonds, 1960). Many studies examining unawareness of memory deficits have followed these early descriptions in an attempt to elucidate what factors underlie this fascinating syndrome. Although unawareness of memory loss can manifest in a variety of etiologies of memory loss, most of the recent literature has focused on patients with AD. Indeed, some of the most influential theoretical models have been developed based on data derived from patients with AD (e.g., Agnew & Morris, 1998; Clare et al., 2011; Mimura, 2008).

The prevalence of anosognosia for memory impairment is also majorly derived from studies with individuals diagnosed with AD. Studies examining patients with AD, show a very variable prevalence of anosognosia throughout the literature with reports from 20% (Clare, 2004a) up to an 80% (Sevush & Leve, 1993). The prevalence of anosognosia for memory loss in patients suffering from Mild Cognitive Impairment (MCI), a condition believed to be a precursor of AD, has been reported as high as 60%

(Vogel et al., 2004). Further a recent paper by Gerretsen et al. (2017) found that the presence of anosognosia was predictive of the conversion from MCI to AD. Within the ABI literature, studies from patients with TBI have shown that between 30 % and 40 % of patients with moderate to severe injuries will have some degree of unawareness of their behavioural and neuropsychological deficits, including memory loss (Fischer, Gauggel, & Trexler, 2004; O'Keeffe, Dockree, Moloney, Carton, & Robertson, 2007; Prigatano, 1996; Prigatano, Altman, & O'Brien, 1990). Studies with other ABIs such as stroke have also observed a variable prevalence of anosognosia for cognitive difficulties, including memory loss, with some studies reporting between 39 % and 72 % of patients as having variable degrees of unawareness (Anderson & Tranel, 1989). When memory in isolation was examined the reported prevalence of unawareness was of 27 % (Hartman-Maeir, Soroker, Ring, & Katz, 2002). The extent of recovery of awareness of memory loss has not been systematically assessed but there is evidence from a single case study that residual unawareness can manifest up to 13 years post a TBI (Hoofien, Gilboa, Vakil, & Barak, 2004).

As for the correlates associated with anosognosia for memory loss, conflicting evidence can be found across studies. For example, although some studies have found an association between severity of dementia and unawareness (Barrett, Eslinger, Ballentine, & Heilman, 2005; Duke, Seltzer, Seltzer, & Vasterling, 2002; Gerretsen et al., 2017; Mangone et al., 1991; Migliorelli et al., 1995; Sevush & Leve, 1993; Starkstein, Sabe, Chemerinski, Jason, & Leiguarda, 1996), others did not find such association (Clare & Wilson, 2006; Correa, Graves, & Costa, 1996; DeBettignies et al., 1990; Kotler-Cope & Camp, 1995; Michon, Deweer, Pillon, Agid, & Dubois, 1994; Reed, Jagust, & Coulter,

1993). Further examinations have explored if specific cognitive dysfunctions in memory and executive abilities are the primary root of the disorder (see Agnew & Morris, 1998; Ansell & Bucks, 2006; Morris & Mograbi, 2013). However, the associations between anosognosia and memory (Derouesne et al., 1999; Reed et al., 1993; Starkstein et al., 1995) and executive function (López, Becker, Somsak, Dew, & DeKosky, 1994; Michon et al., 1994; Reed et al., 1993; Starkstein et al., 1996) have been largely inconsistent, raising the question of what other mechanisms may be at play.

Although differences in sampling and methodologies can partly explain some of the inconsistent results across studies (Brookes, Hannesdottir, Markus, & Morris, 2013; Clare, Marcová, Verhey, & Kenny, 2005; Cosentino & Stern, 2005), several cognitive theories have proposed that processes specific to self-evaluation, that is, metacognitive monitoring processes, may have a unique contributing variance, and hold an instrumental role in the emergence of awareness of one's deficits (see Agnew & Morris, 1998; Chapman et al., 2018; McGlynn & Schacter, 1989; Rosen, 2011). Paradoxically though the notion of the self is at core of this disorder, different evaluative measures of the self, have not been systematically assessed within anosognosia. Experimental self-evaluative paradigms may hold promise in the advancement of what factors interplay in anosognosia (see Chapter 5 where these factors are examined) (Cosentino, Metcalfe, Butterfield, & Stern, 2007). Moreover, as awareness may be a dynamic multileveled phenomenon different factors that contribute towards the expression of this syndrome may co-occur. Underlying correlates of anosognosia may thus go beyond the cognitive or sensory deficits associated with the ABI or dementia and may span into cultural, social and psychological domains (Clare, 2004b; Clare et al., 2011). To this date, no single theory

can explain anosognosia leading to proposals where a more comprehensive examination of different factors are considered (Clare et al., 2011; Clare, Nelis, Martyr, Roberts, et al., 2012).

1.3.2.1. Theoretical landscape of anosognosia for memory loss

1.3.2.1.1. The Conscious Awareness model (CAM)

From a cognitive approach, Agnew and Morris developed a neuropsychological model for anosognosia for memory impairment in AD (Agnew & Morris, 1998; Hannesdottir & Morris, 2007; Mograbi & Morris, 2013; Morris & Hannesdottir, 2004). This model provides a modular view on anosognosia by which different modules collaborate to give rise to self-awareness of memory functioning. As depicted in Figure 1.1., information regarding one's own performance or abilities is initially processed through domain specific modules (i.e., language, visual, and motor) and then encoded in different memory systems based on the qualitative properties of the memories. For example, information regarding past experience is stored in episodic autobiographical memory (i.e., memory of past events relating to oneself) and information not specific to the self is stored in generic memory. Based on the information acquired about one's own abilities over time, the Personal Database (PDB) holds a semanticized (more general and decontextualized) conceptualization of one's abilities. As part of the monitoring processes that give rise to awareness, the CAM model includes central Cognitive Comparator Mechanisms (CCMs) hypothesized to operate underlying executive function control, and local (domain specific) comparator mechanisms (i.e., Cn). These comparators compare information regarding ongoing experience with the information held in memory (e.g., episodic) and in the PDB. If a mismatch is observed, the

information in the PDB gets updated and this information is fed to the metacognitive awareness system (MAS) where the current mismatch and the updated PDB is made conscious (e.g., can be explicitly expressed). This information can also be held at an implicit level which can then be manifested through behaviour (e.g., a patient gets upset when they make a memory mistake without acknowledging explicitly that they made a mistake or that their memory overall has deteriorated). The proposed global and local comparators mechanisms can explain why different monitoring deficits can be observed in anosognosia. For example, if a domain specific comparator (Cn) is impaired then an individual would be unaware of that specific domain (e.g., motor functioning (Cm)). On the other hand, if the central CCMs are impaired the individual would be unaware of all deficits (see description of executive anosognosia below).

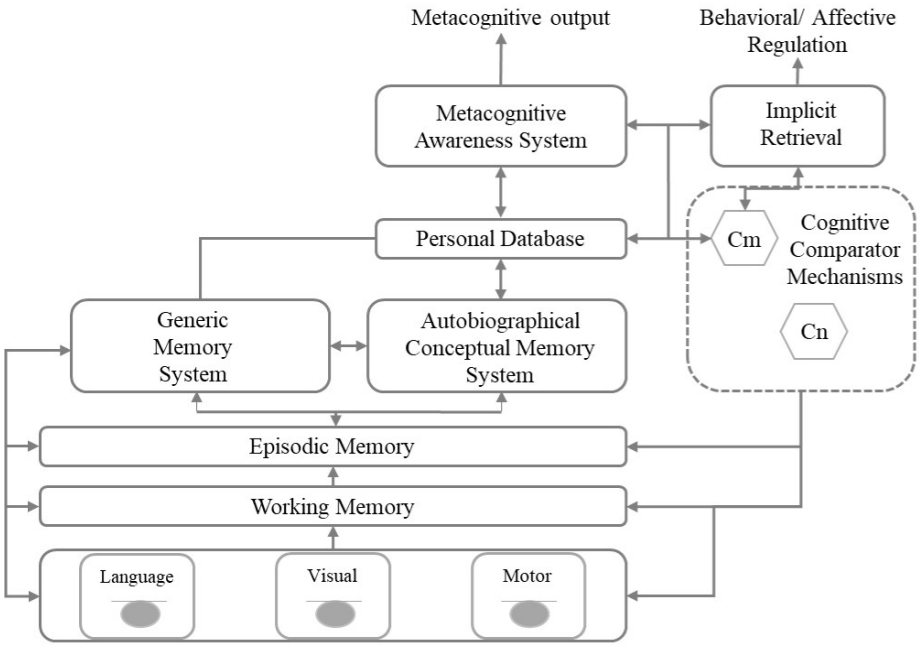

Figure 1.1. A modified version of the Conscious awareness model (CAM) adapted from Morris and Mograbi (2013).

To encompass different features and dissociations found in anosognosia for memory impairment, three types of unawareness of memory difficulties can be discerned in this model: *(i) Mnemonic anosognosia; (ii) Executive anosognosia and (iii) Primary anosognosia.* Individuals suffering from *mnemonic anosognosia*, have an inability to encode and recall the information about their memory mistakes (i.e., they forgot that they forgot). Following the model this translates as a degraded pathway between the CCMs and the PDB. A mnemonic anosognosiac may be able to detect the mistake when they make it, but this cannot translate to a long-lasting change of their own knowledge of their abilities (Ansell & Bucks, 2006). Though individuals may not be able to show long term explicit awareness of their memory failure, they may exhibit some implicit knowledge, as the pathways between implicit memory and the CCMs are theorized to be intact.

Individuals suffering from *executive anosognosia*, won't show awareness within short or long term as their mistakes cannot be compared due to an impaired CCMs at a central level. This means that even if the memory mistake is registered, the monitoring system is not able to detect a mismatch between intentions and performance (memory failures). Individuals with *primary anosognosia,* are defined as having a dysfunctional MAS system, therefore a lack of metacognition is present at an explicit level. These individuals nevertheless may still have some implicit information and may show emotional reactions when confronted with the failure (Mograbi & Morris, 2013).

The variety of presentation in anosognosia for memory deficits is thus represented in this model as different types or subtypes of this disorder. Within AD, these are thought to be representative of the degenerative process and the consequent neuroanatomical damage characteristic of the disease (Agnew & Morris, 1998). For example, *mnemonic anosognosia* has been suggested as especially prevalent at initial stages of AD as earlier stages of the disease are characterized by a decline in new learning and retrieval and atrophy of the hippocampus and medial temporal lobe (Braak & Braak, 1991; Hyman, Van Hoesen, Damasio, & Barnes, 1984; Squire, 1992). *Primary* and *executive anosognosia* will then be more likely to manifest when the progression of AD has reached frontal areas (Ansell and Bucks, 2006). This model has not been systematically assessed except in one paper by Ansell and Bucks, (2006) who showed only partial support for mnemonic anosognosia testing early stages AD's patients and has not been assessed in other patients such as those suffering from ABI.

1.3.2.1.2. Self-monitoring model

The self-monitoring model is a model that builds from the CAM and expands to include factors such as emotional processing that were neglected in the previous model. This model was posited by Rosen (2011) and in line with Morris and Hannesdottir (2004), establishes the basis of awareness on the outcome of performing a determined cognitive task (e.g., forgetting an appointment). Following Rosen's (2011) proposed model every time an individual succeeds or fails at a determined task, they re-evaluate their functioning based on the prior knowledge they have of their performance. If the outcome of the task repeats itself often and is discrepant with the individual's representation of their functions, this representation will eventually be updated with the new information. This evaluative process will then lead to new beliefs and predictions of how well they will do if they encountered a similar task in the future. The novel aspect of the model is that it accounts for the possible mediating role of emotional processes within anosognosia for memory loss (see Chapter 4 for full description of motivational accounts of anosognosia for other deficits). These include motivation and emotional processing that are hypothesized to influence the monitoring processes separately and interactively (see Figure 1.2.).

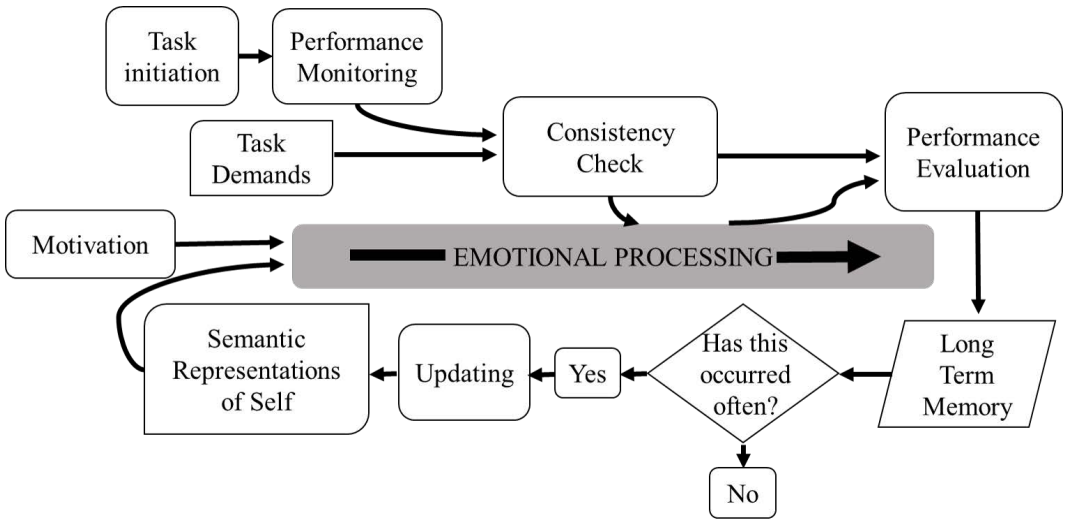

Figure 1.2. The Self-monitoring model – adapted from Rosen (2011).

Motivational factors are proposed to precede and determine how precise and focused the monitoring processes will be ahead of a task. As noted by Rosen (2011), some studies have shown an association of psychological factors such as apathy or depression with anosognosia (Cines et al., 2015; Derouesne et al., 1999; Starkstein, Brockman, Bruce, & Petracca, 2010; Starkstein, Jorge, Mizrahi, & Robinson, 2006). Following Figure 1.2., greater levels of negative mood can affect individuals' initial motivation to closely monitor their performance and consequently diminish their emotional processing when performing a task. Therefore, when an error is committed, a faulty emotional processing fails to flag it as significant and thus impairing a key step in the process by which individuals update their semantic representation of themselves. For example, if a healthy individual has an important appointment of strong emotional significance (e.g., a highly competitive job interview), they would be highly motivated to monitor this process closely; further if they forgot and missed the appointment their error would be flagged as significant and their semantic representation of themselves

updated. This motivation to monitor and in turn flagging of salient errors would be thus affected by mood disorders and an individual with anosognosia will not monitor their appointment as closely and thus when they forgot they would not experience a salient emotional reaction to it.

1.3.2.1.3. Biopsychosocial model

A biopsychosocial model, acknowledges the need to understand not only the physical components of a disease or disorder, but also psychological, social and cultural factors as associated components within each individual (Engel, 1980). Following this framework Clare (2004b), suggested that it is very unlikely that only cognitive or neural factors can explain the complexity of awareness of abilities and that social, cultural and psychological processes may impact the way we evaluate ourselves. These factors were derived from integrating many of the elements proposed in different disciplines such as neurology, neuropsychology, psychology, psychiatry and social constructivism. In the centre of the model of awareness is located the *sense of self.* This sense of self interacts, and becomes affected by factors in biological, social, cultural and psychological levels. Each level contributes a unique set of variances. For example the psychological level would provide the coping mechanisms that help protect the self against the threat of a disability (Weinstein, 1991) interfering with an accurate appraisal of one's abilities. On the biological level, contributions underlie the actual neural injury and the subsequential cognitive deficit. Deficits such as memory or executive impairment can influence the updating of one's abilities (Agnew & Morris, 1998; Mograbi, Brown, & Morris, 2009; Mograbi & Morris, 2013; Mograbi & Morris, 2018; Morris & Mograbi, 2013). At a social

level, interpersonal interactions can determine how much of one's self concept is shared and how it is interpreted (Clare, 2004a; Harre, 1987).

Following nearly 10 years of research, this model has evolved to a succinct conceptualization of levels of awareness and specific associated factors that may affect each level (Clare et al., 2011). As depicted in Table 1.3., this conceptualization specifies different levels of awareness, the operations involved, the commonly used measures, and the types of factors that can affect each. Thus, this conceptualization is an integration of a biopsychosocial approach into awareness. For example, the extent of the neurological damage, cognitive deficits and psychological factors, such as mood and personality, can all interfere at different levels of awareness.

Table 1.3. Biopsychosocial or hierarchical model of awareness – (Modified from Clare et al., 2011).

Level of awareness	Processes involved	Commonly assessed by	Factors associated with awareness
Sensory registration	Registration of basic sensory and perceptual information	Observation of behavioural and/or verbal response	Rate of occurrence of stimuli/events; sensitivity and accuracy of observation
Performance monitoring	Monitoring ongoing task performance as it occurs, and identifying errors	Comparing self-ratings of task performance with objective test scores.	Cognitive function; individual psychological factors; task characteristics; and familiarity with or opportunities to engage in task
Evaluative judgement	Judgements about symptoms, changes or impairments, or specific aspects of one's abilities, performance, functioning, or situation	Comparing self-ratings with informant ratings on a parallel measure.	Cognitive function; individual psychological factors; informant perceptions; informant factors; contextual factors; and characteristics of the measure used
Meta-representation	Reflection on one's situation and changes experienced, self-reflection, considering the perspective of others.	In-depth interview with participant and possibly also informant	Individual psychological factors; cognitive function; context; relationship with interviewer; and interviewer's interpretation

Summary of different levels of awareness, measures and aspects that can influence the expression of awareness.

1.4. Moving forward

Even though there has been a significant advancement in the study of unawareness of memory deficits, our understanding of this construct remains incomplete. Methodological concerns have been raised from the multiple and different measures and sampling processes involved in each study. A push for more reliable assessments is key for the advancement of the field (Cocchini et al., 2012). Taking these limitations into account, theoretical approaches have shown a growing acceptance that underlying

monitoring processes have an important role in how one makes higher order judgements of a specific deficit, such as memory impairment. Further, other factors such as underlying neurological, mood and personality factors can play a role in explaining different levels of awareness and should be considered (Agnew & Morris, 1998; Clare et al., 2011; Cosentino et al., 2007; Cosentino, Metcalfe, Cary, De Leon, & Karlawish, 2011; Rosen, 2011; Rosen et al., 2014; Schacter, 1990). The progressive nature of the AD may present a limitation for the study and the development of the understanding of anosognosia as the progression of cognitive difficulties may cloud the interpretation of results. Other conditions that can also lead to anosognosia of memory impairment include ABIs, of traumatic or vascular nature, and have been quite neglected in the assessment, even though these patients can present with specific impairment that can help elucidate what processes are key for the emergence of anosognosia. This thesis will attempt to overcome some of the methodological concerns in the assessment of anosognosia and explore multifaceted processes that may play a role in patients' unawareness of memory loss.

Chapter 2

Main Research Questions & Methods

Summary of Chapter

Following the general introduction in Chapter 1, this chapter provides an overview of the main research questions included in this thesis. Main methodological aspects relevant to the studies included in this thesis are discussed including ethical approvals, description of participants, main measures used across different studies and main statistical analyses conducted.

2.1. Main Research Questions

2.1.1. Measuring anosognosia for memory loss

2.1.1.1. Measuring Anosognosia: The Visual Analogue Test for Anosognosia for Memory impairment (VATAmem) (Chapter 3)

Although anosognosia as a syndrome was coined over a 100 years ago (Babinski, 1914), the assessment process to measure anosognosia is still underdeveloped (Clare et al., 2002; Clare, Wilson, Carter, Roth, & Hodges, 2002; Cocchini, Gregg, Beschin, Dean, & Della Sala, 2010; Della Sala et al., 2009; Marková & Berrios, 2001). Many authors have expressed concern for the great variety and lack of standardization of measures across studies examining unawareness deficits. The lack of a gold standard has thus clouded the interpretation of underlying factors associated with this phenomenon (Cosentino et al., 2007; Jenkinson et al., 2011). It is also important to consider that different existing measures might be tapping into different mechanisms or levels of awareness, and that these might not share the same contributing mechanisms (Clare et al., 2011; Morris & Hannesdottir, 2004). Thus following McGlynn and Schacter (1989), in order for the field of anosognosia to move forward, a clear conceptualization of the

object of anosognosia (e.g., unawareness of specific deficits versus overall disease) is necessary, along with the production of more specific and quantifiable measures of this disorder (see also Clare et al., 2002; Clare et al., 2005).

As it is unlikely that one measurement will capture all different components or levels of awareness, it is important that future research examines anosognosia with a variety of measures. A combination of measures can help understand how each component contributes to awareness and consequences associated with it (Cocchini et al., 2012; Cosentino et al., 2011). In order to do so, we first need to improve our current measures assessing anosognosia. The first aim of this thesis (Chapter 3) is to review current and past measures of anosognosia for memory loss and to develop a new tool that builds upon existing measures and attempts to improve how we measure anosognosia for memory loss.

2.1.2. Underlying mechanisms in anosognosia for memory loss

As the research of anosognosia moves forward, leading theorists agree that no single factor can explain this disorder and multifaceted approaches are needed to understand how each factor contributes to the presentation of unawareness (Clare, Nelis, Martyr, Roberts, et al., 2012; Cocchini et al., 2012; Gainotti, 2018; Jenkinson et al., 2011). This section is aimed at examining different factors that can contribute towards anosognosia for memory loss, including psychological factors, neuroanatomical factors and self-evaluative or self-monitoring factors.

2.1.2.1. Personality and mood factors in anosognosia (Chapter 4)

Psychological processes such as premorbid personality traits or mood have been proposed as key mechanisms on how we shape our consciously conceived ideas about

ourselves and the world (McCrae & Costa, 1987; Moore & Fresco, 2012; Serfass & Sherman, 2013). Within the study of anosognosia, classic conceptualizations have defined lack of awareness as a protective reaction to the loss of an ability, with those with specific personality traits, such as conscientiousness, being more prone to 'denial' reactions (Nardone, Ward, Fotopoulou, & Turnbull, 2008; Weinstein, 1991; Weinstein & Kahn, 1955). Interestingly, more recent examinations of personality traits and unawareness (Clare, Nelis, Martyr, Roberts, et al., 2012; Colvin, Malgaroli, Chapman, MacKay-Brandt, & Cosentino, 2018) have found seemingly contradictory results to that of the classical proposal of Weinstein and Kahn (1955).

Other factors such as mood, seem to also play a role in how we evaluate our reality. For example, negative mood can affect the way we evaluate ourselves and our outcomes (Msetfi, Murphy, Simpson, & Kornbrot, 2005). With regard to anosognosia, there seems to be an inverse relation between unawareness of deficits and depression (Bertrand et al., 2016; Cines et al., 2015; Conde-Sala et al., 2014). This relation though has not been consistently observed, and other studies have shown no association between negative mood or depression and anosognosia (Cocchini et al., 2013) and thus to this date the role of premorbid personality and mood over anosognosia is still unclear. If personality and mood do indeed affect how we evaluate our abilities, it is thus crucial that we continue our efforts to comprehensively examine this question in patients who are suffering from anosognosia. Chapter 4 presents new results regarding both mood and personality traits in a sample of patients with variable levels of awareness following stroke.

2.1.2.2. Self-Monitoring mechanisms in anosognosia (Chapter 5)

As introduced earlier, the examination of specific cognitive abilities such as memory or executive functions have introduced mixed results (Derouesne et al., 1999; López et al., 1994; Michon et al., 1994; Reed et al., 1993; Starkstein et al., 1996; Starkstein et al., 1995) suggesting that other mechanisms might also play a role in patients' awareness of memory deficits. Several cognitive theories, such as the CAM model, have shared the assumption that processes specific to self-evaluation, that is, monitoring processes can hold an instrumental role in becoming aware of one's deficits (see Agnew & Morris, 1998; McGlynn & Schacter, 1989; Rosen, 2011). Self-monitoring processes can be understood as uniquely self-evaluative, one that operates outside of primary cognitive abilities, and by which an individual evaluates aspects of one's own thoughts, intentions and actions from that of others or the external world (Chapman et al., 2018). Following the CAM model a mnemonic monitoring impairment has been proposed as one underlying process by which anosognosia may manifest (i.e., executive anosognosia (Agnew & Morris, 1998). The extent and the mechanisms underlying this impairment are yet to be examined. Chapter 5 will build on the proposed mnemonic monitoring impairment by the CAM model and examine what specific monitoring processes break down in tandem with anosognosia for memory loss. Three studies are included in this chapter. The first chapter examines if lower levels of awareness (i.e., ongoing memory performance monitoring) are impaired in stroke patients unaware of their memory loss compared to those aware. The second study aims to explore if deficits of lower awareness are domain specific or if they expand to other domains such as ongoing motor monitoring. Finally, study three explores what type of mechanisms

specific to memory monitoring are impaired in patients with anosognosia for memory loss.

2.1.2.3. Neural mechanisms underlying anosognosia (Chapter 6)

Chapter 6 will provide an examination of the most relevant studies examining neurocorrelates of unawareness with memory impairment that have attempted to shed some light on key brain areas correlated to anosognosia of memory loss. Few studies have examined neuroanatomical correlates of anosognosia in patients suffering from memory loss due to other etiologies other than dementia (Anderson & Tranel, 1989; Hartman-Maeir et al., 2002). Examining neural correlates of unawareness of memory loss in other etiologies is important as the progressive nature of dementia disorders may cloud the interpretation of the different regions associated with unawareness (see Chapter 6). Indeed, patients with unawareness of memory loss due to specific brain injuries such as stroke may allow the determination of specific anatomical lesioned regions that may be key for unawareness of memory loss. Although many studies have examined the neuroanatomy of anosognosia in ABI's, these have largely examined anosognosia for motor difficulties (e.g., Moro et al., 2016; Pia, Neppi-Modona, Ricci, & Berti, 2004; Starkstein, Fedoroff, Price, Leiguarda, & Robinson, 1992; Vocat, Staub, Stroppini, & Vuilleumier, 2010; Vocat & Vuilleumier, 2010). This chapter is an attempt to bridge the gap of neural correlates of anosognosia of memory loss following an ABI. This chapter is aimed at providing new results regarding location and extent of the lesion in relation to anosognosia for memory loss. Further vascular burden will be included by examining the integrity of white matter in relation to anosognosia in a sample of patients with memory loss following stroke.

2.2. Methods

2.2.1. Recruitment and site of studies

All studies included in this thesis have been conducted in collaboration with two major sites: St George's stroke unit at the St George's NHS Hospital in London (U.K.) and the Neurological Institute at Columbia University Medical Centre, Columbia University in New York (U.S.) A third site collaborated with this study recruiting participants for the first study included in Chapter 3 at the Neuropsychology Unit of Somma Lombarda Hospital in Italy.

2.2.2. Ethical approvals

Ethical approvals were sought at both main sites and were approved by all recruitment site ethical bodies. Within the U.K., the ethical NHS committee West of Scotland REC 5 provided a favorable ethical opinion by its committee on November 2014 (see Appendix 1). Within the U.S. two separate groups of participants were seen (e.g., Stroke and AD patients). AD patients were recruited as part of a larger project which was approved by The Institutional Review Board (IRB) of Columbia University Medical Centre (see Appendix 2). A different protocol obtained favourable opinion by IRB review for the recruitment of stroke patients (see Appendix 2). The local ethical board at the Neuropsychology Unit of Somma Lombarda Hospital in Italy also approved for this study. This was submitted by Nicoletta Beschin, head of the neuropsychology unit at the site. No major ethical concerns were raised during the design or development of the study. All participants gave written informed consent for the study (see Appendix 3 - 5).

2.2.3. Participants

The overall sample of participants included in this thesis were suffering from memory loss due to ABI or from degenerative disorders such as AD. Each chapter delineates the specifics of the sample included for each study. The overall inclusion criteria that participants follow throughout this thesis is as follows:

Inclusion criteria (patients with ABI)

I. Aged 18 to 90

II. Acquired brain injury

III. Referred as having memory difficulties

IV. Mini Mental Status Examination > 20

V. > 20 days after the acquired brain damage

VI. Patient must be able to provide consent for themselves in accordance with the Mental Capacity Act (2005) guidelines.

VII. Fluent in English or Italian (depending on recruitment site)

Exclusion criteria (patients with ABI)

I. Major Psychiatric disease (excluding depression)

II. Other illness that could have a major effect on cognitive function (i.e. dementia).

Inclusion criteria (patients with AD)

I. Aged 18 to 90

II. Diagnosis of AD following the criteria of the Neurologic Disorders and Stroke - Alzheimer's disease and Related Disorders Association (NINDS-ADRDA).

VI. Patient must be able to provide consent for themselves in accordance with the IRB at Columbia University guidelines.

VII. Fluent in English

Exclusion criteria (patients with AD)

I. Major Psychiatric disease (excluding depression)

II. Other illness that could have a major effect on cognitive function (i.e. acquired brain injury).

III. Mini Mental Status Examination < 20.

2.2.4. Measures

This section will summarize common measures that will be used across several chapters. Some chapters have unique measures and thus will be described within each chapter.

2.2.4.1. Anosognosia

Anosognosia or unawareness of memory loss will be measured across all chapters through the Visual Analogue Test for Anosognosia for memory loss (VATAmem). This measure is fully described in Chapter 3 where its development and psychometric properties are reported. One study (Study 2 in Chapter 5) used a different measure to assess awareness (a modified version of Reed's Clinically Rated Awareness (CRA)

interview; Reed et al., 1993) as data collection started before the final version of the VATAmem. The CRA interview is described in Chapter 5.

2.2.4.2. Cognitive Battery

2.2.4.2.1. BCoS, brain behaviour analysis cognitive screen

The BCoS, developed by Humphreys, Bickerton, Samson, and Riddoch (2012), is a cognitive battery designed to evaluate the neuropsychological profile of individuals who have suffered from a stroke. The battery is designed to assess 5 main domains including 1) Attention and executive functions; 2) Language; 3) Memory; 4) Number skills; and 5) Praxis. This thesis only used the subtest of attention and executive functions, language and memory in most studies described below. Some studies included participants recruited at different times or centres (e.g., study in Chapter 5 and Chapter 3). In these cases different cognitive tasks were used and are described in each study.

The *auditory attention task* provides a measure of sustained and selective attention. In this task 6 pre-recorded words are presented nine times each in a semi random order. For half of the words the participant has to respond by tapping his or her pen (i.e., target), and for the other half of words the participant is instructed to not respond (i.e., distractor). Each target word (‘*no’, ‘please’, ‘hello’*) is related to the distractor word (‘*yes’, ‘thanks’, ‘goodbye’*). Participants assessed undergo three blocks. Executive function is measured through the *rule finding and concept switching task.* This task consists of 17 6x6 grids, presented one at a time, with a black dot and 4 coloured squares (see Figure 2.1.). The participant is instructed that the black dot can move in any direction following a rule, but to be aware that this rule might change. The main goal of the task is to learn to predict where the black dot will move to next, that is to learn the rule that

guides it movements. For example, if the black dot had moved serially from left to right previously, one should predict that the next location would be one square to the right from its current position. In order to successfully complete this task the participant needs to accurately infer three different rules or patterns of movement that the black dot follows.

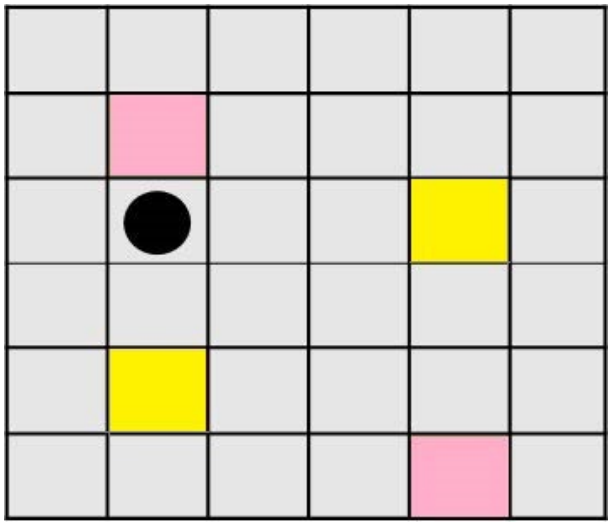

Figure 2.1. Adapted example of the rule finding & switching task (BCoS, Humphrey's et al., 2012)

The language subscale of the BCoS included the *picture naming* task. This consists of 14 pictures of different objects, half living half non-living. This task measures object recognition and access to the semantic knowledge of the object. The memory subscales of the BCoS included in this study are those of story recall and recognition. Specifically, these were used as screeners for inclusion in this study. This task consists of a story with 15 segments to be recalled immediately after the learning trial and after a 20-minute delay. The recognition component is also administered immediately after the recall and at the delay. For the recognition test there are 4 different choices for each segment of the story, one correct answer and three distractors. For purposes of

recruitment only those with impaired scores (i.e., below 1.5 SD) were included in the studies.

2.2.4.2.2. The Rivermead Behavioural Memory Test (RBMT)

In order to assess memory functioning in the majority of the studies included in this thesis, a memory test known for its ecologically valid properties was selected (i.e., The Rivermead Behavioural Memory Test (RBMT)) (Wilson, Cockburn, & Baddeley, 2003; Wilson et al., 2008). The RBMT is a memory test that assesses memory impairment in everyday memory functioning. This test was developed to include tasks that were more representative of real life memory difficulties. Throughout all studies but one (Study two in Chapter 5) the RBMT (second version) is used to measure memory loss in those patients who were enrolled following the screener. The RBMT-II includes a total of 11 items that measure everyday memory mistakes commonly observed in patients with impaired memory described below:

> *1&2. First and second name*: The patient is shown a picture of a person and given their first and last name. They are instructed to remember this as they will be asked to free recall the full name after a delay.
>
> *3. Belonging:* The patient is asked to provide the examiner with a belonging, something that is not too expensive or valuable. The examiner then hides the belonging as the patient observes. The patient is then instructed to ask for the belonging when the examiner states: “We have finished this test”.

4. Appointment: The examiner sets an alarm for 20 minutes and instructs the patient to ask the following question when it rings: “When am I going to see you again?”

5. *Pictures*: The examiner shows a set of 10 pictures for a few seconds each and asks the patient to try to remember all of these as they will be asked to recall later.

6. Story immediate & delayed: A story containing 14 segments is read to the participant who is asked to recall immediately after and after a delay.

7. Faces: A set of 5 faces are presented to the patient who is asked to make a judgement of whether they are male or female and if they are over or under 40 to ensure they encode the faces. They are asked to remember these as they will be assessed after a delay. *8&9. Route immediate and delayed & message*: The patient is shown a small route around the room by the examiner which includes 5 locations including start and finish. The examiner starting point is where an envelope is lying, the examiner then takes the envelope and walks around the room making strategic stops in locations such as the window or the door. The examiner finishes where he or she started and leaves the envelope in the same location. The patient is then asked to mimic the route the examiner just completed and again after a delay.

10&11. *Orientation and date*: The patient is examined in their orientation to time and space. Example of questions include: “What date is it?”; “Where are we now?”; “What is the name of the Prime Minister of Britain?”.

Based on all these items, the RBMT-II provides an overall score ranging from 0-24 that can represent normal memory (range = 22-24), poor memory (range = 17-21), moderately impaired (range = 10-16) or severely impaired memory (range = 0-9). Finally, the first study of this thesis (Chapter 3) included some participants recruited in Italy who had received a newer version of the RBMT (e.g., RMBT-III) (Wilson et al., 2008). Similarly to the RBMT-II the RMBT-III provides an overall score for memory functioning that can be used to categorize memory impairment as with the RBMT-II.

2.2.5. Statistical analysis

2.2.5.1. Power analyses

Three a priori power analyses were conducted for studies exploring underlying mechanisms of anosognosia, one for psychological mechanisms (Chapter 4), one for cognitive mechanisms (Chapter 5) and one for neural mechanisms (Chapter 6). Power calculations were developed using the program G*Power 3.1.9.2. A priori power, effect size and two tailed p value or alpha value were determined to calculate a minimum sample size for behavioural and neuroanatomical studies respectively. A priori power, or the probability of correctly rejecting the null hypothesis of 80% (Suresh & Chandrashekara, 2012) and a two tailed alpha value of .05 were selected (Fleiss, 1981). The a priori effect size was extrapolated from previous and relevant studies examining similar questions as those posed in part two of this thesis.

Two papers were selected for the psychological process study included in chapter

4 (i.e., Bertrand et al., 2016; Conde-Sala et al., 2014). Based on these studies, the average effect size of the relation between mood and anosognosia was calculated. As reported in Table 3 in Conde Sala and colleagues (2014) the effect size averaged to a d = 0.80 and reported in results section in Bertrand and colleagues (2016) the effect size of the relation between mood and anosognosia averaged to d = 1.75. These values reflect high effect sizes, which is not unusual in neuropsychological studies. Two statisticians (Dr. Allen and Mr. Griffiths affiliated with Goldsmiths College, University of London) suggested considering the most conservative value for Cohen's d for the power calculations and thus Cohen's d = .80 was selected. Based on these values a priori correlational power analysis recommended a minimum sample of 7 individuals for studies included in Chapter 4.

One study was selected for the study examining neural correlates of anosognosia in Chapter 6 (i.e., Cosentino et al., 2015). Based on their main significant correlational finding reported in Table 3 the effect size was calculated as d = 0.93. We developed an a priori one tailed power calculation with G*Power 3.1.9.2 establishing a power of 80% which recommended a minimum sample size of 5 participants.

Finally, for cognitive mechanisms, one study (Jenkinson, Edelstyn, Drakeford, & Ellis, 2009) was selected for studies included in Chapter 5. The effect size from this study was calculated from the difference of source proportion between patients aware and unaware of their motor deficits reported in Table 1 in Jenkinson and colleagues (2009). Cohen's d calculated with G*Power 3.1.9.2 resulted in a d = 1.89. Based on these values a priori power analyses for two tailed non parametric Mann-Whitney analyses with 80% power revealed a minimum of 6 individuals per group.

2.2.5.2. Main analyses

Bivariate associations are examined through correlations (Spearman's and Pearson's product-moment correlations). Differences between groups are examined through t tests, ANOVAs, Kruskal Wallis and Mann Whitney U tests, as appropriate. Regression analyses were also be used to examine the association between anosognosia and proposed outcomes including cognitive and metacognitive variables. Non-parametric analyses were conducted when sample sizes are small and data is not normally distributed (i.e., detection of skewness and outliers that can affect the results of the analyses).

Chapter 3

Measuring Anosognosia: The Visual Analogue Test for Anosognosia for Memory impairment (VATAmem)

Summary of chapter

The previous chapter provided a general overview of methodological considerations and main research questions that are included in the following experimental chapters (Chapters 3 to 6). In this current chapter, an examination of the methods of assessing anosognosia for memory loss is presented, together with their most common pitfalls and limitations. In an attempt to overcome some of these limitations, the main aim of this chapter is to report on the development of a new tool for the measurement of anosognosia for memory impairment: The Visual Analogue Test for Anosognosia for Memory impairment (VATAmem).

3.1. Introduction

Early conceptualizations of unawareness of deficits were circumscribed to anecdotal descriptions in the literature, and lacked a clear definition as to what the object of awareness was (e.g., awareness of disease versus awareness of deficit) (Prigatano & Schacter, 1991). Following McGlynn and Schacter (1989), in order for the field of anosognosia to move forward, a clear conceptualization of anosognosia is necessary, along with the production of more specific and quantifiable measures of this disorder (see also Clare et al., 2002; Clare et al., 2005).

Several authors have expressed concern for the great variety and lack of standardization of measures across studies examining unawareness deficits, and its possible impact on the interpretation of underlying factors associated with this phenomenon (Clare, Wilson, et al., 2002; Cocchini et al., 2012; Cocchini & Della Sala, 2010; Cosentino & Stern, 2005; Jenkinson et al., 2011). An important factor, also

commonly neglected, is that each of these measures might be tapping into different mechanisms or levels of awareness, and that these might not share the same contributing mechanisms (Clare et al., 2011; Morris & Hannesdottir, 2004). As it is unlikely that one measurement will capture all the different components or levels of awareness, it is important that studies examining anosognosia use different measures specific to the component or level of interest. For example, in patients with ABI and/or dementia, different deficits can coexist, and awareness for these deficits has been shown to dissociate (e.g., a patient with two deficits, such as language and motor deficits, might be unaware of one deficit and have adequate awareness for the other (Breier et al., 1995; Kinsbourne & Warrington, 1963). Anosognosia for a single deficit can also be measured or observed at different levels. For example, one can measure what a patient says about his or her deficits (i.e., *explicit awareness*), but also how they behave in the context of the deficit (i.e., *implicit awareness*). The underlying mechanisms of anosognosia for different deficits can overlap, and at the same time, the mechanisms underlying anosognosia for one deficit can dissociate (Cocchini et al., 2012). It is thus crucial for research to focus both on awareness of multiple deficits and single deficits, with a combination of measures that can help understand how each component contributes to awareness and consequences associated with it (Cocchini et al., 2012; Cosentino et al., 2011). In order to do so, we first need to improve our current measures for anosognosia.

In the context of memory loss, most instruments assessing anosognosia, as the research focus, have been developed with individuals suffering from AD. In their influential review, Clare et al. (2005) described four main types of paradigms that have been used in the study of unawareness of memory deficits in dementia. These included

(i) Clinical ratings, (ii) Questionnaires, (iii) Objective Performance, and (iv) Phenomenological methods (see Table 3.1. for full description). Traditionally, the most common way of assessing anosognosia for memory deficits has been through unstructured clinical interviews (Schacter, 1991) that measure *explicit awareness*. These measurements, though may reveal interesting qualitative information at an individual level, they lack a systematic procedure to compare and categorize groups of awareness. More structured interview procedures include measures of clinically rated awareness (CRA). In CRA measures, the interviewer or clinician assesses the patient's explicit responses to probes of memory deficits as reflective of different levels of awareness (Cosentino et al., 2007; Reed et al., 1993).

An alternative way of assessing anosognosia is through questionnaires, which were sought by researchers to provide a more ecologically valid measure of awareness of memory deficits (Schacter, Glisky, & McGlynn, 1990). These questionnaires mainly measured anosognosia of memory loss through explicit judgements of specific everyday memory failures (Cosentino & Stern, 2005). These judgements can be compared to an informant's judgement of the person's memory abilities (i.e., Subjective Rating Discrepancy – SRD) (Clare, Wilson, Carter, Roth, & Hodges, 2002), or can be evaluated by a clinician during an interview process (i.e., Clinically Rated Awareness – CRA) (Reed et al., 1993). Following Clare et al. (2011), when studies use explicit measures such as clinical ratings and informant based discrepancy scores, it is likely that they are measuring a global higher order of awareness (i.e., "evaluative judgement"). These measures reliant on the memories of previous memory failures, are lacking the contextual information that one might experience at the exact moment when they make a memory

mistake (e.g., forgetting to take an umbrella with you when it is raining outside). Thus, these judgements, also referred to as *offline judgements,* are likely to be supported not only by an integrative prediction based on episodic memory of these types of events, but also from a general semantic notion of memory function (Agnew & Morris, 1998).

Table 3.1. Description of different measures of anosognosia (adapted from Clare et al., 2005).

Assessment	Description	Pros	Cons
Clinical Ratings	Clinician or experimenter rates the patient based on their response in interview, from records or informant interviews.	(i) Quick assessment of awareness (ii) Flexible interview.	(i) Inter-rater variability. (ii) Normative data lacking. (iii) Self judgements might be biased through factors such as personality, mood etc.
Questionnaires (compared to informant or clinician report)	Specific set of items on memory functioning assessed on patient and informants. The discrepancy scores reflect the unawareness.	(i) Standardization, reliability and validity. (ii) Different domains within one deficit may be explored.	(i) Questionable validity of the informant or the clinician response. (ii) Heavy load in memory or language abilities. (iii) Self judgements might be biased through factors such as personality, mood etc.
Objective performance	Self-reports are compared to objective Memory tasks. Metamemory judgements within a memory task.	(i) Standardized memory tests. (ii) Comparison with objective performance within the task.	(i) Laboratory measures might lack ecological validity. (ii) Self judgements might be biased through factors such as personality, mood etc.
Phenomenological	Awareness is determined through information from psychological and social factors obtained from records and informant reports.	(i) Contextualized assessment of awareness.	(i) No normative data. (ii) Bias of the assessor.

Offline or explicit assessments of anosognosia are generally easy and quick instruments aimed at measuring global judgements of memory performance in general (e.g., Do you have difficulty remembering appointments?). This type of measurement provides a continuous outcome that can represent the directionality and gradients of impairments in awareness (Clare et al., 2005; Clare, Wilson, et al., 2002). Explicit measures also provide the opportunity to explore how individuals endorse different types of memory failures (i.e., prospective or retrospective memory - Crawford et al., 2003; Smith et al., 2000). By using explicit measures of awareness, interesting qualitative responses may also be triggered from the subject being questioned (e.g., justification for deficits) (Bisiach & Geminiani, 1991). Combined with the above, one of the most attractive aspects of these measures is that they provide an easy and quick standardized tool to assess unawareness of deficits that can be administered by both trained and untrained staff.

Though existing explicit questionnaires examining anosognosia for memory impairment offer important information that has been linked to practical outcomes, they are not free from pitfalls. First, valid completion of explicit questionnaires may be challenged by patients' cognitive deficits. For instance, completing a questionnaire (i.e., remembering the questions, the instructions and the procedure) is in itself a memory task, and patients with severe memory difficulties may be unable to complete the form in a valid and reliable manner (Cocchini et al., 2012). Additionally, most explicit measures rely heavily on verbal comprehension, which can be also be disrupted in patients that have suffered ABI. Likewise, individuals with an executive syndrome may show perseveration across responses, patients with neglect may ignore one side of a

questionnaire, and so forth. Finally, many assessments lack normative data, complicating proper interpretation of responses (see Clare et al., 2005; Cosentino & Stern, 2005 for reviews). Relatively few studies have attempted to address these limitations (Clare et al., 2005; Clare, Wilson, et al., 2002; Cocchini et al., 2012; Cocchini, Gregg, et al., 2010; Della Sala et al., 2009). The aim of the VATAmem is to provide a reasonably quick and reliable instrument that introduces visual support in the form of vignettes and visual analogue scales to account for possible language deficits and difficulties to memorize the actual questions. Finally, a critical aspect of the VATAmem is that check questions are included to monitor both the patient's and informant's compliance and response reliability.

A second goal of the VATAmem was to examine potential variability in awareness across specific types of everyday memory failures, namely, prospective versus retrospective memory. Prospective memories can be defined as those pertaining to the future (e.g., remembering to carry out an action), whilst retrospective memories can be defined as those linked to the past (e.g., remembering past actions or events (Einstein et al., 2008) (see section 1.2.1.1, Chapter 1). Although prospective and retrospective memories are likely to be supported by similar underlying memory networks or structures (Einstein et al., 2008; Schacter, Addis, & Buckner, 2007; Underwood, Guynn, & Cohen, 2015), prospective memories differ from retrospective memories in their inherent self-initiated processes that form the intentions to remember something in the future (Craik, 1986). Further, the properties of prospective memories vary from those of retrospective memory, with regard to the types of associations with other memories and aspects of the environment that are required to prompt the individual to remember in the future (Marsh,

Cook, & Hicks, 2006). Interestingly, individuals appear to experience these memory failures differently. Indeed, previous studies examining subjective cognitive complaints with self the Prospective and Retrospective Memory Questionnaire (PRMQ) have found that individuals report prospective difficulties more frequently than retrospective (Crawford, Henry, Ward, & Blake, 2006; Crawford et al., 2003). Such studies, however, are based on reports by healthy older adults and may not translate to amnesic patients with variable degrees of awareness.

The purpose of this chapter is twofold. First, the psychometric properties and normative data for a new tool for the assessment of awareness of memory impairment (the VATAmem) are provided. The VATAmem, based on the PRMQ, attempts to build a new measure of anosognosia improving the existing assessment of anosognosia by tackling some of the most common pitfalls of these measures as described above. If this tool does indeed present an advantage to previous tools such as the PRMQ, a reduced impact of possible associated cognitive deficits (e.g., language impairment) should be observed. Secondly, in an attempt to further the understanding of unawareness of memory loss in patients with ABI, differences in awareness of memory for prospective versus retrospective memory will be examined across the VATAmem and the PRMQ. Results from this study will inform on the use of a novel, practical measure to characterize anosognosia for memory impairment in ABI.

3.2. Methods

3.2.1. Participants

A total of 190 individuals with ABI were initially referred to the study screening phase by consultant neurologists from three sites, the Columbia University Medical Center Department of Neurology Stroke outpatient clinic in the U.S., the NHS St. George's Hospital Stroke outpatient clinic in the U.K., and the Neuropsychology unit of Somma Lombardo Hospital in Italy. Of the initial group, 60 patients were considered for the study as they presented with no evidence of psychiatric illness but with evidence of memory difficulties as determined by age-corrected standardized scores of immediate and delayed story recall (Humphreys et al., 2012). A further 9 patients dropped out of the study due to lack of interest or failure to follow up, leaving a final sample size of 51 patients. The final sample of 51 patients (39% females) had a mean age of 61.40 years (SD = 14.90; range = 22 – 87) and 13.16 years of education (SD = 3.75; range = 4 – 22). Mean time since lesion onset was 2.89 months (SD = 4.85; range = .07 – 22). The majority had stroke (64.7% ischeamic; 11.8% haemorrhagic), 17.6% traumatic brain injury and 5.9% other injuries (i.e., 1 from obstructive hydrocephalus and 2 from hypoxia) (see Table 3.2.).

Table 3.2. Patient lesion description.

Nature of lesion	Unilateral Left hemisphere	Unilateral Right hemisphere	Bilateral	Including Subcortical structures
Vascular (n=39)	17	9	13	18
Traumatic (n=9)	4	2	3	1
Other (n=3)	1	-	2	2
Total (n= 51)	22	11	18	21

Clinical data of n = 51 patients with memory difficulties following ABI. Number of subjects with lesions encompassing left, right or both (bilateral) hemispheres, diffuse brain damage, and lesions that include damage to subcortical structures.

For each participant, an informant was recruited to provide evaluations of the patient's memory ability. For a subset of participants (n = 22), two informants were recruited to enable us to calculate the VATAmem cut-off score as described below in the statistical analysis and results section. This resulted in a total of 73 informants with a mean age of 50.85 (SD = 19.44; range = 18-92) years and 13.30 years of education (SD = 3.34; range = 8 – 23). All informants were people who frequently interacted with the patient on a regular basis.

Fifteen patients and their informants were retested after 48 to 72 hours to examine test re-test reliability.

3.2.2. Measures

3.2.2.1. Cognitive measures

All patients underwent an initial general cognitive assessment and specific cognitive tests to evaluate long- and short-term memory, language, attention, and executive functions. Due to different scoring systems across countries, patients' performance in each measure was converted to standardized z-scores, which were then collapsed to represent each cognitive domain (i.e., memory, language, and executive function).

Patients were assessed with the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975). The score ranges from 0–30. Higher scores represent higher cognitive functioning and a score below 24 has been used as an indicator of general cognitive difficulties (Folstein et al., 1975; Kukull et al., 1994).

Regarding memory, all patients completed the Rivermead Behavioural Memory Test (RBMT) (Wilson et al., 2003; Wilson et al., 2008) described in section 2.2.4.2.2. of Chapter 2. Patients' short-term memory was assessed with Digit and Spatial span tests (Orsini et al., 1987; Randolph, 2012). The digit forward raw scores ranged from 0 to 16 for the English version and from 0 to 10 for the Italian version. Raw scores of the spatial span ranged from 0 to 10 (Corsi, 1972). Visuospatial span was assessed through the Visual Pattern Test in the Italian sample (Della Sala, Gray, Baddeley, Allamano, & Wilson, 1999) where patients have to reproduce a visuospatial matrix. Raw scores range from 2 to 15. For each patient a final z-score for verbal (i.e., Digit span) and visuospatial (i.e., Spatial and Visuospatial spans) short term memory was calculated.

Language was assessed using naming subtests from two measures. English speaking patients were assessed with the naming subtest of the BCoS Battery (Humphreys et al., 2012) described in section 2.2.4.2.1. in Chapter 2. Italian speaking patients' naming abilities were measured with the subtest of the "Esame Neuropsicologico per l'Afasia" (Capasso & Gabriele, 2008). Raw scores range 0-10, with higher scores also representing better naming abilities. Normative data cut-offs were used to classify patients' performance as impaired or not impaired in their language abilities. To compare how the degree of language difficulties mapped on to the degree of unawareness a within sample z-score was also derived.

Finally, measures of rule following and set switching were included for the measurement of executive functions. These included: (i) the executive subtest in the BCoS Battery (Humphreys et al., 2012) also described in section 2.2.4.2.1. in Chapter 2; and (ii) the Trail Making Test (Reitan & Wolfson, 1985), which is composed of two trail making subtests. In Part A, the patient is asked to draw lines linking numbers in ascending order from 1 to 25 in the shortest time possible. In Part B, the patient is asked to repeat the same procedure, but alternating between letters and numbers (i.e., 1–A; 2–B; 3–C). The total raw scores of the executive BCoS Battery test (ranging from 0 to 18) and the Trails B (e.g., time to complete in seconds) were combined to calculate an overall z-score of executive function.

3.2.2.2. Awareness of memory deficit

Self and informant reports of memory performance were obtained through two measures in a counterbalanced order.

3.2.2.2.1. Prospective and Retrospective Memory Questionnaire (PRMQ)

The PRMQ (Crawford et al., 2006; Smith et al., 2000) includes a total of 16 items requiring patients and informants to rate the frequency of the patient's everyday memory mistakes, from 5 (Very often) to 1 (Never). Raw scores are converted to true scores, as reported by Crawford et al., (2003) and Crawford et al., (2006), and can range from 16 to 80 with lower scores representing more difficulties. Discrepancies between patients and informants can thus range from -64 to +64, with a 0 representing perfect agreement. Positive values in discrepancy scores represent an informant rating a subject as having more difficulties than he or she is endorsing, and negative values reflect reports of more difficulty by the patient. The PRMQ provides two cut-off scores to interpret the difference between an individual and their informant ratings that can be used for the assessment of anosognosia (i.e., cut-off of 7 with a significance value of p=.05 for the full scale and a cut-off of 9 for prospective and retrospective subscales; Crawford et al., 2006).

3.2.2.2.2. The Visual Analogue Test for Anosognosia for Memory impairment (VATAmem)

Preliminary phase of the scale.

The final version of the VATAmem was derived following a preliminary phase, consisting on a series of pilot studies, that allowed refinement of questions and vignettes based on feedback from a total of 9 patients with memory disorders (age M = 53; SD = 20.50; range 25- 78; 89% male) and 40 healthy adults (age M = 51.60; SD = 17.37; range: 25-85; 52% male). Based on the outcome of these pilot studies, fifteen questions were selected for the final version.

Final Scale

The VATAmem consists of 15 questions assessing everyday memory situations, 1 practice item to ensure the participant's compliance with the test (i.e., Do you have difficulty watching TV?), and 4 check questions to control reliability of participants' responses, as described below (see Figure 3.1. for an example). As in the PRMQ, the 15 memory-related items explore two different dimensions of memory: prospective and retrospective memory. Prospective memory questions refer to those activities in which an individual needs to remember an intention for a future action (e.g., remembering to call someone later as they did not answer the phone). Retrospective items examined memory for activities in which an individual needs to recall past learned information (e.g., remembering that they have already told a person a story). All items were balanced across items referring to *self versus environmentally cued* activities; that is, those in which an individual relies on internal cues to remember information (e.g., remembering appointments without the help of a calendar) versus remembering information when cued by something in the environment (e.g., remembering to give something to someone when you see them). All items were also balanced across short versus long term memory, that is, memory for information that was just learned versus information that had been learned before. Thus, following similar classification as in the PRMQ, each question represents one aspect of each of the three dimensions. For example, "Do you have problems remembering that you have already told the same story to the same person on a previous occasion?" would represent retrospective, long term memory, and environmentally cued dimensions.

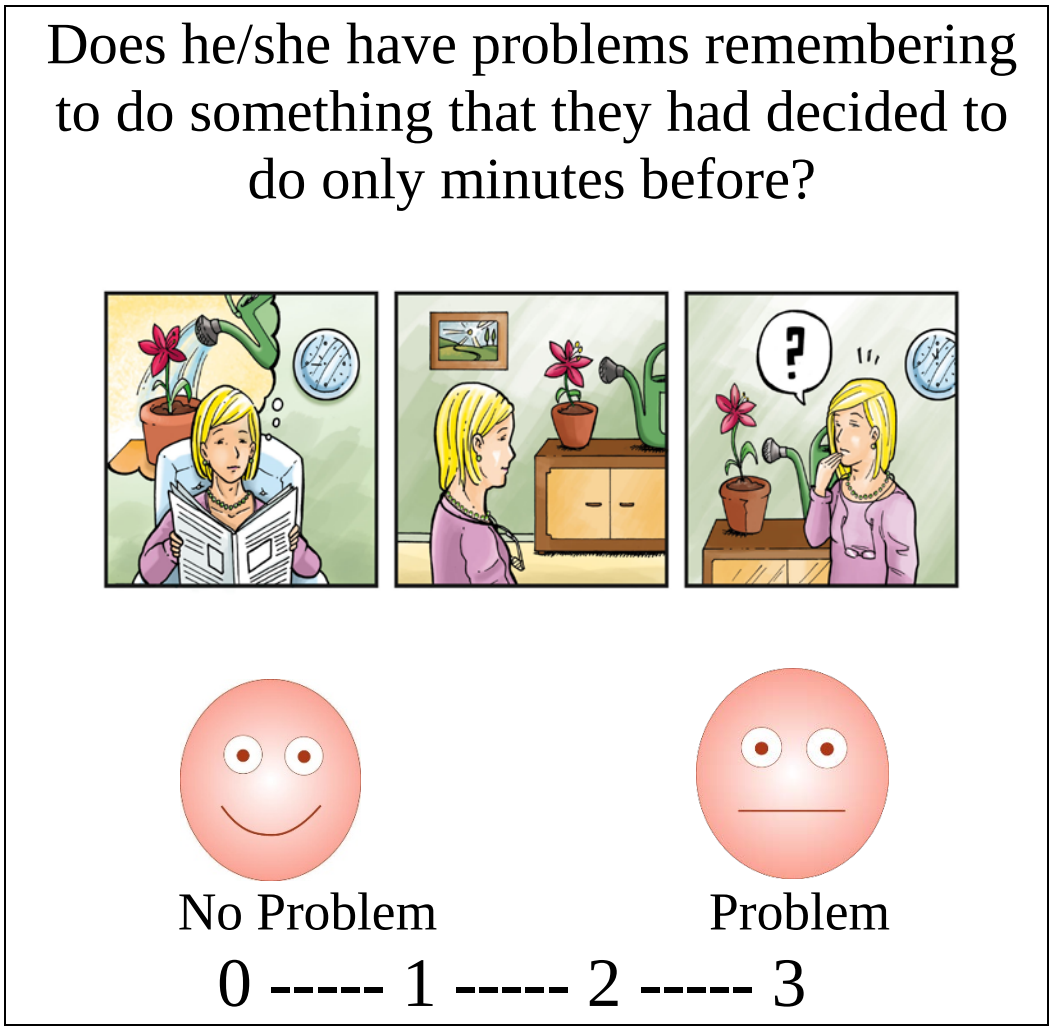

Figure 3.1. Example of a question, vignette and visual-analogue scale from the VATAmem.

Patients were asked to rate their current ability in each task depicted by the vignettes by saying the number or pointing to a specific point on the 4–point scale (Della Sala et al., 2009; Cocchini et al., 2010). Informants rated the participants using the exact same items with slightly varied wording to refer to a third person.

To account for the reliability of responses, 4 “check questions” were evenly distributed throughout the questionnaire (see “Check” questions in Appendix 6). These questions allowed us to account for possible perseveration, lack of comprehension or attentional and visual deficit that may prevent the respondent from attending to one side

of the scale (Cocchini et al., 2010; Della Sala et al., 2009). The check questions were designed to elicit, when appropriately endorsed, scores in one extreme of the scale. Two of these check questions would have their appropriate response on the left end of the scale (0 – no problem or 1 – mild problem; see check question 2 & 3 in Appendix 6) and three on the right end of the scale (3 – problem or 2 – moderate problem; see check questions 1& 4 in Appendix 6). For questions depicting tasks requiring a motor component, two versions were provided with left and right limb affected, to provide reliable check questions for people that may be experimenting weakness or paralysis in one side of the body (i.e., hemiparesis). The ratings of the "check questions" were not included in the final score of the VATAmem; however, participants who failed to provide the expected responses to any of the four check questions were excluded for later analyses as their responses were considered not reliable.

The 15 questions were presented in the same fixed pseudo-random order with memory dimensions (prospective/retrospective, self/environmentally cued and short/long term) evenly distributed throughout the questionnaire, as reported in Appendix 6. To minimise possible associated attentional disorders, such as neglect (Della Sala et al., 2009), participants were shown one question at a time in a plasticised A4 sheet in portrait orientation.

First, a practice question was presented to make sure the participant understood how to use the rating scale. Then the questions were read aloud by the examiner, allowing time for the participant to read them again, if they wished, and to observe the vignettes. Special emphasis was placed during administration that the responses should reflect current abilities.

VATAmem- Total score

The VATAmem total score was calculated on the 15 memory-based questions and it ranged from 0–45. A discrepancy value was obtained subtracting the participant's score from informant's scores. When two informants were available, the mean was calculated and this was compared with the patient's score to calculate the discrepancy value. The discrepancy value ranges from -45 to 45, where a discrepancy value of 0 means perfect agreement. A positive discrepancy means that compared to the informant, the participant has overestimated his/her memory abilities; while a negative discrepancy value indicates that the participant has underestimated his/her own memory abilities. This score may provide information about possible depression or anxiety; however, this is not examined in this study (see Chapter 4 for an examination of mood).

VATAmem- Subscales

As it was my interest to examine variability of awareness across different types of memory failures, two main subscales were devised to measure awareness of prospective and retrospective memory loss. In Crawford and colleagues' (2003) factorial examination of the PRMQ (2003), the authors found that although they included items reflective of various types of memories (i.e., short versus long term memory, self versus environmentally cued memory, and prospective versus retrospective memory), only general memory, prospective memory, and retrospective memory were observed as independent factors. Two subscales were thus examined to measure awareness of prospective and retrospective memory abilities. The Prospective memory subscale includes 7 questions evenly spread across the questionnaire (i.e., see questions 1, 2, 6, 7, 9, 12 & 13 of VATAmem questionnaire in Appendix 6) with a total score ranging from

0 to 21; whilst the Retrospective memory subscale includes 8 questions also evenly distributed (i.e., see questions 3, 4, 5, 8, 10, 11, 14 & 15 of VATAmem questionnaire in Appendix) with a total score ranging from 0 to 24.

3.2.3. Statistical Analyses

In order to validate informants' reports in this study, Spearman correlations were conducted to examine how informants' reports mapped on to actual memory performance measures. Non parametric Spearman correlations were chosen over Pearson product moment correlations in this study when data did not meet the assumptions for parametric correlations (e.g., data not being continuous, outliers > 3 SD, lack of homoscedasticity or normal distribution in the data).

The Crawford and Howell (1998) modified t test was used to develop the VATAmem cut-off for anosognosia in the full memory scale, and for prospective and retrospective subscales. Independent sample t tests were conducted to examine differences of awareness of patients and informants across prospective and retrospective scales. From this cut-off two further severity scores were derived that represented the level of disagreement in all items as follows: (i) mild anosognosia (statistically derived cut-off – disagreement of one point in all items); (ii) moderate anosognosia (disagreement of one point in all items – disagreement of two points in all items); (iii) severe anosognosia (disagreement > two-point disagreement across all items). Examination of reports on prospective versus retrospective memory were compared across both patients and informants through two 2x2 Repeated Measures ANOVA (awareness group x type of memory).

Test-retest of the VATAmem was evaluated through product moment Pearson correlations of overall scores of the VATAmem in patients tested on two separate occasions as all assumptions for parametric analyses were met. Internal consistency was examined for both self and informant reports through Cronbach's alpha and item sensitivity analysis. Construct validity of the VATAmem was examined through Pearson product correlation between self and informant reports in the VATAmem and the PRMQ as all assumptions for parametric analyses were met. Partial and one tailed Spearman correlations were conducted to examine the relationship between cognitive measures and anosognosia as determined by the VATAmem and the PRMQ as cognitive scores of severity were used and data did not meet the assumptions for Pearson correlation (e.g., ordinal measures and not normally distributed). Scatterplots of correlational analyses are included in Appendix 8.

3.3. Results

3.3.1. Cognitive measures

Mean raw score of the sample on the MMSE was 25.94 (SD = 2.87; range = 19-30). Some patients did not complete the full battery of tests (see Table 3.3.). In particular, one patient did not complete the RBMT but he showed evidence of long term memory impairment on the initial Story Recall test.

As shown in Table 3.3., all patients showed a long term memory impairment and executive functions deficits. Nearly half (49%) of our sample also showed language difficulties; whereas short term memory was spared in the majority of the cases.

Table 3.3. Neuropsychological assessment of overall sample of patients with ABI.

Cognitive functions impairment	% of patients showing pathological performance (*n/N*)
Long Term Memory (LTM) impairment	100% (50/50)
Mild	26% (13/50)
Moderate	37% (19/50)
Severe	35% (18/50)
Short Term Memory (STM) impairment	
Verbal STM	2% (1/51)
Visuospatial STM	22% (9/41)
Executive functioning impairment	57% (29/51)
Mild	6% (3/51)
Moderate	6% (3/51)
Severe	45% (23/51)
Language functioning impairment	49% (25/49)

Summary of cognitive abilities of sample of 51 ABI patients. *n* = total patients with cognitive impairment; N = total patients with available data on cognitive measures. LTM: Performance on the RBMT.

3.3.2. Awareness of memory deficits

3.3.2.1. Prospective and Retrospective Memory Questionnaire (PRMQ)

Based on the PRMQ, 54.9% (n = 28) of patients were classified as unaware of their memory deficits following the Crawford et al. (2006) cut-off. Mean discrepancy scores were 20.2 (SD = 9.8; range = 8 - 44) for patients unaware of their deficits and –4.7 (SD = 7.5; range = –21 - 6) for patients aware of their deficits, indicating that patients who were aware of their deficits actually tended to underestimate their memory abilities compared to their informants. Within the subscales, 25 patients were classified as unaware of their retrospective memory failures versus 26 as unaware of the prospective

memory failures. These patients largely overlapped with those classified as unaware by the total scale cut-off; however, two cases were classified as unaware on the prospective or on the retrospective scale but they were not deemed as unaware according to the overall scale's cut-off.

3.3.2.2. Visual analogue Test for Anosognosia (VATA-mem)

3.3.2.2.1. Preliminary version of the scale

A series of Spearman correlational analyses for each of the 15 items was run between pairs of informants rating the same patient. In all cases, the correlation was significant (at least *rho* = .54, p = .01; d = 1.28). This result suggests that the content of the 15 items selected for the final version of the VATAmem was similarly interpreted and rated by different informants.

3.3.2.2.2. Check questions

One informant had to be removed from further analyses as she failed one check question in the VATAmem. In this case, the patient's rating was compared with the other informant's score. One patient was also removed from further analyses due to not passing one check question. The remaining patients and informants provided the expected responses to the check questions.

3.3.2.2.3. Informant report and patient's memory performance

A final total of 72 informants were included in the sample. Informant scores on the VATAmem were compared to the corresponding patients' memory performance measured by the RBMT. Spearman correlation analyses showed a significant association between informants' reports and patients' performance in standardized memory assessments (*rho* =

.33, p = .02; d = .70), suggesting that the more severe the patient's score on memory tasks, the worse informants reported patients' memory to be.

3.3.2.2.4. Unawareness cut-off score

The unawareness cut-off was derived following a similar procedure adopted by Cocchini and colleagues (2010). An "informant discrepancy" score was calculated for the 22 pairs of informants that evaluated the same individual (i.e., two informants per patient). This score ranged from -45 to +45, with 0 meaning perfect agreement and ±45 complete disagreement. The mean and standard deviation of the informants' discrepancy score was used to calculate a "discrepancy threshold".

In order to calculate the discrepancy threshold, Crawford's and Howell's (1998) modified t test was used. The mean value of the discrepancy score between the 22 pairs of informants and the standard deviation was M = 3.75 and SD = 3.44. The critical value of t with d.f.= 21 in a two-tailed test was 2.080. According to the modified t test by Crawford and Howell, the discrepancy value at which we would have this critical value of t with a likelihood of less than 5% was 10.5.

Therefore, an overall cut-off score to indicate a significant discrepancy between the patient and informant was set to 10.5; scores above this value are suggestive of a significant lack of awareness on the part of the patient. Following Della Sala et al. (2009), additional cut-off scores to signify the degree of unawareness were established. The first cut-off represented an average disagreement of 1 point in all 15 items. A discrepancy value between 10.6 and 15.0 included was then considered as indicative of *mild anosognosia*. The second cut-off represented an average disagreement of 2 points in all

15 questions, with discrepancy values between 15.1 and 30.0 included considered to be indicative of *moderate anosognosia*. Finally, a discrepancy value between 30.1 and the maximum discrepancy score of 45 was considered as indicative of *severe anosognosia* (see Table 3.4.).

Two cut-off scores were derived in the same manner as above for the retrospective and prospective sub-scales considering the corresponding memory items. The mean and standard deviation of the informant discrepancy score for the prospective subscale were M = 1.89 and SD = 1.34, and M = 2.23 and SD = 1.90 for the retrospective subscale. The cut-off scores for the prospective and retrospective sub-scales are reported in Table 3.4.

Table 3.4. Awareness cut-off scores for total scale, prospective and retrospective subscales with degrees of severity

		Degree of unawareness		
	Aware	Mild anosognosia	Moderate anosognosia	Severe anosognosia
Total scale	0.0-10.5	10.6-15.0	15.1-30.0	30.1-45.0
Prospective subscale	0.0-4.7	4.8-7.0	7.1-14.0	14.1-21.0
Retrospective subscale	0.0-6.4	6.5-8.0	8.1-16.0	16.1-24.0

Awareness for memory deficits

Nearly a third of the 51 patients were classified unaware of their deficits with discrepancy values above 10.5. Different degrees of severity are reported in the Table 3.5.

Prospective memory questions seemed to elicit disagreement between patient and informant evaluations more often than Retrospective memory questions. A total of 15 patients were classified as unaware of their deficits in the Prospective subscale, in contrast to 9 in the Retrospective subscale. Within patients' reports there was no significant interaction effect between awareness group and type of memory ($F(1, 48) = .21$, $p = .65$). Overall though, both aware and unaware participants endorsed less retrospective memories than prospective memory ($F(1, 48) = 11.83$, $p = .001$). Aware participants endorsed overall more memory difficulties than those unaware of their deficits ($F(1, 48) = 13.78$, $p = .001$). Similarly to patients reports overall prospective memory difficulties were endorsed more frequently than retrospective memory by informants ($F(1,48) = 46.76$, $p < .001$), but opposed to patients informants endorsed

overall more memory difficulties to unaware patients compared to aware patients ($F(1,48) = 44.62$, $p < .001$). No interaction effect between awareness and type of memory was observed ($F(1,48) = 1.36$, $p = .25$).

Table 3.5. Patients classified as aware and unaware of their memory deficits

		Degree of unawareness		
	Anosognosia	Mild anosognosia	Moderate anosognosia	Severe anosognosia
Total scale	15 (29.4%)	6 (11.8%)	8 (15.7%)	1 (2%)
Prospective subscale	15 (29.4%)	5 (9.8%)	9 (17.6%)	1 (2%)
Retrospective subscale	9 (17.6%)	1 (2%)	7 (13.7%)	1 (2%)

3.3.2.2.5. Reliability, sensitivity & validity

3.3.2.2.5.1. Test-retest reliability

A total of 15 patients were retested on a separate occasion between 24 hours and 3 days after first assessment). A Pearson correlation analysis showed a high significant coefficient between test and retest ($r = .92$, $p < .001$; $d = 4.70$).

3.3.2.2.5.2. Internal Consistency and test sensitivity

Internal consistency was evaluated through Cronbach's alpha. The internal consistency of the whole scale for self-evaluations was of $\alpha = .91$ and $\alpha = .90$ for informant evaluations. Internal consistency for subscales was of $\alpha = .88$ and $\alpha = .85$ for self and informants in the Prospective subscale scale and $\alpha = .81$ for self and $\alpha = .81$ for informant report on the Retrospective subscale.

In terms of overall sensitivity, the VATAmem identified 15 patients as being unaware of their memory deficits while the PRMQ identified 28 patients (χ^2= 12.68, p < .001; φ = *.50*), suggesting that the VATAmem diagnostic criteria may be more conservative, but also less prone to false positives than the PMRQ. Of the 15 patients identified by the VATAmem as unaware of their deficits, 93.3% (n = 14) were also classified by the PRMQ. Out of the 28 identified as unaware by the PRMQ 50% (n = 14) were also identified by the VATAmem. Thus 14 patients overlapped as unaware by both scales and 15 mismatched. Out of the 15, 14 were classified unaware only by the PRMQ, and 1 only by the VATAmem. To further explore the reasons underlying the mismatched cases several analyses were conducted. Specifically, the subset of cases that were deemed as unaware by the PRMQ but not the VATAmem were examined in relation to cases deemed unaware by both. No significant differences were observed across all cognitive domains between the groups (p > .05). Following these results, analyses were conducted to examine if differences between these groups lay within the reports of both patients and informants. Results showed that informants reported similarly in the VATAmem and the PRMQ. Specifically, informants on the VATAmem reported significantly less memory difficulties in those that were deemed unaware only by the PRMQ as opposed to those who were deemed unaware by both measures (t (26) = -4.72, p < .001; d = 1.78). Similarly, informants on the PRMQ endorsed less memory difficulties in those deemed unaware only by the PRMQ (t (26) = .82, p = .06; d = .74) in line with informants reports on the VATAmem, though this difference was not significant. Further, Spearman correlations showed that informant's reports mapped on similarly to memory performance on both measures (i.e., *rho* = .33 p = .02, d = .07; PRMQ, *rho* = -.47, p <

.001, d = 1.06). With regard to patient's reports, results showed that patients were endorsing less memory problems on the VATAmem when they were deemed unaware by both the PRMQ and the VATAmem than when they were deemed unaware only by the PRMQ (t (26) = 2.93, p = .007; d = 1.11). Interestingly patients' reports on the PRMQ revealed no significant differences between those deemed unaware only by the PRMQ versus those by both measures (t (26) = .27, p = .79).

Finally, as with the previous VATA's an item level analysis was conducted to examine each item's sensitivity "correctly detected", and specificity "correctly not detected" respective of the overall VATAmem unawareness cut-off (e.g., total scale anosognosia cut-off). That is, the extent to which i) an individual item showed a positive discrepancy (i.e., evidence of over-estimation of own memory ability) between self and informant when a patient was deemed unaware based on the overall VATAmem score (Correctly detected); and ii), when a single item showed no discrepancy or negative discrepancy when the patient was classified as aware based on the overall VATAmem score (Correctly not detected, CND). As reported in Table 3.6., item analysis revealed that on average the items showed a relatively high sensitivity and specificity (M = 74.5; SD = .05) for detecting unawareness as defined by the overall scale. Items such as question 8 "remembering people's names" and question 11 "knowing your way around your home/ward" had the highest sensitivity and specificity.

Table 3.6. Item level percentages of HITS (correct detected) and CND (correct non detected) for total scale and subscales for prospective and retrospective memory.

Items	Total scale HITS + CND %	Prospective HITS + CND %	Retrospective HITS + CND %
Q1. Doing something	66.7 %	70.6 %	-
Q2. Posting a letter	72.5 %	72.5 %	-
Q3. Directions	74.5 %	-	70.6 %
Q4. Drinking coffee	72.5 %	-	72.5 %
Q5. Same story	70.6 %	-	58.8 %
Q6. Turn off the cooker	74.5 %	74.5 %	-
Q7. Appointment	80.4 %	76.5 %	-
Q8. Peoples names	78.4 %	-	74.5 %
Q9. Walking into a room	80.4 %	84.3 %	-
Q10. The time	72.5 %	-	76.5 %
Q11. Home/ward	80.4 %	-	84.3 %
Q12. Umbrella	72.5 %	72.5 %	-
Q13. Saying	74.5 %	74.5 %	-
Q14. Introduced	74.5 %	-	76.5 %
Q15. Names	76.5 %	-	84.3 %

Total scale mean HITS + CND % = 74.5 %; SD = 0.05%. Prospective subscale mean HITS + CND %= 73.1 %; SD = 0.08%. Retrospective subscale mean HITS+ CND % = 74.8 %; SD = 0.08%.

3.3.2.2.5.3. Validity

Self and informant evaluations on the VATAmem were compared to ratings provided in the PRMQ. Both self (r = .64, p < .001; d = .41) and informant (r = .67, p < .001; d = .45) evaluations were significantly associated with those reported in the PRMQ.

Further, patient-informant discrepancy scores for PRMQ and VATAmem were also correlated (r = .68, p < .001; d = .46).

3.3.2.3. Cognitive functions & awareness

Raw scores of global cognition, standardized scores of memory and executive function, and within sample language scores were examined in relation to the overall VATAmem discrepancy scores. Partial correlations adjusted for demographics showed a negative correlation between anosognosia and global cognition (r = -.38, p = .008; d = .82). One tailed Spearman correlations revealed a significant association between the severity of the memory impairment and unawareness (RBMT-2, 3; *rho* =.31, p = .01; d = .65), no significant association was found between the severity of executive functions difficulties and unawareness (Switching task and TMT; *rho* = .22, p = .06; d = .45). No significant association was found between anosognosia and the language index (*rho* = -.12, p = .21; d = .24). The PRMQ was also significantly correlated with global cognition (r = -.28, p = .03; d = .58) and memory (*rho* = .38, p = .003; d = .82). In contrast to the VATAmem, the PRMQ was significantly correlated to language index (*rho* = -.26, p = .04; d = .54) and executive functions (*rho* = .25, p = .04; d = .52).

3.4. Conclusion

The main aim of this study was to develop a measure of explicit anosognosia for memory deficits that can be used in patients presenting with a range of cognitive and language abilities, and that will provide information regarding awareness for both prospective and retrospective memory impairment. As with other similar measures

(VATA-L and VATAm - Cocchini, Gregg, et al., 2010; Della Sala et al., 2009) the main aim was to provide a psychometrically sound measure that could not only detect anosognosia, but also distinguish between different levels of severity of unawareness providing cut-offs for mild, moderate and severe anosognosia. Overall, results suggest that the VATAmem has high validity and reliability, and differentiates between awareness of retrospective and prospective memory failures.

With regard to data obtained from the informants, results showed a significant association between their reports and the patients' memory deficits on neuropsychological testing. Thus, although it has been noted that variables such as caregiver culture, burden and mood related disorders can affect informant reports of someone's memory abilities (Prigatano, 2005, 2010), informants in this sample overall, appeared to be a reasonably reliable source of information regarding patients' level of memory functioning. Further, the VATAmem informant version also requires informants to answer check questions to ensure reliability of their responses. One informant failed the check question. Interestingly, this participant endorsed the majority of the items on the VATAmem as severe, in contrast to the other informant who endorsed items of moderate and mild difficulties in line with the patient's performance on standardized memory assessments. This result suggests that the check questions can provide a useful way to gauge also on informant's reliability, avoiding potential false positives, as it would have been for this patient if the first informant's data were not excluded as unreliable.

Regarding its psychometric properties, the VATAmem has strong internal consistency and reliability across time, rendering it useful as a follow up measure. In

terms of its validity, the VATAmem was associated with the PRMQ, another measure of anosognosia, suggesting that it taps into similar self-reflective abilities captured with the PRMQ. A striking difference though was observed when the cut-offs for each measure were applied. With regard to rates of anosognosia according to the VATAmem based on the cut-offs developed in this study, 27.5% of the sample was classified as unaware of their deficits (7.8% of the sample classified as mildly unaware, 15.7% as moderately unaware and 2% as severely unaware). In contrast, the PRMQ identified more patients as unaware of their deficits (54.9%; n = 28). Although it is possible that the PRMQ represents a more sensitive measure for anosognosia, based on these results, as discussed below it is suggested that the PRMQ may capture impairments other than anosognosia that the VATAmem does not.

Developing on the PRMQ, the VATAmem has been designed to account for possible associated cognitive difficulties following ABI by including visual aids during questioning and check questions for both patients and informants to ensure adequate levels of reliability in their responses. Following ABI, patients with memory difficulties may also have language difficulties, for example, and long written or open-ended questions may limit an accurate communication of their awareness. As the other VATAs for motor and language deficits, this scale was developed to include vignettes depicting common memory related mistakes and a visual analogue scale to reduce the demands on these cognitive functions. Indeed, the PRMQ was associated with language and executive function abilities while the VATAmem was not.

The VATAmem also enables measurement of awareness for prospective versus retrospective memory failures. Interestingly, results showed that more patients were

categorized as unaware of prospective memory deficits (n = 15) than retrospective (n = 9). As noted in previous studies, awareness for prospective and retrospective memory abilities/difficulties can differ (Mäntylä, 2003; Wilkins & Baddeley, 1978), and elderly individuals have a tendency to endorse higher levels of difficulty in prospective memory than in retrospective memory (Crawford et al., 2006; Crawford et al., 2003). In this study, it was observed that patients' reports were comparable across prospective and retrospective scales, but it was the informants who endorsed more problems in prospective than retrospective abilities. Following Mäntylä (2003), informants might be more sensitive to prospective memory failures given the concerning consequences of these memory lapses (e.g., missing a doctor's appointment, forgetting to deliver an important message, etc.). These lapses might be thus more obvious and emotionally salient for informants. Another possibility is that prospective memory failures are more common than retrospective memory failures and thus informants would note these difficulties more frequently. Future studies should examine these two possibilities, along with patient performance and ratings in both retrospective and prospective memories, to determine more precisely the basis of differences in awareness scores for these two types of memory.

Separate analyses were conducted to compare several cognitive measures to the discrepancy values of the VATAmem. A strong relationship between memory functioning and unawareness of memory deficits was shown. These results showed that overall, those that were unaware of their memory difficulties performed worse in memory suggesting a role of memory abilities and overall cognitive deterioration in supporting awareness in this population (see Agnew & Morris, 1998; Ansell & Bucks, 2006;

Mograbi et al., 2009). Finally, although previous reports have found unawareness for memory loss to be associated with executive functions (López et al., 1994; Michon et al., 1994; Reed et al., 1993), this study does not replicate this finding. It is possible that the lack of relationship between anosognosia and executive functions could be due to the fact that the VATAmem minimizes the influence of other associated difficulties. However, this result is not uncommon, as others have also failed to replicate this relationship (Starkstein et al., 1996; Vogel, Hasselbalch, Gade, Ziebell, & Waldemar, 2005). The lack of consistency across studies on anosognosia has been interpreted by some as representative of the multifactorial nature of anosognosia as described in Chapter One (Cocchini et al., 2012; Cocchini et al., 2002; Fotopoulou, 2014; Gainotti, 2018; Marcel et al., 2004; Orfei et al., 2007; Vuilleumier, 2004). That is, anosognosia is not a unitary syndrome and different subtypes of anosognosia may exist (Agnew & Morris, 1998; Gainotti, 2018; McGlynn & Schacter, 1989) and may be linked to different associated cognitive abilities and deficits. Others have also highlighted that although executive functions can contribute to unawareness, processes that are specific to self-evaluation, such as self-monitoring, are more likely to underlie unawareness of memory deficits (see Chapter 5) (Cosentino et al., 2007; Rosen, 2011; Rosen et al., 2014).

This study has several limitations that should be considered, including, a relatively small sample size and a heterogeneous etiology of brain injury. Although the sample was heterogeneous, it was largely formed (>70%) by elderly patients who had suffered from a stroke. This might limit the applicability of this scale to other groups such as young patients with traumatic brain injuries. Further, although informant's reports were correlated with overall memory severity, this study did not assess if their

reports on prospective and retrospective mapped on to prospective and retrospective memory performance respectively. With regard to reliability, test-retest was conducted within 1-3 days. This might present a limitation as it may not reflect clinical settings (e.g., rehabilitation centers) follow up timeframes which may be longer. Overall though, the VATAmem can provide a useful and reliable tool to measure anosognosia for memory loss. The alleviation of language and memory load plus the use of vignettes may provide a more accurate assessment of one's awareness of memory deficits than that obtained from verbally based measures. The VATAmem will thus be used as a measure of anosognosia in the following chapters where different mechanisms suggested to underlie anosognosia will be explored.

Chapter 4

Mood, Personality & Unawareness of Memory Loss

Summary of chapter

The previous chapter presented a new tool for the measurement of anosognosia for memory deficits, The Visual-Analogue Test of Anosognosia for memory impairment (VATAmem). Results supported the VATAmem as a reliable and valid tool that appears to overcome some of the limitations of other existing measures. Therefore, the VATAmem will be used across this chapter and the following chapters as a measure reflective of global awareness and of the clinical syndrome of anosognosia for memory deficits (i.e., the extent to which they are unaware of their overall everyday memory failures).

This chapter is the first of three chapters (Chapters 4 to 6) in which different factors associated with the expression of anosognosia for memory loss are explored, including psychological, cognitive, metacognitive and neuroanatomical factors. Specifically, this chapter will examine the relationship of psychological factors, including personality and mood, in relation to anosognosia for memory loss in a sample of patients with memory loss after stroke.

4.1. Introduction

A classic distinction of the study of anosognosia has been defined between psychological or motivational based theories, and neurological or neuropsychological theories (Bottini et al., 2010). This distinction is commonly used to provide a conceptual categorization of mechanisms proposed to underlie anosognosia and can encompass varied theories and methodologies as outlined in Chapter 1. This chapter is aimed at investigating the most relevant theories and studies examining psychological factors in

relation to anosognosia and introducing new results of the association between anosognosia of memory loss, mood, and personality in a sample of patients with memory deficits following stroke.

There are different ways by which researchers have approached the study of psychological factors in relation to anosognosia. Historically, psychological or motivational proponents such as Weinstein and Kahn (1995) have attempted to explain anosognosia as a psychological reaction to the information of having an acquired deficit (Goldstein, 1939; Sandifer, 1946). The basis of this argument can be understood within Freud's classical psychodynamic theory of self defence mechanisms (Freud, 1946; Freud, 1996). Sigmund Freud, believed that all individuals have predisposing psychological processes that serve to protect the ego, or the self, from information that can affect its own equilibrium or well-being. Ramachandran and Blakeslee (1998), have highlighted the most relevant of Freudian mechanisms with regard to anosognosia as (i) *denial*: the patient denies strongly that there is a problem or a deficit (ii) *repression*: although the patient has access to information regarding the deficit and might admit some difficulty they quickly repress that information and revert to denial; (iii) *reaction formation*: a patient asserts the opposite of what they suspect to be true (i.e., they have a deficit). In this example, a patient with memory deficits might assert that they have unique memory abilities and can remember better than most people; and (iv) *rationalization*: the patient elaborates logical reasoning as to why they are experiencing a deficit. For example, a patient with memory loss might say that they got the year wrong because they are retired and never check the calendar anymore, although they might be 20 years off the actual date. These common psychological mechanisms present in healthy

individuals, have been proposed to be magnified in patients that have anosognosia for their deficits (Ramachandran, 1995).

The above proposition by Ramachandran, was derived from observations and experiments developed as single case studies conducted with patients presenting anosognosia for their hemiplegia (Ramachandran, 1994, 1995; Ramachandran & Blakeslee, 1998). One of the more well-known experiments conducted by Ramachandran was that of vestibular caloric stimulation (Ramachandran, 1995; Turnbull, Fotopoulou, & Solms, 2014). This study, previously conducted by Cappa, Sterzi, Vallar, and Bisiach (1987) and replicated by others (see Rode et al., 1992; Ronchi et al., 2013; Vallar, Sterzi, Bottini, Cappa, & Rusconi, 1990), involved irrigating a neglect and anosognosic patient's ear canal with ice-cold water. The patients who underwent this procedure were reported to overcome their neglect and become aware of their paralysis while the effects of the caloric stimulation lasted, reverting to anosognosia as the effects dissipated. Interestingly, after the patient relapsed to an anosognosic state, they were able to remember specific details of the procedure but failed to report any information regarding their fluctuations in awareness. This lack of acknowledgment was interpreted as support for a "denial" mechanism, one that prevented that patient from accessing negative information about themselves (Ramachandran & Blakeslee, 1998). Another interesting experiment that supported this conclusion, was that of the 'fake paralyzing injection'. In this experiment, Ramachanchran told the patient that she was going to receive an injection that would temporarily paralyze her (already paralyzed) arm. Interestingly, after the patient was given the injection she was able to verbally acknowledge the paralysis, but only in the context of the procedure (Ramachandran & Blakeslee, 1998). Here it

appears that patients who are unaware of their deficits are struggling with the negative valence of the information, and the effect that it can inflict on the image of themselves. The mechanisms by which this might be the case in some patients but not others are though not clear and may not be replicable to other anosognosic patients (see Cocchini et al., 2002).

A recent approach to anosognosia as a 'defence' mechanism has attempted to answer the question posed above (e.g., why do anosognosic patients appear unable to process the negative valence of the loss of an ability, while those who are aware seem to be able to adapt and acknowledge their loss?). This more contemporary approach has moved away from a primarily psychogenic explanation and has tried to integrate cognitive and neurological aspects involved in patients who have ABIs. This position primarily led by Turnbull and colleagues (Turnbull, Evans, & Owen, 2005; Turnbull et al., 2014; Turnbull, Jones, & Reed-Screen, 2002) suggests that anosognosia can be explained as an emotion regulation deficiency. Specifically, these authors propose that spatially based emotional regulation, proposed to be right hemisphere dominant, is impaired following acquired brain injury. Spatially oriented emotion regulation is defined as those processes that regulate our emotional response to events that are circumscribed to the self (i.e., egocentric space) versus others (i.e., allocentric space). In line with Turnbull's and colleagues view (see Turnbull et al., 2014 for full description), patients who are unaware of their deficits due to their brain injury, have difficulty regulating emotional reactions to information regarding their egocentric space, that is, specific to themselves. This conceptualization derives support from previous findings such as (i) anosognosia cannot be explained merely by low-level perceptual or sensory

deficits (Bisiach & Geminiani, 1991; Heilman & Harciarek, 2010); (ii) higher frequency of anosognosia following right sided injury (Orfei et al., 2007); (iii) dissociation between explicit and implicit knowledge of the deficit, suggesting that explicit unawareness can be affected by unique factors (Cocchini, Beschin, et al., 2010; Fotopoulou et al., 2010; Moro, Pernigo, Zapparoli, Cordioli, & Aglioti, 2011; Nardone et al., 2008); and (iv) the extent of the explicit awareness varies in relation to cognitive and subjective factors based on their 'personal significance' or based on their perspective (i.e., egocentric versus allocentric) (Fotopoulou et al., 2010; Marcel et al., 2004).

Although this previous proposal holds promising value in moving forward our understanding of anosognosia, previous studies have also supported how other psychological factors such as different mood states and personality traits, can influence patients' explicit reports of their deficits (Bertrand et al., 2016; Besharati et al., 2014; Gainotti, 2018; Weinstein, 1991; Weinstein & Kahn, 1955). It is therefore important that we also continue our efforts to attempt to understand and account for these processes when examining and studying awareness as it's unlikely that one single mechanism can explain the complexity of the anosognosic syndrome (Cocchini et al., 2012; Cocchini et al., 2002; Fotopoulou, 2014; Gainotti, 2018; Marcel et al., 2004; Orfei et al., 2007; Vuilleumier, 2004).

Studies from healthy older adults support the notion that different mood states can influence awareness of cognitive abilities (Balash et al., 2013; Binder et al., 1999; Pereira et al., 2010). These studies have shown that higher rates of cognitive related complaints are associated with higher endorsement of negative mood such as depression or anxiety. In the anosognosia literature, partial support has been found for this effect,

with some authors showing an association between negative mood and higher degrees of awareness (Bertrand et al., 2016; Besharati et al., 2014; Cines et al., 2015), while others have failed to find this association (Cocchini et al., 2013; Starkstein et al., 1995). This variability of results could be partially explained by differences in sampling and measurements methods (Paolucci, 2008) but further research is needed in order to elucidate what role that mood plays in unawareness.

Similarly to mood, different authors within the ageing and anosognosia literature have hypothesized over the effects of personality traits and awareness of cognitive abilities (Colvin et al., 2018; Weinstein, 1991; Weinstein & Kahn, 1955). One of the most renowned studies examining personality traits in relation to anosognosia is that of Weinstein and Kahn (1995). In their seminal work, Weinstein and Kahn (1955) defined different 'patterns' of explicit denial extrapolated from clinical interviews with 104 patients unaware of their deficits. These included (i) *complete denial:* the patient completely denies they are ill in any respect; (ii) *denial of major disability*: the patient denies a major disability but acknowledges lesser threatening ones; (iii) *Minimization or attribution to some benign caus*e: for example, a patient with AD acknowledges some memory loss but attributes it to ageing rather than the presence of the disease; (iv) *Projection of disability outside the self*: as noted in the introduction, patients might state that the paralyzed arm does not belong to them (i.e., asomatognosia). The authors compared patients endorsing these types of denial with those showing other forms of adaptation to explore possible dissociating factors. To this purpose, they obtained comprehensive interviews with relatives, physicians and friends who were questioned on

the patient's premorbid attributes and any changes after the brain injury in order to characterize the following:

a) Attitudes: Attitudes towards work, neatness, punctuality, money and property, duty, health, illness, food, sex, religion, right and wrong.

b) Character of drive: Creativeness, imaginativeness, competitiveness, compulsiveness, need for superiority, prestige values, reactions to failure.

c) Reaction to stress: Temper outbursts, euphoria, humor, depression, indifference, sleepiness, worry, overt anxiety, physical symptoms and effect of alcohol.

d) Interpersonal patterns: Degree of maturity, capacity for love and interchange of feelings, dependence, passivity, self-sacrifice, domination, manipulation, stubbornness, need to be right, pedanticism, practicality, suspiciousness, jealousy, tolerance, sensitivity, adaptability and self-consciousness.

e) Expressive symbols: sayings, superstitions, resolutions, promises, clichés, confabulations, prayers, profanity, manner of speech, gestures, mannerisms and habits.

Based on these interviews, the authors observed that those who explicitly denied their deficits were more likely to have had negative attitudes towards illness. In particular, the patients who expressed denial for their current deficits were more likely to have denied the existence of illness in the past and to view illness as weakness or imperfection. Other attitudes that were consistent in the anosognosic group were those towards work, where they were characterized as responsible and conscientious. Finally,

other common traits were those of need for prestige and esteem and being rather conventional as opposed to creative or eccentric (Weinstein & Kahn, 1955).

Although Weinstein & Kahn's study provided insightful qualitative information on premorbid attitudes and personality traits, their measures lacked standardization and their results have been hard to replicate. For example, in their results they concluded that individuals who denied their deficits had higher levels of conscientiousness (Weinstein & Kahn, 1955), but when Clare, Nelis, Martyr, Roberts, et al. (2012) attempted to replicate this finding in a sample of patients with AD, they did not find this association. Furthermore, their results supported a negative relation between unawareness of memory loss and conscientiousness. These opposite results were discussed as possibly reflective of sampling differences. Interestingly, results by Clare and colleagues in 2012 were also supported in a recent study with healthy individuals (Colvin et al., 2018). This recent study examining awareness mood and personality traits in older adults showed that awareness of memory ability was more accurate in those individuals with higher traits of conscientiousness, extraversion and lower traits of neuroticism and anxiety. Taken together, these results suggest that conscientiousness may actually have 'preventive' properties against unawareness of deficits, rather than predisposing.

To summarize, it appears that there are specific premorbid factors such as personality, belief systems, defence mechanisms and/or mood that can modulate the expression of awareness. This study is primarily aimed to examine two hypothesized factors that can affect how people report on their cognitive deficits: Premorbid personality traits and mood. Specifically, this study will examine these factors in a sample of patients with variable degrees of unawareness for memory loss following

stroke. As highlighted above, the relation between mood and awareness appears inconclusive. However, if mood does play a role in awareness, differences in how aware and unaware patients endorse emotions would be expected. Based on previous studies, these differences would be expected in relation to negative mood or depression. In this case, patients who are unaware should endorse less depression than patients who are aware of their deficits. With regard to personality, based on previous studies differences could be expected in relation to traits such as Neuroticism, Conscientiousness and Extraversion. Specifically, patients who are unaware of their deficits might be expected to endorse less Neuroticism, Conscientiousness and higher Extraversion than those aware of their deficits. These hypotheses will be examined through correlational analyses.

4.2. Methods

4.2.1. Participants

A total of 34 individuals with ABI following a stroke and memory loss were enrolled in the current study and were referred to the study by consultant neurologists from two international sites including the Columbia University Medical Centre, Department of Neurology, Stroke outpatient clinic in the U.S., and the NHS St. George's Hospital Stroke outpatient clinic in the U.K. Of the initial group, 4 patients did not provide an informant (needed for the VATAmem) leaving a sample size of 30 individuals, 40.0% (n=12) from the UK, 60.0% (n=18) from the USA.

All participants provided full consent and procedures were approved by the Institutional Review Board at Columbia University Medical Centre in US, and the NHS Research Ethical Committee in UK.

4.2.2. Measures

4.2.2.1. Anosognosia

Memory functioning awareness was measured through the Visual Analogue Test for Memory Impairment (VATAmem) (see Chapter 3 for full description).

4.2.2.2. Cognitive measures

Memory was assessed through the Rivermead Behavioural Memory Test – 2, (RBMT – 2) (Wilson et al., 2003). Language, executive functions and attention were measured through the BCoS described in Chapter 2. General cognitive ability was also measures through the Mini Mental State Examination (MMSE) (Folstein et al., 1975).

4.2.2.3. Mood

Mood was assessed by a version of the Visual Analog Mood Scales (VAMS) (Nyenhuis, Yamamoto, Stern, Luchetta, & Arruda, 1997). The VAMS consists of 8 scales measuring different emotions or moods including sadness, fear, tiredness, anger, confusion, tension, happiness, and energetic mood. Each scale is presented individually and consists of a vertical line of 100mm in the middle of an A4 page with a cartoon face at each end. The top cartoon face depicts a neutral face and is accompanied by the word "neutral". The bottom cartoon depicts one of the eight moods with their correspondent word. When administered, the patient is asked to place a mark along the vertical line representing how he or she felt his or her mood was on that day. These scales have been proven to be a reliable and valid measure of mood for patients with ABI (Arruda, Stern, & Somerville, 1999). A total score is then calculated by measuring the distance of the patient's mark and the neutral face, representing how strongly they experience each mood. Higher scores represent more of each of the 8 reported emotions. An overall

composite score representative of depressive mood can also be derived by subtracting positive moods from the negative moods and dividing by the total number of scales. With scores ranging from -100 to 100. Higher scores indicating higher depressive mood.

4.2.2.4. Personality

Personality was assessed via an informant version of the NEO-FFI (Costa & McCrae, 1991). The NEO-FFI is a 60-item version inventory that measures five main domains of personality as defined by the five-factor model: Extraversion, Agreeableness, Openness to experience, Conscientiousness and Neuroticism (McCrae & Costa, 1987). For each item, patients' informants were asked to provide with a rating on a 5-point scale that included the following rating: 0-Strongly Agree, 1-Agree, 2-Neutral, 3-Disagree, 4-Strongly Disagree. Scores were standardized to z-scores to adjust for differences of personality traits observed in different sexes (Weisberg, DeYoung, & Hirsh, 2011). Higher scores represent higher traits of each personality trait assessed.

4.2.3. Statistical Analyses

Pearson product moment and Spearman correlations were conducted to examine the relation between awareness, mood and personality. Pearson correlations were conducted as assumptions for parametric analyses were met (e.g., linear relation of continuous measures, lack of outliers > 3 SD of the mean, homoscedasticity and normal distribution in the data). Scatterplots of correlations are included in Appendix 8.

4.3. Results

4.3.1. Participants

The final sample of 30 patients (40.0% females) had a mean age of 69.0 (SD = 12.3; range = 45-90) years and 14.4 years of education (SD = 4.3; range = 4-23). Regarding ethnicity, 60.0% (n=18) of the sample was classified as White Caucasian, 13.3% (4) as African American, 10.0% (n=3) as White Hispanic, 10.0 % (n=3) as South Asian and 6.7% (n=2) as Black British. All participants had suffered from a stroke (86.7% ischeamic; 13.3% haemorrhagic) (see Table 4.1. for information on the lesions of patients). Mean time since lesion onset was 47.46 months (SD = 72.86; range = 1.38 – 275.27).

Table 4.1. Patient lesion description.

Nature of lesion	Unilateral Left hemisphere	Unilateral Right hemisphere	Bilateral	Including Subcortical structures
Ischeamic (n=26)	11	5	10	11
Haemorrhagic (n=4)	2	1	1	2
Total (n=30)	13	6	11	13

Clinical data of 30 patients with memory difficulties following stroke. Number of patients with lesions encompassing left, right or both (bilateral) hemispheres, diffuse brain damage, and lesions that include damage to subcortical structures.

A total of 30 informants were recruited for this study with a mean age of 58.33 (SD = 18.99; range = 18 – 92) years and 14.26 years of education (SD = 2.88; range = 10 – 20). The informant was someone that frequently interacts with the patient on a daily or weekly basis.

4.3.2. Anosognosia

The mean awareness discrepancy score for the sample was of -1.5 (SD = 16.2, range = -27 – 27). Using the cut-offs described in Chapter 3 (i.e., discrepancy between informant and self-report >10.5), a total of 33.3% (n = 10) participants were deemed unaware of their memory difficulties and 63.3% (n = 19) as aware of their memory difficulties. Regarding severity of unawareness 3.3% (n = 1) patients classified as severely unaware, 20.0% (n = 6) as moderately unaware, and 10.0% (n = 3) as mildly unaware.

4.3.3. Cognitive measures

Of all participants assessed with the RBMT-2, 26.7 % (n = 8) had mild memory difficulties, 40.0% (n = 12) moderate, and 33.3% (n = 10) severe memory difficulties. Regarding language, 40.0% had mild language difficulties, 40.0% had moderate difficulties and 16.7% (n = 5) had severe language difficulties measured with the naming task. One participant did not complete the assessment. Executive functions, measured with the BCoS switching task showed that 60.0% (n = 18) of the sample had mild difficulties, 3.3% (n = 1) moderate difficulties and 36.7% (n = 11) had severe difficulties. Mean performance on the global cognitive measure (i.e., the MMSE) was of M = 26.1 with a standard deviation of SD = 3.1 (range = 18 – 30).

4.3.4. Mood and Personality

The mean score of the overall sample on the composite mood score was of 6.95 (SD = 21.24, range = -23.75 – 49.63). Overall sample means of each emotion and each personality trait included in this study are shown in Table 4.2.

Table 4.2. Overall mean, standard deviations and ranges of emotions in the overall sample of patients (n = 30)

Overall sample means and SD of emotions and personality traits	Mean (SD)	Range
Emotions		
Happiness	60.75 (32.69)	0 – 100
Energetic	44.06 (27.99)	5 – 100
Confusion	28.21 (31.79)	0 – 98
Sadness	24.14 (25.46)	0 – 82
Anger	20.04 (29.34)	0 – 96
Tension	25.46 (29.20)	0 – 99
Tiredness	46.86 (31.86)	0 – 100
Fear	15.70 (20.92)	0 – 65
Personality traits z-scores		
Neuroticism	-.15 (1.19)	-2.09 – 2.60
Agreeableness	.35 (1.15)	-3.56 – 2.20
Conscientiousness	.15 (1.30)	-2.20 – 2.24
Extraversion	.30 (1.12)	-1.75 – 2.38
Openness	-.54 (.87)	-2.08 – 1.03

4.3.5. Mood, Personality & Awareness

Pearson correlations revealed no significant associations between awareness and the different emotional states assessed via the VAMS. Specifically, our discrepancy measure of awareness was not associated with happiness (r = - .01, p = .97), energy (r = .02, p = .92), confusion (r = -.28, p = .16), sadness (r = - .02, p = .91), anger (r = -.18, p

= .37), tension (r = - .13, p = .51), tiredness (r = .09, p = .66) or fear (r = - .06, p = .75). The composite score of the VAMS was also not associated to awareness (r = -.09, p = .66).

With regard to personality, when the relationship between awareness and the 5 domains of personality were assessed, only conscientiousness was found to be negatively associated with anosognosia (r =.43, p = .02; d = .95) (see Figure 4.1.).

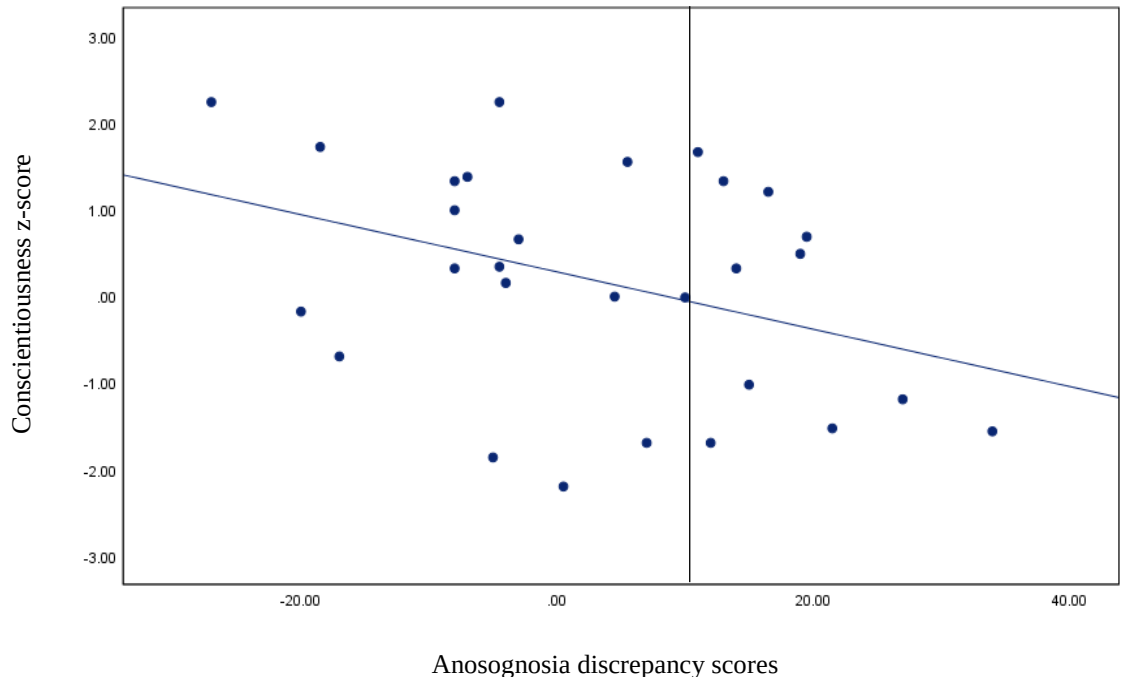

Figure 4.1. Scatterplot of the relation between conscientiousness (standardized z-score) and awareness of memory loss. Middle black line represents unawareness cut-off as determined by the VATAmem (i.e., 10.5).

4.4. Conclusion

Traditional accounts of the relation of psychological factors and anosognosia have proposed defence or reactive processes to protect the self from negative information (Goldstein, 1939; Ramachandran, 1995; Sandifer, 1946). Though more contemporary

accounts have moved away from motivational based accounts (see Turnbull et al., 2014 for a recent 'defence' proposition), it is clear that psychological factors can have an impact on how individuals report on their cognitive abilities and thus should be studied (Balash et al., 2013; Binder et al., 1999; Clare, Nelis, Martyr, Roberts, et al., 2012; Colvin et al., 2018; Gainotti, 2018; Pereira et al., 2010). The effects of these specific psychological mechanisms in patients with variable degrees of awareness after acquired brain injury remains though unclear (see Rosen, 2011 for a recent proposal; section 1.3.2.1.2., Chapter 1). This study was aimed at examining these two main mechanisms, mood and premorbid personality, proposed to modulate awareness of deficits in a sample of patients with memory loss following acquired brain injury.

All participants included in this study were assessed with the VATAmem, an explicit measure of awareness described in Chapter 3. Based on the VATAmem's cut-off, 33.3% of the sample was deemed as unaware of their deficits. This prevalence is on average slightly lower than in other recent studies examining anosognosia for memory loss in patients with AD (Chapman et al., 2018; Cosentino et al., 2007; Cosentino et al., 2011). As discussed in the previous chapter though, these studies used different measures of awareness that can be sensitive to biases and may be tapping into different factors concomitant with unawareness (e.g., cognitive difficulties).

As part of the main aim of this study, the discrepancy score of the VATAmem was used to examine the relation of both mood (The VAMS) (Nyenhuis et al., 1997) and personality factors (The NEO-FFI) (Costa & McCrae, 1991) in relation to anosognosia. Regarding mood, results from this study showed no association between mood and awareness memory deficits. Indeed those aware and unaware of their deficits expressed

comparable endorsement across different emotions including individual positive and negative emotions, and overall depressive mood. Findings within this study thus do not support a clear relation between different mood states and awareness for memory deficits. These results are in line with previous studies which have shown that anosognosic patients display a 'normal range of emotions' (Gainotti, 1972, 1997, 2018; Turnbull et al., 2005; Turnbull et al., 2014; Turnbull et al., 2002; Turnbull & Solms, 2007).

Regarding overall depressive mood, results are also in line with some previous studies that found no association negative mood and anosognosia (Cocchini et al., 2013; Dalla Barba, Parlato, Iavarone, & Boller, 1995; López et al., 1994; Passard, Mantelet, Hervy, Rigaud-Monnet, & Hardy, 2001), but not all (Bertrand et al., 2016; Besharati et al., 2014; Chapman et al., 2018; Cines et al., 2015). These inconsistent results across studies examining overall negative mood or depression and anosognosia can reflect methodological differences such as measuring mood across different samples or at different time points (Paolucci, 2008). Negative mood may thus modulate the way awareness is expressed (e.g., depressive realism), but these modulatory effects may vary at different stages of the disease and/or may be diminished or clouded by concomitant deficits such as cognitive impairments or even unawareness of negative mood (see Cocchini et al., 2013).

With regard to personality, differences were found between patients aware and unaware of their deficits regarding premorbid personality traits, specifically within the conscientiousness trait. Interestingly, no other personality traits appeared to be associated with anosognosia for memory loss, these results might though reflect smaller effect sizes of these traits in relation to anosognosia that this study might not have been powered to

detect (see Chapter 7 for further discussion). Contrary to what Weinstein and Kahn (1955) proposed, results reported in this study showed a positive association between anosognosia and the trait of conscientiousness. As Clare, Nelis, Martyr, Roberts, et al. (2012) point out differences found in personality traits in relation to anosognosia could be due to the sampling differences. Further, in Weinstein and Kahn's (1955) study, personality was not assessed using a standardized personality measure, such as the Neo-FFI (Costa & McCrae, 1991), used in this study. It is also not clear how they quantified consciousness and if any psychometric or statistical analyses were conducted.

To conclude it appears that premorbid personality has an effect on how individuals report their deficits following an acquired brain injury. Results from this study though highlight the unique role that conscientiousness may play on awareness. Specifically, individuals with higher traits of conscientiousness are less likely to overestimate their abilities. Further, those with the highest scores of conscientiousness were more likely to underestimate their abilities. The underlying processes by which the trait of conscientiousness affects anosognosia, as opposed to other traits, is not clear and will be further discussed in the general discussion (Chapter 7).

Chapter 5

Monitoring mechanisms

Summary of chapter

The previous chapter examined psychological factors, including personality and mood, in relation to anosognosia for memory loss. Results from this study showed that higher levels of neuroticism were associated with increased awareness of deficits, supporting a role for psychological factors in the expression of awareness. This chapter's main aim is to further examine other factors hypothesized to influence awareness of memory abilities. Specifically, this chapter will examine different cognitive and metacognitive processes with the main focus on monitoring mechanisms. Three studies are included in this chapter in which (i) memory performance monitoring abilities; (ii) motor monitoring abilities; (iii) source and temporal mnemonic monitoring abilities will be assessed in relation to anosognosia.

5.1. Introduction

Revisiting one of the most influential models of unawareness of memory impairment (see section 1.3.2.1.1 in Chapter 1), the Conscious Awareness Model (CAM) was developed to be applicable to mnemonic dysfunction regardless of its etiology (Agnew & Morris, 1998; Mograbi & Morris, 2013). A strength of this model relies on its ability to encompass the variability observed in anosognosia for the memory deficit by proposing distinct types of anosognosia that rely on different impaired processes. Three main types of anosognosia are characterized under this model: i) *global anosognosia* (e.g., a failure integrating higher order processes involved in becoming aware); (ii) *mnemonic anosognosia* (e.g., due to impaired memory, patients do not remember their failures and fail to update their self-concept of memory abilities); and iii) *executive*

anosognosia (e.g., monitoring impairment leads to undetected errors in memory performance and thus individuals' self-concept of memory abilities is never updated). Embedded within this model lies a hierarchical structure of awareness. This hierarchical structure can be interpreted as representing different levels of awareness (see Clare et al., 2011), such as local online levels where the ongoing experience is monitored, and higher global offline levels where more stable information of the self is stored and updated. Deficient higher levels of awareness, in which deficits are never updated can thus be interpreted as representative of anosognosia.

Traditionally, many of the studies examining underlying mechanisms of anosognosia have focused on examining the association between memory and executive functioning using standardized neuropsychological assessments in patients with anosognosia for memory loss (e.g., Reed, Jagust, & Coulter, 1993; Starkstein et al., 1995). These studies though informative, are mainly focused on degenerative disorders such as AD, and lack experimental examination of those mechanisms proposed by the CAM or other theoretical approaches. Indeed, although this model is a useful characterization of the anosognosia syndrome, it has only been empirically assessed with regard to the mnemonic subtype of anosognosia, and only within the context of AD (see Ansell & Bucks, 2006). Unawareness of memory impairment though does not only occur in the context of dementia (Hartman-Maeir et al., 2002). In order to obtain a model for unawareness of memory impairment, assessment of different amnesic disorders should be studied, and theoretically driven experimental examinations of mechanisms included.

This chapter is largely focused on the proposed subtype of *executive anosognosia*. This subtype of anosognosia has been suggested as an underlying failure in the central

Cognitive Comparator Mechanisms (CCMs). The assumption is that this impaired centralized monitor is no longer able to detect a mismatch between the desired or intended outcome, and the actual performance across different domains, leading to unawareness across different deficits (see McGlynn & Schacter, 1989; Rosen, 2011; Schacter, 1990 for similar proposals). Underlying this centralized CCMs are domain specific cognitive comparators (Cn) which if selectively impaired, lead to domain specific anosognosia. These impairments can be considered as representative of impairments at lower levels of awareness (online or local), which would contribute towards an impairment at a higher levels (global or offline) as errors of performance cannot be detected by the monitors and thus the higher order awareness is never updated (Agnew & Morris, 1998). Impairments in lower levels of awareness (e.g., ongoing memory performance monitoring) have been examined in relation to anosognosia in patients with AD (Cosentino, Metcalfe, Butterfield, & Stern, 2007). Results from this study, recently replicated, supported an association between lower levels and higher levels of awareness (Cosentino, 2014; Cosentino et al., 2007; Cosentino et al., 2011). These findings have yet to be assessed in the context of other etiologies leading to anosognosia for memory loss such as ABIs. This will be examined in study one of this chapter where ongoing memory performance monitoring is assessed in a group of patients with and without anosognosia for their memory loss following an ABI and compared to patients with AD.

Based on the CAM model's assumption summarized above, monitoring impairments can lie at a central comparator or at a domain specific comparator. Studies examining underlying monitoring impairments in anosognosia for memory loss have

done so by focusing on the domain of memory only. It is not clear thus if these deficits would expand to other domains and reflect a global monitoring impairment or if these deficits are domain specific and reflective of an impaired memory comparator (Cn) (Drakeford et al., 2006; Venneri & Shanks, 2004). This assumption will be examined in study two, where monitoring deficits across domains are explored.

Finally, if indeed a mnemonic specific monitoring deficit is present in patients with anosognosia; what are the specifics of this impairment? That is, what aspects of the monitoring process are dysfunctional? Many definitions of mnemonic monitoring can be found across the literature from both healthy individuals and clinical populations (Johnson & Raye, 1981; Mitchell, 2017; Nelson & Narens, 1990; Schnider, 2013). Each definition highlights a specific aspect or quality of the mnemonic monitoring process assumed to be key for an adequate evaluation of one's own reality, that is the process by which we distinguish what is 'real' versus what is not.

Much of the research developed in clinical populations has focused on patients with schizophrenia (Simons, Garrison, & Johnson, 2017) and confabulators (Schnider, 2008). Similarly to patients with anosognosia, patients with hallucinations, delusions, or confabulatory phenomena show a marked difficulty in appraising the feasibility or the adequacy of their thoughts and beliefs (Jenkinson et al., 2009; Saj, Vocat, & Vuilleumier, 2014; Schnider, 2008; Simons et al., 2017; Venneri & Shanks, 2004). Different mnemonic monitoring mechanisms have been proposed to underlie specific impairments including difficulty with determining the temporal relevance of a memory (Schnider & Ptak, 1999; Schnider, Ptak, von Daniken, & Remonda, 2000) or determining the appropriate source of a memory (Johnson & Raye, 2000; Mitchell, 2017). The aim of

study three is to examine these potential mechanisms underlying impaired monitoring processes in relation to anosognosia for memory loss in an attempt to advance our understanding of the basis of anosognosia for memory loss.

5.2. Study One – Memory performance monitoring & anosognosia

5.2.1. Introduction

Monitoring of one's own memory performance, first described by Hart (1965a, 1967) as the "memory monitoring system", is a conceptualized system that oversees the functioning of our memory processes. This system can, for example, monitor what information has been learned and stored, and provide conscious predictions of what is known and what is not. A similar concept was proposed by Nelson and Narens (1990), who theorized a general metacognitive system that oversees our cognitive abilities, including memory. Within this system, two main levels can be identified: The *Object-level* and the *Meta-level.* These levels translate to the actual cognitive performance (e.g., memory performance) and a higher order knowledge of what individuals perceive their performance to be (e.g., a mental representation of performance). Communication between these two levels is hypothesized to be bidirectional, from Object-level to Meta-level and vice versa. The pathway from the Meta-level to the Object-level is referred to as control (i.e., the behaviour or decisions based on the knowledge of performance). The pathway from the Object-level to the Meta-level is referred to as *monitoring* (i.e., knowledge of the performance). The concept of monitoring will be used throughout this chapter, and thesis, as the ability to monitor one's own ongoing memory performance

across different tasks and situations (Clare et al., 2005). This ability is interpreted within the hierarchical conceptualization of awareness (described in Section 5.1.). Ongoing monitoring of one's ability is therefore considered a lower level of awareness, one that is local or contextually (online) driven. In contrast, anosognosia is measured and interpreted as a deficit of higher level of awareness (also referred to as a global level), as it is measured as an offline judgement of memory abilities with no contextual details to aid self-judgements. The purpose of this study is to examine the relation between these two levels of awareness in a sample of patients with memory difficulties after stroke compared to patients with AD.

Ongoing monitoring of memory performance can be assessed through a variety of paradigms depending on the specific mechanism under study. Several studies have focused on pre and post estimations of performance on a given cognitive task, including memory (Ansell & Bucks, 2006; Duke et al., 2002). Performance predictions are believed to represent a generalized self-efficacy representation of oneself, combined with online monitoring (Kaszniak & Zak, 1996). Meanwhile post-dictions are believed to represent a purer self-monitoring process regarding the cognitive ability at test. A recent example using this paradigm can be found in Duke and colleagues (2002) study. In their design, they used both an anosognosia questionnaire discrepancy approach (e.g., patient versus informant ratings) and memory monitoring pre- and post-diction tasks with a group of 24 early stage AD patients, and their informants. Both patients and informants predicted (i) their own performance, (ii) the other's performance (e.g., the patient predicted the informant's ability and vice versa), and (ii) the performance of a fictional patient with memory difficulties. These predictions were measured at pre- and post-performance in a

fluency test and a delayed-recall list. Results from the anosognosia discrepancy questionnaire showed that AD patients overestimated their functional memory abilities compared to the ratings of their informants. Similarly, results from the memory monitoring pre- and post-diction task showed that AD patients overestimated their abilities. Interestingly, patients were able to reduce the overestimation after being presented the task (e.g., for their post-dictions). Similar findings were observed in a later study by Ansell and Bucks (2006) who assessed 18 patients with early AD and their informants. In line with Duke et al.'s (2002) study, they included a measure of anosognosia (e.g., global awareness of functional abilities) and a context specific memory monitoring measure (e.g., task specific evaluations of performance). Patients were asked to provide ongoing pre and post-dictions of performance on word learning trials, specifically at an immediate recall and after a 20-minute delay. Although patients tended to overestimate their performance across the task, they were able to increase their awareness with exposure to the task. Further, their improved awareness was largely maintained after the 20-minute delay. These results thus partially supported the notion of mnemonic anosognosia, as patients begin a task predicting that they would do much better than they actually did but with experience they were able to adjust their predictions. Although this result indeed supports the notion that patients had forgotten their current memory abilities, the fact that their 'improved' awareness was still present after a 20-minute delay goes against the idea that memory degradation was underlying this initial overconfidence. Alternatively, a delay of 20 minutes may not be long enough for the degradation of the recently acquired 'improved' awareness. This notion is supported by a more recent study that also showed 'improved' awareness immediately after being

exposed to a memory task but not after a longer delay (1 hour) (Stewart, McGeown, Shanks, & Venneri, 2010). Indeed, Stewart and colleagues (2010) found that after this longer delay patients reversed to their initial overestimations of abilities.

Similar to pre and post-dictions on specific cognitive tasks, other paradigms can be derived from the metacognitive literature (see Nelson & Narens, 1990). Two examples of these paradigms are the *feeling of knowing (FOK)* and the *judgement of learning (JOL)* tasks. These paradigms have been commonly used to assess memory monitoring in healthy young and older adults (Eakin, Hertzog, & Harris, 2014; Metcalfe, 1986, 2000; Sacher, Isingrini, & Taconnat, 2013; Sacher, Landre, & Taconnat, 2015; Thomas, Bulevich, & Dubois, 2011), and have been believed to be a useful framework to gain understanding of unawareness in patients with AD (Cosentino et al., 2007). FOK and JOL can refer to judgements about future performance on specific previously presented items (e.g., "if I give you 5 options, will you know which answer is right?") and items that have yet to be learned (e.g., "of a list of 20 words, how many do you think you will remember?"). These tasks normally test performance in semantic memory or episodic memory (Hart, 1965a, 1965b, 1967; Leonesio & Nelson, 1990; Nelson, 1984; Nelson & Narens, 1990). Both FOK and JOL provide information on two aspects of memory monitoring: i) "*resolution*" or relative accuracy (e.g., the ability to adapt your prediction in line with your performance) and ii) "*calibration*" or absolute accuracy (Cosentino et al., 2007). Several studies have explored these paradigms in patients with AD patients finding primarily that monitoring impairment seems to be specific to episodic memory (Ansell & Bucks, 2006; López et al., 1994; Moulin, Perfect, & Jones, 2000; Souchay, Isingrini, & Gil, 2002). It was not until 2007 that anosognosia (clinically rated) and the

paradigm of FOK were compared within patients with AD by Cosentino et al. (2007) and were shown to be associated constructs.

Earlier studies have used these types of paradigms to examine the integrity of memory monitoring in patients suffering from other forms of memory loss. One of the earliest was that of Shimamura and Squire (1986), who measured abilities to monitor ongoing memory performance through a FOK task (Hart, 1965b) across three groups of amnesic patients. Although this study did not measure anosognosia, it revealed interesting results when comparing different etiologies of memory loss. The authors compared patients with memory loss due to Korsakoff's syndrome (n = 7), electroconvulsive therapy (n = 8), and mixed etiologies (e.g., anoxia, ischemia; n = 4), with a group of alcoholics acting as controls (n = 7). Results showed that compared to controls and amnesic patients, patients with Korsakoff's syndrome had impaired abilities for monitoring their ongoing memory performance. Interestingly, patients with Korsakoff's syndrome and other confabulatory patients have systematically been reported as being anosognosic for their memory difficulties as opposed to other amnesic patients who can show variable degrees of awareness Feinberg, 2007; Feinberg et al., 1994; McGlynn & Schacter, 1989), potentially reflecting the selective monitoring deficit observed in this group.

As mentioned above, more recent studies have supported the association of monitoring of ongoing performance and anosognosia in patients with AD (Cosentino et al., 2007; Cosentino et al., 2011). In their 2007 paper, Cosentino et al., using a modified FOK task, compared different aspects of memory monitoring (e.g., resolution and calibration) to clinically rated awareness (e.g., anosognosia) in a sample of patients with

AD. Their results confirmed that those patients who were less aware at a global level (e.g., showed higher degrees of anosognosia for their memory loss) were also more likely to have difficulty with local or contextually driven awareness (e.g., monitoring of memory performance). These results, though replicated in patients with AD (Cosentino et al., 2007; Cosentino et al., 2011), have yet to be demonstrated in patients with other etiologies such as ABI.

Following the premises of the CAM model of awareness, in order to provide a comprehensive model of the variable presentation of anosognosia for memory loss, different etiologies must be examined (Agnew & Morris, 1998). As noted by Agnew and Morris (1998), it is not clear that the mechanisms of anosognosia in patients with memory loss due to an ABI would parallel those observed in patients with AD. For example, cognitive profiles of a patient with AD might be different than those observed in ABI. As described in the general introduction, following the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the AD and Related Disorders Association (ADRDA) criteria, in order to have a diagnosis of AD, patients must show evidence of impairments across a minimum of two cognitive domains (McKhann et al., 2011) while ABI patients may experience memory impairments in isolation or with a variable cognitive profile dependent on the location of the injury (Wilson, 2013). Further memory difficulties observed in patients showing early signs of AD commonly reflect failure at an encoding level (Broadbent et al., 2002; Libon et al., 1998) and they might also experience difficulties in implicit memory (e.g., priming) which are normally spared in ABI amnesic patients (Fleischman & Gabrieli, 1998; Fleischman et al., 2005). Within patients with ABI, memory difficulties may also be reflective of retrieval difficulties and

not an encoding deficit per se as frontal regions are selectively affected (Depue, 2012; Shimamura, 1995). Another core characteristic of AD that distinguishes it from ABIs is the progressive nature of this disease where impairments will become more significant across time in AD as opposed to ABI were they can remain static or improve with time. This heterogeneity of presentation may translate into different mechanisms for anosognosia depending on the distribution of pathologies within a given sample. It is thus important to examine both groups' cognitive profiles and other possible underlying mechanisms of anosognosia. The main aim of this study is to examine if the previously shown association between anosognosia in AD and deterioration in lower levels of memory awareness (i.e., memory monitoring) is also present in the context of ABI. To do so, results from patients AD from an existing data set shared by Dr. Cosentino at Columbia University Medical Centre will be compared to results in patients with stroke. This data was collected as part of a larger study examining different correlates than from those examined in this study. If patients with anosognosia following a stroke also have an impairment in ongoing memory performance such as the observed in the AD patients, they will have increased difficulties in metamemory abilities compared to stroke patients aware of their memory difficulties.

5.2.2. Methods

5.2.2.1. Participants

A subgroup of 20 stroke patients from those recruited for the VATAmem study (see Chapter 3), were also recruited for this study. The patients were recruited from the stroke outpatient clinics at Columbia University Medical Centre, US. All participants were referred by consultant neurologists as having suffered a stroke and showing memory

impairment on initial clinical screening. All participants gave full verbal and written consent. Out of these, 19 had one or two informants who reported on their everyday memory functioning resulting in a total of 21 informants.

A total of 51 participants with mild to moderate AD were recruited through the Department of Neurology at the Columbia University Medical Centre as part of a larger study conducted by Dr. Cosentino. Participants had a diagnosis of AD following the criteria of the NINDS-ADRDA. Participants were excluded from the study if there was evidence of moderate to severe psychiatric illness, history of acquired brain injury (traumatic and vascular), or any other neurological conditions that may have had an impact on cognition. Participants were also excluded if they scored under 20 on the Mini-Mental State Examination (Folstein et al., 1975) to ensure comprehension of the tasks. Participants with atypical presentations of AD that were not characterized primarily by memory loss (i.e., language or frontal variant AD) were excluded. All participants provided informed consent and all procedures were approved by the Institutional Review Board at Columbia University Medical Centre. Of the original sample size of 51 participants, 16 (31.4%) cases dropped out of the study and failed to complete the three visits and had missing data. This resulted in a final sample size of 35 participants.

5.2.2.2. Measures

5.2.2.2.1. Anosognosia

Stroke patients' memory awareness was measured through the Visual Analogue Test for Anosognosia for memory impairment (VATAmem). The VATAmem consists of 15 questions exploring everyday memory failures that map on to prospective and retrospective memory functioning (see Chapter 3 for full description).

Due to the data being obtained prior to the development of the VATAmem, patient's levels of anosognosia were measured through a different measure in AD patients. Anosognosia was thus measured through a brief interview at the beginning of each of the three study visits, generating a Clinical Rating of Awareness (CRA) of memory functioning. A modified version of Reed et al's. (1993) clinical awareness scoring categories was used. Participants were asked an open-ended question about their memory (i.e., "how is your memory?"). Based on participants' responses, the examiner rated their awareness with the following scoring system: 1.00 = Full Awareness (Patient spontaneously complains of significant memory loss and may discuss memory loss as consequential of the disease); 2.00 = "Moderate Awareness" (Patient spontaneously admits significant memory loss but attributes it to normal ageing); 3.00 = "Shallow Awareness" (Patient is inconsistent or uncertain about memory loss); 4.00 = "No Awareness" (Patient denies memory loss). Repeated measures examined if there were significant differences of awareness across the three visits before averaging these into one score. For the purposes of this study, the scoring ratings were then collapsed into two categories (1-2 = "Aware"; >2- 4 = "Unaware") in line with previous publications (Cosentino et al., 2016).

5.2.2.2.2. Cognitive measures

Stroke patients were assessed with measures of long term memory (i.e., Rivermead Behavioural Memory Test – 2, RBMT – 2) (Wilson et al., 2003), short term memory (i.e., digits forward – Wechsler Memory Scale, WMS; (Wechsler, 1945), executive function, and attention (i.e., BCoS, cognitive battery described in Chapter 2)

(Humphreys et al., 2012). General cognitive ability was also measured through the MMSE (Folstein et al., 1975).

AD patients were assessed with a measure of long term memory, the Philadelphia Verbal Learning Task (PVLT) (Price et al., 2009). The PVLT is a list learning task in which patients have to learn 9 words across 5 trials and need to recall them after a long delay. A single total raw score was derived by averaging scores of the 5 learning trials and the long delay trial. Executive function measures included a verbal fluency task (i.e., FAS) (Stuss & Benson, 1986). In this fluency task the patient is required to say as many words as possible starting with the letter F, A and S within 60 seconds per letter. A single total score was derived by averaging total words provided across the three letters. Short term memory was assessed with the Digit forward span from the WMS (Wechsler, 1945). Raw scores represent total string of numbers remembered. Attention was assessed with a visual scanning task. This task consists of a set of distractors and stimuli spread across a horizontal A4 page. Patients are required to find as many targets as possible within 60 seconds. Raw scores represent total number of targets found within the 60 seconds.

For purposes of comparing cognitive functioning across awareness status in AD and stroke patients, within sample z scores for memory (short and long term), executive functions, and attention were calculated.

5.2.2.2.2.1. Training to use the task.

Prior to commencing the FOK task, all participants underwent a training procedure to familiarize them with the rating procedure. This rating procedure was a Likert three-point scale in which respondents could choose from *No, Maybe* and *Yes* as their responses. The training procedure includes 16 items to which participants had to

respond using one of the three answers above. For example, a question that required a response of *Yes* was "*Are you seated?*" a question requiring a response of *No* was *"Are we at a sporting event*?", and a question that required a response of *Maybe* was "*Will it be sunny three weeks from today?*".

5.2.2.2.2.2. General knowledge FOK task.

The general knowledge section was comprised of thirteen items that assessed general knowledge (i.e., What is the crime by which one purposefully betrays his own country?). At the same time that participants were shown the questions, the instructor read, "*Here is the question. Don't answer out loud. There are 8 possible answers on the next page. Will you know which one is right? Yes, Maybe, or No"*. The questions were designed to have variable difficulty based on the accuracy of healthy adults previously reported by Nelson and Narens (1980). Prior to commencing the general knowledge section, two practice items were provided (i.e., *What is the liquid portion of blood?*).

5.2.2.2.2.3. Episodic memory FOK task.

The episodic FOK task was composed of four trials with five items per trial. Prior to commencing all trials, participants were instructed: "*During this task, I am going to tell you about five people. I will tell you their names and something about their background. Your task is to try to remember this information as best you can. Please listen carefully*". After hearing the information read aloud, participants were asked to give a global judgement of learning (JOL) (i.e., "*Now I am going to test your memory for those names, giving you answer choices. Of the five names, how many do you think you will get right*?"). Then, for each of the five items, participants were shown the individual question and asked to estimate the likelihood of knowing the right answer (FOK

judgement; i.e., "*There are eight possible answers on the next page. Will you know which one is right – Yes, Maybe, or No?*"). After each FOK judgement, participants were shown eight answer choices which included the correct answer as well as seven distractors. These seven distractors included the other four names that had been presented in the learning trials, and three novel distractors. Each of the four global JOLs provided before each trial ranged from 0 to 5. Item level prediction judgements were given ordinal values of 0 = No; 0.5 = Maybe and 1 = Yes. Performance (i.e., memory) accuracy had values of 0 = incorrect and 1 = correct for each item (20 total) to enable the calculation of the measures below.

AD patients received the same procedure as above (standard condition), in addition to two other conditions (query and feedback). The overall task is the same for each condition except for the query and feedback conditions, in which one more element was included. In the query condition, participants were also asked to make a judgement, after each item, regarding the accuracy of their answer. In the feedback condition, the examiner provided participants with verbal feedback on the accuracy of their memory performance after each item.

5.2.2.2.2.4. Outcome measures

5.2.2.2.2.4.1. Calibration

Calibration scores reflect the extent to which individuals are generally over or under confident in their predictions. For this study, two measures of calibration were obtained, global calibration judgements and item level calibration.

Global calibration judgements reflect the overall level of predictive confidence

participants had in their upcoming performance for each 5-item learning trial. These scores were calculated for each of the four trials by subtracting predictions of accuracy (ranging from 0-5) from total accuracy (ranging from 0-5) and dividing by 5 (the total number of items in the trial). The Global calibration judgements represent the average score across all four trials. Values close to 0 represent accurate judgements. Positive values indicate overconfidence, and negative values indicate under confidence.

Item level calibration indicates the extent to which participants are under or over confident in their performance at the item by item level (i.e., "Will you know whether this item is right? Yes? Maybe? No?"). Predictions were given a score of 0 if the participant stated they would not recognize the correct choice, 0.5 if they were not sure and stated "maybe", and a score of 1 if they were sure they would recognize the right answer. Memory recognition accuracy was scored 0 if they chose the wrong answer, and 1 if they chose the correct answer. Item level calibration was calculated by adding all predictions for performance within all trials, subtracting the sum of accuracy scores, and dividing by the total number of items (e.g., ($\sum$ prediction – $\sum$ accuracy)/ total items). The resulting measure reflects the extent to which a patient is overconfident (positive values), or under confident (negative values) in their item-level predictions compared to their actual performance. Item level calibration was calculated across each of the four trials and averaged to create a single score.

5.2.2.2.2.4.2. Resolution

Resolution reflects the extent to which participants are able to adjust their predictions for performance on each item in line with actual memory performance on that item. Resolution was measured with the Goodman-Kruskal gamma statistic, a rank order

correlation that is based on the total amount of ***concordances*** across the test (*C*; predictions for performance on an item are heightened when performance on that item is high, and vice versa) and the total number of ***discordances*** (*D;* predictions for performance on an item are lowered when performance on that item is high, and vice versa). Gamma is calculated as (C-D)/(C+D). Following this formula, more concordances will result in a value of gamma closer to 1 (perfect resolution), whilst the opposite will result in a value of gamma closer to -1. This calculation does not take into account the number of "ties" where predictions and accuracy are equal in two pairs. Therefore, if someone "ties" across all pairs, gamma cannot be calculated. To avoid losing data in these cases, a formula was developed so that a value of 0 was assigned to gamma, representing the randomness or no association between predictions and actual accuracy (see Cosentino et al., 2015).

5.2.2.3. Statistical analyses

In order to examine if there were intrinsic differences between the stroke and AD patient groups, independent sample t test and chi squared analyses were conducted. As the AD group had a measure of anosognosia that was assessed in three different sessions, a non-parametric Friedman test for repeated measures was conducted to examine if these scores could be collapsed into one. As in previous chapters, non-parametric analyses were chosen when assumptions for parametric analyses were not met. Chi squared analyses were conducted to examine differences of anosognosia frequencies between the stroke and AD groups. Differences of cognitive abilities between the groups were examined in relation to awareness classification. As parametric assumptions were met a one-way ANOVA was conducted to explore differences of general cognitive functioning

(i.e., MMSE) across the 4 groups (e.g., aware stroke, unaware stroke, aware AD and unaware AD). As assumptions were not met with other cognitive variables, Kruskal Wallis tests were run instead for the comparison of memory, executive functions and attention abilities.

With regard to the metamemory test (e.g., FOK task), preliminary analyses included Mann Whitney U tests that assessed if there were mean differences in overall performance on the training section of the FOK task in stroke patients. As patients in the AD group were also assessed with the FOK task three times, GLM repeated measures were conducted across the three outcome measures (e.g., item calibration, global calibration and resolution) to explore if these scores could be collapsed into composite scores. These collapsed metacognitive scores were then examined in relation to awareness within each diagnostic group through independent sample t tests. Finally, in order to examine if there were differences in metacognitive abilities specific to a diagnostic group (e.g., stroke versus AD) a two-way ANOVA was conducted.

5.2.3. Results

5.2.3.1. Participants

The 19 stroke patients were on average 67.2 (SD = 13.8) years old, had 16.3 (SD = 3.5) years of education, and were 52.6% (n = 10) female. 63.2% (n = 12) were classified as Caucasian, 26.3% (n = 5) as African American, and 10.5% (n = 2) as south Asian. The majority of participants 94.7% (n = 18) were right handed. All participants had suffered from a stroke (78.9% ischeamic, 21.1% haemorrhagic), with 3 participants having had several strokes ranging from 2 to 3 strokes in total. Mean time since lesion onset is

provided for first ever stroke and was 43.94 (SD = 62.3) months. Lesion location is provided in table 5.1.

Table 5.1. Patient lesion description.

Nature of lesion	Unilateral Left hemisphere	Unilateral Right hemisphere	Bilateral	Including Subcortical structures
Ischeamic (n = 15)	7	1	7	8
Haemorrhagic (n=4)	1	2	1	1
Tota1 (n=19)	8	3	8	9

Clinical data of n = 19 patients with memory difficulties following stroke. Number of patients with lesions encompassing left, right or both (bilateral) hemispheres, and lesions that include damage to subcortical structures.

The 35 AD patients were on average 77.7 years old (SD = 9.4; range = 57-99), had 16.3 years of education (SD = 2.9) and were 68.6% female (n = 24). Over 91% (n = 32) of the AD participants were Caucasian; the remaining 9% (n = 3) were African American. All participants were assessed across three visits.

There were no significant differences between AD and Stroke patients regarding education (t (53) = -.02, p = .99), sex (χ^2 (1) = 1.01, p = .31) or race (χ^2 (3) = 7.64, p = .054). AD patients were though on average older (M = 77.7, SD = 9.4) than stroke patients (M = 68.2, SD = 14.1; t (26.9) = 2.64, p = .01; d=.79).

5.2.3.2. Anosognosia

Stroke patients' mean awareness discrepancy score, as measured through the VATAmem, was of -1.5 (SD = 16.2, range = -27 – 27). Using the cut-offs described in Chapter 3 (i.e., discrepancy between informant and self-report >10.5), a total of 31.6 % (n = 6) participants were deemed unaware of their memory difficulties and 68.4% (n = 13) as aware of their memory difficulties. Regarding severity of unawareness 5.3% (n = 1) patient was classified as severely unaware, 15.8% (n = 3) as moderately unaware, and 10.5% (n = 2) as mildly unaware.

AD patients' awareness was examined through a CRA at each of the three visits. A non-parametric Friedman test for repeated measures revealed no significant difference of awareness ratings across the three sessions (χ^2 (2) = .95, p = .62). The scores of the three visits were averaged to provide a composite score, and the scores were then collapsed into two categories described in the methods (aware and unaware). 57.1% (n = 20) of the sample was classified as unaware (shallow or no awareness) and 42.9% (n = 15) as aware of their memory deficits (full or moderate awareness).

Although more patients were classified as unaware of their memory loss in the AD sample this difference was not significant (χ^2 (1) = .66, p = .42).

5.2.3.3. Cognitive measures

Stroke participants had an overall mean raw score on the MMSE of 25.3 (SD = 3.4; range = 18-30). AD patients had an overall MMSE of 25.1 (SD = 2.0; range = 21-30). Overall cognitive functioning as measured by the MMSE was not significantly different across stroke and AD patients (t (50) = -.32, p = .79). Table 5.2. summarizes

cognitive performance across both stroke patients and AD patients across those aware and unaware of their memory loss as determined by the VATAmem and the CRA.

Table 5.2. Cognitive measures across patients unaware and aware of their deficits by diagnosis.

Cognitive performance	**Unaware AD (n=20)**	**Aware AD (n=15)**	**Unaware Stroke (n=6)**	**Aware Stroke (n=13)**
MMSE (0-30)	25.05 (1.93)	25.07 (2.18)	22.33 (3.39)	26.91 (2.12)+
LT-Memory (Z score)	-.15 (.94)	-.02 (.74)	-1.05 (.56)	.49 (.75)+
ST-Memory (Z score)*	.43 (1.03)	-.45 (1.25)	.28 (2.10)	-.38 (1.21)
Executive functions (Z-score)	-.05 (1.66)	.09 (1.23)	.85 (1.98)	.06 (1.66)
Attention Z score*	.20 (1.34)	-.11 (1.79)	-.58 (2.35)	.60 (.36)

Mean and standard deviations of global cognition (MMSE) in participants unaware and aware of their memory difficulties. *Non normal data is reported as medians and interquartile ranges in LT-Memory= Long term memory; ST-Memory= Short term memory. + Statistically significant difference between unaware and aware stroke patients.

One-way ANOVA analyses revealed significant differences across groups in global cognition as measured by the MMSE (F (3, 48) = 5.46, p = .003; r^2 = .25). Bonferroni post hoc analyses with corrected p-values showed significant differences between stroke patients unaware of their deficits versus stroke patients aware of their deficits (see Table 5.2.). Kruskal Wallis analyses revealed significant differences across groups in long term memory performance (X^2 (3) = 11.95, p =.008). Post hoc Mann Whitney U test with Bonferroni corrected p value revealed that this difference between the groups was significant between stroke patients aware of their memory difficulties and stroke patients unaware of their memory difficulties (U = 5.0, p =.001).

5.2.3.4. Memory performance monitoring task (FOK task)

5.2.3.4.1. Training to use the task

Within the stroke sample, out of the 19 patients, 4 patients answered one question incorrectly in the training session. Within the AD patients, out of the total 35 patients, a total of 9 patients answered incorrectly one question and one patient answered incorrectly two questions. There was no significant difference between those aware of their memory difficulties (Mdn = 16.00) and those unaware (Mdn = 16.00) in their overall accuracy across the 16 training questions ($U = 36.50$; $p = .76$) in stroke patients and in AD patients (Mdn = 16.00, Mdn = 16.00, $U = 191.0$; $p = .18$).

5.2.3.4.2. General knowledge and episodic memory FOK task

Metacognitive scores (calibration and resolution) described above were calculated for both the general knowledge and episodic memory scores and were compared across patients aware of their memory difficulties and unaware of their memory difficulties.

As noted in the methods section, the data from AD patients is part of a larger study, and participants were exposed to three different FOK conditions (standard, query and feedback). GLM Repeated measures corrected for Green House Geisser showed no difference in memory monitoring as measured by episodic gamma across the conditions (F (1.62, 50.24) = 1.72, $p = .19$). Similarly, GLM repeated measures for prospective global calibration judgements revealed no differences across conditions for either the global or item level predictions (F (2, 56) = .64, $p = .53$; F (2, 62) = 1.26, $p = .28$). These metacognitive metrics were therefore averaged across visits to create composite scores.

5.2.3.4.3. Outcome measures

5.2.3.4.3.1. Calibration and resolution

Item level calibration was calculated by subtracting the average predictions from the average performance of all items. Global calibration scores were calculated by subtracting patients' judgements of overall performance prior to each trial from their overall performance in that trial. These scores were calculated for the episodic memory FOK task. Gamma scores were calculated through a rank order correlation described in the methods section. These scores were available for both the general knowledge and episodic memory task.

AD patients showed no differences in semantic or episodic memory item calibration (t (33) = -.67, p = .51; t (33) = .27, p = .78). No differences were observed on episodic global calibration (t (33) = .37, p = .72) or resolution during the general knowledge test (t (33) = .57, p = .58) as a function of their awareness. Significant differences were observed though on episodic memory resolution in which unaware AD patients performed significantly worse than those aware of their deficits (t (33) = 3.0, p = .005).

Similar to AD patients, stroke patients showed no differences on item calibration, or resolution on the semantic memory task as a function of their awareness (t (17) = .21, p = .83; t (17) = .63, p = .54). No significant differences were observed though on episodic memory item calibration (t (17) = .38, p = .71) or global calibration (t (17) = .04, p = .97). Significant differences were observed though for resolution on episodic

memory with lower performance if they were unaware of their deficits versus if they were aware of their deficits (t (17) = 3.79, p = .001) (see Table 5.3.).

Table 5.3. Metacognitive measures across patients unaware and aware of their deficits by diagnosis.

Metacognitive measures of memory monitoring	**Unaware AD (n=20)**	**Aware AD (n=15)**	**Unaware Stroke (n=6)**	**Aware Stroke (n=13)**
Gamma GK (-1–1)	.59 (.29)	.64 (.23)	.38 (.56)	.31 (.08)
Gamma EM (-1–1)	.18 (.34)	.50 (.26)^	.10 (.49)	.77 (.29)+
Global calibration EM (-1–1)	.07 (.18)	.10 (.18)	.19 (.13)	.20 (17)
Item level calibration GK	.01 (.16)	-.03 (.16)	.07 (.17)	.09 (.17)
Item level calibration EM (-1–1)	.01 (.12)	.02 (.08)	.20 (.23)	.24 (.21)

Means and standard deviations of performance memory monitoring presented for AD and stroke patients aware and unaware of their memory difficulties at a global level (anosognosia). ^ Significant differences between aware and unaware within the AD group. + Significant differences between aware and unaware within the Stroke group.

A two-way ANOVA showed no significant interaction effect between group membership (i.e., stroke versus AD) and awareness (i.e., aware versus unaware) (F (1, 50) = 3.18, p = .34, partial η^2 = .06).

5.2.4. Conclusion

The purpose of this study was to examine the relation between online lower levels of awareness (memory monitoring) and global awareness (anosognosia) in patients that had a diagnosis of AD and patients that had a diagnosis of Stroke. Results showed that patients who were classified as having anosognosia were more likely to have difficulties adjusting their prediction on an ongoing memory task regardless of their neurological condition. These results appear to suggest that, despite the nature of the memory

impairment ongoing memory monitoring processes are impaired in both ABI and AD patients.

Findings of this study showed that although more patients were classified as unaware in the sample of AD patients, this difference in the prevalence of anosognosia was though not significantly different from the sample in stroke. As described in section 1.3.2. (Chapter 1), variable prevalence reports of the prevalence of anosognosia for memory loss can be found across both AD and ABI samples. As reported in Chapter 3, existing measures such as the CRA may be sensitive to biases such as cognitive impairments that reduce its specificity towards detecting anosognosic only. This limitation must be considered across the interpretation of results within this study.

Regarding cognition, stroke patients who were unaware of their memory loss had significant lower global cognitive and memory function compared to those who were aware of their memory difficulties. These differences were not observed in patients with AD, who did not differ across any cognitive domain as a function of awareness, suggesting that neither overall cognition nor memory could explain the monitoring impairment in these patients.

With regard to memory monitoring metrics, no differences were observed in calibration across either group as a function of anosognosia. These results go against those by Duke et al. (2002) and Ansell and Bucks (2006) who found that patients who were unaware tended to overestimate their ongoing performance (i.e., they had poor calibration). In the case of the Ansell and Bucks (2006), this pattern of performance was interpreted as reflective of a *mnemonic anosognosia*, in which memory loss prevents patients from updating their semantic self and thus it remains 'petrified' in time (Mograbi

et al., 2009). In contrast, both AD and stroke patients with anosognosia were impaired in memory monitoring, as measured by the resolution score of gamma. These results move away from the proposed mnemonic type of anosognosia and suggest that at least in this sample, impaired awareness cannot be solely explained by a memory impairment. Interestingly though, significant differences could be observed in unaware stroke patients who were performing worse both in long term memory and memory monitoring than those aware. This significant difference in memory functioning was though not observed in patients with AD. These results suggest that memory deficits can partially contribute to impairments in performance memory monitoring but are not the primary root of impaired awareness in this sample.

This study has several limitations. For example, the use of two different scales of awareness may have influenced the results. As data collected from the AD sample preceded the development of the VATAmem another measure of awareness was used. As discussed in Chapter 3, measures such as clinical interviews often lack normative data and can be prone to interviewer bias therefore, by including such measure this bias might be present and one must exercise caution in comparing results across samples one must exercise caution in comparing results. Another limitation of this study is the inclusion of a heterogeneous stroke sample that could have also affected the results (see limitations section of Chapter 7 for further discussion).

To conclude, results from the current study suggest that being able to monitor predictions in line with performance is impaired in anosognosic patients, supporting the hypothesis of an impairment in a mnemonic monitoring mechanism ‘Cm’ as proposed in the CAM model. However, this study was not able to completely support the specificity

of the monitoring mechanism for the memory domain as it did not include any monitoring measures outside the memory domain. If a mnemonic monitor is indeed impaired in patients unaware of their deficits, these deficits should not expand to other domains. If, on the other hand, monitoring deficits do expand, the failure would then appear to lie at a global monitoring level across lower levels of awareness. This will be examined in the following study where memory monitoring, motor monitoring, and anosognosia are studied in a sample of AD patients.

5.3. Study Two – Memory performance monitoring, motor monitoring & anosognosia

5.3.1. Introduction

The previous study examined if online monitoring of one's memory performance was associated with how one evaluates one's memory in a more general less context dependent manner. These two types of evaluations, as noted earlier, are considered to be different levels of self-evaluation. The local context dependent monitoring processes are considered to represent a lower level of awareness, meanwhile general judgements are considered higher levels of awareness which represent the clinical syndrome of anosognosia. In line with studies with patients with AD (Cosentino et al., 2007; Cosentino et al., 2011), these judgements are related within a memory domain across stroke and AD patients (see study one of this chapter) supporting an impaired mnemonic comparator (Cm). An interesting question that can be raised is whether these deficits are specific to memory monitoring or if they extend beyond this domain and represent a more general impairment at a local level of awareness (i.e., online self-monitoring across domains).

In the current study, the association between anosognosia for memory loss, memory monitoring, and motor monitoring (i.e., agency judgements, or the extent to which individuals perceive themselves to be the agent of a determined outcome or action) is examined (Gallagher, 2000) in AD patients. There is an inherent necessity of accessing self-specific information when making a judgement of agency related to an action or thought, and agency tasks have been used to understand unawareness of hemiplegia and other motor deficits following stroke (Fotopoulou et al., 2008), providing an ideal framework with which to examine self-referential monitoring in a non-memory domain. Indeed, much of the work dedicated to modeling anosognosia and examining the role of monitoring difficulties has occurred in the context of impaired motor functioning, specifically in individuals who are unaware of hemiplegia following stroke (Jenkinson et al., 2009; Saj et al., 2014; Venneri & Shanks, 2004; Vocat, Saj, & Vuilleumier, 2013). Conceptually, it has been proposed that difficulty detecting discrepancies in monitoring between one's intentions (i.e., motor plan) and one's actual motor performance may result in unawareness of hemiplegia (Berti, Spinazzola, Pia, & Rabuffetti, 2007; Cocchini, Beschin, et al., 2010; Fotopoulou et al., 2008; Moro et al., 2011). The *Comparator Model* of motor control posits that for each produced movement, an individual *implicitly* monitors their intentions and predicted outcome in relation to sensory and perceptual feedback about the actual outcome (Blakemore, Wolpert, & Frith, 2002). The comparison between these two processes allows the detection of a mismatch that would occur in the context of a movement error, and therefore allows correction of the error. The comparison also provides a neural basis for the perception of a distinction

between internally driven movements (where the match between the two processes is high) and those movements caused by an external source (Feinberg, 1978; Frith, 2005).

Another explanatory model of judgements of agency or judgements of motor monitoring is the *Theory of Mental Causation* (Wegner, 2002; Wegner & Wheatley, 1999). This theory proposes that individuals *consciously* assess the relationship between intentions and actions and infer causal judgements of agency. This conceptualization moves away from the idea of an underlying unconscious process of motor monitoring, and proposes that individuals utilize conscious processes such as the intention associated with the action and contextual cues of the outcome itself, to derive an inferential judgement of agency or judgements of motor monitoring (Haggard & Tsakiris, 2009; Metcalfe, Eich, & Castel, 2010; Moore, 2016; Synofzik, Vosgerau, & Newen, 2008; Wegner, 2002; Wegner & Wheatley, 1999).

Several studies have supported the association of motor monitoring and anosognosia for hemiplegia (e.g., Jenkinson & Fotopoulou, 2010; Vocat et al., 2013). Interestingly, monitoring deficits in patients unaware of their motor deficits seem to relate to monitoring deficits in other cognitive domains (Feinberg et al., 1994; Jenkinson et al., 2009; Venneri & Shanks, 2004). These cross-domain associations suggest that at least in the case of anosognosia for motor deficits, its underlying mechanisms may not be domain specific and that a combination of different processes may be key to the emergence of impaired awareness (e.g., deficient error prediction, encoding, monitoring and premorbid factors; Cocchini, Beschin, & Sala, 2002; Davies, Davies, & Coltheart, 2005; Fotopoulou, 2014; Levine, 1990; Marcel, Tegnér, & Nimmo-Smith, 2004; McGlynn & Schacter, 1989; Vuilleumier, 2004). The association between self-

monitoring abilities across different task domains has also been demonstrated in non-demented cohorts in which the integrity of memory monitoring and motor monitoring (i.e., *agency*) judgements have been linked (Cosentino, Metcalfe, Holmes, Steffener, & Stern, 2011).

To my knowledge, there are no previous studies examining judgements of agency in AD. Given the cross-domain monitoring deficits seen in individuals with anosognosia for hemiplegia, and the link between memory monitoring and agency monitoring in older adults, one might hypothesize that anosognosia in AD may be associated with compromised agency in AD. However, there is also reason to believe that these processes may be dissociated. While they are both self-referential, the substrates that contribute to each judgement are seemingly very different. For example, memory monitoring has been hypothesized to rely on memory abilities, executive functioning, and underlying implicit internal monitoring of mnemonic processes such as familiarity and partial access to information (Cosentino, Metcalfe, Holmes, et al., 2011; Koriat, 1993; Koriat & Levy-Sadot, 2001; Metcalfe, Schwartz, & Joaquim, 1993; Reder & Ritter, 1992; Schnyer et al., 2004; Schwartz & Metcalfe, 1992). In contrast, judgements of agency have been hypothesized to rely on the monitoring of sensory and perceptual stimuli of the action, and the integration of different contextual cues such as perceived success, temporal delay between intention, outcome and reward (Blakemore et al., 2002; Frith, Blakemore, & Wolpert, 2000; Kirkpatrick, Metcalfe, Greene, & Hart, 2008; Metcalfe, Van Snellenberg, DeRosse, Balsam, & Malhotra, 2014; Michotte, 1963; Moore, 2016; Schlottman & Shanks, 1992).

The purpose of this study is to clarify the association between different domains and levels of awareness in AD patients by examining the relationship between anosognosia for memory loss, memory monitoring, and agency. For this purpose, regression models were conducted to examine the associations among these three self-evaluative measures including covariates such as memory, executive functions, and mood (Ansell & Bucks, 2006; Bertrand et al., 2016; Cines et al., 2015; Clare et al., 2012; Conde-Sala et al., 2014; Cosentino, Metcalfe, Holmes, et al., 2011; Mograbi & Morris, 2013; Perrotin, Isingrini, Souchay, Clarys, & Taconnat, 2006; Reed et al., 1993). If a memory performance monitoring impairment is present in patients with stroke (examined in study one) and this deficit is underlying a 'Central Comparator' deficit, memory monitoring deficits should expand to other domains. That is, anosognosic patients would have impaired monitoring deficits across various domains compared to those aware of their deficits. On the other hand, if anosognosic patients have a memory performance monitoring impairment that underlies a specific deficit in the 'mnemonic comparator', only memory monitoring abilities would be associated with unawareness.

5.3.2. Methods

5.3.2.1. Participants

A sample of 51 participants described in the previous study (study 1) were recruited through the Department of Neurology at the Columbia University Medical Centre. Participants had a diagnosis of Alzheimer's Disease following the criteria of the NINDS-ADRDA. Participants were excluded from the study if there was evidence of moderate to severe psychiatric illness, history of acquired brain injury (traumatic and vascular), or any other neurological conditions that may have had an impact on cognition.

Participants were also excluded if they scored under 20 in the Mini Mental State Examination (Folstein et al., 1975) to ensure comprehension of the tasks. Participants with atypical presentations of AD that were not characterized primarily by memory loss (i.e., language or frontal variant AD) were excluded. All participants provided informed consent and all procedures were approved by the Institutional Review Board at Columbia University Medical Centre. As part of the larger study, participants were asked to complete three structured sessions, with the main measures of interest for this study administered across the three sessions.

5.3.2.2. Measures

5.3.2.2.1. Anosognosia

Like study one, to ensure correct completion of a larger study, anosognosia was evaluated via a brief interview at the beginning of each of the three study visits, generating a Clinical Rating of Awareness (CRA) of memory functioning. As in study one, patients were classified as Aware and Unaware (see section 5.2.2.2.1. in study one).

5.3.2.2.2. Cognitive measures

Participants underwent neuropsychological examination, which included measures of global cognition, memory, executive functions, and attention. Memory measures consisted of the Philadelphia Verbal Learning Task (PVLT - Price et al., 2009) for verbal memory and the Biber Figure Learning Test (Glosser, Goodglass, & Biber, 1989) as a nonverbal memory measure. Executive function measures included a design fluency task (Glosser & Goodglass, 1990), a verbal fluency task (i.e., FAS - Stuss & Benson, 1986), and the Digit and Spatial backward spans from the Wechsler Memory Scale (WMS; Wechsler, 1997). Attention was assessed with a visual scanning task.

Cognitive index scores were obtained from these measures to represent three main cognitive domains: memory, executive functions, and attention. A memory index score was obtained by averaging z-scores of the total immediate recall and long delayed recall of both the PVLT and the Biber Figure learning memory tests. An executive index score was derived from an average of the Digit and Spatial spans backward, FAS, and Design fluency z-scores. Finally, an attention score was the z-score of performance on the visual scanning task (Cosentino, Metcalfe, Holmes, et al., 2011).

5.3.2.2.3. Self-monitoring measures

5.3.2.2.3.1. Memory Monitoring Task

A modified Feeling of Knowing or FOK task was used in this study (described in section 1.2.2.3. of study one). AD participants received three versions of the episodic FOK task. As reported in study one, no differences were found across conditions and the three versions were collapsed to provide a single score for episodic memory item calibration, global calibration and resolution (gamma). Only episodic memory metrics were explored in this study.

5.3.2.2.3.2. Agency Task

A computer task was used to measure patients' ability to monitor when they were or were not in control of motor outcomes whilst playing a simple computerized game. A modified version of Metcalfe and Greene (2007) task was used (see Cosentino, Metcalfe, Holmes, et al., 2011). In this task, participants were required to move the cursor of a computer horizontally across the bottom of the screen to try to "catch" as many "X"s as possible whilst avoiding the "O"s, both of which were falling vertically from the top of

the screen. At the end of each trial, participants were required to make a judgement of agency (i.e., “who was in control”) between two dichotomous choices of themselves or the computer as being in control. In the modified version of Metcalfe and Greene's task, on some of the trials, participants were in complete control of the computer mouse, and so they should have said that they were 'in control'; on other trials, the computer interfered with the position of the cursor, and so on these trials, to the extent that they correctly recognized their own lack of control over the cursor, they should have said that the computer was ‘in control’. Participants were given 1 practice trial, 8 trials in which they were in complete control of the cursor, 8 trials in which the computer controlled the cursor, and 8 mixed trials in which they were in control half of the time and the computer took over the other half. These mixed trials were introduced to enhance uncertainty. In computer controlled trials, the cursor on the screen moved directly towards the proximal target in a linear fashion without actively attempting to avoid O’s. The person's own mouse movements had no effect on this trajectory. The trials were presented in random order and each had a duration of 10 seconds. To begin each trial, the participant had to move the cursor. If they failed to do so, a message would inform them that the game would not begin if they did not perform a movement. This avoided the strategy of waiting to see if the computer moved the cursor.

Agency judgements, or motor monitoring, were measured as the total accuracy of all judgements on self-and computer-based trials. A combined score of both trial types ranged from 0 to 16. Accuracy for each type of trial (self and computer) was also derived which ranged from 0 to 8 in each. Mixed trials were excluded from analysis. The

inclusion of trials in the analysis followed that of Cosentino et al., (2011) to allow comparison of our results with those of healthy ageing individuals.

5.3.2.2.4. Computer Experience Questionnaire

Three questions regarding computer experience were presented to participants about how often and how comfortable they felt using a mouse: (i) “How often did you use a mouse before the study?”, responses were recorded in a Likert scale from 0 = Never, 1 = A few times, and 2 = Many times; (ii) “How comfortable are you using a mouse ?”, responses were recorded in a Likert scale from 0 = Not comfortable, 1 = Somewhat comfortable, and 2 = Very comfortable; (iii) “How often did you use a mouse last year?”, responses were recorded in a Likert scale from 0 = Never, 1 = A few times, 2 = Several times a month, 3 = Several times a week, and 4 = Daily. A composite score, used as a measure of overall computer experience, was developed by averaging the results of the three questions.

5.3.2.3. Statistical analyses

As anosognosia was assessed through various visits a non-parametric Friedman test for repeated measures was conducted to ensure these scores could be collapsed into a composite score. Independent sample t tests were conducted to examine cognitive abilities in relation to awareness. With regard to the motor monitoring task a Pearson product moment correlation was run between the two types of trial to examine if these could be collapsed into a composite score as conditions for parametric analyses were met. Two further correlations were conducted to examine if performance in these trials was correlated to our computer experience questionnaire. Performance on the motor

monitoring task across both trials was then compared in relation to awareness with a 2x2 repeated measures ANOVA (awareness group x trial type). Memory monitoring outcomes (item calibration, global calibration and gamma) were first correlated to each other to examine if these scores were independent. Memory monitoring outcomes were then also assessed in relation to awareness with independent sample t tests. Finally, regression models were conducted to further understand which correlates were predictive of each awareness measure (e.g., anosognosia, motor monitoring outcomes and memory monitoring).

5.3.3. Results

5.3.3.1. Anosognosia

Anosognosia was examined through CRA at each visit. A non-parametric Friedman test for repeated measures revealed no significant difference of awareness ratings across the three sessions (χ^2 (2) = .95, p = .62). The scores of the three visits were averaged to provide a composite score, and the scores were then collapsed into two categories described in the methods (aware and unaware). Up to 57% of our sample was classified as unaware (shallow or no awareness) and 43% as aware of their memory deficits (full or moderate awareness). The awareness groups did not differ significantly in demographic variables (see Table 5.4.).

With regard to cognitive tasks, unaware participants appeared to perform somewhat worse on memory tasks, though this qualitative difference was not significant (t (33) = -1.69, p = .10). No differences were found in executive functions (t (29) = .11, p =.90), or attention (t (32) = 1.61, p = .11).

Table 5. 4. Mean and standard deviations of demographic and neuropsychological variables in participants unaware and aware of their memory difficulties.

Demographics details and neuropsychological performance	**Unaware (n=20)**	**Aware (n=15)**	**Sig. Two tailed**	**95 % Confidence intervals**
Age	79.94 (8.02)	74.78 (10.54)	.10	1.21, 11.54
Education	16.00 (2.73)	16.73 (3.10)	.46	-1.55, 11.87
Gender (female/male)	14/6	10/5	.94	-
Race (Caucasian/African American)	19/1	13/2	.38	-
MMSE (0-30)	25.05 (1.93)	25.07 (2.18)	.98	-1.43, 1.40
Memory index (Z score)	-.20 (.58)	.19 (.79)	.10	-.86, .07
Executive Index (Z score)	.01 (.89)	-.01 (.80)	.69	-.28, .41
Attention Index (Z score)	.11 (1.03)	-.15 (1.02)	.48	-.49, 1.00

Higher scores on MMSE and Z scores reflect better performance.

5.3.3.2. Memory Monitoring Task

Within the memory monitoring scores, resolution (i.e., gamma) was not significantly correlated with item calibration (r = .28, p = .11) or global calibration judgements (r = -.11, p = .55).

5.3.3.3. Agency Task

Bivariate Pearson's correlation revealed no association between accuracy of agency judgements in self trials and computer trials (r = - .10, p = .54). Therefore, agency was broken down into two scores reflecting each trial type and examined separately in subsequent analyses. Overall, both unaware and aware participants performed

significantly better on self trials (M = 6.02, SD = 1.69) as compared to computer trials (M = 2.40, SD = 2.38) (t (34) = 7.02, $p < .001$; d = 1.75).

5.3.3.4. Computer Experience Questionnaire

Computer mouse experience data was available for 25 participants. Out of these, 44% reported using a mouse before the study many times, whilst 24% had used it a few times, and 32% had never used one. More specifically, 64% of participants reported using the mouse at least once within the last year. Finally, participants were asked how comfortable they felt using a mouse, and 36% reported being very comfortable, 24% somewhat comfortable and 40% not comfortable. The relationship between computer experience and agency was not significant for self (r = 0.00, p = .99) or computer trials (r = .33, p = .11).

5.3.3.5. Bivariate Relationships between Awareness Measures

Comparison of the three memory monitoring metrics (gamma, global, and item level calibrations) between unaware and aware participants showed a significant difference only for the gamma score (t (33) = -3.02, p =.005; d = 1.06; see Table 5.5.) such that participants who were unaware of their deficits tended to have lower resolution scores—that is, unaware participants showed greater difficulties in predicting their memory performance. This difference remained significant after Bonferroni correction for multiple comparisons. Repeated measures 2x2 ANOVA showed no differences of performance across computer or self trials in relation to awareness between trial type and awareness, that is there was no interaction effect (F(1,33) = 0.08, p = .79) (see Table 5.5. for means and SDs). Total judgements of agency showed a qualitative not significant association with gamma (r = .28, p = .0501; d =.58). Although the correlation between

the accuracy of the agency judgements on the computer trials and the resolution gamma correlations was not significant (r = .11, p = .25), an association was found between the accuracy of agency judgements for self trials and the resolution gamma correlations (r = .30, p = .04; d = .63).

Table 5. 5. Mean and standard deviations of metacognitive measures for memory and agency in participants unaware and aware of their memory deficits. Significance and 95 % Confidence intervals included when independent sample t test were conducted.

Metacognitive measures of memory and motor domains (range)	**Unaware (n = 20)**	**Aware (n = 15)**	**Sig. Two tailed**	**95% Confidence intervals**
Gamma (-1–1)	.18(.34)	.50(.26)	.005	-.53, -.10
Global calibration (-1–1)	.07(.18)	.09(.18)	.72	-.15, .10
Item level calibration (-1–1)	.01(.12)	.02(.08)	.78	-.08, .06
Agency total (0-16)	8.30(2.61)	8.60(3.04)	.76	-2.25, 1.65
Agency computer trials (0–8)	2.40(2.11)	2.40(2.77)	-	-
Agency self trials (0–8)	5.90(1.74)	6.20(1.65)	-	-

5.3.3.6. Regression analyses

In order to explore the relation between the three measures of self-evaluation (i.e., memory monitoring as measured by gamma, CRA, and agency), these variables were included in each model as dependent measures. Predictor variables were selected on theoretical basis and based on previously shown associations. The first linear regression was conducted to examine the extent to which gamma could be predicted by scores on agency self trials, CRA, memory, and executive function indices, entered in a single block. Results indicated that the overall model was significant and explained 53 % of the

variance (R^2 = .53, F (5, 28) = 6.41, p < .001). It was found that higher memory (B = .20, p = .01), greater accuracy for agency self trials (B = .07, p = .04), and higher clinical rated awareness (B = .21, p = .04) significantly predicted higher gamma. When controlling for demographics, including age, sex and education, the model remained significant, as did the three predictors.

Two additional linear regressions were conducted to examine the predictors of accurate judgements of agency in the self trials and in the computer trials. These predictors included the executive function index, gamma, CRA, and computer experience. The overall model, however, was not significant for either the self (R^2 = .30, F (5, 19) = 1.68, p =.19) or the computer trials (R^2 = .21, F (4, 20) = 1.31, p =.30).

Finally, a logistic regression was conducted to explore the extent to which CRA could be predicted by gamma, agency accuracy for self trials, memory, and executive function, entered in one block. Results indicated that the overall model was significant (χ^2 (4) = 8.58, p =.02) and explained 30 % of the variance (Nagelkerke R^2) in clinically rated awareness. Increasing accuracy in gamma was associated with increased likelihood of being aware of their memory deficits (B = 3.43, Wald χ^2 (1) = 4.31, p = .04). No other predictors were significant. When controlling for demographics, only gamma remained a significant predictor of clinically rated awareness. All predictors, for each model, are summarized in Table 5.6.

Table 5.6. Regression models of self-awareness measures of memory monitoring (gamma), anosognosia (CRA), and the accuracy of agency judgements in self trials and in computer trials.

Predictors of memory monitoring (gamma), CRA and agency	**Gamma** B (Std. error)	**CRA** B (Std. error)	**Agency self trials** B (Std. error)	**Agency computer trials** B (Std. error)
Gamma	-	**3.43 (1.65)**	1.47 (1.47)	2.10 (1.87)
CRA	**.21 (.10)**	-	.23 (.82)	- .81 (1.05)
Agency self	**.07 (.03)**	-.002 (.25)	-	-
Executive functions	- .15 (.09)	.69 (.80)	- .01 (.77)	.69 (.97)
Memory	**.20 (.07)**	.23 (.69)	-	-
Computer experience	-	-	- .03 (.13)	.24 (.16)

Unstandardized betas and standard errors of the individual predictors are included. Significant predictors are shown in bold ($p < .05$).

5.3.4. Conclusion

This study examined the extent to which anosognosia (i.e., a global marker of awareness) in AD is characterized by deficits in specific aspects of online self-monitoring (i.e., lower level of awareness) across domains. Moreover, this study explored if specific forms of self-monitoring deteriorate in tandem or are dissociable processes.

The main question that was attempted to answer was the extent to which individuals with anosognosia for memory loss in AD demonstrated deficits at the lower level of awareness in self-monitoring mechanisms beyond memory. This was explored by assessing agency judgements in relation to anosognosia. If monitoring deficits underlying anosognosia are not domain specific, agency should be distorted in anosognosic patients. The lack of an observed association between anosognosia and

judgements of agency in this study suggests that the mechanisms of awareness in AD are modular, at least to some extent, across the domains of memory and motor functioning. The pattern of performance on the agency task was very similar in both aware and unaware patients, with a clear trend for higher performance on self trials than computer trials in both groups. In computer trials, both aware and unaware participants performed below chance. A similar pattern of findings has been previously observed in controls (i.e., healthy ageing adults), who completed the same agency task, performing worse on computer trials than self trials (Cosentino, Metcalfe, Holmes et al., 2011). Interestingly, previous literature has supported the idea that agency changes with age, specifically that, as people age, they tend to disregard or become more resistant to external cues when making judgements of agency (Cioffi, Cocchini, Banissy, & Moore, 2017; Metcalfe et al., 2010). Participants in this study were indeed older than the healthy ageing participants studied in the previous study, and thus they might be showing an exacerbated inability to appropriately weigh external cues when making these judgements.

Taken together, the current results support the notion that within-domain awareness such as for the domain of memory, may be associated across levels (i.e., CRA and gamma), but cross-domain monitoring (e.g., motor versus memory monitoring) may occur only within a given level of awareness (i.e., gamma and agency). Based on the CAM model (see introduction for full description) and our findings, monitoring of performance depends on domain specific monitors (i.e., CCMs), identified as unconscious processes that can lead to a local metacognitive output of performance (e.g., context local judgement of motor or memory monitoring). At the same time, these monitors are part of the evaluative process by which an individual makes more global

and stable judgements of their own abilities. Specific deficits to each CCM would contribute to a domain specific anosognosia. Following the CAM and the motor literature of anosognosia, some individuals may instead have a more generalized impairment in executive control, leading to a generalized impairment of monitoring across domains (see section 1.3.2.1.1. in Chapter 1 for full description). In our sample of individuals suffering from AD, results support a domain specific CCM deficit (i.e., Cm) contributing to a specific global awareness deficit. The relationship between Cm (memory) and Cn (motor), however, speaks to shared variance at a local level of awareness.

Finally, the examination of the cognitive correlates of each self-evaluation measure revealed different predictive factors associated with different levels of memory awareness. Specifically, within the cognitive factors, poorer memory performance was a significant predictor of deficits in memory monitoring (i.e., gamma). People who were less able to monitor their memory functioning were also more likely to have lower memory scores. This relationship between memory and awareness went in the same direction for CRA but was not statistically significant. The association between memory and monitoring can be interpreted through the *memory-constraint hypothesis* for example, which assumes that memory monitoring relies on an inferential process by which one derives a judgement based on different cues such as familiarity or accessibility of target. These cues are, themselves, hypothesized to be byproducts of the retrieval process (Koriat, 2000; Metcalfe, 2000; Metcalfe et al., 1993). The quality of the cues retrieved by people with memory difficulties would be hampered, resulting in a blurring of the distinctiveness between what is known and what is not. Thus, the memory-constraint hypothesis predicts that poor memory would lead to poor memory monitoring

(Hertzog, Dunlosky, & Sinclair, 2010). As with anosognosia, the relation of memory function and memory monitoring is inconsistent and though some studies have found support for this relation (Chapman et al., 2018; Gallo, Cramer, Wong, & Bennett, 2012; Hannesdottir & Morris, 2007), others have not (Cosentino et al., 2007; Michon, Deweer, Pillon, Agid, & Dubois, 1994; Shaked et al., 2014; Souchay, Isingrini, & Espagnet, 2000; Souchay, Isingrini, Pillon, & Gil, 2003).

To conclude, this study supported a mnemonic-specific monitoring deficit as contributing to anosognosia. However, the precise mechanism by which memory monitoring fails is not clear. When monitoring one's memories, individuals rely on ample characteristics of memories such as temporal relevance or source of memory. These characteristics are monitored in order to make decisions on what is currently relevant or what is real versus what is not. It is not clear though, which specific mnemonic monitoring mechanisms are more relevant in relation to awareness. This question will be examined in the following study in an attempt to elucidate the role of underlying memory monitoring mechanisms in producing anosognosia.

5.4. Study Three – Memory monitoring mechanisms & anosognosia

5.4.1. Introduction

Following the findings from study one, anosognosia for memory loss and ongoing memory performance monitoring appear to be associated. In study two of this chapter, deficits on ongoing self-evaluative processes were examined across domains in order to understand if they were impaired in a domain specific manner or extended to other

domains such as motor abilities. Results showed that in the context of anosognosia of memory loss, these monitoring processes deteriorate in a domain specific manner. Therefore, it appears that being able to consciously track and control certain elements of the ongoing memory experience, may be crucial for the emergence of awareness of memory deficits. Further, the evidence for impairments in lower levels of awareness (i.e., online memory performance monitoring) in relation to anosognosia can be contextualized within the CAM proposal of an impaired mnemonic comparator. But what specific monitoring processes are critical for the emergence of awareness? Would all types of memory related monitoring processes be impaired in patients who are unaware of their deficits? In an attempt to answer this question and elucidate what elements play a stronger role in supporting one's awareness of memory abilities, this study looks specifically at two memory monitoring mechanisms that could lead to impairment of the comparator; a failure of *reality filtering*, or a failure of *reality monitoring* (Johnson & Raye, 1981, 2000).

Reality *filtering* refers to the ability to monitor the temporal relevance of a memory (Schnider & Ptak, 1999; Schnider, von Däniken, & Gutbrod, 1996). Impairments in the ability to know when a thought or memory relates to the present or the past have been proposed as one of the primary deficits in patients who express confabulations (Schnider, 2008). This monitoring process is hypothesized to rely on frontal cortices, specifically on the anterior limbic system including the posterior medial orbitofrontal cortex (Schnider, 2013). Failure in reality filtering has been reported repeatedly in patients with confabulatory phenomena and has been proposed as the mechanism by which these patients are unable to monitor what information is relevant to

the present moment (Schnider, 2008, 2013; Schnider & Ptak, 1999; Schnider et al., 2000; Schnider et al., 1996). Within the context of self-awareness of memory performance, the ability of knowing if a memory relates to the past or the present seems key in those patients who are learning that their memory is not what is used to be. That is, knowing what your abilities were, versus knowing what your abilities are in the present moment, could explain why some patients have difficulties identifying their current abilities. This assumption will be assessed via a Continuous Recognition Test (CRT) where patients have to identify recurring targets that are relevant for a present trial, disregarding those that are no longer relevant (Schnider & Ptak, 1999).

Reality *monitoring* on the other hand, refers to a source attribution process by which we can make distinctions of memories that stemmed from an internal or an external source (i.e., imagined vs. seen; Johnson, 1991; Johnson & Raye, 1981, 2000). Failures in these monitoring abilities have been associated with memory and perceptual disturbances such as those experienced by patients with mental disorders and acquired brain injury (Brébion et al., 2000; Johnson, 1991; Radaelli, Benedetti, Cavallaro, Colombo, & Smeraldi, 2013; Turner & Coltheart, 2010). Further, within anosognosia for motor deficits, previous authors such as Venneri and Shanks (2004) have hypothesized that anosognosia could be explained as a deficit in monitoring the veracity of one's beliefs. In a more recent study, Jenkinson et al., (2009) assessed monitoring deficits through experimental paradigms and showed that patients anosognosic for motor deficits had difficulties distinguishing between self-generated information (imagined actions) versus externally experienced (seen actions). Others have also shown a deficit in action-monitoring in patients with anosognosia for hemiplegia following stroke, a deficit that

was not mediated by other neuropsychological deficits (Saj et al., 2014). The overall conclusion of these studies is that these monitoring deficits reflect an impaired "prediction-reality" monitoring system that prevents patients from becoming aware that their predictions did not match reality (i.e., they didn't move even though they intended to do so). When predicting one's abilities there is a delicate interplay between what one desires and intends to perform and how one actually performs. In order to be able to correctly adapt our predictions based on our performance, or our feeling of knowing one's performance, one must be able to discern an intentioned or desired outcome from what the outcome itself is. Similarly to patients with anosognosia for hemiplegia, patients with anosognosia for memory loss might have difficulties discerning their intentions or desired outcomes from their performance on a given memory task. Following Jenkinson's et al., (2009) study, this study uses a modified Henkel, Johnson, and De Leonardis (1998) task to test the assumption that patients with unawareness of memory deficits following stroke will show impaired reality monitoring deficits compared to patients aware of their memory deficits.

If anosognosics are having difficulties in accurate temporal identification of memories, they will have greater difficulties identifying temporally relevant items and suppressing the proactive interference of previous items (e.g., filtering out temporally irrelevant items) compared to the aware group. On the other hand, if anosognosics are having difficulty in monitoring internally versus externally generated memories, higher error rates when discriminating between these items (e.g., internal versus external memories) would be expected, compared to those who are aware of the memory deficits.

5.4.2. Method

5.4.2.1. Participants

A total of 43 participants were recruited for this study which included the subgroup of 31 patients also recruited for the VATAmem study reported in Chapter 3. The patients were recruited from both stroke outpatient clinics at St. George's NHS hospital, U.K. and at Columbia University Medical Centre, US. All patients were referred by a consultant neurologist as having suffered a stroke and showing memory impairment on initial clinical screening. All participants gave full verbal and written consent. Out of these, 6 did not have an informant and had to be excluded from analysis resulting in a sample of 37 patients. As some provided two informants, a total of 51 informants were included in this study.

5.4.2.1. Measures

5.4.2.1.1. Anosognosia

Memory functioning awareness was measured through the Visual Analogue Test for anosognosia for memory impairment (VATAmem) (see Chapter 3 for full description).

5.4.2.1.2. Cognitive Measures

Patients were assessed with measures of memory (Rivermead Behavioural Memory Test – 2, RBMT – 2; Wilson et al., 2003), language, executive functions and attention were measured through the BCoS, described in Chapter 2 (Humphreys et al., 2012). General cognitive ability was also measures through the Mini Mental State Examination (MMSE) (Folstein et al., 1975).

5.4.2.1.3. Reality filtering

Reality filtering was explored through a Continuous Recognition Test (CRT). Specifically, an adapted version from Schnider and Ptak (1999) by Cocchini, Lello, McIntosh, and Della Sala (2014) was used in this study. This test measures the ability to distinguish between information obtained at different moments in time also referred to as temporal monitoring. Four runs were displayed to the participant with different intervals between the runs varying from 0 to 30 minutes. The first and second runs were presented immediately after each other, the third run after a 5-minute delay and the fourth run was presented 30 minutes after the third run. In every run, 80 stimuli were presented, composed of coloured Snodgrass pictures (Rossion & Pourtois, 2004), in which 30 items were recurrent and 50 items had not been shown before (see Figure 5.1.). The same stimuli were used for all runs, however, different items were recurrent in each run. The stimuli were presented in a single random order for all patients.

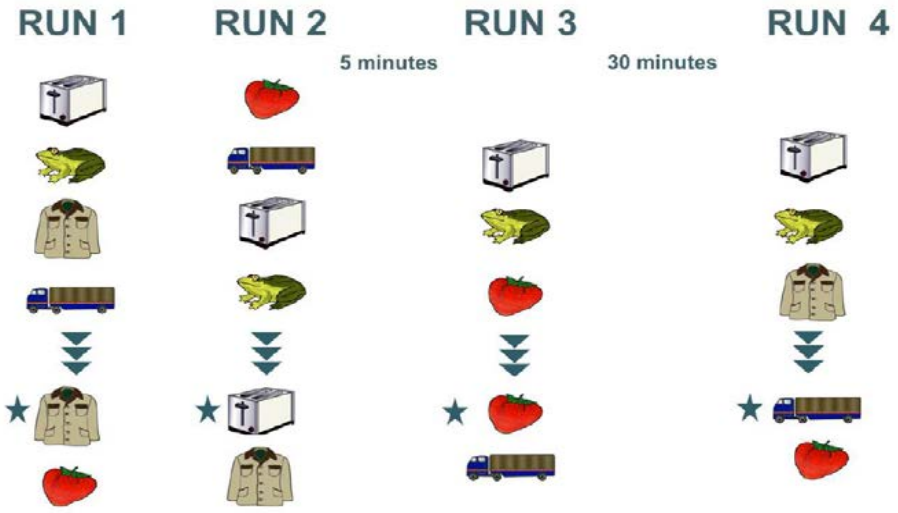

Figure 5.1. Depiction of the CRT 4 runs. The participant must continuously identify the item (here indicated with a *) that has already been presented within that run.

Patients were explicitly instructed to focus on the ongoing run only and to forget about stimuli presented in previous runs. Within each run they were instructed to identify whether they had seen the picture before or not (Figure 5.1.). All runs were preceded by 4 practice items, which were repeated until instruction comprehension was ensured. If patients exhibit a temporal monitoring deficit, they will experience incremental false alarms across runs as they will experience difficulties discerning which item they previously saw repeated from the ones that are currently relevant. This difficulty is interpreted as a failure to monitor the temporal relevance of newly learned information (Schnider & Ptak, 1999).

5.4.2.1.4. Reality monitoring

An adapted and modified version of the Henkel et al. (1998) Reality Monitoring Test (RMT) was used to measure the ability to distinguish between internally and externally generated memories also referred to as source monitoring (Cocchini, Lello, McIntosh, & Della Sala, 2014). In the encoding phase (Figure 5.2. A), patients are presented with 30 object words of which half (15) were accompanied with a Snodgrass picture of the object (Snodgrass & Vanderwart, 1980). When the picture is not shown underneath the word, patients were explicitly instructed to create an image of the object in their head. Furthermore, patients are encouraged to focus on the object characteristics and their appearance by asking them to estimate how long it would take to draw the perceived or imagined object (Henkel et al., 1998).

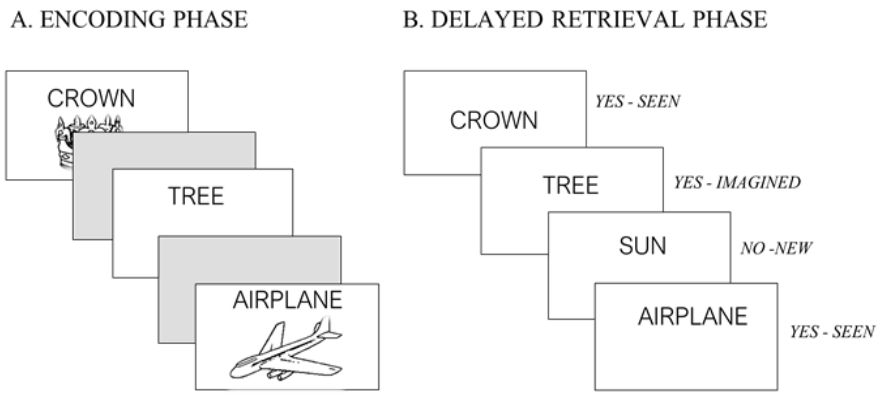

Figure 5.2. Depiction of the RMT encoding (A) and delayed (B) retrieval phases.

The encoding phase is preceded by a practice run of 4 words; two with and two without object pictures. After a 15-minute delay, a surprise recognition test is conducted in which patients are presented with 45 object words (Figure 5.2. B). Of these words, 15 are new, 15 were presented in the encoding phase with a picture and 15 were presented in the encoding phase without a picture. Patients are asked to indicate for each word whether it was a perceived, imagined or new object. Written instructions are provided during the recognition test listing these three options. The stimuli of the RMT are presented in a single pseudorandom order for all patients.

5.4.2.1.5. Outcome measures

For both monitoring measures total Hit and False Alarm rates were calculated. To further examine how patients responded to the items, Pr (discrimination accuracy) and Br (response bias) were calculated following the two factor theory of memory which is recommended when the number of targets and distractors are uneven (Corwin, 1994; Jenkinson et al., 2009). Pr represents how well the patient can distinguish between targets and distractors. Br represents the tendency by which the patient responds (i.e., more conservative or more liberal). These were calculated as follows:

Pr = (total hits + 0.5 / total targets + 1) - (total false alarms + 0.5 / total distractors +1)

Br = (total false alarms + .05 / total distractors + 1) / (1 – Pr)

Three more scores were calculated for the source monitoring data following Jenkinson et al. (2009). A Source Proportion (SP) score was developed to capture patients' ability to monitor if the information learned was imagined (internal) or seen (external). To examine if there were different biases in source categories between those unaware and aware of their memory deficits, an Externalization Bias (EB) and an Internalization Bias (IB) were also derived. These scores were calculated as follows:

SP= total correct source assignation / total hits

EB= ∑ erroneous external source assignation

IB= ∑ erroneous internal source assignation

5.4.2.2. Statistical analyses

Patients were classified as aware or unaware following the VATAmem's cut-off. Differences across cognitive abilities were explored through independent sample t tests and Mann Whitney U tests when data did not meet assumptions for parametric analyses. With regard to the reality filtering task mixed effects repeated measures ANOVA were conducted to examine if there were any differences of overall Hits, FA's, Pr and Br across the four runs in relation to awareness. As outliers and deviations of normality were detected in the data, these analyses were rerun excluding outliers and with transformed variables to examine the effect of the violation of these assumptions on the results. With regard to the reality monitoring task differences in overall Hits,

FA's, Pr, Br and Source Proportion were examined in relation to awareness through independent sample t tests and Mann Whitney U tests. Finally, Spearman correlations were conducted to examine the directionality of source proportion bias (e.g., external versus internal) in relation to awareness.

5.4.3. Results

5.4.3.1. Participants

The 37 patients included in this study were on average 67.5 (SD = 12.7) years old, had 13.9 (SD = 3.7) years of education, and were 43.2% (n = 16) female. 67.6% (n = 25) classified as Caucasian, 24.3% (n = 9) as African American or Black British, and 8.1% (n = 3) as south Asian. Most patients 97.3% (n = 36) were right handed. All patients had suffered from a stroke (83.8% ischeamic, 16.2% heamorrhagic), with 3 patients having had several strokes ranging from 2 to 3 strokes in total. Mean lesion onset is provided for first ever stroke and was 39.9 months (SD = 67.3). Lesion location is provided in Table 5.7. Informants were on average 53.0 years old (SD = 12.9) and had 14.0 mean years of education (SD = 2.5).

Table 5.7. Patient lesion description

Nature of lesion	Unilateral Left Hemisphere	Unilateral Right Hemisphere	Bilateral	Including Subcortical Structures
Ischeamic (n = 31)	15	5	11	14
Haemorrhagic (n = 6)	2	2	2	2
Total (n=37)	17	7	13	16

Clinical data of N = 37 patients with memory difficulties following stroke. Number of patients with lesions encompassing left, right or both (bilateral) hemispheres, and lesions that include damage to subcortical structures.

5.4.3.2. Anosognosia

The mean awareness discrepancy score for the sample was 3.3 (SD = 13.5, range = -27 – 34). Using the cut-offs described in Chapter 3 (i.e., discrepancy between informant and self-report >10.5), a total of 34.2 % (n = 13) patients were deemed unaware of their memory difficulties and 63.2% (n = 24) as aware of their memory difficulties. Following the severity cut-offs of the VATAmem, 2.6% (n = 1) patient classified as severely unaware, 13.2% (n = 5) as moderately unaware, and 18.4% (n = 7) as mildly unaware.

5.4.3.3. Cognitive measures

Mean raw score of the sample on the MMSE was 26.0 (SD = 3.0; range = 18-30). All patients had impaired memory performance in the study screener described in Chapter 2 (i.e., BCoS episodic memory story immediate and delayed). Patients' performance on the RBMT-2 showed that 34.2% (n = 13) of the patients were classified as having severe memory problems, 42.1% (n = 16) as having moderate memory impairment and 23.7% (n = 9) as having poor memory or mild memory impairment. Short term memory as measured with the digit span subtest of the RBANS (Randolph, 2012) showed that 5.4% (n = 2) had severe difficulties, 27% (n = 10) had moderate memory difficulties and 67.6% (n = 26) patients had mild short term memory difficulties. Visuospatial short term memory as measured with the Wechsler Memory subscale of visuospatial functioning and with the Corsi visuospatial test (Corsi, 1972; Wechsler, 1997). These showed that 27 % (n = 10) patients had severe visuospatial short-term

memory difficulties, 13.5 % (n = 5) had moderate difficulties and 40.5 % (n = 15) had mild difficulties.

On the naming test, 18.9 % (n = 7) had severe language difficulties, 35.2 % (n = 13) had moderate language difficulties, and 43.2% (n = 16) had mild language difficulties (Humphreys et al., 2012). Scores on executive function tests showed that 5.3% (n = 15) had severe executive function difficulties and 40.5 % (n = 22) had mild executive function difficulties.

Cognition was also examined as a function of awareness to explore if there were any cognitive functions that were selectively impaired in those considered unaware versus those aware by the VATAmem (see Table 5.8). Results showed that those unaware of their deficits had overall worse cognition as measured by the MMSE and worse memory abilities as measured by the RBMT-2 ($p < .01$). No other differences were observed (see Table 5.8.).

Table 5.8. Mean and standard deviations of cognitive variables in patients unaware and aware of their memory difficulties.

Cognitive performance	**Unaware (n=13)**	**Aware (n=25)**	**Sig. Two tailed**	**95 % Confidence intervals**
MMSE (0-30)	24.15 (3.13)	27.15 (2.46)	.004+	-4.95, -1.03
Memory – RBMT (0-24)	7.85 (5.58)	14.13 (3.78)	.008+	-5.11, -.87
Short term – Verbal (Z score)*	-.55 (1.60)	-.63 (1.78)	.32	-
Short term – Visuospatial (Z score)*	.30 (2.30)	-.40 (1.03)	.44	-
Executive function (Z score)	-.55 (1.86)	-1.13 (2.08)	.38	-.77, 1.94
Attention (Z score)*	-2.70 (9.39)	.11 (2.73)	.16	-
Language (Z score)*	-1.05 (2.86)	-1.05 (3.66)	.49	-

Higher scores on MMSE and all cognitive domains reflect better performance. *Non normal data is reported as median and interquartile ranges. Exact significance is reported (Dinneen & Blakesley, 1973). + Significant results between those aware and unaware of their deficits.

5.4.3.4. Reality filtering

Performance on the TMT was analyzed in relation to awareness. Total hit rates and false alarm rates were compared across both aware and unaware patients (see Figure 5.3.). Repeated measures mixed ANOVA showed that there were no group differences (aware vs. unaware) in their overall hit rates across the four runs (F (1, 34) = 1.14, p = .29). Further, although hits were significantly different in relation to time (run 1 – 4; F (3,102) = 5.40, p = .002) there was no significant interaction between group and time (F (3, 102) = 1.81, p = .15). Several outliers (> 3 SD) were observed in the residuals of this model. As such, these analyses were conducted excluding those outliers above 3 SD which also improved normality in all distributions assessed through visual inspection. Results remained and there were no significant group differences in relation to overall

hits (F (1, 30) = 1.02, p = .32) nor an interaction between group and time (F (3, 90) = 2.05, p = .11). With regard to false alarms, repeated measures mixed ANOVA showed that there were significant group differences (aware vs. unaware) in overall false alarms across the four runs (F (1, 34) = 35.34, p = .007). Although false were significantly different in relation to time (run 1 – 4; F (3, 66.28) = 7.21, p < .001) there was no significant interaction between group and time (F (3, 66.28) = .77, p = .46). As with the Hits analysis, several outliers were observed and analyses were conducted excluding these cases to investigate their possible influence on the results. Results remained and though unaware participants had increased overall false alarms (F (1, 32) = 7.51, p = .01), no interaction between group and time was observed (F (3, 96) = .93, p = .43).

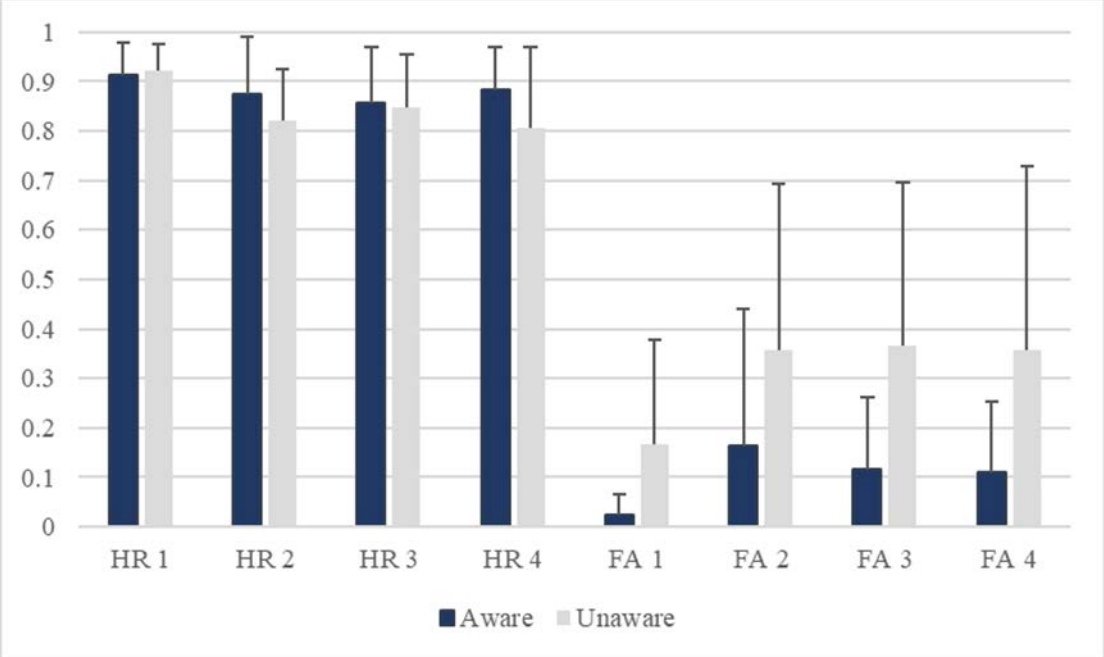

Figure 5.3. Mean and standard deviations of Hit rates (HR) and False Alarm rates (FA) in patients aware versus unaware of their memory deficits.

Further analyses were conducted to examine if there was an overall difference in patients' discrimination accuracy and their response bias (i.e., Pr and Br calculations

described in the methods section) in relation to their awareness status. Overall, neither discrimination accuracy (Pr) nor Response bias (Br) were significantly different in patients aware versus unaware of their memory (Pr, $U = 94$, $p = .07$; Br, $U = 94$, $p = .18$). Figure 5.4 depicts discrimination accuracy and discrimination bias run by run. Although differences are not significant (i.e., $p > .05$), patients who are unaware of their memory deficits displayed a trend to have worse discrimination accuracy and a more liberal response bias.

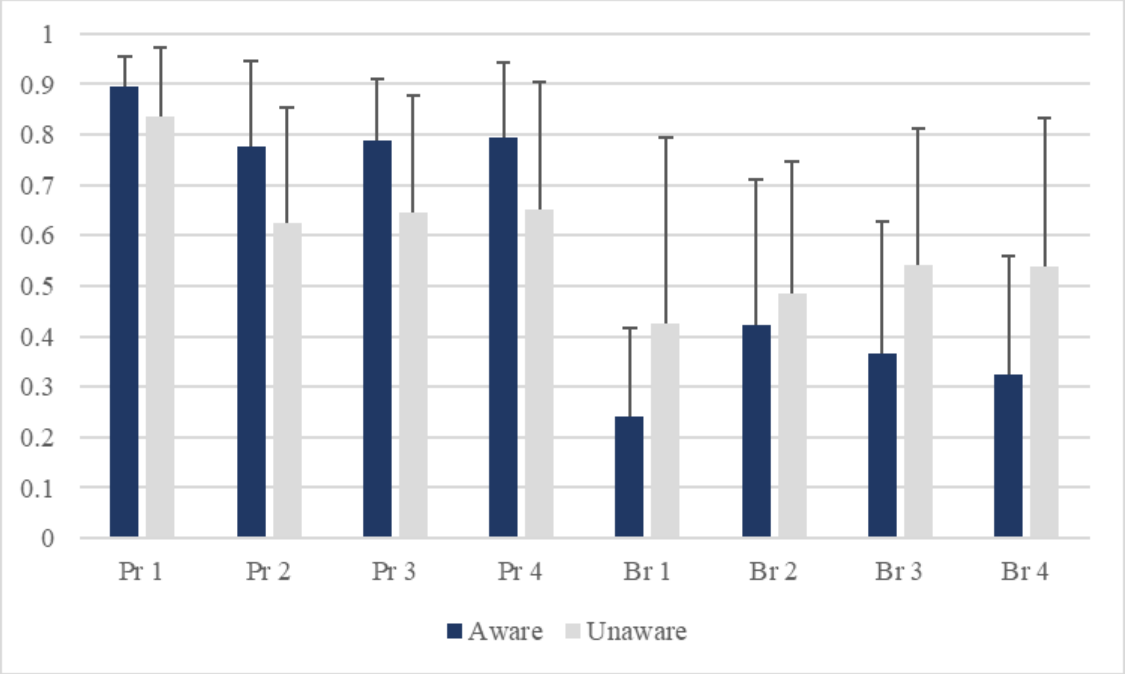

Figure 5.3. Mean and standard deviations of discrimination accuracy (Pr) and response bias (Br) in patients aware versus unaware of their memory deficits across runs 1-4 of the TMT.

5.4.3.5. Reality monitoring

Results of reality monitoring as measured by the reality monitoring task (RMT) were also analyzed in relation to awareness. Overall hit rate was not significantly different between those aware and unaware of their deficits (t (35) = 1.56, $p = .13$). False alarms, however, were significantly different with unaware patients making more false

alarms (Mdn = .13) than those aware (Mdn = .07; U = 87.0, p = .03, r = .37). Analysis regarding discrimination accuracy and response bias revealed that those unaware of their deficit did not differ from those aware in the response bias (Br) (t (35) = -1.84, p = .21) but they had significantly worse discrimination accuracy (Pr) (U = 74.5, p = .008, r = .43) (see Figure 5.5).

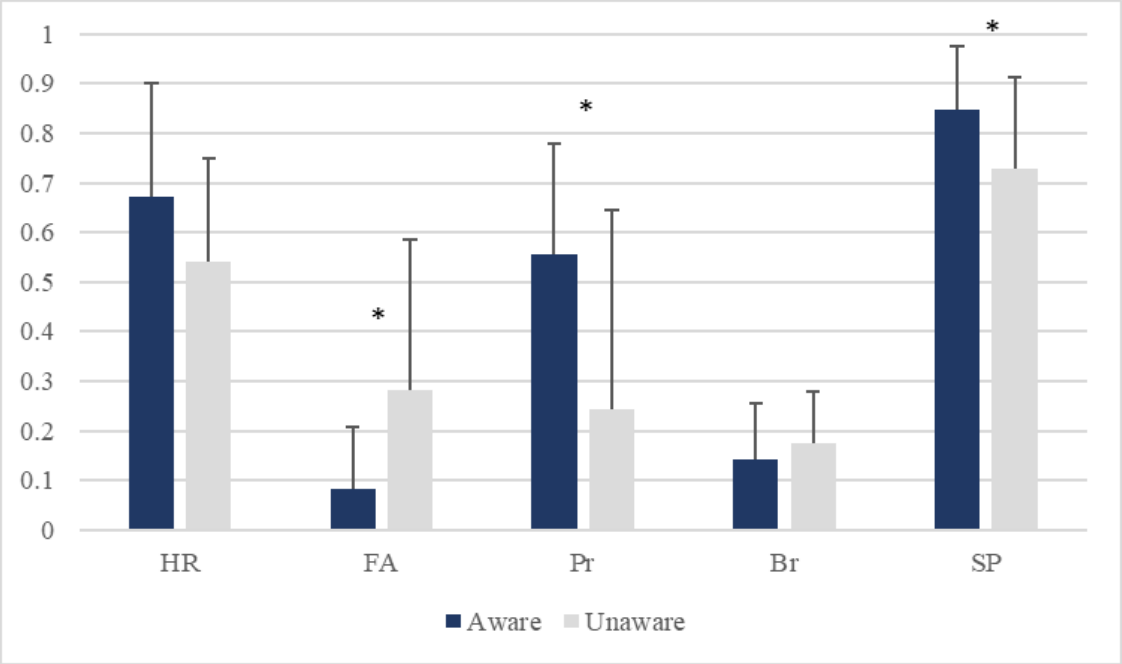

Figure 5.4. Mean and standard deviations of Hit Rate (HT) False Alarm rate (FA), discrimination accuracy (Pr), response bias (Br) and Source Proportion (SP) in patients aware versus unaware of their memory deficits on the RMT. * Significant differences (p <. 05).

Analyses specific to the patient's ability to monitor the source of the information (i.e., internal versus external information) showed, as depicted in Figure 5.5., that those unaware of their deficits had more difficulty discerning the source of the targets (Mdn = .70) than those aware of their deficits (Mdn = .85; U = 94.0, p = .049, r= .32). Spearman correlations were conducted to examine the direction of the source bias (i.e., internalization or externalization bias) in relation to awareness (see scatterplots in

Appendix 8). Results showed a significant correlation between unawareness and externalization bias (Aware, Mdn. = 2.00, range 0 – 8; Unaware, Mdn. = 3.00, range 0 – 23) (*rho* = .38, *p* = .02; *d* = .82) but not internalization (Aware, Mdn. = 2.00, range 0 – 8; Unaware, Mdn. = 2.00, range 0 – 14) (*rho* = .12, *p* = .48).

5.4.4. Conclusion

This study's main goal was to assess, contextualized within the proposal of the CAM model (Agnew & Morris, 1998), what type of mnemonic monitoring failures were observed in patients unaware of their memory difficulties. To this purpose, two main monitoring processes were explored, reality filtering and reality monitoring (Johnson & Raye, 1981; Schnider, 2008).

Based on the discrepancy values of the VATAmem, a total of 34.2 % (n = 13) patients were deemed unaware of their memory difficulties. Patients deemed unaware by the VATAmem were more likely to have impaired global cognition and memory than those aware of their difficulties. Results of previous studies in this chapter and this current study support a more complex picture than the idea that because patients have bad memory, they are unable to remember their mistakes and thus never become aware. Indeed, these findings support an association between specific mnemonic monitoring failures and anosognosia of memory loss.

The examination of reality filtering showed no differences in the ability to monitor the temporal relevance of stimuli as a function of anosognosia. Although overall patients unaware of their deficits were more likely to have more false alarms, there was no significant interaction between awareness and time (e.g., runs). When examining the

overall recognition (Pr) and response bias (Br) no significant differences were observed. Indeed, the pattern of results across aware and unaware patients was similar. Both groups of patients experienced more difficulties in run 2 (as expected), similar difficulties in run 2 were observed across groups in run 3 (with anosognosic patients having more FAs than aware), and a decrease of FAs was observed in both groups in run 4. This pattern of results does not appear to support a temporal monitoring deterioration in patients unaware of their memory loss. As described in the methods section, patients with temporal monitoring deficits should show incremental difficulties across runs as they cannot rely on the temporal characteristics of the information learned (Schnider, 2008). Decreased FAs in run 4 though could be more reflective of memory abilities than of temporal monitoring abilities (e.g., information learned in previous runs is forgotten and patients may experience run 4 as if it were a new run). The fact that patients are showing an overall increased FAs rate across trials may suggest a degradation of their ability discerning temporal characteristics of memories although no significant differences were found when increases from trial to trial were examined. Another possible explanation is that these patients are experiencing deficits in more general cognitive abilities such as inhibition. Impairments in inhibition are well known to produce difficulties in suppressing proactive interference from recently learned information and thus could explain these results (Anderson, 2003; Anderson, Bjork, & Bjork, 2000). Further research should examine through experimental paradigms the possible role that inhibitory processes play in degrading memory monitoring in patients unaware of their memory loss trying to minimize the impact that memory impairment may have on these tasks.

With regard to reality monitoring, results from this study support a relation between the ability of monitoring internal versus external information and anosognosia for memory loss. This pattern of results corroborates impairments in reality monitoring that have been proposed and observed in patients suffering from anosognosia of motor deficits (see Jenkinson et al., 2009; Venneri & Shanks, 2004; Saj, Vocat & Vuilleumier, 2014). Within the RMT task, patients did not differ in total hits, but they did in the overall total FAs. Patients unaware of their deficits showed significantly more FAs and a worse recognition memory discriminability index. These results were expected given the differences observed in memory performance in their general cognitive assessment. Interestingly though, when the total hits and FAs were controlled for (i.e., through the calculation of the source proportion index) patients who were unaware appeared to have more difficulties than the aware group in determining the source memories. A further intriguing result was the difference found in the type of misattributions in anosognosic patients. Patients unaware of their memory deficits committed external misattributions with higher frequency than those aware of their deficits. These results are in line with a previous study with patients unaware of their motor deficits (see Jenkinson et al., 2009). Further, there is a long-standing association of the External Bias (EB) and positive symptoms in schizophrenia (i.e., Bentall, Baker & Havers, 1991; Brébion et al., 2000; Woodward, Menon & Whitman, 2007). Some authors suggest that within this disorder, the EB serves a protective function of the ego avoiding negative connotations associated with the self (Langdon, Corner, McLaren, Ward, & Coltheart, 2006). From a more cognitive approach, Garrison, Bond, Gibbard, Johnson, and Simons (2016) suggested a perceptual threshold that a determined memory must hold to reach an internal source

level (see also Bentall & Slade, 1985). This is exemplified by the idea that internally produced memories are associated with a higher certainty (e.g., I would know if I were the agent that produced that thought versus someone else saying it). This approach would suggest that anosognosia in part reflects a deficiency in experiencing the perceptual richness that is necessary to attribute memories to an internal source (see Chapter 7 for further discussion). Future research should continue to examine the nature of this bias in patients with anosognosia as it may present an interesting venue to examine both cognitive and motivational accounts of anosognosia for memory loss. As previously highlighted the heterogeneity in sampling ranges of stroke onset and frequencies should be taken into account when extrapolating conclusions from this study (see Chapter 7 limitations section for further discussion).

As an overall conclusion of this chapter, findings supported a mnemonic monitoring deficit that appears to be domain specific and does not include motor monitoring deficits. When these mnemonic monitoring deficits were further explored, results supported an association between difficulties in reality or source monitoring. Indeed, patients who were unaware of their overall memory difficulties, had more difficulty discerning if previously acquired information was internally versus externally produced. Further, it appears that unaware patients tend to have an externalization bias. These results have important implication for current models of awareness and will be discussed in depth in the conclusion Chapter (Chapter 7; Relevance and implications section).

Chapter 6

Neuroanatomical Correlates

Summary of chapter

The previous chapter examined monitoring deficits in relation to anosognosia for memory loss. Findings supported that ongoing performance memory monitoring abilities (e.g., how well they are performing on an ongoing memory task) were associated with anosognosia for memory loss. Further, anosognosic patients appear to have an impaired ability to discern the source of memories (i.e., internally produced versus externally produced). Together with Chapter 4, in which the trait of neuroticism was associated with awareness, results support multifactorial factors underlying unawareness for memory loss in patients with ABI. This chapter's main aim is to further examine different factors that can influence awareness of memory loss with a main focus on neuroanatomical factors. Within this chapter, a summary of some of the most relevant studies examining neuroanatomical correlates of anosognosia for memory loss across different samples will be presented and the extent to which neurovascular disease is associated with anosognosia of memory loss will be assessed in a sample of patients with memory loss following a stroke.

6.1. Introduction

The examination of neuroanatomical correlates of anosognosia for cognitive failures, including memory loss, has mainly focused on patients suffering from dementing processes such as AD or FTD (see Zamboni & Wilcock, 2011 for recent review) with few studies examining other etiologies such as ABIs (see Hartman-Maeir et al., 2002; Hibbard, Gordon, Stein, Grober, & Sliwinski, 1992; Wagner & Cushman,

1994). Indeed, studies examining unawareness in ABIs have mostly focused on anosognosia for motor deficits following stroke (see Moro et al., 2016; Pia, Neppi-Modona, Ricci, & Berti, 2004; Starkstein, Fedoroff, Price, Leiguarda, & Robinson, 1992; Vocat, Staub, Stroppini, & Vuilleumier, 2010; Vocat & Vuilleumier, 2010) neglecting other deficits that patients can experience unawareness of, and that can have important consequences on patients' clinical outcomes.

Table 6.1. provides some of the most relevant studies that have explored the relation between neuroanatomical correlates and anosognosia of memory loss across both degenerative diseases and ABIs such as stroke. To this date, although several regions have been proposed to support anosognosia for memory loss, no specific area or structure has been systematically associated with it, possibly due to variable approaches used from study to study (Cosentino et al., 2015; Zamboni & Wilcock, 2011). Following Zamboni & Wilcock (2011), important methodological aspects that differ across studies can be specific to (i) the object of awareness (ii) the assessments used to determine awareness, (iii) the chosen neuroimaging measures and techniques, and (iv) the overall study design. One must thus exercise caution when extracting overall conclusions from different studies. For example, as observed in Table 6.1., although some studies examine unawareness for memory loss only (e.g., Cosentino et al., 2015; Hanyu, Sakurai, Hirao, Shimizu, & Iwamoto, 2007; Reed et al., 1993; Ries et al., 2007; Shibata, Narumoto, Kitabayashi, Ushijima, & Fukui, 2008; Vogel et al., 2005), others have conceptualized the object of awareness as a combination of different cognitive abilities and/or the overall dementing process including memory loss (e.g., Hartman-Maeir et al., 2002; Mendez & Shapira, 2005; Rosen et al., 2010; Salmon et al., 2006). The inclusion of awareness of

different cognitive abilities can produce biased results as anosognosia of each domain might be dependent on different mechanisms (e.g., see Study Two, Chapter 5). Another important factor to take into consideration, is the assessment used to determine awareness. Out of the nine studies examining unawareness for memory deficits only, six studies used patient-informant discrepancy scores, two studies used evaluations of memory performance in different tasks and one study used a clinical rating. Collapsing results from these studies can also be problematic as different measures of anosognosia have their own limitations and might tap into different forms of awareness for which specific regions might be necessary (see Chapter 3). Finally, the way that neuroanatomical correlates have been examined also varies across these studies as different measures of brain pathology or dysfunction have been used. For example, those studies examining neural correlates of anosognosia in ABI patients are more likely to report on the structural injury (i.e., broad location of lesions) (see Hartman-Maeir et al., 2002; Hibbard et al., 1992; Wagner & Cushman, 1994), while those studies focusing on degenerative diseases are more likely to report on functional markers, (i.e., cerebral blood flow and metabolic markers), or on volumetric differences of specific regions of interest (see Reed et al., 1993; Vogel et al., 2005; Zamboni & Wilcock, 2011). In this case reconciling results from different studies can also be difficult as studies using metabolic markers infer regions to be key for awareness but cannot specifically pinpoint at a concrete damaged region such as those observed in patients with ABIs.

Taking in account the previous limitations, although no single region has been found to be related to unawareness across all studies (see Table 6.1.), several studies have found support for a right lateralization of anosognosia for memory loss (Anderson &

Tranel, 1989; Cosentino et al., 2015; Derouesne et al., 1999; Harwood et al., 2005; Marshall et al., 2004; Ott, Noto, & Fogel, 1996; Reed et al., 1993; Rosen et al., 2010; Starkstein et al., 1995; Vogel et al., 2005), though others have failed to observe this (Hanyu et al., 2007; Hartman-Maeir et al., 2002; Shibata et al., 2008; Zamboni et al., 2013). This lateralization of anosognosia has also been reported in other studies examining anosognosia for hemiplegia following stroke (Orfei, Robinson, Bria, Caltagirone, & Spalletta, 2008; Orfei et al., 2007). These results may be partially reflective of a sampling bias, as patients with language difficulties are rarely included in these studies (Cocchini et al., 2012; Cocchini & Della Sala, 2010). Interestingly, within cognitive theoretical accounts, no theory has yet proposed underlying mechanisms specific to the right hemisphere. In contrast, motivational theoretical accounts such as that proposed by Turnbull et al. (2014), have proposed that unawareness of hemiplegia underlies an impaired right sided emotional processing and regulatory system (see Chapter 4 for description).

Table 6. 1. Summary of studies examining neurocorrelates of unawareness of deficits adapted from Zamboni & Wilcock, 2011.

Study	Sample	Domain of awareness	Awareness measure	Imageing measure	Study design	Neuroanatomical correlates
Anderson and Tranel, 1989	32 Stroke	Cognition	Self-evaluation-cognitive performance discrepancy	CT	Groups comparison: patients divided in two groups on unawareness score	Right hemisphere lesions more likely than left
Hibbard et al., 1992	82 Stroke	Cognition	Self-evaluation-cognitive performance discrepancy	Structural (not specified)	Groups comparison: patients divided in two groups (Right ABI versus left ABI)	No differences in awareness between left and right sided injuries
Reed et al., 1993	20/57 AD	Memory	Clinical rating	Functional: SPECT	Group comparison: patients divided in three groups on unawareness score	Right dorso-lateral frontal cortex
Wagner et al., 1994	108 Stroke	Cognition	Self-evaluation-cognitive performance discrepancy	CT/MRI	Interaction effects of lesion location on level of awareness	Cortical and posterior circulation strokes associated with unawareness
Starkstein et al., 1995	24/46 AD	Cognition and behaviour	Patient-informant discrepancy	Functional: SPECT	Groups comparison: patients divided in two groups on unawareness score	Right inferior-orbitofrontal and right frontal-superior frontal cortex
Ott et al., 1996	40 (AD, depression PS, FTD)	Global insight /cognition	Clinical rating	Functional: SPECT	Correlation between unawareness and hypo-perfusion	Right temporo-occipital cortex
Derouesne et al., 1999	78/88 AD	Cognition	Patient-informant discrepancy and Clinical rating	Functional: SPECT	Groups comparison: patients divided into two groups on imageing pattern	Right frontal lobe
Hartman-Maeir et al., 2002	60 Stroke	Cognition	Self-evaluation-cognitive performance discrepancy	CT	Groups comparison: patients divided in two groups on unawareness score	Cortical involvement and lesion size
Marshall et al., 2004	26 AD	Global insight	Clinical rating	Structural histopathology	Groups comparison: patients divided in two groups on unawareness score	Right hippocampal presubiculum
Vogel et al., 2005	39 FTD (frontal variant)	Memory	Patient-informant discrepancy	Functional: SPECT	Correlation between unawareness and hypo-perfusion	Right inferior frontal gyrus
Harwood et al., 2005	41 AD	Global insight	Clinical rating	Functional: FDG-PET	Correlation between unawareness and hypo-metabolism	Right lateral and dorsolateral frontal cortices
Mendez and Shapira, 2005	29 FTD (frontal variant)	Global insight	Clinical rating	Functional: SPECT or FDG-PET	Group comparison: patients divided into four groups on imageing pattern	Right frontal lobe
Mimura and Yano, 2006	24 AD 16 controls	Memory	Performance judgements	Functional SPECT	Correlation between unawareness and hypoperfusion	Medial frontal lobe right precuneus and right inferior frontal gyrus

Table 6.1. (Continued)

Study	Sample	Domain of awareness	Awareness measure	Imageing measure	Study design	Neuroanatomical correlates
Salmon et al., 2006	209 AD	Cognition	Performance judgement & Patient-informant discrepancy	Functional: SPECT or FDG-PET	Correlation between unawareness and hypometabolism.	*Self-performance:* right parahippocampus and left orbitofrontal cortex; *Discrepancy:* left temporo-parietal junction inferior temporal
Ries et al., 2007	16 MCI 16 controls	Memory	Patient-informant discrepancy	Functional MRI, task related	Group comparison on self-awareness task & correlation between unawareness and functional activation.	*Controls>MCI*: medial frontal cortex and posterior cingulate; *Correlation:* medial frontal cortex and posterior cingulate
Hanyu et al., 2007	43 MCI	Memory	Patient-informant discrepancy	Functional: SPECT	Group comparison based on imageing pattern	Bilateral parietotemporal or posterior cingulated areas
Shibata et al., 2008	29 A	Memory	Patient-informant discrepancy	Functional: SPECT	Correlation between unawareness and hypo-perfusion	Left orbitofrontal cortex
Hanyu et al., 2008	38 AD	Memory	Patient-informant discrepancy	Functional: SPECT	Groups comparison based on unawareness scores	Bilateral lateral and medial frontal lobes, bilateral anterior and posterior cingulate and left inferior parietal cortex
Rosen et al., 2010	39 (2 controls, 9 ASL, 9 AD, 2 MCI, 20 FTD, 4 CBS)	Cognition	Performance judgements	Structural: MRI	Correlation between unawareness and grey matter volume	Right orbito-medial frontal cortex
Zamboni et al., 2010	64 (38 FTD and 26 CBS)	Behaviour	Patient-informant discrepancy	Structural: MRI	Correlation between unawareness and grey matter volume	Right temporo-parietal junction and right superior temporal sulcus
Amanzio et al., 2011	29 AD	Cognition & behaviour	Patient-informant discrepancy	Functional: MRI	Group comparison, based on awareness, of cluster of activation in the inhibition go-no-go task.	Right anterior cingulate, rostral prefrontal cortex, right post-central gyrus, parieto-occipital gyrus left temporal gyrus in the striatum and in the cerebellum
Zamboni et al., 2013	51 (17 healthy elderly, 17 MCI, 17 AD)	Cognitive, behavioural and physical traits	Self-evaluation & Patient-informant discrepancy	Functional: MRI	Group comparison, based on diagnosis, of activation clusters of self and others evaluations	Dorsal medial prefrontal cortex and left anterior temporal lobe
Cosentino et al., 2015	14 AD & 30 healthy adults	Memory	Metamemory FOK task	Structural: MRI	Correlation grey matter volume with gamma scores	Right insula
Fujimoto et al., 2017	49 mild AD	Memory	Patient-informant discrepancy	Structural: MRI	Correlation of grey matter volumes with unawareness scores	Left superior frontal gyrus

AD, Alzheimer's disease; MCI, mild cognitive impairment; FTD, frontotemporal dementia; CBS, corticobasal degeneration syndrome; SPECT, single photon emission computed tomography; FDG-PET, Fluedeoxyglucose-photon emission tomography; MRI, Magnetic resonance imaging; Cognition: This term is used when several cognitive domains were assessed in the study.

Similar to the proposed right lateralization of anosognosia, although variable regions have been observed, unawareness of memory loss does appear to be more frequently associated with cortical regions (i.e., the dorsolateral frontal cortex, the medial and orbitofrontal cortex, the inferior frontal gyrus and the temporo-parietal junction), and some subcortical regions (i.e., insula and cingulate) (see Table 6.1.). As highlighted earlier, these studies are though largely focused on one etiology (degenerative disorders). The few existing studies examining anosognosia for memory loss in ABIs such as stroke have only reported on the extent of the injury (overall stroke burden) and on broad localizations of these injuries (e.g., cortical versus subcortical; right versus left; anterior versus posterior). In order to bridge the gap between studies examining anosognosia for memory loss in degenerative disorders and stroke more studies need to provide a more comprehensive examination of neurovascular pathology.

As described in Chapter 1, one of the most common cause of ABI in ageing populations is that of stroke (see section 1.2.1.1.2.) which can be classified as haemorrhagic and ischeamic, with ischeamic occurring more frequently (WHO, 2006). Ischeamic strokes can include cortical or subcortical strokes (e.g., lacunar infarcts) and can be commonly accompanied by what are believed to be ischeamic lesions of white matter (e.g., White Matter Hyper Intensities (WMHs) or Leukoaraiosis) (Brookes et al., 2013). As previously noted, deficits arising from an ischeamic stroke are dependent on the location of the injury and can include memory, executive functions, attention, language etc. (Markus et al., 2010), while WMHs have commonly been associated to cognitive difficulties such as executive functions and processing speed (Charlton, Morris, Nitkunan, & Markus, 2006; Nitkunan, Barrick, Charlton, Clark, & Markus, 2008). It is

not clear if WMHs contribute to anosognosia of memory loss, but deficits proposed to underlie WMHs (i.e., executive functions) can be key in some forms of anosognosia (i.e., executive anosognosia, see Chapter 5) and thus should be examined. Further, as proposed by Pacella et al. (2018) the variability of correlates associated with anosognosia can suggest a disconnection of different regions due to damage to the white matter tracts that connect them.

In an attempt to advance the understanding of how neurovascular pathology relates to anosognosia, this study aims to examine both ischaemic stroke lesion burden and disruptions to white matter integrity also known as White Matter Hyperintensities (WMHs). To this purpose, overall lesion volume and WMHs volume will be explored in relation to anosognosia. If the extent of tissue damage is important for awareness, one could expect that larger lesion and WMHs volume would be associated with higher levels of unawareness. Further, as described above, a lateralization of lesions and an association of specific cerebral regions with anosognosia has been observed, hence regional specificity could also be expected in relation to unawareness. This study will examine 6 regions of interest (i.e., Frontal lobe, temporal lobe, parietal lobe, limbic lobe, cerebellum and insula) in relation to anosognosia in an attempt to replicate findings observed in patients with neurodegenerative diseases such as AD.

6.2. Methods

6.2.1. Participants

A total of 43 participants with memory loss following a stroke were recruited for this study. Imaging scans (e.g., MRI, CT) were available in 23 participants. For purposes

of this study, only those patients that had available FLAIR scans were selected. These images were available for 21 individuals, one individual was excluded from analyses as they had an artifact and one individual was excluded from the analyses as they failed to provide an informant for our anosognosia measure (The VATAmem) leaving a total of 19 participants 42.1 % (n = 8) from the U.S., 57.9 % (n = 11) from the U.K all of whom had suffered from a ischeamic stroke.

6.2.2. Measures and procedure

6.2.2.1. Anosognosia and cognition

As in the previous chapter anosognosia was measured through the Visual Analogue Test for Anosognosia for memory impairment (VATAmem) (see chapter 3 for full description).

Cognition was assessed via the BCoS battery, the RBMT-2 and the MMSE (see chapter 2 for full description).

6.2.2.2. Lesion analyses

Images were acquired at two different institutions (St. George's hospital in London and CUMC in New York) and different scanners were used to obtain the images with the magnetic field varying from 1.5 to 3 Teslas. The whole brain was acquired for all images and slice thickness varied from 1 to 5 millimeters.

Preprocessing stream for images was developed in collaboration with Kay Igwe (imaging technician at CUMC). First, intensity inhomogeneity correction was applied to all FLAIR images using ANTs N4BiasFieldCorrection (Avants et al., 2011). An automated brain extraction tool, FMRIB's BET (Smith et al., 2004), was then used for

brain tissue extraction. As available images were collected at different institutions, variability of scanners introduced bias in the histogram intensity across scans. In order to correct for this, an intensity normalization algorithm for histogram matching was applied to all images using the scan with the largest variation of intensity values as the reference. Following Collewet, Strzelecki, and Mariette (2004), histogram matching is used for correcting the variations in scanner sensitivity due to differences in scanner performance (Sun et al., 2015). A semi-automated algorithm, as proposed in Brickman et al. (2011) was applied to the histogram matched images for segmentation of both WMHs and ischeamic cortical and lacunar strokes in native space. False positives were manually corrected by myself after visual inspection using itk-SNAP software (Yushkevich et al., 2006). Manual correction of ischeamic strokes and WMHs was derived from the information provided in patients' clinical radiological reports. In order to enable group analyses all images were converted into standard space. As some patients did not have a structural T1 to transform to standard space, a linear transformation was applied to each image using a flair template (Winkler, Kochunov, & Glahn, n.d.) using the FSL-FLIRT tool (FMRIB's Linear Image Registration Tool) and FSL-APPLYXFM was applied to all lesions in order to bring to them into flair template space. Finally, a nonlinear transformation was applied to each image using FSL-FNIRT and FSL-APPLYWARP was applied to all lesions (Smith et al., 2004; Woolrich et al., 2009). Lesion location for group analyses were derived using the Talariach atlas as reference (Lancaster et al., 2000).

6.2.2.3. Statistical analyses

In order to examine if there were any significant differences in cognitive functioning across awareness groups as determined by the VATAmem, Mann Whitney U tests were conducted. Due to limited sample sizes, non parametric analyses were conducted throughout this study. In order to examine the extent of damage or lesion volume and the volume of WMHs in relation to awareness two Mann Whitney U tests were also conducted. These analyses were conducted for whole brain and for both left and right hemispheres to assess if there was a lateralization effect. In order to further explore if there was a directionality effect of overall stroke and WMHs volume in relation to awareness, Spearman correlations were conducted (scatterplots included in Appendix 8). Region specific analyses were conducted across main cerebral lobes previously implicated in awareness of memory loss (e.g., frontal, temporal, parietal and limbic lobes) as well as specific regions such as the cerebellum and the insula also shown to be associated with unawareness of memory loss (see Table 6.1.). These analyses were specific to stroke lesion volumes and were examined through Mann Whitney U tests.

6.3. Results

6.3.1. Anosognosia and cognition

Based on the VATAmem's discrepancy score (see Chapter 3) a total of 8 patients were deemed unaware of their deficits and 11 as aware of their deficits. Mann Whitney U tests revealed no significant differences in global cognition, long term and short-term memory, executive functions, or attention abilities ($p > .05$). Table 6.2. provides a summary of patients' cognitive profile in relation to their awareness status.

Table 6.2. Cognitive measures across patients unaware and aware of their deficits.

Cognitive performance	**Unaware (n = 8)**	**Aware (n = 11)**	**U (p)**
MMSE (0-30)	24. (4.75)	26 (2.0)	18.5 (.28)
LT-Memory score (0-24)	7 (11.5)	14 (5.0)	16 (.06)
ST-Memory Z score*	-.15 (2.32)	-.56 (1.6)	50 (.20)
Executive Z score*	.68 (4.32)	0 (3.87)	39 (.81)
Attention Z score*	.59 (.95)	-.68 (2.36)	19 (.34)

Data is reported as medians and interquartile ranges in MMSE= global cognition; LT-Memory= Long term memory; ST-Memory= Short term memory. *P*-values of Mann-Whitney U test are also shown.

6.3.2. Lesion analyses

Ischeamic strokes and WMHs volumes were examined in relation to awareness status. Correlational analyses were also conducted to explore the association of overall lesion volume with unawareness. As shown in Figure 6.1., lesions in aware participants included bilateral frontal and parietal cortices, bilateral white matter tracts in the MCA territory, and subcortical structures such as the left puntamen and left insula. Lesions in the unaware group included left frontal, parietal and inferior right temporal cortices, left white matter tracts in the MCA territory, subcortical structures such as bilateral basal ganglia, left insular regions, the pons and the cerebellum. Overall ischeamic stroke volume and WMHs volume was not significantly different across aware and unaware patients ($U = 48$, $p = .80$; $U = 43$, $p = .87$). Regarding ischeamic strokes, no significant differences of overall volume was found in right ($U = 41$, $p = .74$) or left hemispheres ($U = 48$, $p = .80$). Whole group Spearman correlations were conducted to examine the

overall association of unawareness with ischeamic strokes and WMHs volumes. Results showed that ischeamic strokes volumes were not significantly associated with anosognosia for memory loss as measured by the VATAmem (*rho* = .15, *p* = .54). Overall WMHs burden was also not significantly associated with overall awareness (*rho* = .14, *p* = .55). When considering both the stroke and WMHs burden the association with unawareness of memory loss remained non-significant (*rho* = .19, *p* = .42).

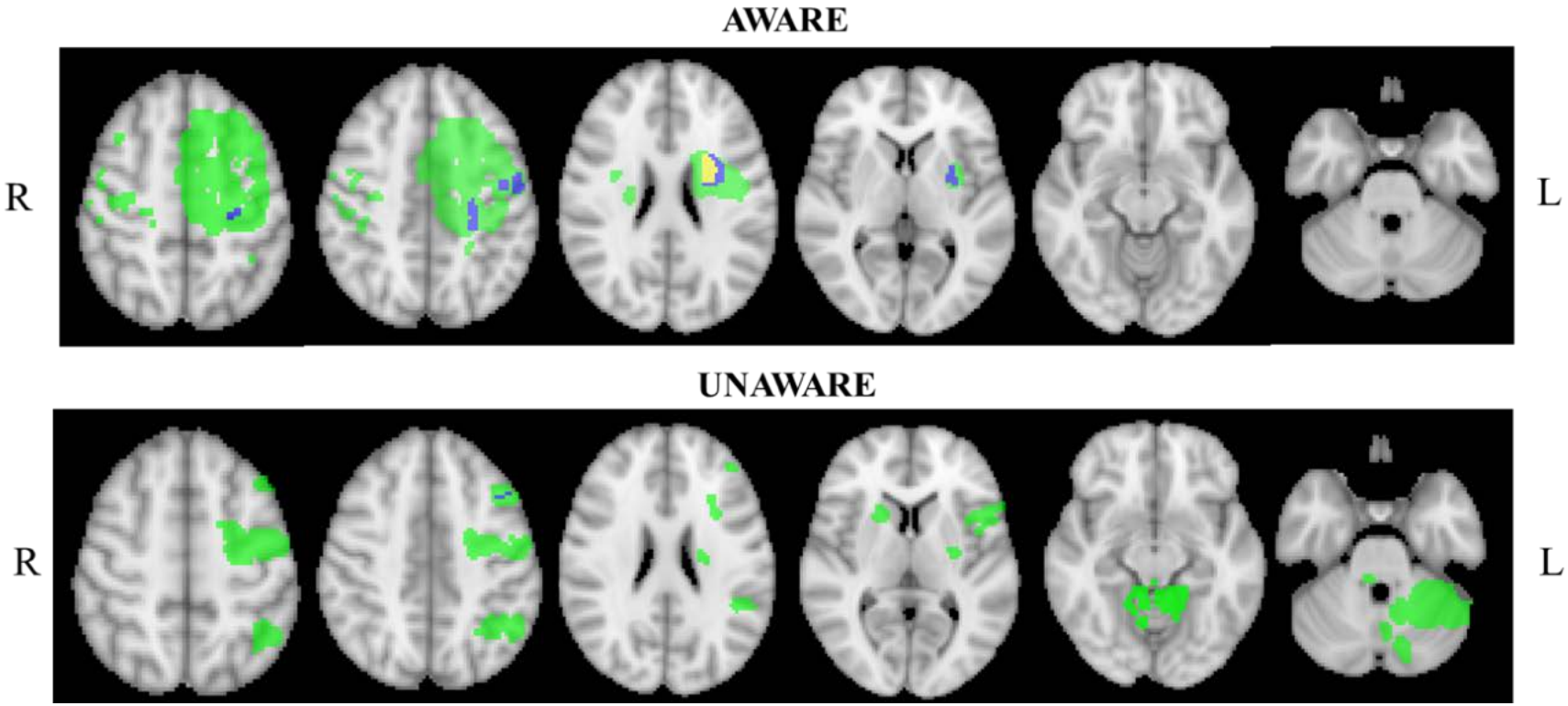

Figure 6. 1. Lesion overlay of patients aware (n = 10) and unaware (n = 9) of their memory difficulties. L = left side of the brain; R = right side of the brain. Green represents single lesions; Blue represents when two lesions overlapped in one region; Yellow represent when three lesions overlapped in one region.

Mann-Whitney U test were conducted to examine differences across overall volume of ischeamic stroke across different regions of the brain. Regions were selected based on the distributions of lesions within this sample and previously reported regions as associated with awareness. As observed in Table 6.3., the only significant difference across groups was found regarding the cerebellum ($p < .05$).

Table 6. 3. Mann-Whitney U test results comparing ischeamic strokes volumes across different brain regions between patients aware and unaware of their memory difficulties.

Brain regions	**Unaware (n = 8) Mdn (IQR)**	**Aware (n = 11) Mdn (IQR)**	**U (p)**
Frontal lobe	10.46 (15.84)	11.2 (49.25)	33 (.36)
Temporal lobe	5.42 (8.06)	.74 (18.22)	49 (.78)
Parietal lobe	2.52 (4.44)	3.66 (14.04)	36 (.49)
Limbic lobe	2.52 (4.94)	1.70 (15.30)	47 (.90)
Cerebellum	.40 (5.53)	0	70 (.04)+
Insula	.08 (.47)	.04 (.17)	51.5 (.60)

Data is reported as medians (Mdn) and interquartile ranges (IQR) across selected brain regions. P-values of Mann-Whitney U test are also shown. Significant difference between aware and unaware patients.

6.4. Conclusion

This study attempted to provide a comprehensive examination of neurovascular burden in patients unaware of their memory loss following a stroke. As noted in the introduction, although variable methodologies have been used in previous studies, some critical areas have emerged in relation to awareness including frontal, temporal and

parietal cortices and subcortical regions such as insular regions, parahippocampal presubiculum, cingulate and the cerebellum with a predominance of right sided lesions (see Table 6.1.). These areas have been extrapolated from studies including only degenerative disorders and it is not clear if they would correspond to those found in patients with ABIs such as stroke.

Results from this study showed significant differences of ischeamic stroke burden in the cerebellum. No significant lateralization effect was found of overall ischeamic stroke burden. No significant differences were observed of overall ischeamic stroke or WMHs burden between those aware and unaware of their deficits. Although the cerebellum has been traditionally understood as being involved in motor planning and control (see Manto et al., 2012), recent studies have supported the idea that the cerebellum is also involved in cognitive and limbic functions (Middleton & Strick, 2000a). Within previous studies examining anosognosia for memory loss, the cerebellum has been identified in one study as possibly underlying anosognosia in patients with AD (see Table 6.1.). This study by Amanzio and colleagues (2011), examined brain functional activation during an inhibition (go, no-go) task across aware and unaware patients with AD. The authors hypothesized that patients unaware of their deficits would experience hypometabolism in frontal cingulate pathways known to be involved in two possible correlates of anosognosia (i.e., apathy and inhibition). Their findings implicated these structures but also extended to limbic structures such as the putamen and the globus pallidus and the cerebellum suggesting an underlying degraded pathway between all these structures. Indeed Pacella et al. (2018) showed that, between others, disconnection to the limbic system was associated with anosognosia for hemiplegia.

Previous studies have supported that both cerebellar and limbic structures include outputs to frontal, prefrontal, inferotemporal and posterior parietal cortices forming loops that support functions that go beyond that of motor abilities (Middleton & Strick, 1996, 1997a, 1997b, 1997c, 2000b). Therefore, the cerebellum may play a role in known major limbic frontal loops. Three major limbic frontal circuits have been identified as those described by Bonelli and Cummings (2007). These circuits are hypothesized to be involved in complex cognitive and mood processes that could, if disrupted, contribute towards anosognosia of memory loss. The three frontal limbic circuits identified are : (i) the dorsolateral prefrontal circuit, hypothesized to mediate executive functions such as planning and monitoring of errors (Cummings, 1993; Cummings & Bogousslavsky, 2000); (ii) the medial frontal circuit, hypothesized to mediate mood (Starkstein, Fedoroff, Price, Leiguarda, & Robinson, 1993); and (iii) the orbitofrontal circuit, hypothesized to mediate the integration of visceral information of bodily functions and the integration of emotion into appropriate behaviour (Eslinger & Damasio, 1985; Mega, Cummings, Salloway, & Malloy, 1997). Pathological changes of these circuits can lead to impairments in executive function, mood (e.g., apathy) and behaviour regulation (i.e., disinhibition) which have been previously proposed as correlates of anosognosia (see Amanzio et al., 2011).

If the cerebellum is indeed part of a frontal-limbic-cerebellar pathway disruptions to it may lead to deficits described above. For example, deficits in executive functions have been found to have an equivocal relation with anosognosia for memory loss, with some studies finding an association while others, including this current study, have not (see Chapter 5). These unclear results can speak to a partial involvement of executive

functions that in addition to other processes can lead to unawareness of memory loss. Another possible contributor towards unawareness is that of mood dysregulation. Indeed, previous studies in patients with anosognosia for hemiplegia have argued that lesions in the basal ganglia structures known to be involved in motivation and detection of errors can lead to an inability to verify the contents of one's experience (Fotopoulou et al., 2010; Vuilleumier, 2004). Similarly, dysfunctional motivation or apathy has also been suggested as an underlying mechanism for unawareness of memory loss in patients with degenerative disorders such as AD and FTD (see Rosen's self-monitoring model in section 1.3.2.1.2., Chapter 1). This theory proposes that dysfunctional mood regulation can lead to suboptimal levels of motivation that are necessary for successful monitoring of one's own performance. Lack of motivation and an inability to integrate emotion into monitoring processes can lead to undetected errors, as they are not identified as emotionally salient. This study unfortunately did not include measures of apathy or motivation and thus could not provide evidence to support this theory.

To conclude although overall stroke and WMHs burden was not significantly associated with anosognosia for memory loss there was a positive trend between these. The lack of significant results might be reflective of the relatively small sample size included in this study which as noted in the general limitation sections (Chapter 7) may have impacted the results. Similarly, this study did not find support for a right lateralization of anosognosia for memory loss. Significant associations were found when examining the relation between specific regions affected by stroke and anosognosia for memory loss. Findings showed that the cerebellum were associated with anosognosia for memory loss. These lesions are interpreted in the context of cortical-subcortical circuits

that are critical for processes key for self-awareness (Fotopoulou et al., 2010; Rosen et al., 2010; Vuilleumier, 2004). Results from this study must be interpreted with caution as ABIs can affect many other brain regions not affected in this sample. Further, although this is the first study examining regional lesion mapping to unawareness of memory loss following a stroke, the use of other more updated lesion techniques such as Voxel-based Symptom Mapping (VSLM) (Bates et al., 2003) could have strengthened analyses in this study. These techniques allow a more refined examination of lesioned areas and can overcome some of the pitfalls of other techniques such as the one used in this study. For example, VSLM and similar techniques overcome the challenge of finding patients with similar lesions, allow for a voxel by voxel examination in a more specific manner than a priori large regions of interest, and avoid the loss of information that comes from using binary data (see Geva et al., 2012). Future studies should examine these correlates in a larger sample of individuals with anosognosia for memory loss following stroke and other ABIs including measures that reflect processes underlying limbic frontal loops and using more updated lesion mapping techniques (See also the limitations section of Chapter 7).

Chapter 7

General Discussion

Summary of chapter

This chapter provides a general conclusion that ties together the different studies developed as part of this thesis. Firstly, results from the study included in Chapter 3 (development of a new measure of awareness, the VATAmem) are presented and reviewed. Secondly, results from studies examining factors associated with anosognosia for memory loss (psychological, monitoring and neuropathological factors) are presented and reviewed. This section is followed by a review of the relevance and implications of findings across all studies included in this thesis. Finally, limitations encountered in each study are presented followed by suggested future steps and a general conclusion of the work and results presented in this thesis.

7.1. Measuring anosognosia for memory loss

One of the main aims of this thesis was to develop a new measuring tool for the assessment of anosognosia of memory loss (The VATAmem) that would build upon existing measures and overcome some of the pitfalls commonly observed across studies examining anosognosia for memory loss. Many of the existing measures rely heavily on cognitive abilities that may be impaired in patients who have suffered from an ABI or have a degenerative disease such as AD or FTD. For example, many measures rely heavily on verbal or memory abilities that may be impaired in patients with anosognosia (Cocchini et al., 2012). Other concomitant deficits such as attention deficits, lack of motivation or neglect can affect the reliability of patient responses, especially when these are in the form of a questionnaire. When carefully developed, structured questionnaires provide ideal grounds to measure explicit anosognosia for deficits as it allows a

standardized assessment from which validity and reliability metrics can be obtained. A structured questionnaire also allows a clear definition of the object of awareness under measure. As highlighted in Chapters 3 and 6, awareness of deficits is proposed as a multileveled construct and different measures can be developed to capture the different aspects of awareness (see section 1.3. in Chapter 1). Within this thesis anosognosia has been conceptualized as the higher order awareness, one that is less dependent on ongoing contextual cues and has been formed over past experiences (i.e., the semantisized notion of the self across different abilities). The VATAmem aims to assess this higher level of awareness by selectively asking questions regarding commonly experienced memory mistakes in everyday life.

The VATAmen has been developed based on previous existing measures of awareness, the PRMQ (Smith et al., 2000), which had already provided factor analytic studies supporting the distinction of awareness for prospective and retrospective memories (Crawford et al., 2006; Crawford et al., 2003). The VATAmem builds on these questions and aids comprehension by providing a visual analogue scale and vignettes that depict each question. To further aid reliability, check questions are added to capture unreliable responses due to attentional disorders, perseveration or poor compliance. These check questions are also included for informants. Results from study in Chapter 3 suggest that these check questions can indeed provide a useful way of assessing both patients and informants response reliability.

The nonverbal aid of the images not only alleviates the load of memory processing in these patients, but also allows less direct questioning. Following Clare, Nelis, Martyr, Whitaker, et al. (2012), when a patient is directly questioned about a

deficit, psychological processes may cloud self-report. For example, different patients may have different conceptualizations of what is appropriate to share, or they might be worried about revealing too much of a deficit and what consequences might follow. Denial mechanisms at a pre-conscious level have also been suggested as underlying unawareness of memory deficits (Turnbull et al., 2002; Weinstein, 1991). By providing examples of memory failures in the third person, patients might feel less threatened by the inquiry and thus provide self-reports that are a closer representation of their actual knowledge of their deficits (Clare, Nelis, Martyr, Whitaker, et al., 2012). By supporting the patient with visual information and offering them an opportunity to gain distance from the topic discussed, the VATAmem might be accessing a more accurate measure of patients' true knowledge of their deficit. This might aid in minimizing the risk of false positives, which as Baier and Karnath (2005) point out is a serious caveat of traditional measures of anosognosia.

To conclude, results from Chapter 3 supported the use of the VATAmem as a useful and reliable measure of anosognosia for memory loss. This measure was thus used in the following chapters as a measure of anosognosia with the exception of two studies where data was collected from AD patients prior the development of the VATAmem.

7.2. Mechanisms underlying anosognosia for memory loss

A second aim of this thesis was to explore possible underlying mechanisms that contribute to anosognosia for memory loss both in patients that had suffered a stroke and patients with AD. One of the aspects that has intrigued researchers in the field of anosognosia including myself, is the intrinsic complexity and variable presentation of this disorder (see section 1.3. of Chapter 1). This has led several authors to conclude that

anosognosia may indeed be a multifarious syndrome and that different subtypes may exist (Agnew & Morris, 1998; Cocchini et al., 2012; Cocchini et al., 2002; Fotopoulou, 2014; Gainotti, 2018; Jenkinson et al., 2011; Marcel et al., 2004; Vuilleumier, 2004). As highlighted by McGlynn and Schacter (1989) in order for our understanding of anosognosia to move forward, we need to clearly define our object of study and take theoretically based approaches to understanding the condition (see also Agnew & Morris, 1998; Ansell & Bucks, 2006; Clare et al., 2011; Clare, Nelis, Martyr, Roberts, et al., 2012). Following this statement is at the core of this thesis.

With regard to theoretical approaches of anosognosia, although traditional proposals for anosognosia have delineated a distinction between motivational and cognitive theoretical accounts (see section 1.3. and 1.3.2.1 in Chapter One), it has become clear that this distinction does not reflect the complex interplay of factors that can affect how individuals perceive their abilities, and new models have been proposed to account for this complexity (Agnew & Morris, 1998; Clare et al., 2011; Clare, Nelis, Martyr, Roberts, et al., 2012; Fotopoulou, 2014; Gainotti, 2018).

Results from studies included in this thesis support several contributing factors that can affect patients' awareness of memory loss. For example, results from Chapter 4 showed an inverse relation between the personality trait conscientiousness and the degree of unawareness for memory loss. These results were interesting as the most cited authors referring to personality and anosognosia (i.e., Weinstein & Kahn, 1995) had indeed predicted the opposite. In their seminal work, Weinstein and Kahn (1955) observed that those patients that were more likely to be unaware after a brain injury were also reported by their informants as having more conscientiousness traits. This study, as noted in

Chapter 4, lacked the use of a standardized measure of personality thus it is not clear if the construct of conscientiousness was fully captured. Following results found in this thesis, it appears that high levels of premorbid conscientiousness are associated with more accurate and in some cases underconfident evaluations of memory abilities. Previous studies have shown an association between higher levels of conscientiousness with academic and occupational achievement, health and longevity (Digman & Takemoto-Chock, 1981; Ozer & Benet-Martinez, 2006). Further, conscientiousness has also been observed to protect against MCI and AD (Wilson, Schneider, Arnold, Bienias, & Bennett, 2007). Having higher levels of conscientiousness might thus predispose an individual to have a more successful and enriched experience with the environment which in turn will strengthen their neural networks making them more resilient to pathology related changes. This hypothesis would support the idea that patients who are aware are so because they were able to maintain or compensate for the injury more effectively than those unaware of their deficits. This hypothesis though would not explain why some individuals with the highest scores of conscientiousness are also underconfident in their evaluations of their memory. An alternative explanation could be derived from the operationalization of individuals with the trait conscientiousness. Those that are categorized as having higher traits of conscientiousness are defined as being very organized, disciplined and goal oriented (Costa & McCrae, 2003). These characteristics could make these individuals prone to meticulously assess their abilities and develop more accurate perceptions of their cognitive abilities than those with average or lower ranges of this trait (e.g., stringent criterion for errors) (Colvin et al., 2018). No other personality traits were found to be associated with unawareness. This lack of association

could represent that other personality traits have smaller effects on unawareness, and that the study presented in this thesis was not powered to detect these associations. Further, the heterogeneous sample in terms of lesions onset, frequency and location may have also impacted results. This possibility should be considered when extracting conclusions about the role of personality on unawareness for memory deficits. Future studies should examine the possible role of awareness in larger and more homogeneous samples to discern if other traits such as neuroticism or extraversion have some effect on how self awareness is expressed.

The examination of mood in this thesis revealed no differences between stroke patients aware and unaware of their memory loss (see results section in Chapter 4). These results are in line with some studies (Cocchini et al., 2013; Starkstein et al., 1995), but not all (Bertrand et al., 2016; Besharati et al., 2014; Cines et al., 2015). As described in Chapter 4, differences found across studies could be due to sampling differences and timing of the assessment of mood (see Paolucci, 2008). Another possibility for conflicting results is described in the study developed by Cocchini et al. (2013), who provided an interesting insight into the relation between depression and awareness. Their study found that although awareness of language impairment was associated with self-reported depression on a questionnaire, it was not associated with depression as determined through clinical evaluation. Specifically, participants who hadn't reported depression by questionnaire were sometimes determined to be depressed on evaluation. The authors raised a rarely assessed issue, that is, patients who are unaware of their cognitive or motor deficits might also experience unawareness of their depression (see also Verhulsdonk, Quack, Hoft, Lange-Asschenfeldt, & Supprian, 2013). Unawareness

of mood disturbances can thus cloud our understanding of the relation between mood and anosognosia for cognitive difficulties. The fact that patients can be unaware of their depression or negative mood speaks to a much more complex interplay between mood and awareness. Though it appears that being depressed can lead to more complaints in the healthy ageing population (e.g., Balash et al., 2013), this association can become hard to disentangle in the presence of pathology with different results observed from sample to sample.

Finally, within the exploration of contributing cognitive or metacognitive factors to anosognosia for memory loss, this thesis explored, through three different studies, how different ongoing monitoring processes relate to unawareness of memory loss (see Chapter 6). These mechanisms were explored within the framework of awareness as a multileveled and multifaceted construct proposed by Agnew and Morris (1998). These authors proposed the CAM model (see section 1.3.2.1.1, Chapter 1) in which three specific subtypes or mechanisms are hypothesized to lead to anosognosia for memory loss (e.g., mnemonic, executive and global anosognosia) (Agnew & Morris, 1998). Although partial support has been found for one of the mechanisms (e.g., mnemonic anosognosia) (Ansell & Bucks, 2006) no studies have systematically assessed the executive or global anosognosia subtypes. Chapter 5 aimed to further explore executive anosognosia, hypothesized to develop following an impairment in a mnemonic comparator (Agnew & Morris, 1998). This impairment manifests as an inability to monitor ongoing memory performance, as opposed to mnemonic anosognosia where patients can monitor their ongoing performance but are not able to store this information, and therefore cannot permanently integrate this information into higher levels of

awareness (i.e., overall memory awareness). Preliminary evidence for executive anosognosia has been provided in studies with patients with AD where more accurate ongoing memory monitoring was associated with more accurate levels of awareness (Cosentino et al., 2007; Cosentino et al., 2011). Study One in Chapter 5 (Memory performance monitoring & anosognosia) replicated these findings in both a sample of AD patients and a sample of patients with memory loss following a stroke. Interestingly, there was no etiology group effect on memory monitoring, even though the cognitive profiles across the groups differed. For instance, stroke patients who were unaware of their deficits were performing significantly worse in memory and global cognitive tasks than those aware of their deficits. This difference was not observed in patients with AD. These results supported the idea that memory could play a partial role in ongoing memory performance monitoring but, as argued throughout this thesis, it is not sufficient to explain these monitoring deficits.

As noted in the previous paragraph, findings in study one supported an impairment in a mnemonic monitor. It was not clear if this deficit was specific to memory or expanded to other domains such as motor monitoring. Study Two in Chapter 5 (Memory performance monitoring, motor monitoring & anosognosia) assessed this issue. In this study, the relation between memory performance monitoring, motor monitoring and anosognosia was examined in a sample of patients with AD. Results from this study indicated that although memory monitoring and motor monitoring were associated with each other, only memory monitoring was associated with anosognosia for memory loss in this sample. These results are interesting as they support the existence of a lower level of awareness in which monitoring of different ongoing experience occurs but that these

monitors can act independently one from another. Further, these results support the specificity of a memory monitoring impairment for producing anosognosia for memory loss.

Based on results from Study Two, Study Three in Chapter 5 (Memory monitoring mechanisms & anosognosia) aimed at examining the specific type of mnemonic monitoring impairment in an attempt to elucidate further which aspects of memory monitoring processes are most relevant for anosognosia for memory loss. Toward this purpose, two main mnemonic monitoring processes were assessed (e.g., reality filtering and reality monitoring). Reality filtering refers to the ability to monitor temporal aspects of memories in order to determine if they are currently relevant or not (Schnider, 2008). As introduced in study three, this ability could be crucial for patients who have acquired a new deficit and need to be able to discern past versus current experiences with memory when producing a global self-evaluative judgement as the ones elicited when examining anosognosia. Reality monitoring on the other hand, refers to the ability to monitor source aspects of memories, specific to whether the memory was generated internally or externally (Johnson, 1991; Johnson & Raye, 1981). Being able to know if memory of one's performance reflects reality (e.g., actual memory performance) or instead reflects intended or expected memory performance (e.g., what I would like or expect my memory performance to be) can also be key for an individual's awareness of their memory loss.

Results in study three suggested partial support for an association between a temporal monitoring deficit of memories and anosognosia. Indeed, anosognosic patients showed an increased difficulty in discerning currently relevant items in the third run of the temporal monitoring task. Within this run (run 3) a 5-minute gap is provided between

runs which reduces the temporal ambiguity between the previous runs. Within the second run an increase of FAs are expected as the temporal gap between runs 1 and 2 was minimal (i.e., they occurred consecutively) and thus an increase interference effect was apparent for both aware and unaware patients. As the gap of the runs extends in run 3 (e.g., the temporal ambiguity lessens), FAs are expected to decrease. No differences were found when the increases of FAs were assessed across runs or in run 4 where both aware and unaware patients showed reduced FAs. In run 4 the temporal gap is increased to a 30-minute gap and thus patients should benefit even more of the temporal clarity between what was relevant before and what is relevant now. These results suggest that unaware patients were able to benefit from the increased time lapse and discern which items were temporally relevant. Alternatively, as unaware patients had worse memory functioning a 30-minute gap might have been long enough for the information learned in the previous runs to degrade and thus their performance was not based on temporal monitoring. Results from this study thus need further examination to determine if a temporal monitoring deficit (e.g., reality filtering) has a partial role in the memory monitoring difficulties that these patients experience (as shown in Study One, Chapter 5).

Regarding reality filtering, findings supported a relation between unawareness of memory loss and difficulties in monitoring internally versus externally generated memories. Indeed, patients who were unaware of their deficits had lower source proportion scores compared to those aware of their memory deficits in line with Jenkinson et al., (2009) who examined reality monitoring in patients unaware of their motor difficulties. Interestingly, as in the current study, these authors also found an externalization bias (EB), such that patients unaware of their deficits were more likely to

ascribe an external source to both internally sourced and new items. As described in the conclusion section of study three, deriving from the schizophrenia literature, two interesting proposals can be found for EB: a motivational account, and a cognitive account (Garrison, Bond, Gibbard, Johnson, & Simons, 2016; Langdon, Corner, McLaren, Ward, & Coltheart, 2006). From a motivational perspective, in patients with reality monitoring deficits, an EB bias serves as a protective mechanism from the negative information provided by the environment (Langdon et al., 2006). For example, patients with schizophrenia may experience social rejection or isolation and in turn rely on internal generated memories of themselves in a much more positive light. In the case of patients with newly acquired deficits, psychological processes to protect the ego from harm might promote internally produced memories over those externally produced and which reflect a difficult new reality. A cognitive account suggests that patients with schizophrenia have poorly formed internally produced memories which lack the perceptual richness to be distinguished from externally produced memories (Bentall, Baker, & Havers, 1991; Garrison et al., 2016). Following Jenkinson et al., (2009), similar processes could be used to explain reality filtering deficits in patients with anosognosia for motor deficits. These authors suggest that difficulties with attention, arousal and/or social interaction can lead to impairments in the ability to discern internally from externally produced motor imagery. This explanation can be extrapolated to patients who are anosognosic for memory loss. Further, impairments at encoding or retrieval stages can further affect the richness of internally produced memories, which would in turn be perceived as externally produced. Further examinations are needed to elucidate what factors contribute to this deficit in patients unaware of memory loss.

Finally, it should be noted that results from the current study showed that patients also had a worse discriminability index as they had difficulties discerning between targets and distractors. These results were expected given the lower performance of unaware patients in overall memory performance (i.e., RBMT-2). Although memory deficits could have affected the results of this study, it is unlikely that they can alone account for differences found in source proportion across participants. As described in chapter six, source proportion is calculated taking into account each individual's total hits. Though patients in the unaware group did on average worse than the aware group, they were not performing at floor effects and thus their ability to discern sources of memories was still captured.

Within the specific examination of neurocorrelates within this thesis results showed that the burden of stroke in cerebellar areas was significantly associated with unawareness of memory loss. Such that those with higher degrees of anosognosia had a greater stroke burden in this region. These results were interpreted in the context of cortical-subcortical neural circuits such as frontal limbic circuits (see conclusion section, Chapter 6). These circuits can be critical for the emergence of one's awareness as they are responsible for monitoring and integration of errors and mood modulatory processes that can affect how an individual evaluates their performance or general ability (Amanzio et al., 2011; Fotopoulou et al., 2010; Pacella et al., 2018; Rosen et al., 2010; Vuilleumier, 2004). Further, although WMHs can be an important marker to examine in relation to anosognosia, other more comprehensive examinations of white matter integrity such as Diffusion Tensor Imaging (DTI) can provide more informative results regarding white matter abnormalities and their relation to complex cognitive processes such as

unawareness (e.g., Charlton, Barrick, et al., 2006). This study as discussed below Future studies should

7.3. Relevance and implications

As discussed in Chapter One (section 1.3.), the study of anosognosia has important clinical implications. This disorder can have devastating consequences in those that suffer from it. For example, patients unaware of their deficits are more likely to progress from MCI to dementia (Gerretsen et al., 2017), are more likely to become involved in activities that may cause them harm (Cotrell & Wild, 1999; Cotrell & Wild, 1999), be less likely to engage in treatment and therapeutic decisions (Cosentino et al., 2011), and those that care for them experience higher levels of burden (Kelleher et al., 2016). It is therefore crucial that we advance our understanding of this disorder in order to establish grounds for the development of preventive and intervention programs to ameliorate these detrimental effects. These intervention programs can thus be targeted at both individuals suffering from unawareness and those who care for them.

Sporadic cases can be found in the literature with regard to treatments that can alleviate unawareness of deficits. For example, temporary reinstatement of awareness for motor impairment has been reported following caloric vestibular stimulation (e.g., Cocchini et al., 2002; Ramachandran, 1995; Rubens, 1985) or when presented with dangerous actions for the paralysed limb (D'Imperio et al., 2017). In many of these cases though, unawareness returned to baseline after the procedure. To my knowledge, there is only one long lasting treatment that has been reported in the literature as effectively improving awareness. This study developed by Besharati, Kopelman, Avesani, Moro, and Fotopoulou (2015), used third person perspective to improve awareness in an

anosognosic hemiplegic patient. Interestingly, as the patient observed herself in a video, she immediately acknowledged that she "had not been very realistic" in her self-evaluations. This improvement of awareness was maintained after 48 hours and at a 6 month follow up as reported in the study. The effectiveness of this treatment though has only been reported in this single case study and has not yet been replicated. To date thus, there are no standardized recommended treatments. This scarcity of available treatments could be due to the lack of understanding of the complex underlying mechanisms for anosognosia. This thesis attempts to provide a comprehensive examination of possible processes responsible for this disorder that could lead the way to more treatment avenues. In terms of impaired mechanisms that could be targeted as potential therapy, this thesis revealed that patients unaware of their memory loss have impairments in lower levels of awareness (i.e., memory performance monitoring). This finding supports that unaware patients are having difficulty adjusting their predictions to their ongoing performance (e.g., they have impaired resolution). As noted earlier, FOK judgements are hypothesized to partially rely in different processes such as general memory and executive abilities and mnemonic monitoring processes such as familiarity and partial access to information (Cosentino, Metcalfe, Holmes, et al., 2011; Koriat, 1993; Koriat & Levy-Sadot, 2001; Metcalfe, Schwartz, & Joaquim, 1993; Reder & Ritter, 1992; Schnyer et al., 2004; Schwartz & Metcalfe, 1992). Interestingly, aware and unaware patients had similar calibration scores, thus it appears that unaware participants are able to predict their performance accurately to start with, but are unable to combine contextual details from the task and internal factors such as familiarity cues to make appropriate consecutive judgements. In line with this idea, Cosentino et al., (2007) found that unaware

participants differed from aware participants in the strategies they utilized during the FOK task. Their study showed that aware patients relied on previous performance as a marker to estimate following performance (i.e., memory for the past test (MPT) heuristic). For example, if they made an error in the previous trial their confidence levels were more likely to be lower than if they had been correct (Cosentino et al., 2007). If indeed this is the case, unaware patients could be specifically trained at using strategies such as the MPT to help improve their online monitoring of their memory performance. This in turn would translate to increased awareness at a global level as predicted by the CAM model (Agnew & Morris, 1998).

Another mechanism that was found to be associated to anosognosia for memory loss was reality monitoring (the process by which individuals discern internal from external produced memories). This failure could be led by two mechanisms as proposed above: (i) motivational and (ii) cognitive. From a motivational perspective, if patients are having difficulty recognizing externally learned information because it is too painful to manage, psychotherapeutic approaches could be beneficial as they can provide vulnerable patients with a safe space to explore this new negative information about themselves. From a cognitive perspective, patients may be relying erroneously on internal information as it were external information (i.e., what is 'real') as the strength of these memories are subdued due to poor encoding or retrieval strategies. In this case promoting strategies for patients to enhance their ability to discern from these types of memories could be at the core of an interventive program (see also Jenkinson, 2008). Finally, therapies attempting to increase awareness of deficits should also offer psychotherapy sessions to guide the patients with the difficult transition of becoming

aware of the loss of an ability. This might enhance how individuals react to the deficit and how they further engage in rehabilitative or compensatory interventions.

From a more theoretical standpoint, results of this thesis inform on our current understanding of how self-awareness operates. They build upon existing models of awareness such as the Biopsychosocial model or the CAM model (Agnew & Morris, 1998; Clare et al., 2011; Mograbi & Morris, 2013) and provide evidence for some of the hypothesized factors proposed in these models. This thesis approached anosognosia for memory loss from a multilevel and multifaceted perspective and results indeed supported that different factors can contribute to the emergence of awareness. Results from Chapters four to six revealed that psychological processes, cognitive or metacognitive factors and neuroanatomical factors can all play a role in this fascinating disorder. Patients who were unaware of their deficits were shown to have decreased trait levels of conscientiousness suggesting that premorbid levels of this trait can affect the accuracy of self-awareness. Results of this study are opposed to the earlier proposition of conscientiousness as predisposing anosognosia (i.e., Weinstein & Kahn, 1955). On the contrary, it was found that lower levels of conscientiousness were associated with anosognosia. This result is in line with more recent examinations of the accuracy of self-awareness and personality traits across both patients with AD and healthy ageing adults (e.g., Clare et al., 2012; Colvin et al., 2018; Chapman et al., in prep). A shift in the interpretation of conscientiousness in relation to anosognosia may thus be necessary. For example, a recent proposal of conscientiousness suggested that this trait may be crucial for monitoring the salience of stimuli for one's own goals as well as knowing when to pay or not attention to distracting stimuli (Rueter, et al., 2018). These skills are crucial

for monitoring one's own performance (examined in Chapter 5). Patients unaware of memory loss might be at an increased risk for anosognosia because they might have decreased abilities to detect the saliency of important stimuli and ignore distracting stimuli when confronted with their newly acquired deficit. Their premorbid levels of monitoring determined by their level of consciousness may thus make it difficult to detect errors in performance and update their long term semantic database of their memory abilities. Future longitudinally based studies should be conducted to examine this hypothesis.

In line with the argument above, results in Chapter 5 supported that deficits in *local awareness* (context/task dependent notion of abilities) were associated with higher levels of awareness or *global awareness* (general notion of abilities). Further, this association was observed to be domain specific, such as deficits in memory monitoring were only associated with anosognosia for memory loss. These results integrate and extend current theoretical models of anosognosia for memory loss such as the CAM model (Agnew & Morris, 1998; Hannesdottir & Morris, 2007; Mograbi & Morris, 2013; Morris & Hannesdottir, 2004). For example, findings from studies included in Chapter 5, support a shared variance between ongoing monitoring of performance across different domains such as the proposed Cognitive Comparator Mechanisms (CCMs). These as described in section 1.3.2.1.1, operate under executive control and if impaired, monitoring deficits across domains should be observed which would then translate to anosognosia across domains (i.e., executive anosognosia). Study two in Chapter 5 is the first to experimentally assess the proposed CCMs in relation to anosognosia for memory loss and find support for shared variance between different domain monitors. With regard

to anosognosia for memory loss, results showed a Cn deficit specifically of the memory domain that did not expand to other domains (e.g., CCMs). This pattern of results suggests that each monitoring domain is dissociable and in the case of anosognosia for memory loss an impairment at the mnemonic Cn level may underlie its expression. The memory monitoring processes that rely on a mnemonic Cn and are important for anosognosia have not been specified in the CAM model. Study three in Chapter 5 attempted to explore this and examined two different types of mnemonic monitoring abilities (reality monitoring and filtering) in relation to anosognosia for memory loss. This study showed that only difficulties pertaining to reality or source monitoring were significantly associated with anosognosia for memory loss. These findings highlight the need to further clarify what specific mechanisms are impaired in relation to anosognosia in order to further understand this disorder and target tailored interventions.

Limitations and future research

The research included in this thesis builds upon existing studies and provides new findings that further clarify some of the underlying mechanisms of anosognosia for memory loss. Research presented in this thesis though has some limitations that should be taken into account when interpreting findings reported.

Sample size in some of the studies was small and thus the power to detect an association or a difference between groups was reduced. One caveat of small sample sizes is that they are sensitive to bias, therefore when only small sample sizes (Chapter 6) were available and/or data was non normal more robust analyses were conducted such as non-parametric tests (e.g., Mann Whitney U tests and Spearman correlations).

Another limitation of this thesis is that different participants were enrolled across studies with different measures of anosognosia. Some studies included patients with ABI assessed with the VATAmem while others included patients with AD who were assessed via a clinical rating of anosognosia. Ideally, all patients would have been enrolled in all studies allowing for comparison of all mechanisms studied in this thesis and would have received the same diagnostic tool. Additionally, with regard to sampling strategies, a large range of lesion onset for stroke patients was included across several studies (e.g., VATAmem, mood and personality, monitoring and lesion studies). Further, some patients had suffered several strokes. This sampling heterogeneity could have impacted results in various ways. Indeed, patients with a stroke onset under 6 months may still have been adjusting to their new cognitive difficulties, while those with stroke onsets of over a year may have had more time to adjust and be exposed to their deficits (e.g., through their own experience and/or via feedback of others). Levels of awareness between these patients may thus differ due to the variable onsets. For example, one potential confounder of awareness status in patients with larger onsets is that they might have learned through their caregivers and doctors that they have a deficit (e.g., "my wife says I have a problem and hence I say I have a problem"). This 'learned awareness' though may not have been internalized and even though they might endorse explicitly some difficulties, in actuality, they do not believe they have a problem. Therefore, such patients may be categorized as aware when they are truly unaware (e.g., false negative). Further limitations with regard to heterogeneity of sampling could manifest through the inclusion of some patients who had several strokes. Patients with several strokes might be at a higher risk of developing dementia and thus represent a different

neuropathological process than those who have only suffered one stroke. Therefore, more stringent inclusion criteria should be endorsed by future research, limiting the range of the onset and frequency of strokes. For example, future studies could examine patients who have suffered from one stroke only and stratify by onset (e.g., within 1– 6 months; 6 months – 1 year etc.). This design could help tease apart if there are any effects of length of onset in relation to awareness.

Another limitation can be found in terms of the variable presentation of ABIs in terms of lesion location and lesion size which had an impact in the results of the study examining neuroanatomical correlates, limiting the extrapolation of findings to other samples. Another limitation can be found in terms of the variable presentation of ABIs lesion location and lesion size which impacted results of the study examining neuroanatomical correlates limiting the extrapolation of findings to other samples. Further, as noted in the conclusion of Chapter 6, more recent imaging techniques could have provided a more extensive examination of the lesion burden in patients with anosognosia for memory loss following stroke. For example, choosing large regions of interest and overlapping lesions might miss important information regarding which specific regions are affected and which are spared. This limitation impacts the ability of the neuroanatomical examination in Chapter 6 to provide a robust conclusion of what regions may be relevant for anosognosia for memory loss. Indeed, it is recommended that future studies examine lesion burden with voxel based techniques such as Voxel-based Symptom Mapping (VSLM) (Bates et al., 2003) in larger and more homogeneous samples.

7.4. Conclusion

Results from this thesis can help optimize the way anosognosia for memory loss is assessed and extend theoretical implications of some of the most relevant proposed models of anosognosia for memory loss (e.g., CAM model and hierarchical biopsychosocial model) (Agnew & Morris, 1998; Clare et al., 2011). The first study of this thesis (Chapter 3) reports on the development of a new measure of awareness (The VATAmem) which is designed to account, through visual aids and check questions, for possible associated cognitive deficits commonly observed after an acquired brain injury. Findings supported this new measure as valid, reliable and possibly reflecting more accurate self-evaluations of memory deficits. Results from following studies (described in Chapters 4 to 6) showed how different factors contribute towards the expression of awareness.

The study described in Chapter 4, showed how personality traits, specifically conscientiousness, affect the way self-awareness is expressed. Indeed, those with higher levels of conscientiousness were more aware of their deficits. Studies described in Chapter 5 showed that mnemonic monitoring deficits are also associated with self-awareness. Specifically, deficits in online memory monitoring resolution, or the way that one adjusts predictions in line with performance, is associated with anosognosia for memory loss. Further, reality monitoring deficits were also found to be associated with anosognosia for memory loss such that patients unaware of their memory deficits had more difficulties discerning between memories from internal and external sources. Finally, results from Chapter 6 showed that neuroanatomical regions such as the midbrain and basal ganglia may contribute towards awareness, though limited sample size and a

heterogeneous lesions location limit the generalization of these results. Taken together these findings support anosognosia as a multifaceted syndrome. Results from this thesis can help shape new therapeutic interventions as well as inform the current understanding of anosognosia for memory loss.

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Appendix

Appendix 1
REC letter of approval for NHS St George's hospital recruitment site

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 5 Ground Floor - Tennent Building Western Infirmary
38 Church Street Glasgow
G11 6NT

Date 18 November 2014

Direct line 0141 211 2102
E- mail WoSREC5@ggc.scot.nhs.uk

Study title:	**Unawareness (anosognosia) of memory impairment following stroke.**
REC reference:	**14/WS/1073**
Protocol number:	**N/A**
IRAS project ID:	**77480**

Dear Dr Cocchini

Thank you for your letter of 1 November 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and Statistician.

As a suggestion **only**, the Statistician has asked me to pass on the following advice:

"Thank you for your care in your response which I now accept. However, I would ask you to note that you have computed a sample size for a one-tail test, i.e. you are pre-specifying the direction of the difference between the two means. This is not wrong, and may well be exactly what you wish, but it is more common at this stage to use two-tail tests, for which the necessary sample size is 12, giving a total of 36 rather than 30,

and leaving much less room for drop-out in your proposed 40. You may wish to consider this and/or consult your statistician(s)."

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mrs Sharon Macgregor, WoSREC5@ggc.scot.nhs.uk.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Cover letter of amendments]	1	01 June 2014
Covering letter on headed paper [Cover letter of amendments]	2	01 September 2014
Covering letter on headed paper [Cover letter of amendments]		
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity liability]	1	01 June 2014
GP/consultant information sheets or letters [GP letter feedback of results.]	1	01 June 2014
IRAS Checklist XML [Checklist_11092014]		11 September 2014
IRAS Checklist XML [Checklist_12112014]		12 November 2014
Other [Safety protocol.]	1	01 June 2014
Other [PMVA training certificate]	1	
Other [Unfavourable opinion letter previous REC review]	1	29 May 2014
Other [Paper for Cohen's d calculation on Emotional denial mechanism]		
Other [Paper 1 of 2 for calculating Cohen's d for Misleading memory traces mechanism]		
Other [Paper 2 of 2 for calculating Cohen's d for Misleading memory traces mechanism]		
Other [Paper for Cohen's d calculation on Monitoring deficits mechanism]		

Participant consent form [Patient Consent form.]	2	01 September 2014
Participant consent form [Classic controls consent form.]	2	01 September 2014
Participant consent form [Proxy raters controls consent form.]	2	01 September 2014
Participant information sheet (PIS) [Patient Information Sheet.]	2	01 September 2014
Participant information sheet (PIS) [Classic control information sheet.]	2	01 September 2014
Participant information sheet (PIS) [Proxy raters information sheet.]	3	01 November 2014
REC Application Form [REC_Form_04082014]		04 August 2014
Referee's report or other scientific critique report [External review letter.]	1	21 June 2014
Research protocol or project proposal [Protocol version 1; 01.06.1]	1	01 June 2014
Summary CV for Chief Investigator (CI) [Chief Investigator CV; 01.06.14]		01 June 2014
Summary CV for student [PhD student CV 01.06.14]		01 June 2014
Summary CV for supervisor (student research) [Supervisor CV; 01.06.14]		01 June 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please

use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality- assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

14/WS/1073	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Appendix 2
IRB letters of approval for Columbia University Medical Center recruitment site

COLUMBIA|RESEARCH
Human Research Protection Office
Institutional Review Boards

January 12, 2018

Stephanie Cosentino
758200X - SGV Sergievsky Center

Protocol Number: IRB-AAAB4726
Title: Metacognition and Memory Functioning
Approval Date: 01/10/2018 Expiration Date: 01/09/2019 Event Identifier: Renewal (Y14M00)

The above-referenced event was reviewed by Columbia University IRB 1. Level of

review and outcome: Approved by Expedited review

To view a list of documents that were included in this approval (if applicable) and all other currently approved documents for this study, please refer to the Print Menu for this Event in Rascal. It is important to confirm the status of each document, e.g., active, stamped, etc. Only stamped, active documents can be used with research participants.

Study Status: Closed to further enrollment: remaining research activities are limited to data analysis only

Important Reminders:

F- Subjects: Please update the "How many remain on the study?" field to reflect zero for accuracy.

G- Privacy & Data Security section: As previously noted your previous

submissions indicate that PHI/PII will be collected. In your next submission, please respond YES to “Does this study involve the receipt or collection of Sensitive Data?” then answer the subsequent questions to indicate that sensitive data (PHI and PII) will be collected and stored on an encrypted endpoints.

Electronically signed by: Lesmes, Diana

IRB-AAAB4726 **Renew al (Y14M00)**

Researcher Responsibilities:

Any proposed changes in the protocol must be immediately submitted to the IRB for review and approval prior to implementation, unless such a change is necessary to avoid immediate harm to the participants.

Any unanticipated problems that involve risks to subjects must be reported to the IRB in accordance with the Unanticipated Problems: Reporting to the IRB of Unanticipated Problems Involving Risks policy. All submissions for modifications and unanticipated problems must be submitted through Rascal.

Renewal applications should be submitted 60 days before the expiration date of this study through Rascal. Failure to obtain renewal of your study prior to the expiration date will require discontinuance of all research activities for this study, including enrollment of new subjects.

You must file a Closure Report in Rascal when your study has been completed.

COLUMBIA|RESEARCH
Human Research Protection Office
Institutional Review Boards

April 4, 2016

Stephanie Cosentino 758100X - TBI Taub Institute

Protocol Number: IRB-AAAQ6952
Title: Perception of memory following stroke Protocol Version #: 1; 01/06/16
Approval Date: 04/01/2016 Expiration Date: 03/31/2017 Event Identifier: New Protocol (Y01M00)

The above-referenced event was reviewed by Columbia University IRB Exp. Level of

review and outcome: Approved by Expedited review

To view a list of documents that were included in this approval (if applicable) and all other currently approved documents for this study, please refer to the Print Menu for this Event in Rascal. It is important to confirm the status of each document, e.g., active, stamped, etc. Only stamped, active documents can be used with research participants.

Consent Requirements:
Informed consent with written documentation will be obtained from the research participant or appropriate representative

HIPAA Authorization: Authorization will be obtained

Important Reminder:
1) Please make all necessary formatting adjustments to ensure that the Statement of Consent is located on the same page as the signature lines. This update can be made

at the time of the next submission.

Electronically signed by: Santos, Rafael

IRB-AAAQ6952 Protocol (Y01M00)

Researcher Responsibilities:

Any proposed changes in the protocol must be immediately submitted to the IRB for review and approval prior to implementation, unless such a change is necessary to avoid immediate harm to the participants.

Any unanticipated problems that involve risks to subjects must be reported to the IRB in accordance with the Unanticipated Problems: Reporting to the IRB of Unanticipated Problems Involving Risks policy. All submissions for modifications and unanticipated problems must be submitted through Rascal.

Renewal applications should be submitted 60 days before the expiration date of this study through Rascal. Failure to obtain renewal of your study prior to the expiration date will require discontinuance of all research activities for this study, including enrollment of new subjects.

You must file a Closure Report in Rascal when your study has been completed.

Appendix 3
REC approved stroke patient's and informant's information sheet and consent forms for NHS St George's hospital recruitment site

Goldsmiths UNIVERSITY OF LONDON
New Cross, LONDON SE14 6WN

St George's University Hospitals NHS
NHS Foundation Trust
St George's Hospital
Blackshaw RoadLondonSW17 0QT

PATIENT INFORMATION SHEET (Version 2; 01/09/2014)

Dear Sir/Madam,*You are being invited to take part in a **RESEARCH** study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.*

Anosognosia for memory impairment following stroke

PROJECT DESCRIPTION

People that have suffered from a stroke sometimes may experience some difficulties with their memory.
Clinical experience and research studies have revealed that some patients with memory difficulties can experience **problems in being fully aware** of their **memory difficulties** and that this situation can slow down or prevent recovery of memory ability.

Why have I been chosen?

Information on memory ability from people who have suffered a stroke can guide rehabilitation approaches. We will like to **investigate**, with your help, how **people perceive their own memory ability.**

What will I have to do if I take part?

The study will consist of **simple tests** that comprise **two questionnaires** in which you will be asked to rate your memory ability in tasks such as remembering an appointment or a name. We will also ask your relative and/or your clinician to rate your abilities in these tasks in order to

obtain one or two independent evaluations.
You will also be asked to perform other paper and pencil tests or computerized tests where accuracy or reaction times will be recorded. The overall participation time in this study will be from 118 to 178 minutes. Your participation will be divided into several blocks. You will have several choices about where you complete the study, such as the clinic where you are being recruited, Goldsmiths College University of London or your own home. Any travel costs if the first two are chosen will be covered, including car expenses. Please note that if you choose your home as the assessment location we will ask someone involved in your care, a relative or a friend to be present too.
We would like to **video or tape record** your responses in order to allow us to analyze your data later, but also to allow you to watch or listen to your performance. We would like to access some of your medical information such as when you had the stroke and any scans that you may have already had. We will not ask you to have a scan as part of your participation in this study.
All personal details and results will be stored in the researcher's office and will remain confidential. When the study has been completed, data will remain in the researcher's office for 6 months. **Anonymity will be assured** during and after the study by allotting an anonymous code (that is your initials plus a number) to your results and details that will be kept in locked cabinets at Goldsmiths University of London. If any clinically significant results are found your care team will be informed.

Do I have to take part?

You are **not obliged** to take part in this study, and are **FREE TO WITHDRAW AT ANY TIME** during the tests. Should you choose to withdraw from the program you may do so without disadvantage to yourself and without any obligation to give a reason.

What are the potential benefits?

There are no specific direct benefits for your treatment or care from participating in this study. However, research does deliver wider benefits to society / others with a similar condition and some indirect benefits might be foreseeable for participants themselves.

What are the potential risks?

There are no foreseeable risks in this study as all tests are paper and pencil or computerized with non invasive procedures. But you might experience some tiredness or find some of the assessments frustrating. For this reason the assessment has been structured to allow for as many rests as you feel you may need. It is also important to note that there are no right or wrong answers in these assessment s and the outcome of them won't interfere with your treatment or care.

Who should I contact about the study?

This is a **STUDENT PROJECT** developed in fulfillment of the requirements of the PhD in Psychology program at Goldsmiths, University of London. This project is supervised by Dr Gianna Cocchini and Dr Rebecca Charlton professors at Goldsmiths, University of London, Dr Usman Khan Principal Investigator and Rebecca Brookes research psychologist, St Georges, University of London. For any queries please contact any of the following:

Student contact details
Silvia Chapman
Email: ps201sc@gold.ac.uk

Principal Investigator contact details
Dr Usman Khan
Stroke Unit, St George's Hospital
St George's Healthcare Services NHS Trust
E-mail: Usman.khan4@nhs.net

Academic supervisors contact details
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Goldsmiths UNIVERSITY OF LONDON
New Cross LONDON SE14 6NW

St George's University Hospitals NHS
NHS Foundation Trust
St George's Hospital
Blackshaw RoadLondonSW17 0QT

PATIENT CONSENT FORM (VERSION 2; 01/09/2014)

Project Title

Anosognosia for memory impairment following stroke.

Please initial the boxes to confirm

- I have read the information sheet for the above study. ☐
- I have had the opportunity to ask questions about and discuss the study. ☐
- I understand the purpose of the study, and how I will be involved. ☐
- I understand that all information collected in the study will be held in confidence and that, if it is presented or published, all my personal details will be removed. ☐
- I confirm that I will be taking part in this study of my own free will, and I understand that I may withdraw from it, at any time and for any reason, without my medical care or my legal rights being affected. ☐
- I agree to be contacted for a repeat test at some time within the next year. ☐
- I agree for my scans if developed to be used by researchers in this study. ☐
- I agree to be videotaped in some tasks of the study. ☐
- I would like for the results of the assessments to be sent to my GP ☐
  If ticked this box please provide details of contacts
  GP name _____
  GP address _____
  _____

I agree to take part in the above study.

_____ _____
Signed Date

_____ _____
Person taking consent Date

Patient ID _____

Goldsmiths UNIVERSITY OF LONDON
New Cross LONDON SE14 6NW

St George's University Hospitals NHS
NHS Foundation Trust
St George's Hospital
Blackshaw Road
London
SW17 0QT

PROXY RATER CONTROL INFORMATION SHEET (Version 3; 01/11/2014)

Dear Sir/Madam,

*You are being invited to take part in a **RESEARCH** study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.*

Anosognosia for memory impairment following stroke

PROJECT DESCRIPTION

People that have suffered from a stroke sometimes may experience some difficulties with their memory**.** Clinical experience and research studies have revealed that some patients with memory difficulties can experience **problems in being fully aware** of their **memory difficulties** and that this situation can slow down or prevent recovery of memory ability. To this aim we will **investigate**, with your help, **people's level of awareness of memory ability**, and the mechanisms underlying the process of becoming aware.

Why have I been chosen?

In this study we are carrying out different assessments in memory and other cognitive abilities in patients with stroke such as your patient, relative, friend or person you care for. We are asking you if you would like to take part as to provide scoring for your

relatives performance on several tests that measure everyday memory problems.

What will happen to me if I take part?

You will be asked to complete some tests of your patient, relative, friend of person you take care of, memory abilities. Testing will take around 25 minutes.

Do I have to take part?

It is entirely up to you to decide whether or not to take part. If you do decide to take part you will be asked to sign a consent form. We will be repeating the test in a subgroup of people to see how reliable it is and we will ask permission for us to contact at some time in the next year for this. If you decide to take part you are still free to withdraw at any time and without giving a reason.

Will my taking part in this study be kept confidential?

All information collected about you during the course of the research will be kept strictly confidential. Only the research team here and at the coordinating centre (St. George's) will have access to your personal information which is securely stored. Any results which are published from the study will be entirely anonymous.

Will I be reimbursed for my travel expenses?

As this is a research study we will pay travel expenses (public transport or car) for you to come back to clinic to complete the tests on production of receipts.

Whom should I contact for further information?

This is a **STUDENT PROJECT** developed in fulfillment of the requirements of the PhD in Psychology programme at Goldsmiths, University of London. This project is supervised by Dr Gianna Cocchini and Dr Rebecca Charlton professors at Goldsmiths, University of London and Dr Usman Khan Principal Investigator. For any queries please contact any of the following:

Student contact details
Silvia Chapman
Email: ps201sc@gold.ac.uk

Principal Investigator contact details
Dr Usman Khan
Stroke Unit St George's Hospital
Telephone: 0208 672 1255
E-mail: usman.khan4@nhs.net

Academic supervisors contact details
Dr. Gianna Cocchini (Chief Investigator)
Psychology Department
Goldsmiths, University of London
Telephone: 020 07 8524
E-mail: g.cocchini@gold.ac.uk
Dr. Rebecca Charlton
Psychology Department
Goldsmiths, University of London
Telephone: 0207 919 7222

Goldsmiths UNIVERSITY OF LONDON
New Cross LONDON SE14 6NW

St George's University Hospitals NHS
NHS Foundation Trust
St George's Hospital
Blackshaw RoadLondonSW17 0QT

CONTROL CONSENT FORM (VERSION 2; 01/09/2014)

Project Title

Anosognosia for memory impairment following stroke.

Please initial the boxes to confirm

- I have read the information sheet for the above study. ☐
- I have had the opportunity to ask questions about and discuss the study. ☐
- I understand the purpose of the study, and how I will be involved. ☐
- I understand that all information collected in the study will be held in confidence and that, if it is presented or published, all my personal details will be removed. ☐
- I confirm that I will be taking part in this study of my own free will, and I understand that I may withdraw from it, at any time and for any reason. ☐
- I understand that the results of the tests I will take as part of my participation in the study will not be feedback to my GP. ☐
- I agree to be contacted for a repeat test at some time within the next year. ☐

I agree to take part in the above study.

_____ _____

Signed Date

_____ _____Person taking consent Date

Participant ID_____

Appendix 4
IRB approved stroke patient's and informant's information sheet and consent forms for Columbia University Medical Center recruitment site

Columbia University Medical Center Consent Form

Attached to Protocol: IRB-AAAQ6952
Principal Investigator: Stephanie Cosentino (sc2460)
IRB Protocol Title: Perception of memory following stroke

Consent Number: **CF-AAAT3605**
Participation Duration: 3-4 hours
Anticipated Number of Subjects: 30

Contact

Contact	Title	Contact Type	Numbers
Silvia Chapman	Scholar	Co-Investigator	Telephone: 212-342-1969 Cell: 732-669-2397
Stephanie Cosentino	Assistant Professor	Principal Investigator	Telephone: 212-342-0289

Research Purpose
The purpose of this study is to explore people's perceptions of memory after stroke.

Information on Research
Dear Sir/Madam,
You are being invited to take part in a RESEARCH study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your primary physician if you wish. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

PROJECT DESCRIPTION

People that have suffered from a stroke sometimes experience some difficulties with their memory, and can have quite different perceptions of their memory.

We are interested in understanding the factors that contribute to people's perception of their memory.

Why have I been chosen?

We will like to investigate, with your help, how people who have experienced a stroke perceive their own memory ability.
Information on memory ability from people who have suffered a stroke can guide rehabilitation

What will I have to do if I take part?

The study will consist of assessments that comprise cognitive testing and questionnaires in which you will be asked to rate your memory ability in tasks such as remembering an appointment or a name. We will also ask your relative and/or your clinician to rate your abilities in these tasks in order to obtain one or two independent evaluations.

You will also be asked to perform other paper and pencil tests or computerized tests where accuracy or reaction times will be recorded. The overall participation time in this study will be approximately 3 to 4 hours. Your participation will be divided into several sessions.

With your permission we will use a tape recorder to record your responses during portions of cognitive testing and interviews. Only your voice will be recorded. The audio tape will be identified by a random study ID number, with no identifying information attached to the tape. The recording will be maintained indefinitely to allow for future analysis. This recording will be used for research purposes only. You are not required to have your responses recorded in order to participate in the study. Recording is optional. Please initial one of the lines below:

_____You may record my responses

_____You may NOT record my responses

With your permission we will need to access some of your medical information such your previous clinical brain scans that you may have already had. We will not ask you to have a scan as part of your participation in this study.

_____You may access my clinical brain scans

_____You may NOT access my clinical brain scans

Risks

Procedures

There are no foreseeable risks in this study as all tests are paper and pencil or computerized with non invasive procedures. But you might experience some tiredness or find some of the assessments frustrating. For this reason the assessment has been structured to allow for as many rests as you feel you may need. It is also important to note that there are no right and wrong answers in these assessments and the outcome of them won't interfere in your medical treatment or care.

Confidentiality

We will do everything we can to keep your data secure, however, complete confidentiality cannot be promised. Despite all of our efforts, unanticipated problems, such as a stolen computer may occur, although it is highly unlikely. However, all of our computers are encrypted so that information stored on stolen computers cannot be accessed.

Benefits

What are the potential benefits?

There are no specific direct benefits for your treatment or care from participating in this study. However, research does deliver wider benefits to society and others with a similar condition and some indirect benefits might be foreseeable for participants themselves.

Alternative Procedures

This is not at treatment study. Information is collected for research purpose. The alternative of participating will be simply not participating in this study.

Confidentiality

All personal details and results will be stored in the researcher's office and will remain confidential. Anonymity will be assured during and after the study by allotting an anonymous code (research ID number) to your results and details that will be kept in locked cabinets at the Gertrude H. Sergievsky Centre. If any clinically significant results are found your care team will be informed.

All information collected about you in this study will be analyzed with those of other research participants and the results will be combined in such a way that your information cannot be specifically identified and linked to you personally.We will do everything we can to keep your data secure, however, complete confidentiality cannot be promised. Despite all of our efforts, unanticipated problems, such as a stolen computer may occur, although it is highly unlikely.

on stolen computers cannot be accessed.

The following individuals and/or agencies will be able to look at and copy your research records:

- The investigator, study staff, Columbia University staff, New York Presbyterian Hospital staff, and other medical professionals who may oversee the study
- Authorities from Columbia University and New York Presbyterian Hospital, including the Institutional Review Board ('IRB').
- The Office of Human Research Protections (OHRP).

When the study has been completed, data will remain in the researcher's office indefinitely.

Compensation

If you agree to come to Columbia Medical Center for you visits you will be reimbursed for any travel costs. Up to $30 dollars a visit.

Voluntary Participation

Taking part in this study is your choice. You can decide not to take part in or stop being in the study any time. Your choice will not affect the treatment you receive from doctors and staff and Columbia University Medical Center and New York Presbyterian Hospital.

Additional Information

Withdrawing from the Study

You may withdraw your consent to be in this study. If possible, any data collected will be discarded if you request this. Your withdrawal from the study will in no way affect your access to medical care for which you are otherwise eligible. Should you choose to make your data to not be associated with you, no one, including the Principal Investigator will be able to link back your data your identifying information.

If you decide to withdraw from the study, destroy the cognitive testing data, or remove your association with your data, you should contact Dr Stephanie Cosentino (Telephone: 212-342-0289) or Silvia Chapman (Telephone: 212-342-1969). This decision will not affect your medical care at Columbia Medical Center.

If you have any questions about your rights as a subject, you might contact:

Institutional Review Board
Columbia University Medical

154 Haven Ave, 1st Floor
New York, NY 10032
Telephone: 212-305-5883

Satement of consent

"I have read this consent form and the research study has been explained to me. I agree to be in the research study described above. A copy of this consent form will be provided to me after I sign it. By signing this consent form, I have not given up any of the legal rights that I would have if I were not a participant in the study".

Signature

Study Subject
Print Name_____Signature_____Date_____

Person Obtaining Consent
Print Name_____Signature_____Date_____

Columbia University Medical Center Consent Form

Attached to Protocol: IRB-AAAQ6952
Principal Investigator: Stephanie Cosentino (sc2460)
IRB Protocol Title: Perception of memory following stroke

Consent Number: **CF-AAAT3606**
Participation Duration: 30 minutes
Anticipated Number of Subjects: 60

Contact

Contact	Title	Contact Type	Numbers
Silvia Chapman	Scholar	Co-Investigator	Telephone: 212-342-1969 Cell: 732-669-2397
Stephanie Cosentino	Assistant Professor	Principal Investigator	Telephone: 212-342-0289

Research Purpose
The purpose of this study is to explore people's perceptions of memory after stroke.

Information on Research
Dear Sir/Madam,
You are being invited to take part in a RESEARCH study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your primary physician if you wish. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

PROJECT DESCRIPTION

People that have suffered from a stroke sometimes experience some difficulties with their memory, and can have quite different perceptions of their memory.
We are interested in understanding the factors that contribute to people's perception of their memory.

Why have I been chosen?
We will like to investigate, with your help, how people who have experienced a stroke perceive their own memory ability.
Information on memory ability from people who have suffered a stroke can guide rehabilitation approaches.

The study will consist of several questionnaires in which you will be asked to rate your relative/ person you care for/friend's memory ability in tasks such as remembering an appointment or a name, activities of the daily living (e.g. how much help they need going up and down the stairs) and a personality questionnaire.

The overall participation time in this study will be approximately 30 minutes.

With your permission we will use a tape recorder to record your responses during portions of cognitive testing and interviews. Only your voice will be recorded. The audio tape will be identified by a random study ID number, with no identifying information attached to the tape. The recording will be maintained indefinitely to allow for future analysis. This recording will be used for research purposes only. You are not required to have your responses recorded in order to participate in the study. Recording is optional.

Please initial one of the lines below:

_____You may record my responses

_____You may NOT record my responses

Risks

Procedures

There are no foreseeable risks in this study within the procedures as all tests are paper and pencil questionnaires which will take approximately 30 minutes to complete.

Confidentiality

We will do everything we can to keep your data secure, however, complete confidentiality cannot be promised. Despite all of our efforts, unanticipated problems, such as a stolen computer may occur, although it is highly unlikely. However, all of our computers are encrypted so that information stored on stolen computers cannot be accessed.

Benefits

There are no specific direct benefits for yourself by participating in this study.
However, research does deliver wider benefits to society and others with a similar condition and some indirect benefits might be foreseeable for participants themselves.

Confidentiality

All personal details and results will be stored in the researcher's office and will remain confidential. Anonymity will be assured during and after the study by allotting an anonymous code (research ID number) to your results and details that will be kept in locked cabinets at the Gertrude H. Sergievsky

Study Closed to Enrollment

01/05/2018

Centre.

All information collected about you in this study will be analyzed with those of other research participants and the results will be combined in such a way that your information cannot be specifically identified and linked to you personally. We will do everything we can to keep your data secure, however, complete confidentiality cannot be promised. Despite all of our efforts, unanticipated problems, such as a stolen computer may occur, although it is highly unlikely. However, all of our computers are encrypted so that information stored
on stolen computers cannot be accessed.

The following individuals and/or agencies will be able to look at and copy your research records:

- The investigator, study staff, Columbia University staff, New York Presbyterian Hospital staff, and other medical professionals who may oversee the study
- Authorities from Columbia University and New York Presbyterian Hospital, including the Institutional Review Board ('IRB')
- The Office of Human Research Protections (OHRP).

When the study has been completed, data will remain in the researcher's office indefinitely.

Compensation

If you agree to come to Columbia Medical Center for you visits you will be reimbursed for any travel costs. Up to $30 dollars a visit.

Voluntary Participation

Taking part in this study is your choice. You can decide not to take part in or stop being in the study any time. Your choice will not affect the treatment that your relative/person you care for/friend receives from doctors and staff and Columbia University Medical Center and New York Presbyterian Hospital

Additional Information

Withdrawing from the Study
You may withdraw your consent to be in this study. If possible, any data collected will be discarded if you request this. Your withdrawal from the study will in no way affect your access to medical care for which you are otherwise eligible. Should you choose to make your data to not be associated with you, no one, including the Principal Investigator will be able to link back your data your identifying information.

If you decide to withdraw from the study, destroy the questionnaire data, or remove your association with your data, you should contact Dr Stephanie Cosentino (Telephone: 212-342-0289) or Silvia Chapman (Telephone: 212-342-1969). This decision will not affect your or your relative/person you

care for/friend's medical care at Columbia Medical Center.

If you have any questions about your rights as a subject, you might contact:

Institutional Review Board
Columbia University Medical Center
154 Haven Ave, 1st Floor
New York, NY 10032
Telephone: 212-305-5883

Statement of Consenrt
"I have read this consent form and the research study has been explained to me. I agree to be in the research study described above. A copy of this consent form will be provided to me after I sign it. By signing this consent form, I have not given up any of the legal rights that I would have if I were not a participant in the study".

Signature

Study Subject
Print Name_____Signature_____Date_____

Person Obtaining Consent
Print Name_____Signature_____Date_____

Study Closed to Enrollment

01/05/2018

Appendix 5
IRB approved Alzheimer's disease patient's and informant's information sheet and consent forms for Columbia University Medical Center recruitment site

Columbia University Medical Center Consent Form

Attached to Protocol: IRB-AAAB4726
Principal Investigator: Stephanie Cosentino (sc2460)
IRB Protocol Title: Metacognition and Memory Functioning

Consent Number: **CF-AAAM1304**
Participation Duration: 6 hours
Anticipated Number of Subjects: 513

Contact

Contact	Title	Contact Type	Numbers
Stephanie Cosentino	Assistant Professor of Neurops	Principal Investigator	Telephone: 212-342-0289

Research Purpose
The goal of this study is to understand metacognition in people with and without memory loss. Metacognition refers to our own knowledge of how well or how poorly we perform various abilities in our daily lives.

Information on Research Study Procedures
The entire study will be conducted over the course of two to three study visits. Each visit will last approximately two hours and visits will be spaced over the course of two weeks.

At each visit, you will partake in a brief interview regarding your memory. You will also undergo several different tests of thinking abilities. For example, you will be asked to remember various types of verbal and visual information, like words and pictures. You will also be asked to make periodic judgments about your ability to remember these words and pictures throughout the session. Several tests will be on the computer, however, you do not need any knowledge of computers to participate.

At the first visit, you will also complete several questionnaires regarding your mood and your life in general, and you will be interviewed regarding your ability to perform a specific task in every day life such as managing your finances, managing your medication, or preparing meals. With your permission, we will speak separately with someone who knows you well, such as a spouse or child, to ask them their opinion regarding your ability to perform the same task in every day life. Please initial one of the lines below:

You may speak with someone who knows me well _____

withdraw fully from participating.

Benefits

There are no direct benefits to you from these procedures. Results of this study may improve scientific knowledge regarding metacognitive abilities, and the way such abilities are affected by neurologic disease.

Compensation

Upon completion of each study visit, you will be paid $30.00 cash for your participation.

Additional Costs

There will be no additional costs incurred as a result of participating in this study.

Additional Information

If you have any questions, please ask. Should you have any questions in the future, please call the Principal Investigator, Dr. Stephanie Cosentino, at 212-342-0289, and she will do her best to answer them. If you have any questions on your rights as a research subject, you can call the Institutional Review Board at 212-305-5883 for information.

Confidentiality

All records will be kept confidential to the extent permitted by law. Your identity and participation in this study will be kept confidential.

Your test results and questionnaire responses will be assigned a code number, and separated from your name or any other information that could identify you. The research file that links your name to the code number will be kept on a secure computer and only the investigator and study staff will have access to this computer. Information gathered from this study will be used for scientific publications or presentation, however, your name will not be mentioned.

We will do everything we can to keep your data secure, however, complete confidentiality cannot be promised. Despite all of our efforts, unanticipated problems, such as a stolen computer may occur, although it is highly unlikely.

The following individuals and/or agencies will be able to look at and copy your research records:
- Authorities from Columbia University and New York Presbyterian Hospital, including the Institutional Review Board ('IRB')
- The Office of Human Research Protections ('OHRP')

No other person shall be permitted access to information obtained from you without your written consent.

Voluntary Participation

Your participation in this study is completely voluntary. You can refuse to participate or withdraw from the study at any time. You may continue to participate in our other research programs whether or not you agree to take part in this study. Such a decision will not affect your medical care at Columbia-Presbyterian Medical Center now or in the future.

Research Related Injuries

I have been informed that if I believe I have sustained injury as a result of participating in this research study, I may contact the Principal Investigator, Dr. Stephanie Cosentino, at 212-342-0289, or the Institutional Review Board, at 212-305-5883, so that I can review the matter and identify the medical resources which may be available to me.

Consent to Participate

I have discussed this study to my satisfaction with Dr. Stephanie Cosentino or one of her research associates. I understand that my participation is voluntary and that I can withdraw from the study at any time without prejudice. I have read the above and agree to enter this research study. Signing this form does not waive any of my legal rights.

Signature

Study Subject

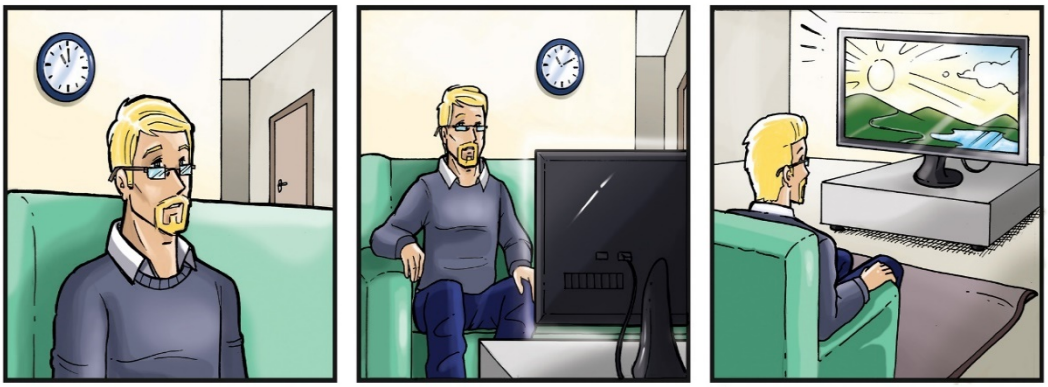
Print Name_____ Signature_____ Date_____

Person Obtaining Consent

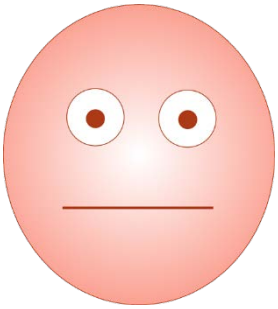
Print Name_____ Signature_____ Date_____

Appendix 6
The Visual-analogue test for anosognosia for memory impairment (VATAmem)

Do you have difficulty watching TV?



No Problem

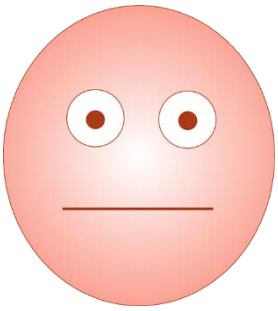


Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering to do something that you had decided to do only minutes before?

No Problem

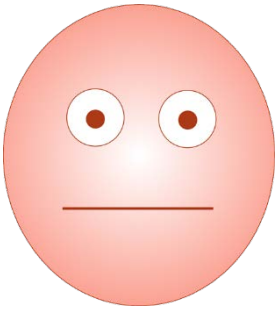


Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering to post a letter even when you walk past a post box?

No Problem

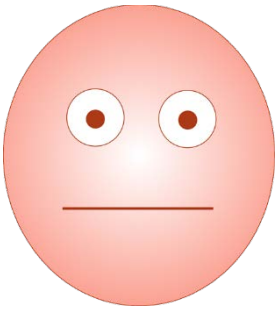


Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems jumping over a lorry?

No Problem

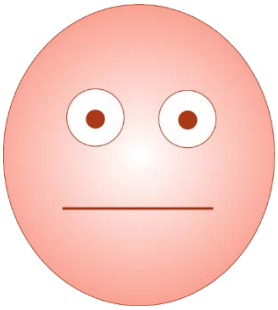


Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering directions, moments after they have been given to you?

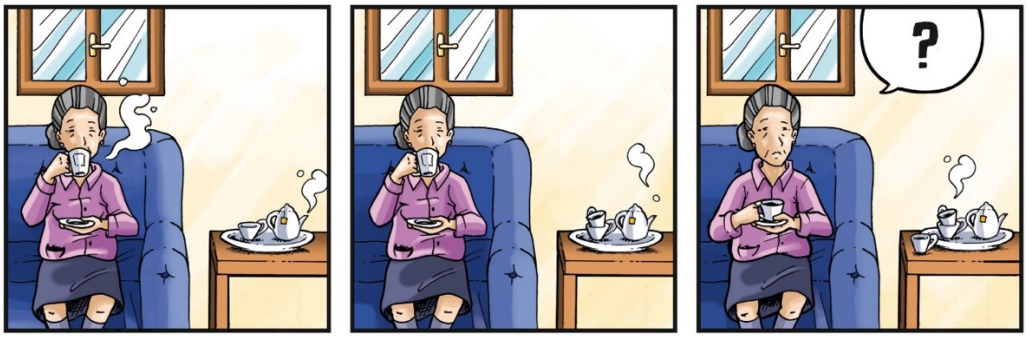
No Problem



Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering the last time you had a cup of tea?



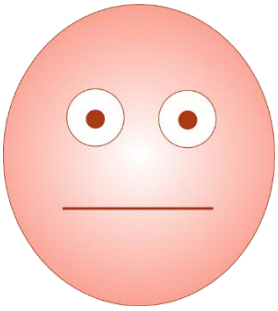
No Problem

Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering that you had already told the same story to the same person on a previous occasion?

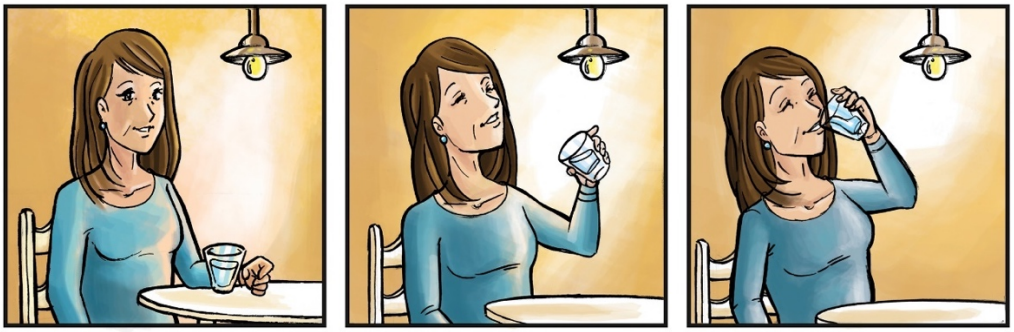
No Problem



Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have difficulty drinking from a glass?



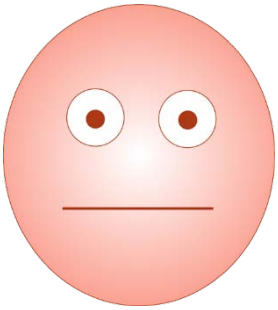
No Problem

Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have difficulty drinking from a glass?

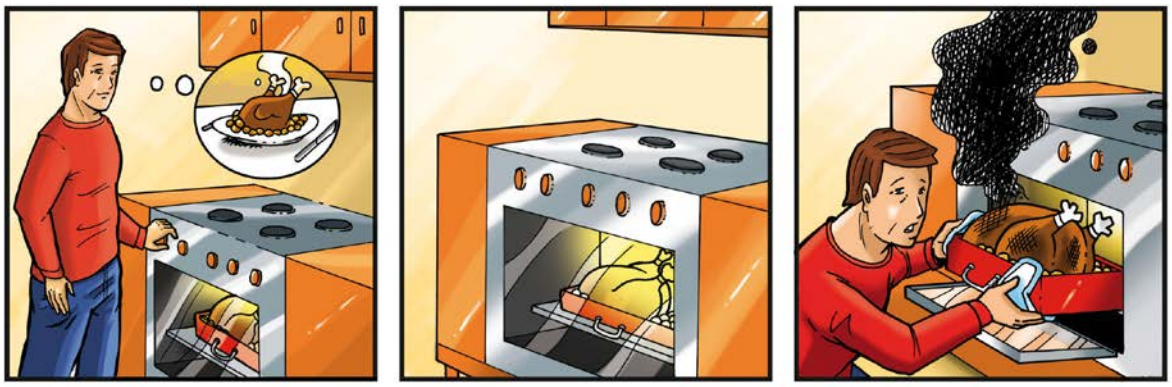
No Problem



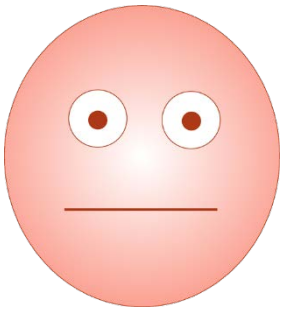
Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering to turn off the cooker at the correct time when cooking?



No Problem



Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering appointments if not prompted by someone else?

No Problem

Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering two digits, such as 6 and 4, for a few seconds?

No Problem

Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering people's names soon after they have been introduced to you?

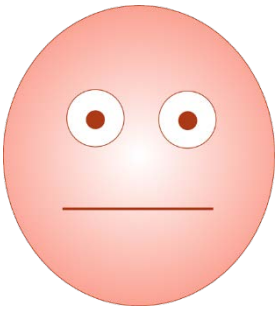
No Problem

Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering to do something you meant to do once you have entered a room?

No Problem

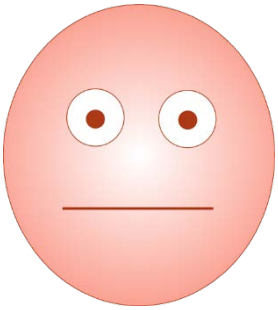


Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering the time even if you have just checked it?

No Problem

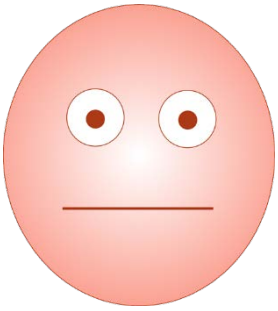


Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering your way around in your ward/home?

No Problem

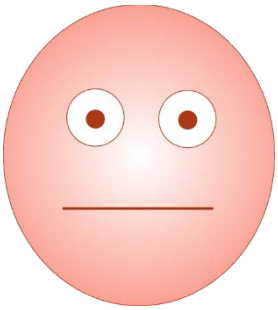


Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems waving with your left hand?

No Problem

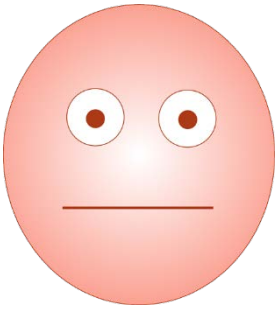


Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems waving with your right hand?

No Problem

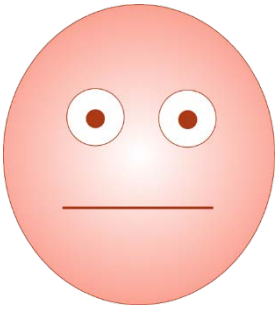


Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering to take something with you even if you pass by it, like an umbrella before going out?

No Problem

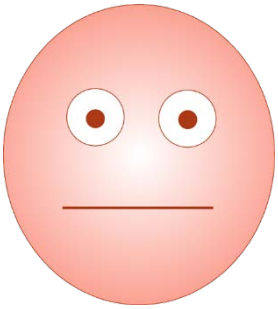


Problem

0 --------- 1 --------- 2 --------- 3

Do you have problems remembering to mention something or to give something to someone?

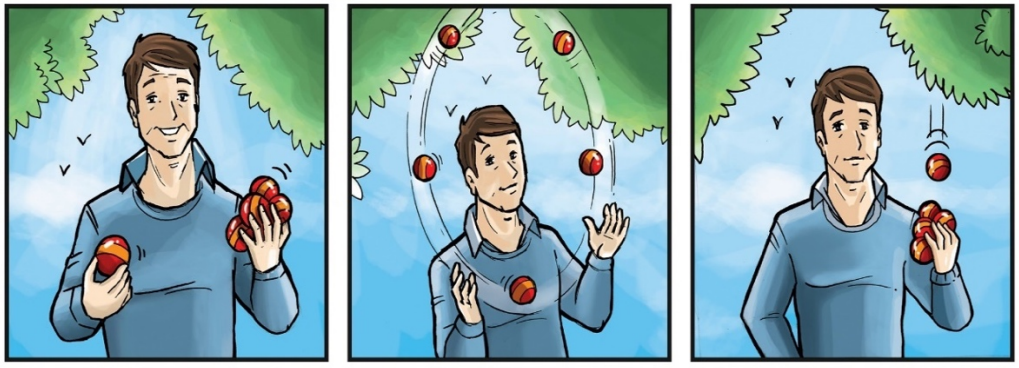
No Problem



Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have difficulty juggling five balls in the air?



No Problem

Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering that you have already introduced yourself to a person?

No Problem

Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering relatives' or friends' names?

No Problem

Problem

0 ---------- 1 ---------- 2 ---------- 3

Do you have problems remembering all names listed in the yellow pages?

No Problem

Problem

0 --------- 1 --------- 2 --------- 3

Appendix 7
Scoring sheet and distribution of items in the VATAmem

VATAmem

Score sheet

Patient name: _____Age: _____ Gender: ___ Formal educ. (years): _____

Clinician: _____Age: _____ Gender: ___Formal educ. (years): _____Relationship_____

Carer:_____Age:_____Gender:____Formal educ. (years):_____Relationship_____

		Patient's rating	Carer 1 / Carer 2
rating Example.	…		
Question 1.	Doing something	_____	_____/_____
Question 2.	Posting a letter	_____	_____/_____
Check question 1.	*Jumping over a lorry*	_____	_____/_____
Question 3.	Directions	_____	_____/_____
Question 4.	Drinking a coffee	_____	_____/_____
Question 5.	Same story	_____	_____/_____
Check question 2.	*Drinking from a glass*	_____	_____/_____
Question 6.	Turn off cooker	_____	_____/_____
Question 7.	Appointment	_____	_____/_____
Check question 3.	*Two digits*	_____	_____/_____
Question 8.	People names	_____	_____/_____
Question 9.	Walking into a room	_____	_____/_____
Question 10.	The time	_____	_____/_____
Question 11.	Home	_____	_____/_____
Check question 4.	*Waving*	_____	_____/_____

Question 12.	Umbrella	_____	_____/_____
Question 13.	Saying	_____	_____/_____
Check question 4.	*Juggling*	_____	_____/_____
Question 14.	Introduced	_____	_____/_____
Question 15.	Names	_____	_____/_____
Check question 6.	*Yellow pages*	_____	_____/_____

Correct check questions *(Expected scores)*	*1(2-3)*	*2(0-1)*	*3(0-1)*	*4(0-1)*	*5(2-3)*	*6(2-3)*
Patient	_____	_____	_____	_____	_____	_____
Carer 1	_____	_____	_____	_____	_____	_____
Carer 2	_____	_____	_____	_____	_____	_____

Total rating (without check questions): Patient: _____/48 Carer 1:_____/48 Carer 2:_____/48 **Discrepancy score** (patient's rating *minus* carer's rating): _____

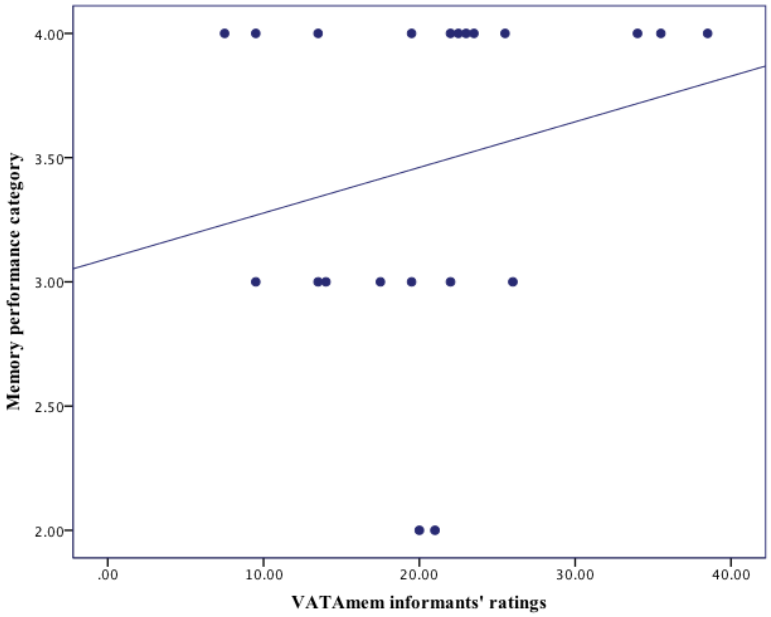
Classification of the type of memory (Smith et al., 2000)

Prospective (P) *versus* Retrospective (R)
Short-term (ST) *versus* Long-term (LT)
Self-cued (SC) *versus* Environmental cued (EC)

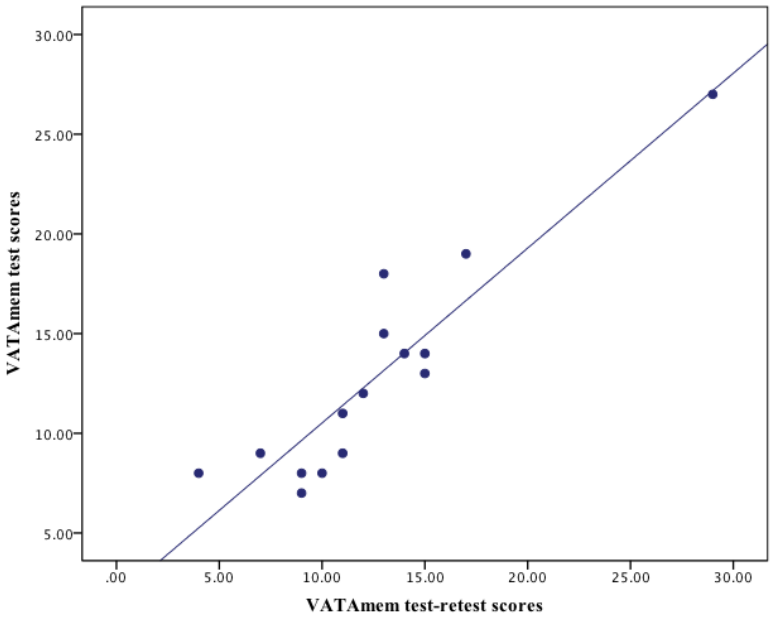
1 – doing something - **P; ST, SC**
2 – postbox - **P; ST; EC**
3 – directions - **R; ST; SC**
4 – cup of tea - **R; LT; SC**
5 – Story - **R; LT; EC**
6 – cooker- **P; ST; EC**
7 – appointments - **P; LT; SC**
8 – introduced - **R; ST; EC**
9 - room - **P; ST; EC**
10- time **R; ST; EC**
11- home/ward - **R; LT; EC**
12 - umbrella - **P; ST; EC**
13 – saying/giving - **P; LT; EC**
14 – introduced - **R; LT/ST; EC**
15 – names - **R; LT; SC/EC**

Appendix 8
Scatterplots of correlational analyses

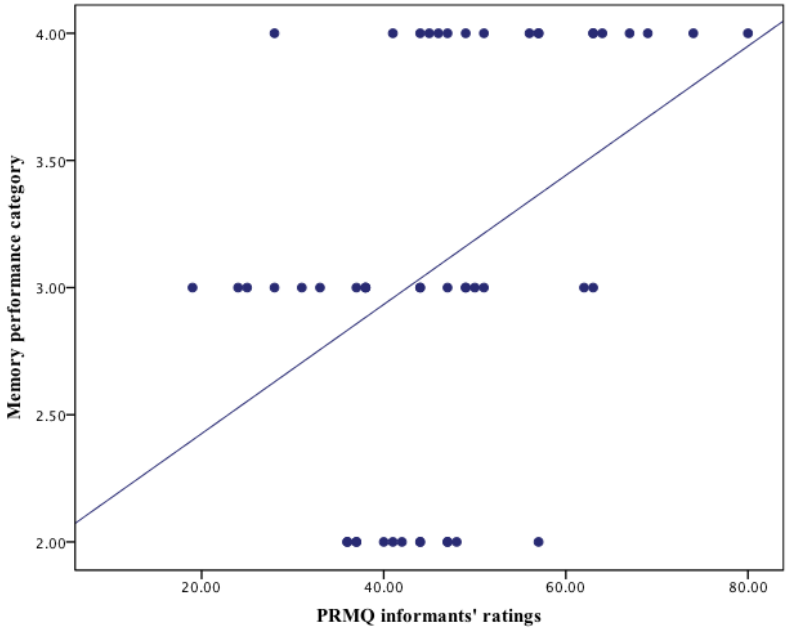
Chapter 3



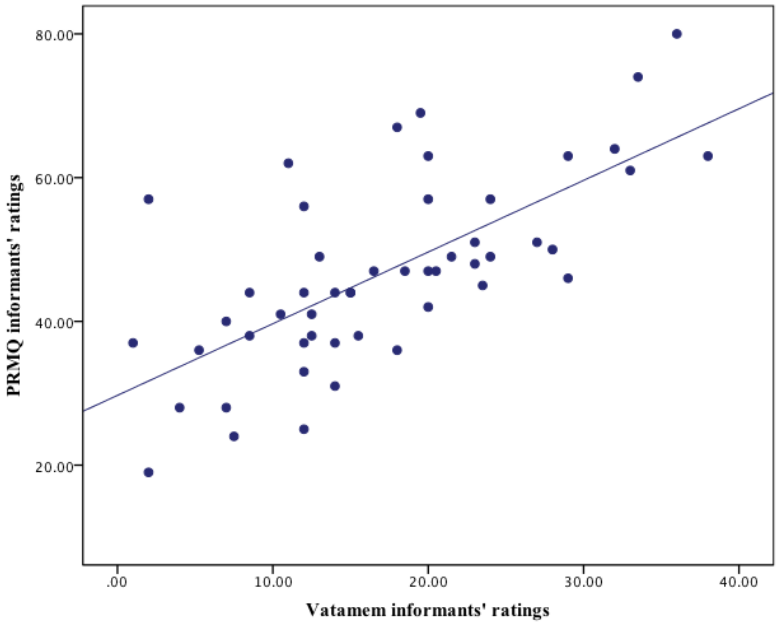
Scatterplot 3.1. Memory performance and informant reports on the VATAmem.



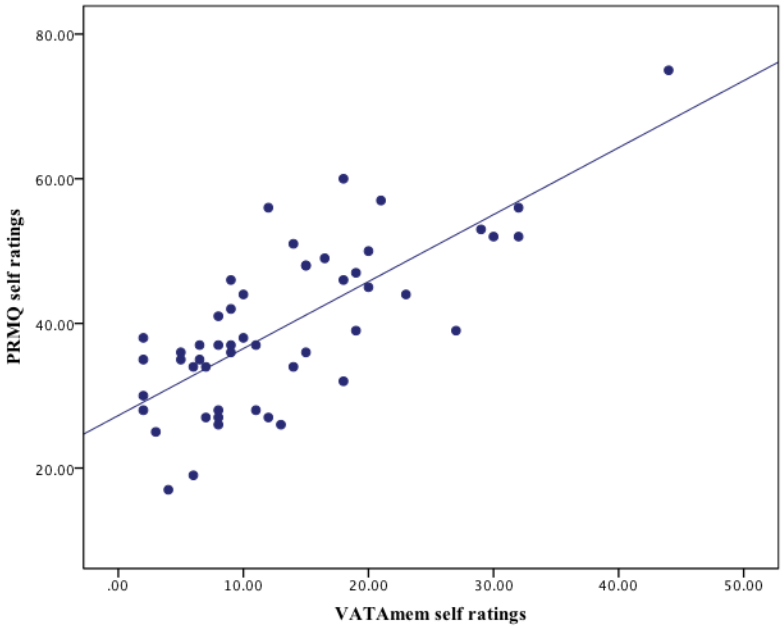
Scatterplot 3.2. Patient VATAmem test retest.



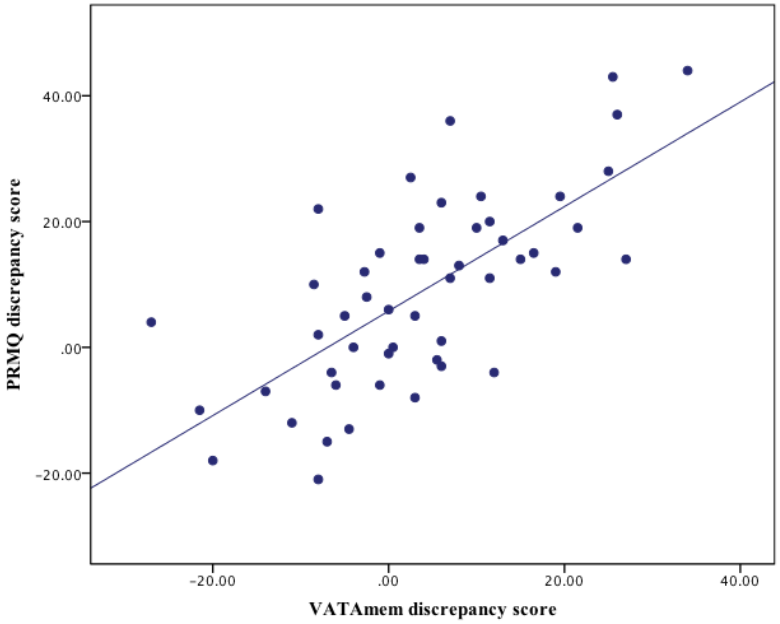
Scatterplot 3.3. Memory performance and informant reports on the VATAmem.



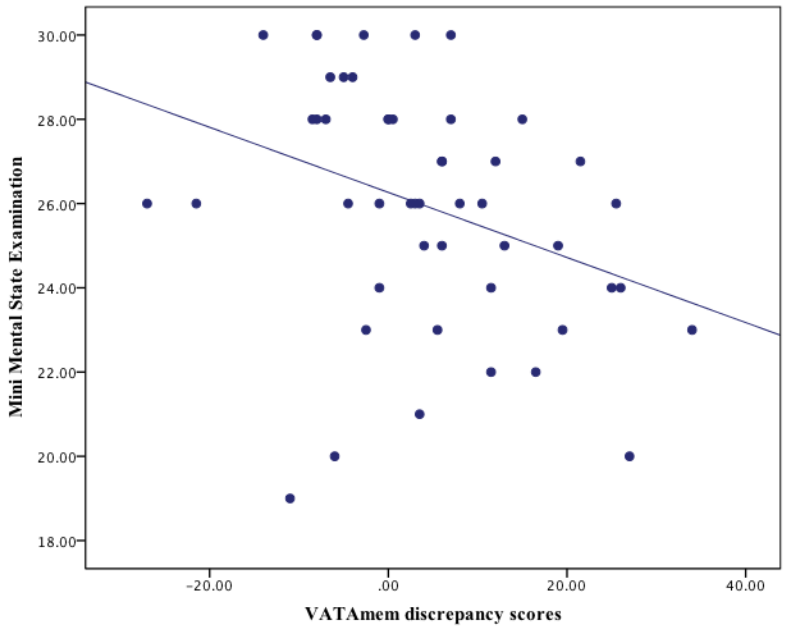
Scatterplot 3.4. Informants' ratings on the VATAmem and PRMQ.



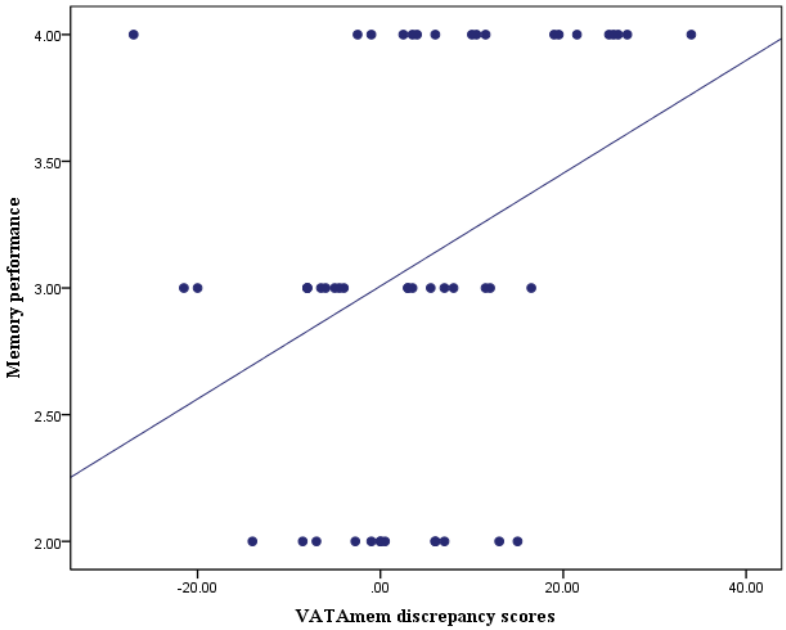
Scatterplot 3.5. Self ratings on the VATAmem and PRMQ.



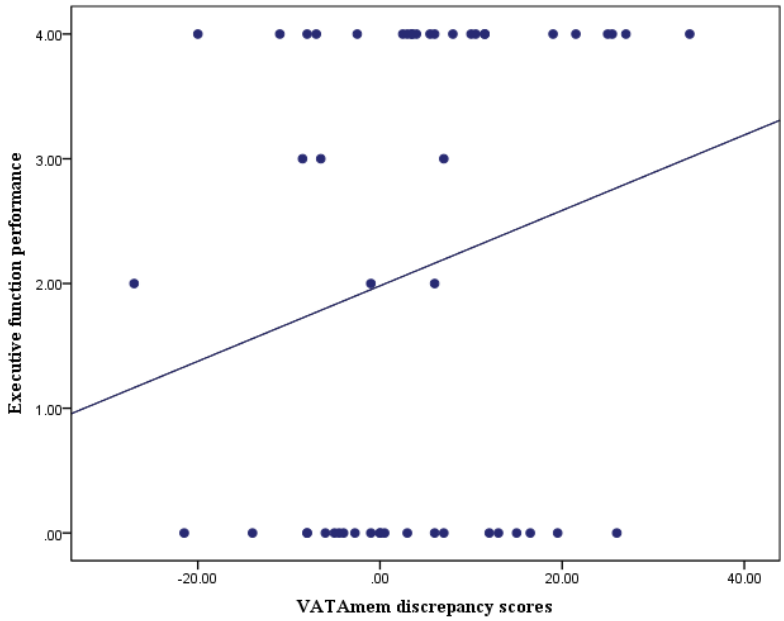
Scatterplot 3.6. Discrepancy scores of the VATAmem and PRMQ.



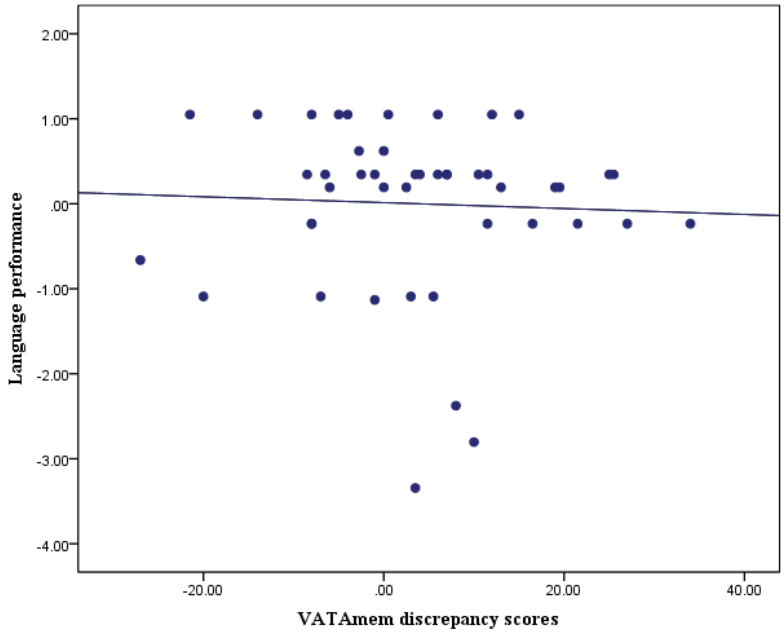
Scatterplot 3.7. Global cognition and discrepancy scores of the VATAmem.



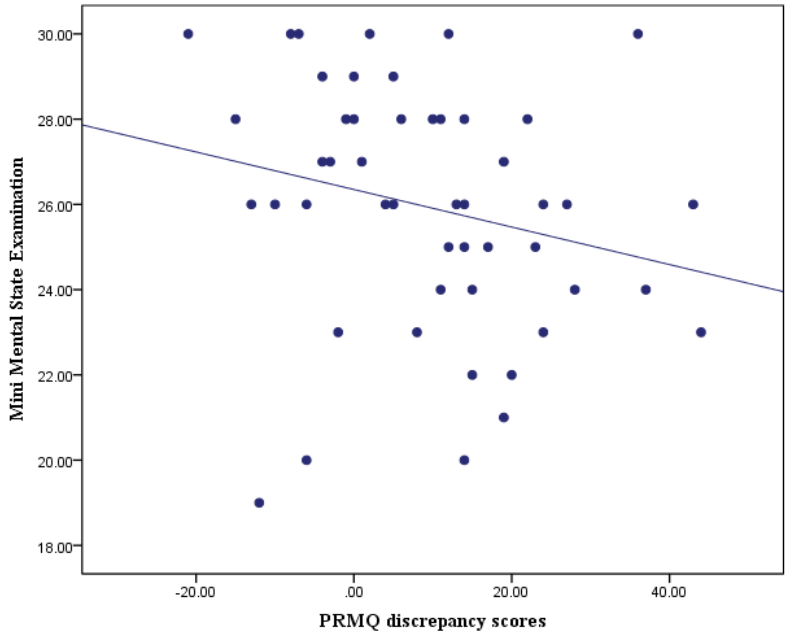
Scatterplot 3.8. Memory performance and discrepancy scores of the VATAmem.



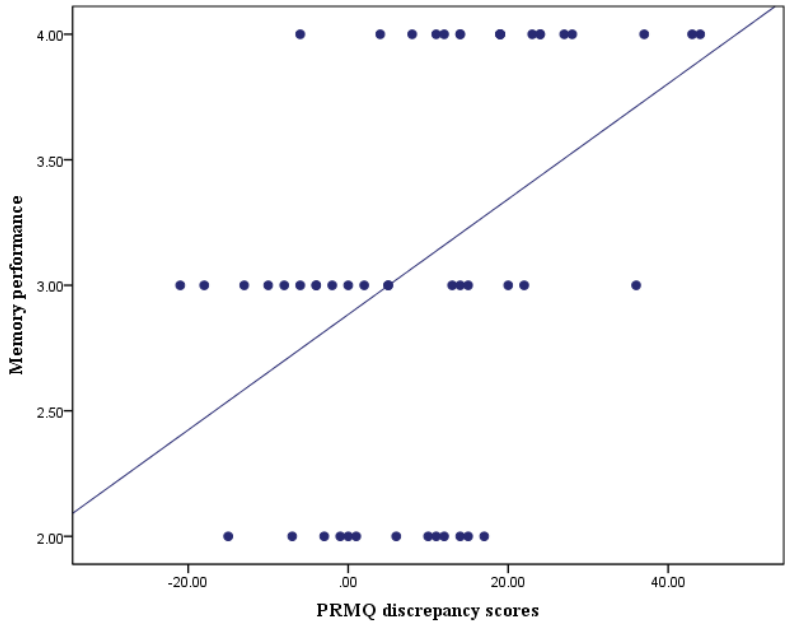
Scatterplot 3.9. Executive function performance and discrepancy scores of the VATAmem.



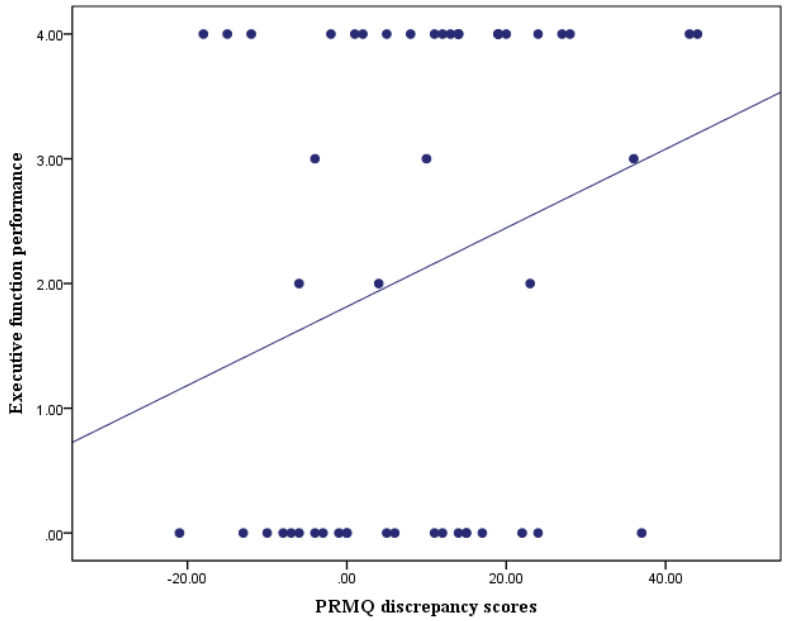
Scatterplot 3.10. Language performance and discrepancy scores of the VATAmem.



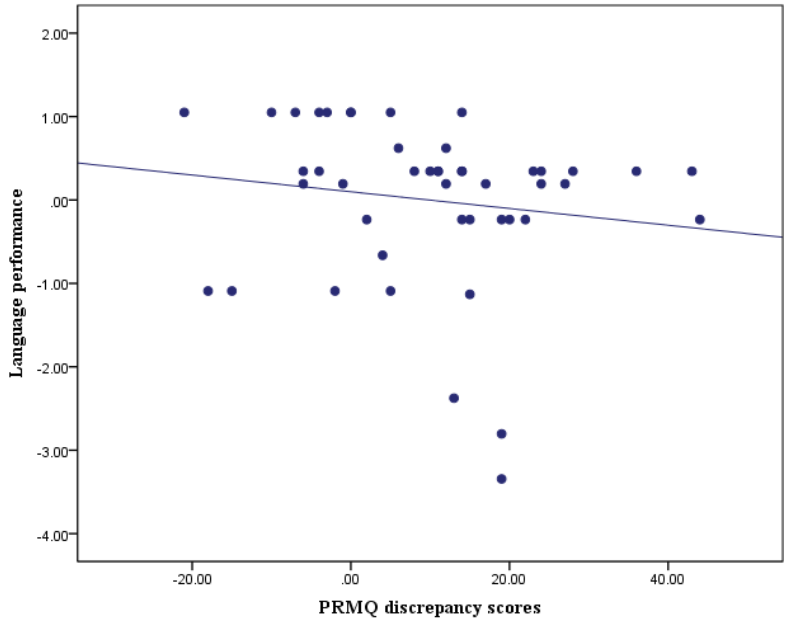
Scatterplot 3.11. Global cognition and discrepancy scores of the PRMQ.



Scatterplot 3.12. Memory performance and discrepancy scores of the PRMQ.

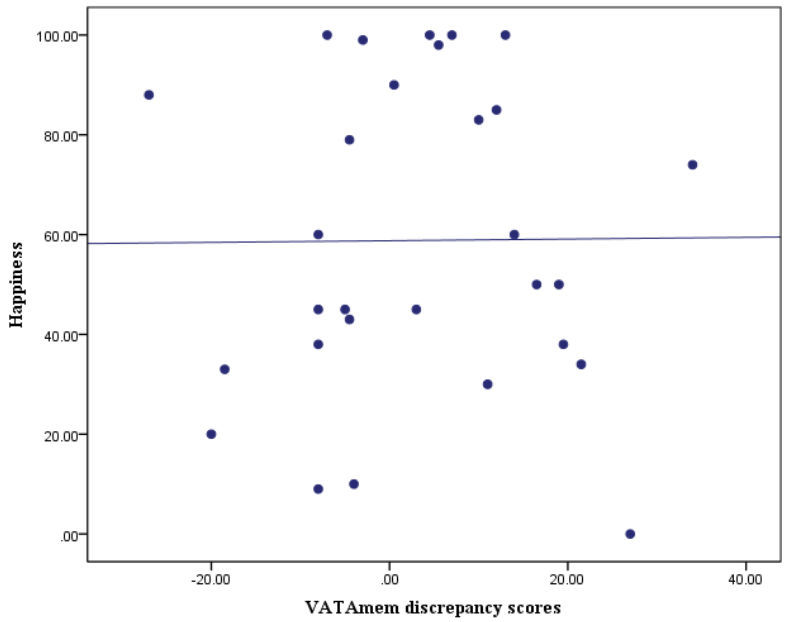


Scatterplot 3.13. Executive function performance and discrepancy scores of the PRMQ.

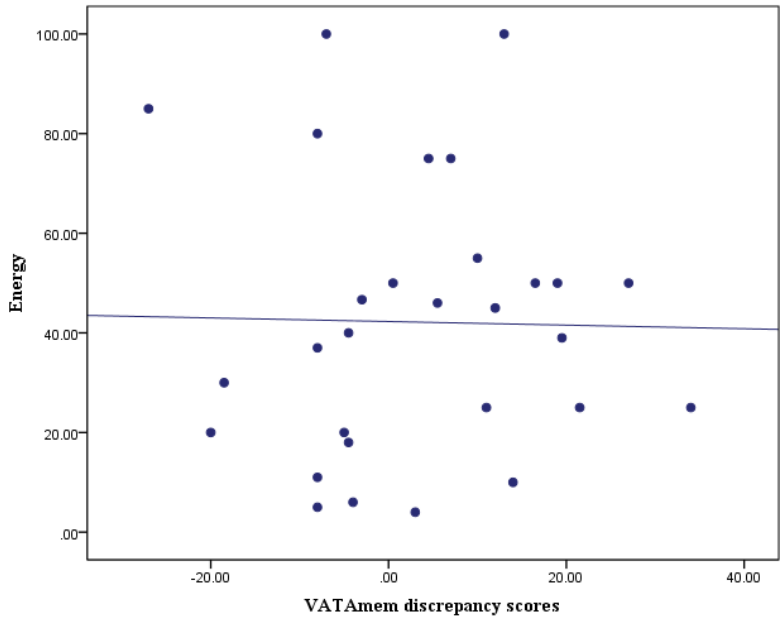


Scatterplot 3.14. Language function performance and discrepancy scores of the PRMQ.

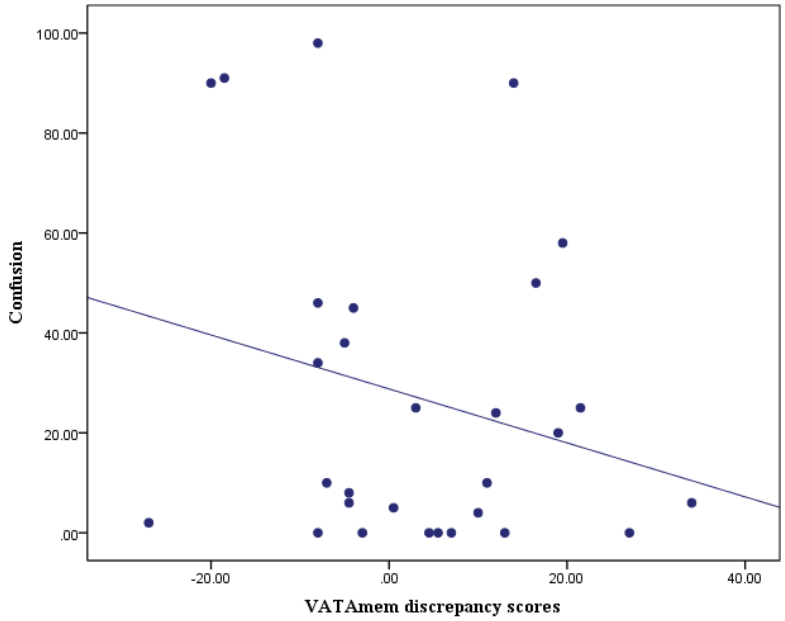
Chapter 4



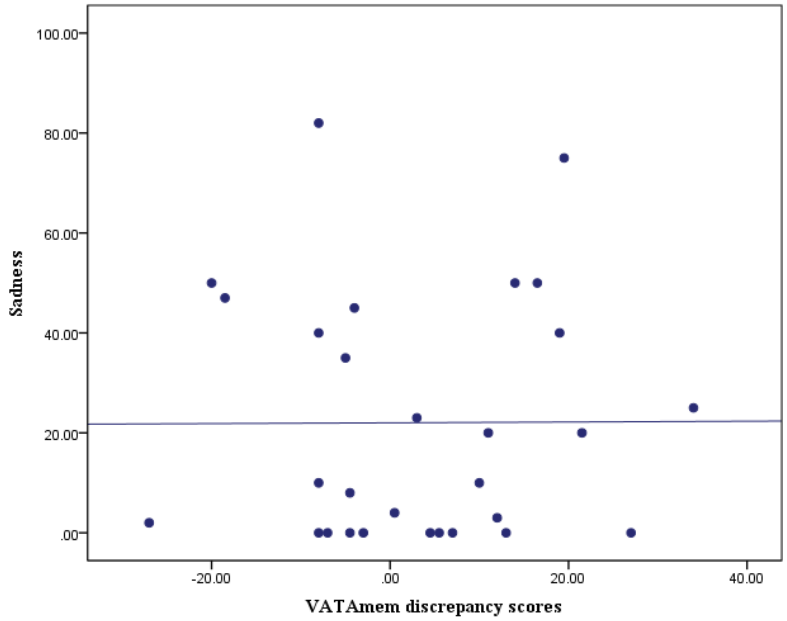
Scatterplot 4.1. Happiness endorsement on the VAMS and discrepancy scores of the VATAmem.



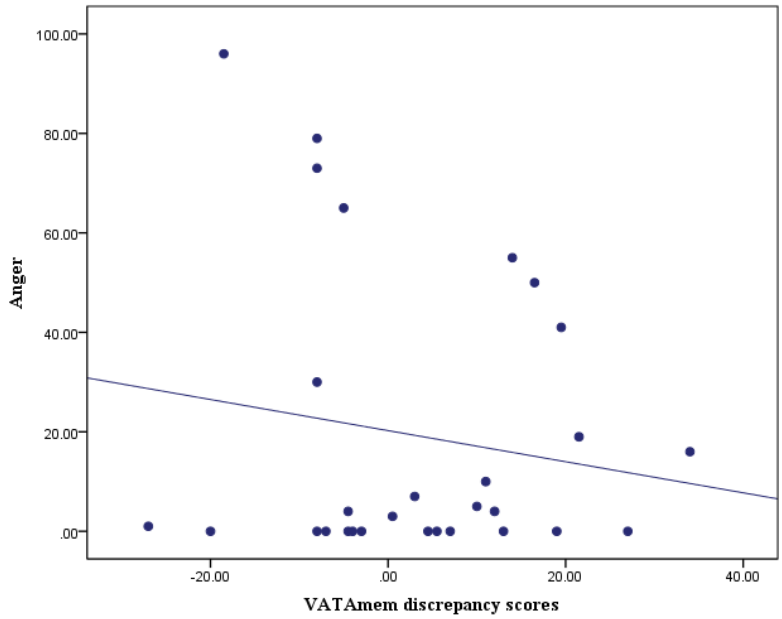
Scatterplot 4.2. Energy endorsement on the VAMS and discrepancy scores of the VATAmem.



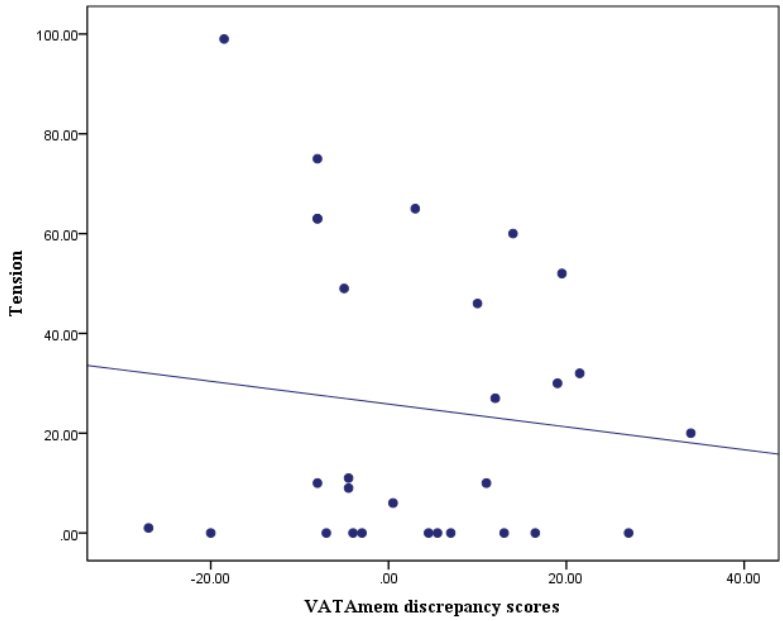
Scatterplot 4.3. Confusion endorsement on the VAMS and discrepancy scores of the VATAmem.



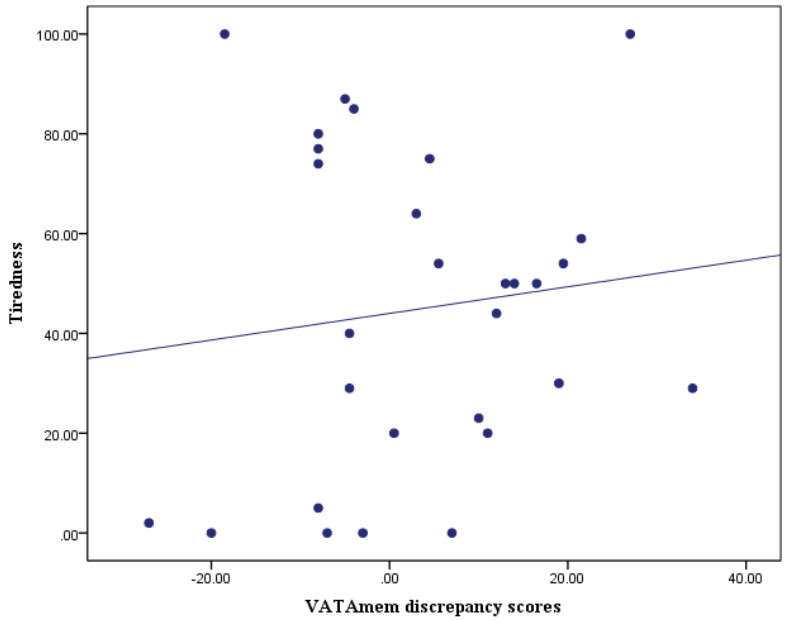
Scatterplot 4.4. Sadness endorsement on the VAMS and discrepancy scores of the VATAmem.



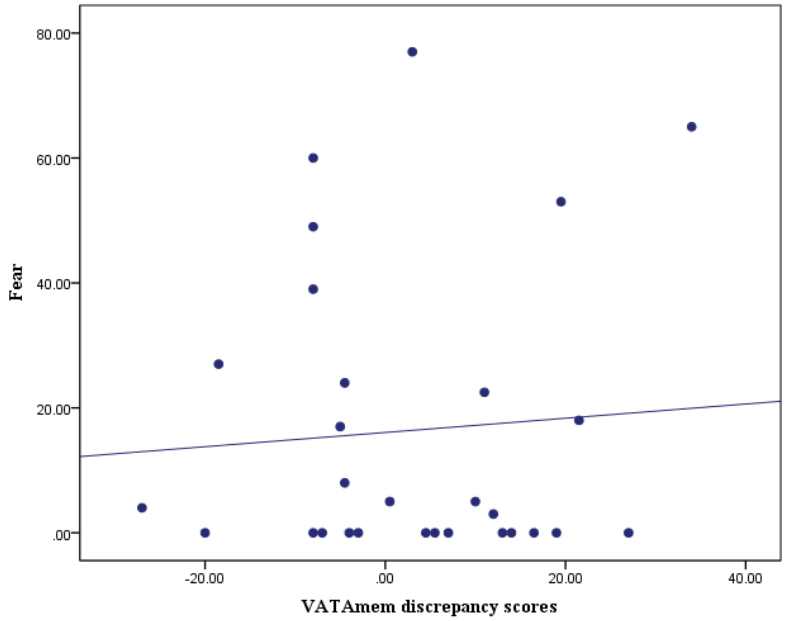
Scatterplot 4.5. Anger endorsement on the VAMS and discrepancy scores of the VATAmem.



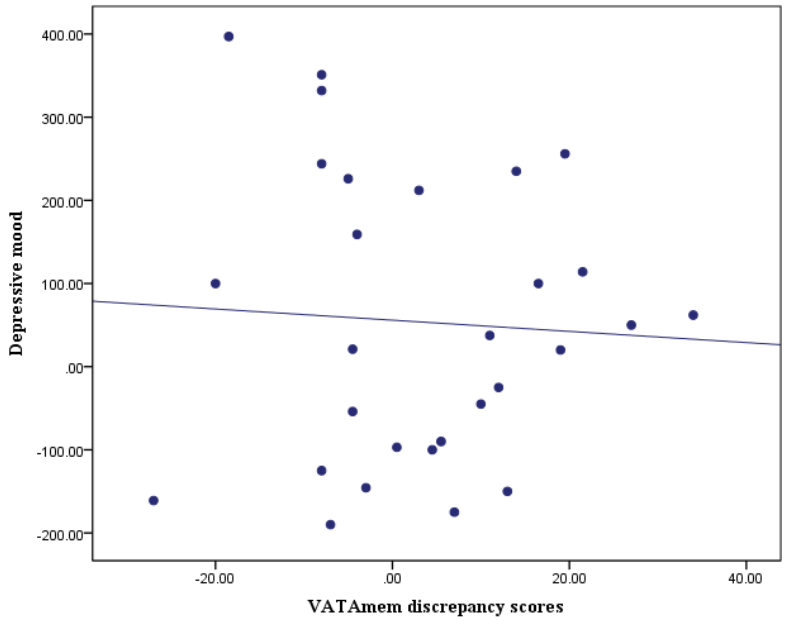
Scatterplot 4.6. Tension endorsement on the VAMS and discrepancy scores of the VATAmem.



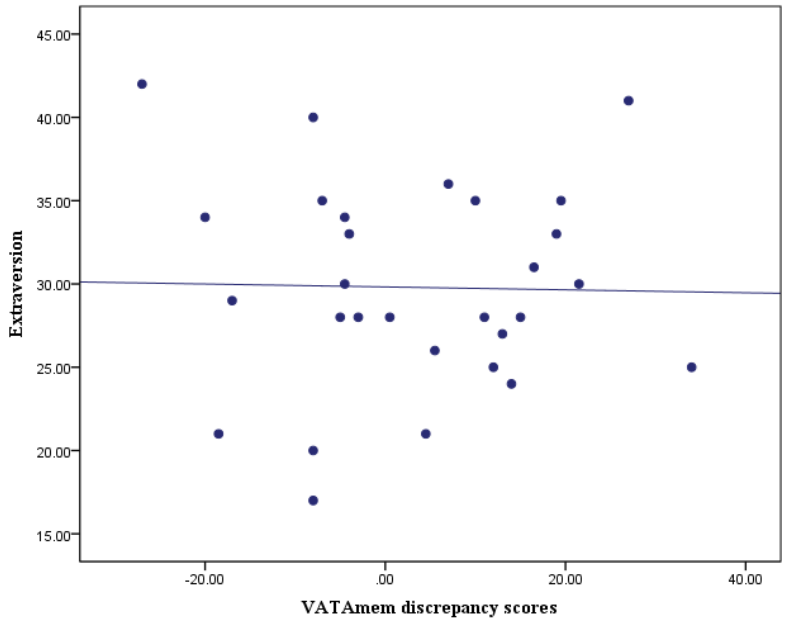
Scatterplot 4.7. Tiredness endorsement on the VAMS and discrepancy scores of the VATAmem.



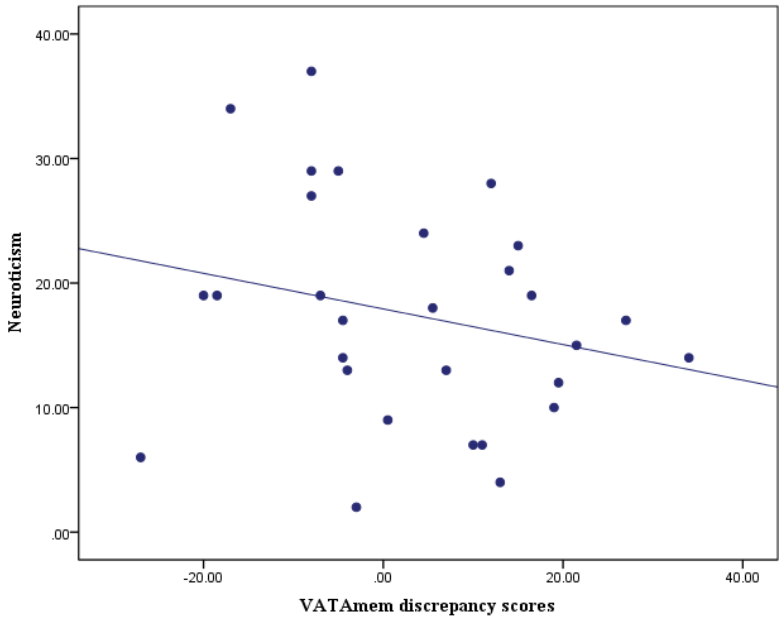
Scatterplot 4.7. Fear endorsement on the VAMS and discrepancy scores of the VATAmem.



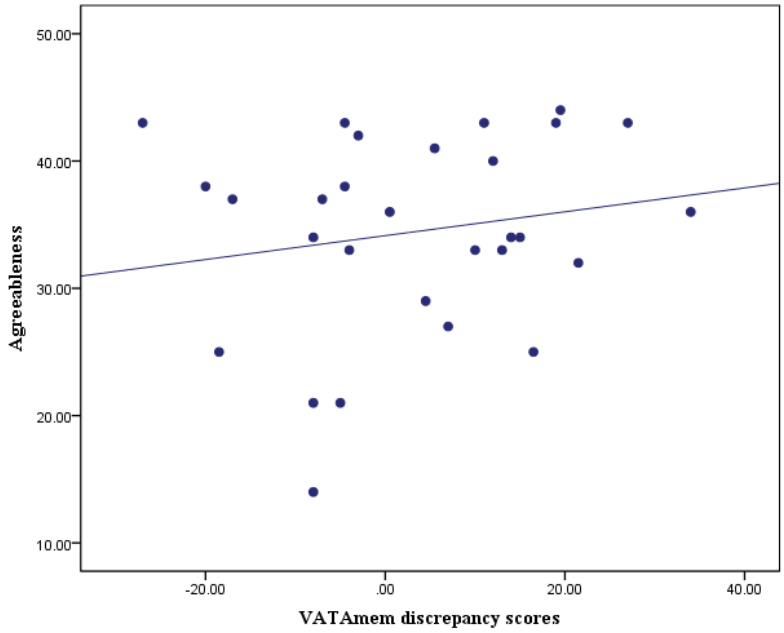
Scatterplot 4.8. Depressive mood (VAMS composite scores) and discrepancy scores of the VATAmem.



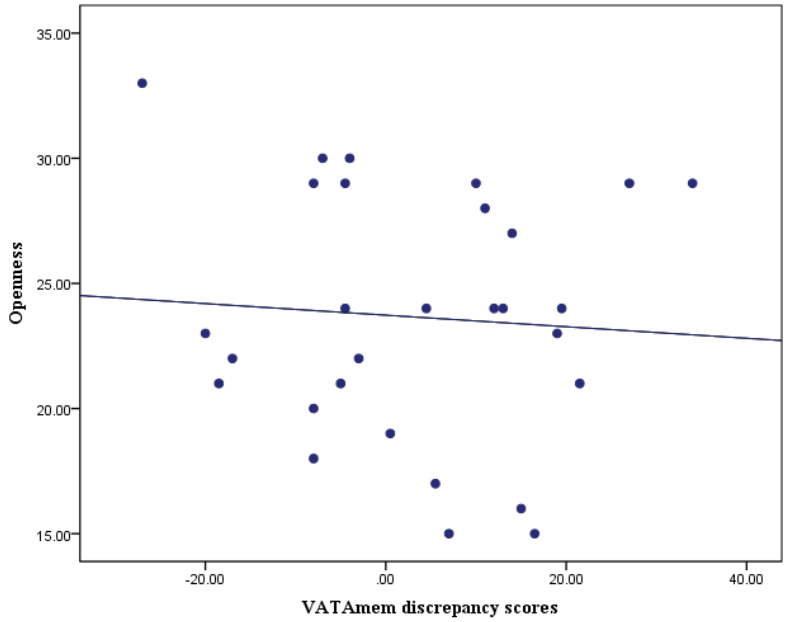
Scatterplot 4.9. Extraversion and discrepancy scores of the VATAmem.



Scatterplot 4.10. Neuroticism and discrepancy scores of the VATAmem.

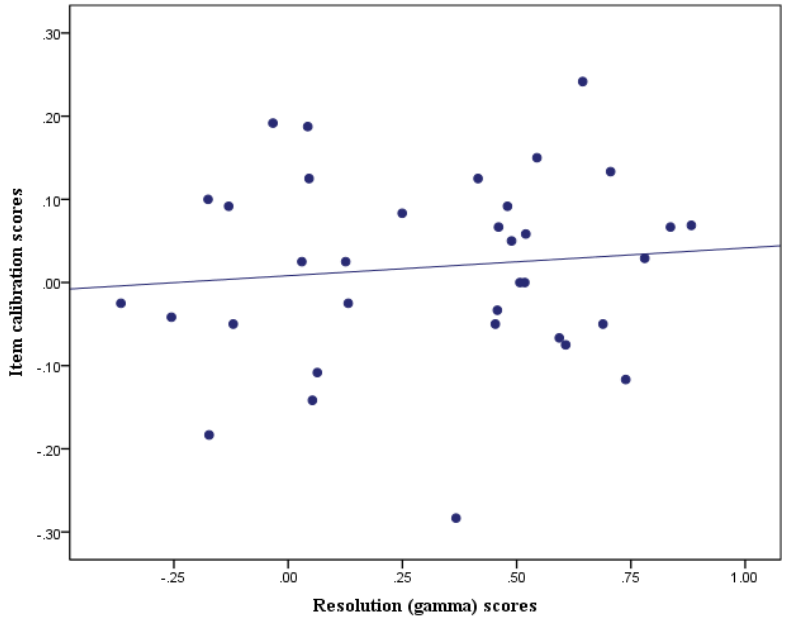


Scatterplot 4.11. Agreeableness and discrepancy scores of the VATAmem.

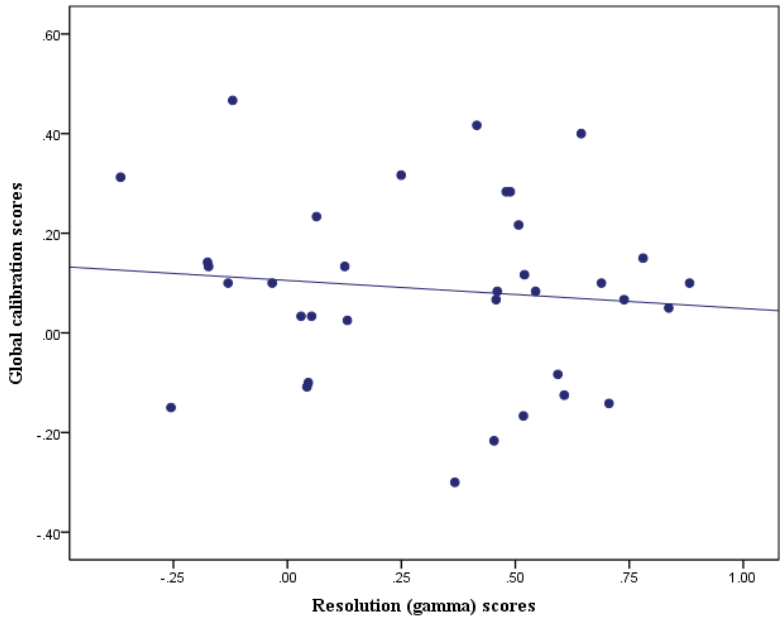


Scatterplot 4.12. Openness and discrepancy scores of the VATAmem.

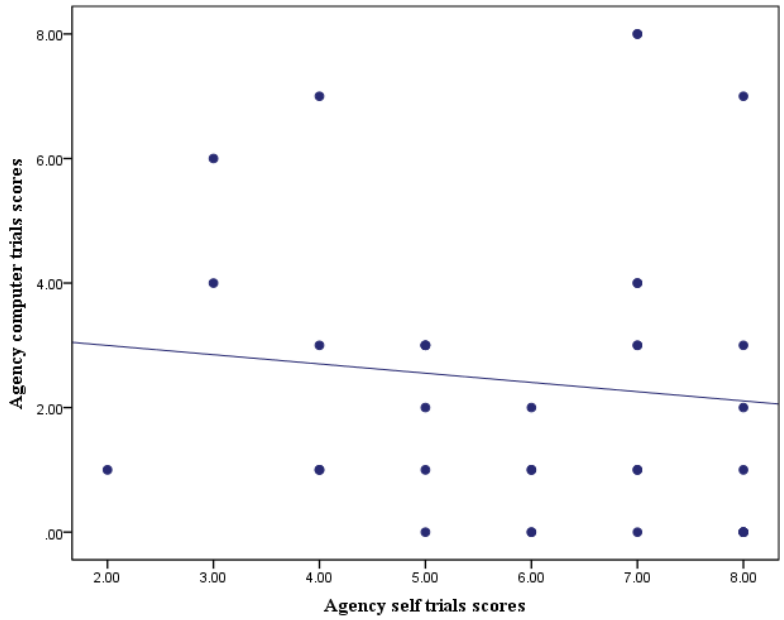
Chapter 5



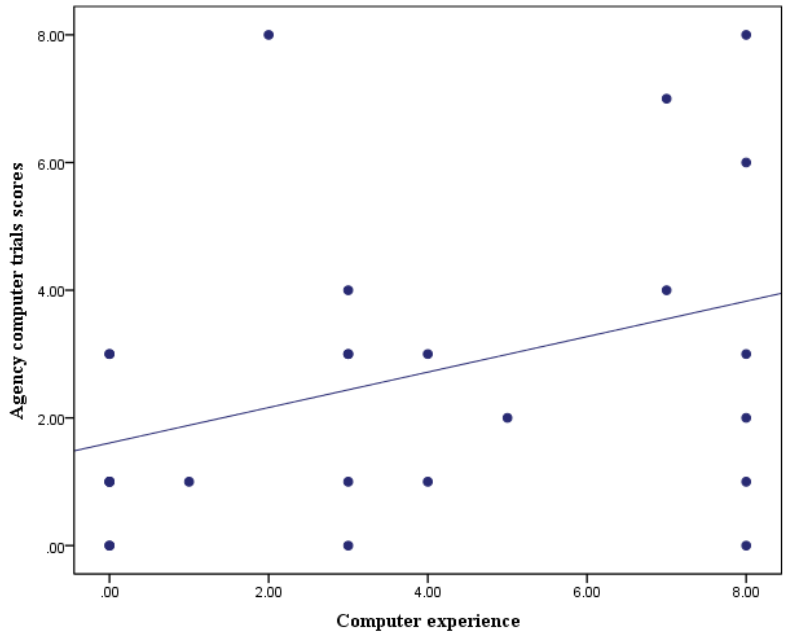
Scatterplot 5.1. Item calibration and resolution scores.



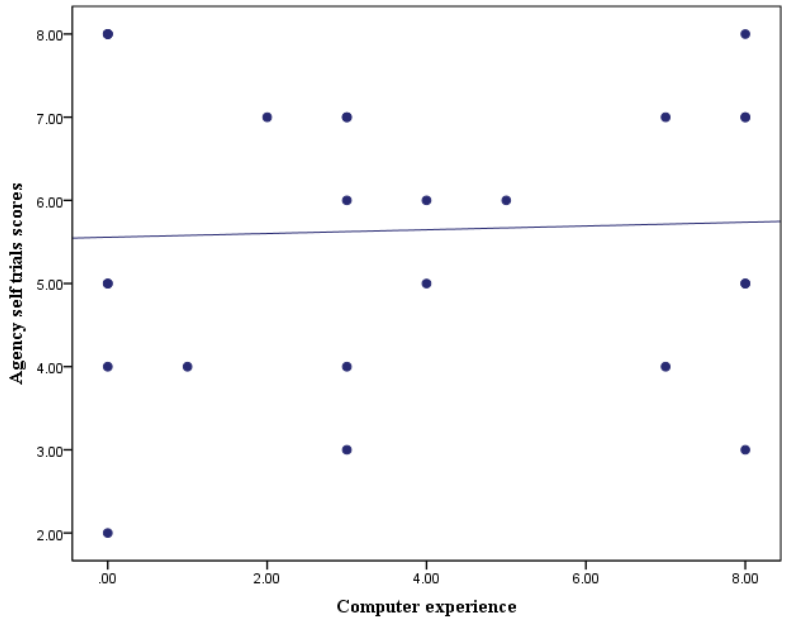
Scatterplot 5.2. Global calibration and resolution scores.



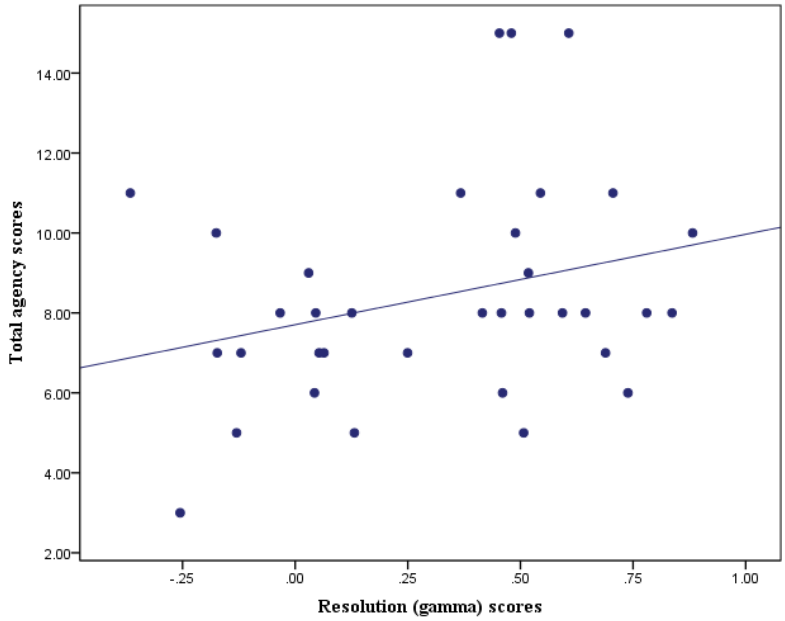
Scatterplot 5.3. Agency computer trials scores and agency self trials scores.



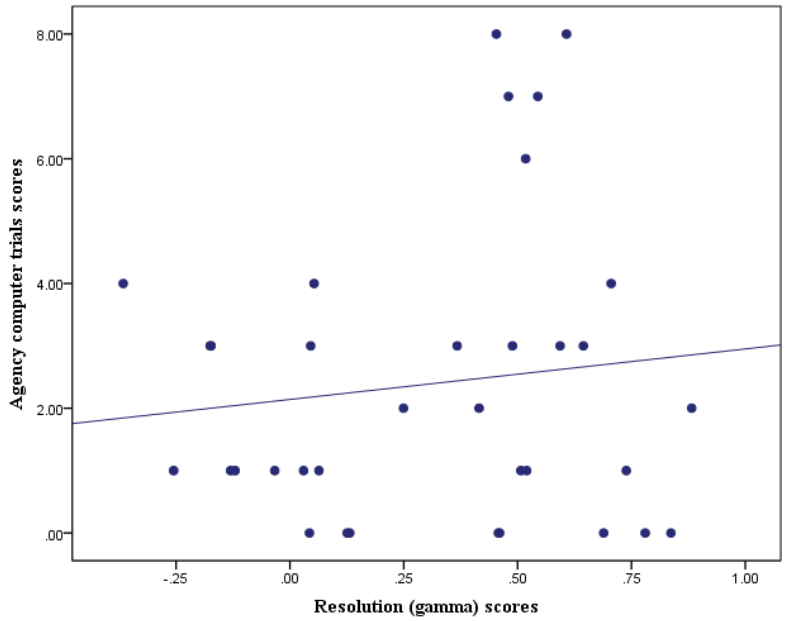
Scatterplot 5.4. Agency computer trials scores and computer experience.



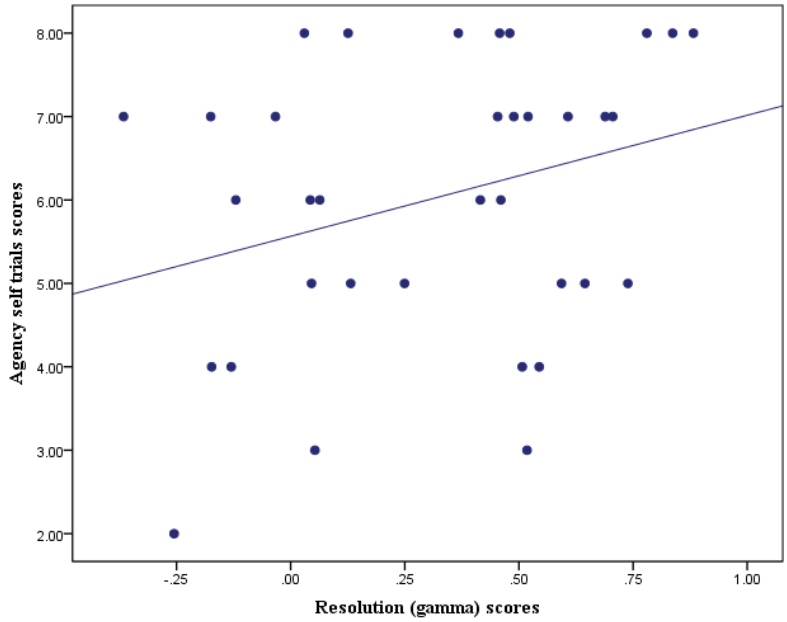
Scatterplot 5.5. Agency self trials scores and computer experience.



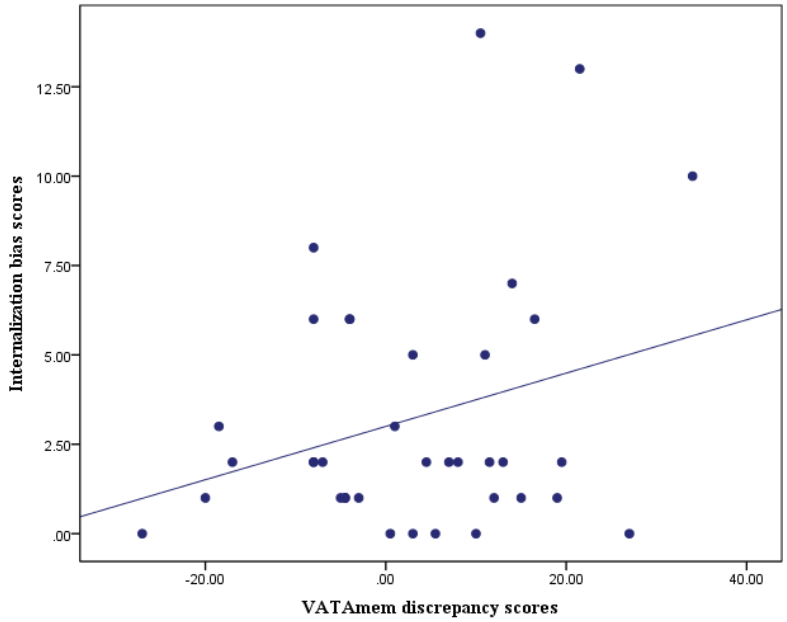
Scatterplot 5.6. Total agency scores and resolution scores.



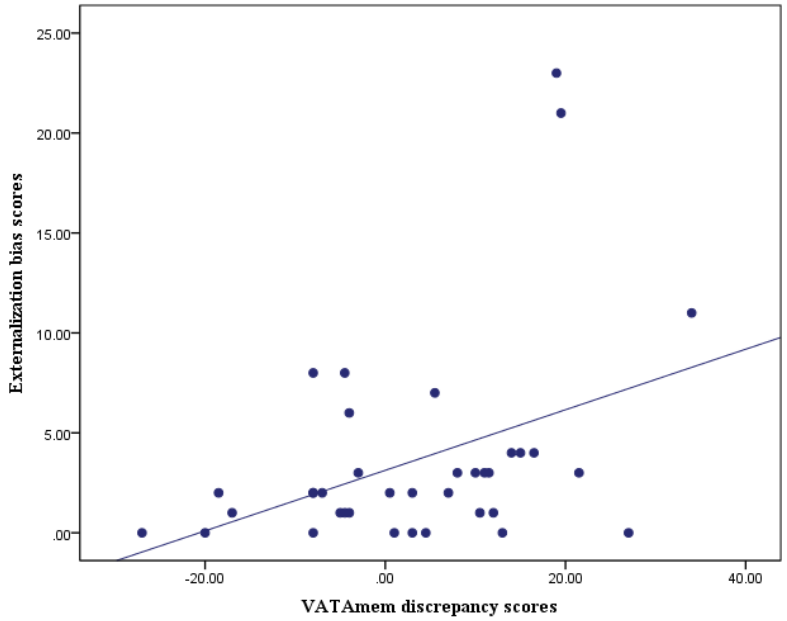
Scatterplot 5.7. Agency computer trials scores and resolution scores.



Scatterplot 5.8. Agency self trials scores and resolution scores.

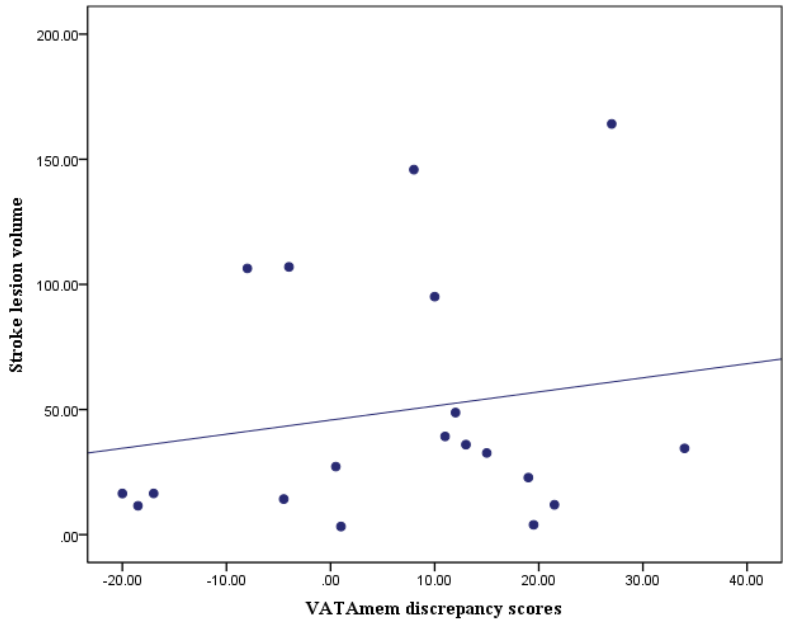


Scatterplot 5.9. Internalization bias scores and VATAmem discrepancy scores.

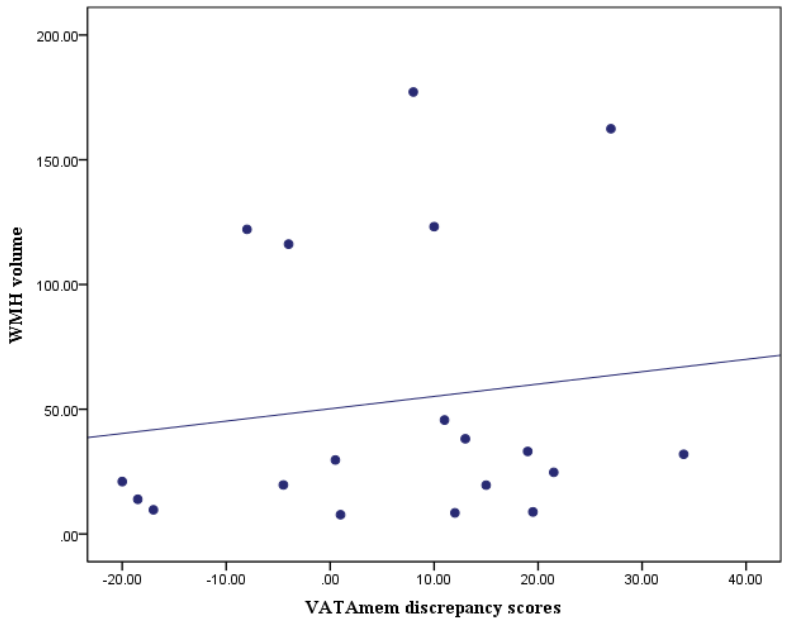


Scatterplot 5.10. Externalization bias scores and VATAmem discrepancy scores.

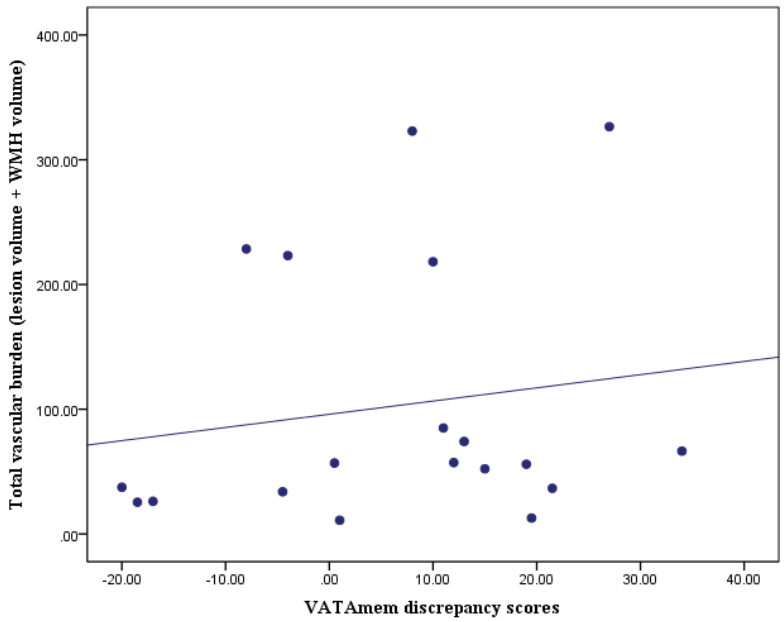
Chapter 6



Scatterplot 6.1. Stroke lesion volumes and VATAmem discrepancy scores.



Scatterplot 6.2. White Matter Hyperintensities (WMHs) and VATAmem discrepancy scores.



Scatterplot 6.3. Total vascular burden and VATAmem discrepancy scores.