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Behavioral and Neurophysiological Mechanisms of Recovery Post-Stroke

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Lenny Eveline Ramsey

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Dedicated to my grandmother

who always puts others first and makes me want to be a better person every day

Abstract of Dissertation

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Dr Maurizio Corbetta, Chair

Strokes can affect very different behavioral domains causing deficits in language, memory, visual attention and movement. This range of deficits is caused by stroke lesions that occur in different locations, and it reflects both the local structural damage as well as remote and widespread neurophysiological abnormalities of structurally normal regions of the brain. The recovery of behavioral deficits depends both on psychosocial factors like age and education, whose brain substrates are presently poorly defined, structural variables such as lesion size and location, and neurobiological repair mechanisms both locally near the lesion and network-wide.

In the current work we hypothesized that behavioral recovery can be divided in two classes: 'domain-general' that influence recovery of deficits across multiple domains of function; and, 'domain-specific' that differ in different functions. At the neurobiological level, we test the hypothesis that domain-specific normalization of abnormal patterns of synchronization occurring across multiple networks at the acute stage represents one of the major neurophysiological correlates of behavioral recovery. Specifically, I will focus on the recovery of attention deficits post-stroke, as seen in the syndrome of hemispatial neglect.

Recovery of neurological deficits reaches a maximum by 3 months post-stroke, and then plateaus in a similar manner across domains without reaching normal performance. The best predictor of chronic performance in each domain of function is the severity of initial deficit that relates proportionally to the amount of recovery (domain-general). However, specific variables such as education level and lesion location differentially improve the prediction of recovery in specific domains (domain-specific). Domain general components likely reflect mechanisms of spontaneous recovery that are activated after a stroke, whereas the domain-specific factors may include those related to compensatory strategies.

Independent of initial severity, the improvement of acutely depressed inter-hemispheric functional connectivity or synchrony across attention, sensory, and motor networks, and a restoration of the normally negative (anti-) correlation between dorsal attention/motor regions and default-mode/frontoparietal regions, robustly predicts recovery of attention deficits post-stroke. These findings are consistent with a normalization of neurophysiological patterns in relationship to behavioral recovery, and a tendency of damaged brain networks to return to normal levels of integration/segregation, which are optimal for information processing.

Chapter 1: Introduction

1.1 Why study stroke?

A stroke occurs when the blood supply to a part of the brain is interrupted (see box 1). While mortality due to stroke has declined in recent years, it is still the fourth leading cause of death in the United States and about 795,000 people suffer from a stroke each year, which has lead to an estimated 6.8 million people currently living with the effects of a stroke (Go et al., 2013). Having had a stroke has a huge effect on the quality of life of the patient, including self-care, communication and eating and many need short or long term care (de Haan, Limburg, Van der Meulen, Jacobs, & Aaronson, 1995). This resulted in an estimated cost of $71 billion in 2012 alone and as the population is growing older and with that an expected increase of the number of stroke patients this is expected to rise up to $184 billion in 2030 (Ovbiagele et al., 2013).

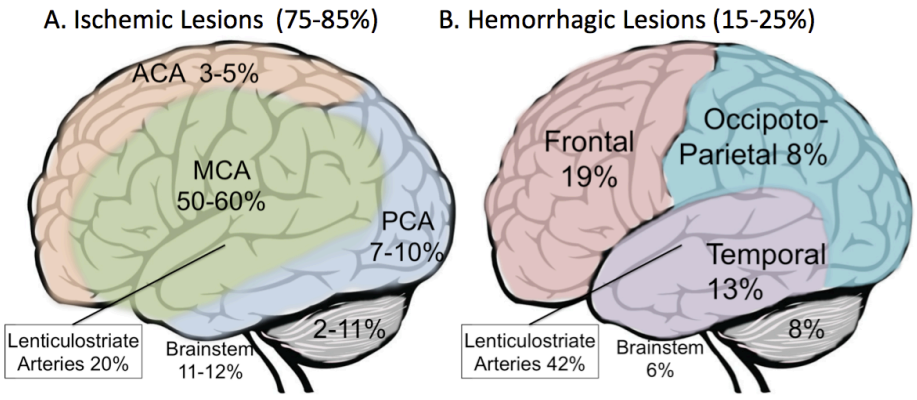

Figure 1.1 Occurrence of lesion by location.
The approximate percentages of lesions for Ischemic lesions by vascular distribution (A) and hemorrhagic lesions by lobe (B). The lenticulostriate arteries supply the deep structures such as the putamen, caudate nucleus internal capsule. ACA anterior cerebral artery, MCA middle cerebral artery, PCA posterior cerebral artery. (Bogousslavsky, Van Melle, & Regli, 1988; Y. S. Ng, Stein, Ning, & Black-Schaffer, 2007; O'Donnell et al., 2010; Sudlow & Warlow, 1997)

Many factors can increase the chances of a stroke, some are modifiable, while others are not. Non-modifiable stroke risk factors include higher age, male gender, race (1:2.4:1.6 for white:AA:Hispanic), ethnicity and heredity (Sacco et al., 1997; Sacco, Kargman, & Zamanillo, 1995; Sudlow & Warlow, 1997). The most important modifiable risk factors for strokes are hypertension, smoking, abdominal obesity, diet and physical activity, followed by other factors such as diabetes mellitus, alcohol intake, stress, cardiac disease, illicit drug use, oral contraceptives, migraines (O'Donnell et al., 2010; Sacco et al., 1997). Disruption in bloodflow to a part of the brain can be caused by an ischemic or hemorrhagic stroke (Box 1). These types of strokes have different underlying causes and occur at different frequencies in different parts of the brain (Box 1, figure 1.1) (Bogousslavsky et al., 1988).

Understanding the risk factors is necessary for the prevention of stroke, but with the inevitable rise in stroke patients a better understanding of behavioral recovery and the changes in the brain that underlie this recovery are essential to developing therapies and improving treatment outcomes.

Box 1: Basic information on lesions caused by stroke

A. What causes a lesion?

Ischemic strokes are caused by an obstruction within a blood vessel that supplies blood to the brain. This is often caused by thrombosis, in which a blood clot develops at the location where the vessel is clogged, or an embolism, in which the blood clot forms at a different location, breaks off, enters the bloodstream and gets stuck in a vessel too small to let it pass.

During a hemorrhagic stroke a weakened spot of a vessel ruptures, causing it to bleed into the surrounding parts of the brain, resulting in pressure on and disruption of this tissue. These

types of strokes are either within the brain (intracerebral), or between the brain and the tissues that cover the brain (subarachnoid). The rupture locations are frequently due to either an aneurism, in which the weakened region balloons and breaks (often because of sustained high blood pressure), or an arteriovenous malformation (AVM), a cluster of abnormally formed blood vessels.

B. What does a lesion damage?

A stroke causes energy levels to drop in the area of disrupted bloodflow, which leads to a complex series of pathobiological events including ionic imbalance, neurotransmitter release and the loss of ion transporter function, resulting in cell death in the core and cell damage in neighboring regions (for a review see Dirnagl, Iadecola, & Moskowitz, 1999). The damage caused by a stroke can involve cell body loss of grey matter as well as damage to white matter connections.

Classically the deficits caused by a stroke were thought to be due to damage to focal grey matter regions. Before neuroimaging methods, single patients were used to identify distinct syndromes caused by damage to specific cortical locations (e.g. Broca's aphasia causing deficits in speech production).

White matter damage causes interruptions in the tracts that connect the same cortical areas in opposite hemispheres (commissural tracts), different regions of the brain within a hemisphere (association tracts) or the brain to and from lower brain areas and the spinal cord (projection tracts). A disruption to one of these tracts disconnects multiple different brain regions.

C. Vascular distributions

The damage caused by a stroke does not adhere to a functional network, but is dependent

on the vascular territory of the vessel affected. The cortex is supplied through three major arteries, the anterior (ACA), posterior (PCA) and medial cerebral arteries (MCA) (figure 1.1).

The lenticulo-striate arteries are small branches off of the MCA, supplying the basal ganglia, caudate nucleus and internal capsule. The cerebellum is supplied through the anterior (AICA) and posterior inferior cerebellar artery (PICA) as well as the superior cerebellar artery (SCA). Finally, the pons and medulla receive their blood supply from branches of the basilar and vertebral arteries respectively.

The size of an ischemic stroke and the particular location damaged depends on the specific branch of the artery that is obstructed, the degree of vascularization and the collateral circulation in that region.

1.2 What behavioral deficits does a stroke cause?

After a stroke patients present with different deficits depending on the location and size of the infarct (table 1.1) (Appelros, Karlsson, Seiger, & Nydevik, 2002; Buxbaum et al., 2004; Nys et al., 2007; Rathore, Hinn, Cooper, Tyroler, & Rosamond, 2002; Ringman, Saver, Woolson, Clarke, & Adams, 2004). Behavioral deficits have frequently been investigated in isolation, but in reality patients often display multiple deficits that fall into several behavioral categories due to the fact that vascular territories include multiple functionally distinct regions (box 1 and table 1.1). A single function is controlled through the interaction of multiple regions, that together form a network. A stroke rarely affects complete networks, but it does damage regions that are part of a network (or networks) which in turn are linked to behavioral domains. Thus, the development of an accurate framework for deficits following stroke requires an understanding of the cortical and subcortical brain networks.

Table 1.1 Types of deficits, their occurrence and artery distribution.

Deficit	Occurrence (%)	Artery distribution
Motor	80-85	ACA, MCA
Sensory	40-50	ACA, MCA
Visual	15-20	PCA
Memory	15-25	MCA, PCA
Aphasia (language)	20-25	MCA, PCA
Neglect (attention)	25-30	MCA, PCA

1.2.1 Motor

The motor system controls the muscles of the body, and does so in a hierarchical fashion, with primary neurons innervating muscles (M1, cerebellum), and increasingly integrating regions that regulate complex integrated movements (secondary and higher order regions). Movement is controlled through a bilateral system of highly studied cortical and subcortical regions. Penfield and Boldrey used electrical stimulation in epilepsy patients to map out the somatotopy of the primary motor cortex (M1) in the precentral gyrus (Penfield & Boldrey, 1937). They mapped the motor (and somatosensory) organization of the representation of body parts, which is referred to as the homunculus. This has since been confirmed with neuroimaging methods such as fMRI (e.g (Rao et al., 1995)). Secondary cortical motor regions include the posterior parietal cortex (involved in visuomotor integration), the supplementary motor area (SMA) and premotor cortex, which are involved in motor action selection and planning (for an in depth review see Rizzolatti, Luppino, & Matelli, 1998). From M1, SMA and the premotor cortex projections go through the cortico-spinal tract (CST) down to the spinal cord. Multiple other regions are important for the control of movement, including the thalamus, cerebellum and the basal ganglia. The thalamus

acts as a relay, the cerebellum is important for the fine tuning and coordination of movement, and the basal ganglia, comprised of the striatum, globus pallidus, substantia nigra and subthalamic nuceus, inhibits competing motor programs.

Strokes to specific regions of the basal ganglia can cause rare movement disorders such as hemiballism or hemidystionia, which cause undesired or abnormal movements in the contralesional parts of the body (Bansil et al., 2012). Damage to secondary motor areas in the frontal and parietal cortices can cause deficits in motor planning or apraxia, which is a deficit affecting skilled and learned movements of limbs or speech (for a review see Koski, Iacoboni, & Mazziotta, 2002 or Leiguarda & Marsden, 2000). However, the most common deficit caused by stroke is hemiparesis, a deficit in the execution of actions, caused by damage to the primary motor cortex or corticospinal tract. Based on studies of patients with hemiparesis, deficits of the distal parts of limbs are thought to be more severe and show worse recovery than more proximal motor deficits (Twitchell, 1951). This could be caused by the fact that distal control is highly dependent on corticospinal tract fibers whereas more proximal control could benefit from ipsilateral innervation (Jankowska & Edgley, 2006). Additionally, lower extremity deficits have been suggested to recover better than upper extremity deficits, but this might be dependent on the types measures used (Box 2) (Olsen, 1990; Twitchell, 1951).

1.2.2 Language

The language system controls the production and the understanding of words and sentences as well as non-verbal aspects of speech. The original Wernicke-Geschwind model of language identified Broca's area for language production, Wernicke's area for comprehension and the arcuate fasciculus as the main white matter connection between the two. This has been expanded into a more complex network with regions of the insular cortex, basal ganglia and

association cortices (for more detail see Damasio & Damasio, 1992)). Damage to this language system causes aphasia, most often due to lesions of the left hemisphere, but also in a subset of patients with right hemisphere damage (Wade, Hewer, & David, 1986). Based on focal lesion studies, the most common subtypes are expressive (or Broca's), receptive (or Wernicke's), conduction and global aphasia. Conduction aphasia is the inability to repeat words or sentences and is caused by damage to the arcuate fasciculus, damaging the connection between Broca's and Wernicke's area. Other less common subtypes of aphasia include anomic (difficulties in word finding) and transcortical sensory or motor aphasia (difficulty in understanding or producing speech, but still being able to repeat words or sentences). Aphasias can generally be classified as fluent (including receptive and conduction aphasia) or non-fluent (including expressive and global aphasia).

The different sub-types of aphasia show similar patterns of improvement (Prins, Snow, & Wagenaar, 1978), but the most common language deficit, global aphasia, can result in one of the more specific types of aphasia with recovery (Laska, Hellblom, Murray, Kahan, & Arbin, 2001; Pedersen, Vinter, & Olsen, 2004). Chronically (after the first 3 months), the largest improvements are found in measures of comprehension (Prins et al., 1978), however these changes are likely due to improvements in non-verbal communication strategies (Sarno & Levita, 1981), suggesting that these are learnt compensatory strategies rather than actual recovery of the impaired language system (Box 2).

1.2.3 Memory

The memory system is responsible for encoding, storing and retrieving of information and comprises multiple different aspects of memory, from short-term active rehearsal to the long-term storage of past events. Memory is considered a sub-measure of cognition that can be

classified in multiple ways, and because of this it is not as clearly defined as the other behavioral modalities. The most common distinction is made between long term and short-term (or working) memory, but this distinction is still under debate as they might be more closely related than previously thought (Nee, Berman, Moore, & Jonides, 2008). Other distinctions have been developed based on theoretical knowledge as well as human and animal studies involving lesions and functional mapping (Squire, 2004).

The memory that is referred to in everyday language is declarative memory, a subcategory of long-term memory that consists of semantic (facts) and episodic memory (events). The other category of long-term memory is non-declarative memory, which is the subconscious process related to performance and the ability to gradually extract common elements from separate events. The different types of non-declarative memory are procedural learning (skills and habits), priming, classical conditioning and non-associative learning (reflexes) (Squire, 2004). Declarative memory, the type of memory most affected by amnesia, has been localized to the medial temporal lobe (including the perirhinal cortex and hippocampus (Brown & Aggleton, 2001) and midline diencephalon (more specifically the mammilary bodies and anterior thalamic nuclei (Vann & Aggleton, 2004). Even in severely amnesic patients the non-declarative memory such as the learning of new skills and priming are still intact. Procedural memory, which relies on gradual learning based on feedback and forms habits, is related to the striatum, whereas priming is attributed to the neocortex. The amygdala responds to classical conditioning based on emotions such as fear, but more skeletal responses, such as eye blink conditioning, rely on the cerebellum (reviewed in Thompson & Steinmetz, 2009).

The classical model for short term memory was conceptualized by Baddeley and colleagues (Baddeley, 1992), making a distinction between visuo-spatial and verbal memory. A

separate component, the central executive, is an attention driven system for the manipulation of the information held in either of the two systems. Object memory is often explored as a third memory component and these three components are supported by regions in the frontal, parietal and temporal cortices. The verbal memory system is thought to be lateralized to the left hemisphere and spatial memory to the right hemisphere (Smith & Jonides, 1998). Interestingly a meta-analysis conducted by Wager & Smith (Wager & Smith, 2003) found only weak lateralization effects that were driven by task demand. Verbal memory was lateralized to the left inferior frontal cortex only during simple tasks and a right-hemisphere lateralization was found in the frontal cortex for spatial memory, only when there was a high executive demand (Wager & Smith, 2003). This suggests that observed verbal versus spatial memory lateralization differences might be driven by differences in demand.

The distinction between spatial and object memory has been confirmed by differences in localization in the brain that are similar to the dorsal "where" and ventral "what" streams proposed in the macaque's visual system (Ungerleider & Mishkin, 1982; Goodale & Milner, 1992) . Spatial memory activates the parietal cortex as well as the dorsal prefrontal cortex, whereas object memory has been mapped to regions in the temporal and ventral frontal cortex (Courtney, Petit, Haxby, & Ungerleider, 1998; Wager & Smith, 2003).

As there are multiple ways to classify memory, the recovery of these distinct components has not been well studied. Interestingly, education has been identified as a protector against memory and cognitive deficits in Alzheimer's disease, multiple sclerosis (MS) and traumatic brain injury (Bonnet et al., 2006; Nunnari, Bramanti, & Marino, 2014; Stern, 2006; Stern, Albert, Tang, & Tsai, 1999). This suggests that recovery of memory deficits might be dependent on the ability to learn and use compensatory strategies (Walker, Sunderland, & Sharma, 2004).

1.2.4 Attention

Attention allows us to focus on specific parts of the sensory system, to select behaviorally relevant stimuli, and is necessary for memory processing. Guiding of attention can be top down (goal driven), or bottom up (stimulus driven). Stimulus driven attention is short lasting and reorients by interrupting the current state of focus and redirecting to the novel or behaviorally relevant stimulus.

Damage to the attention system causes hemispatial neglect, a syndrome characterized by a failure to report, respond, or orient to novel or meaningful stimuli on the side opposite to the lesion and accompanied by a non-spatial decrease in arousal. Neglect is most common and severe after right hemisphere lesions (Stone, Patel, Greenwood, & Halligan, 1992b; Weintraub & Mesulam, 1987), yet it can occur after left hemisphere damage as well (Kleinman et al., 2007; Stone, Halligan, Marshall, & Greenwood, 1998). In general, damage to the right posterior parietal lobe, particularly superior temporal gyrus, the temporo-parietal junction, the inferior parietal lobule and sulcus have been identified as the most likely to cause hemispatial neglect (Mort et al., 2003; Ptak & Schnider, 2011; Rorden & Karnath, 2004). In addition, damage to the middle frontal gyrus as well as the right pulvinar, caudate nucleus and putamen, which are subcortical regions connected to the superior temporal gyrus, can cause neglect symptoms (Karnath, Himmelbach, & Rorden, 2002; Karnath et al., 2005; Ptak & Schnider, 2011).

Lesions to a variety of regions cause similar attention deficits, yet there is some dissociation between locations of damage and the resulting sub-types of neglect (Vaessen, Saj, Lovblad, Gschwind, & Vuilleumier, 2016; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010). The classical distinction is between egocentric neglect, where patients ignore the contralesional side in space, and allocentric neglect, which is object centered and leads to

patients ignoring the left side of each object (Binder, Marshall, Mohr, Benjamin, & Lazar, 1992; Stone et al., 1998). These forms of neglect are associated with parietal and temporal damage respectively (Hillis et al., 2005). Similarly, a distinction has been proposed between personal (the space of the body surface) and extrapersonal space (space surrounding the person) that are correspondingly mapped to parietal and temporal lesions (Halligan & Marshall, 1991; Vuilleumier, Valenza, Mayer, Reverdin, & Landis, 1998)

Finally, a separation between perceptual versus (pre)motor neglect has also been suggested (Bisiach, Geminiani, Berti, & Rusconi, 1990; Buxbaum et al., 2004), finding that more frontal lesions are related to premotor neglect, which involves an impairment in initiating actions into the neglected side, and more parietal lesions to perceptual neglect, resulting in deficits in guiding attention into the neglected side of space. However, this distinction is controversial as designing a task to separate the groups is complicated and the attempts to do so have given inconsistent results (Harvey, Krämer-McCaffery, Dow, Murphy, & Gilchrist, 2002).

Independent of these different types of 'spatial' deficits hemispatial neglect is also associated with a non-spatial, bilateral decrease in arousal that is more apparent in patients with larger temporal lesions involving the periventricular white matter (Samuelsson, Hjelmquist, Jensen, Ekholm, & Blomstrand, 1998). This non-spatial deficit often accompanies neglect and stays stable over time, whereas the spatial deficits show improvement within the first weeks after a stroke (Farne et al., 2004).

The mapping of the subtypes of hemispatial neglect is however not absolute and there is a common functional disruption between attention regions associated with neglect. Non-spatial attention activates ventral attention regions in the right hemisphere (the ventral attention

network), whereas spatial attention is related to a bilateral system of dorsal attention regions. Damage to the ventral attention network is thought to cause an imbalance between the regions of the dorsal attention system, which has been related to the neglect deficits (Corbetta & Shulman, 2011).

1.3 Specific deficits or syndromes?

The distinctions described in the previous section within each domain of function are often based on specifically selected or small groups of patients with similar lesions and deficits. In large patient groups with heterogeneous lesions of different sizes and in different locations, these specific categorizations of deficits are not as apparent. Moreover, in studies it has been underappreciated that patients often present with more than one specific deficit. Studies on the NIH Stroke Scale have for example shown that the majority of variation in neurological deficits can be explained by two components, one for left hemisphere damage and one for right hemisphere damage (Lyden, Claesson, Havstad, Ashwood, & Lu, 2004; Zandieh et al., 2011), which suggests more broad ranges of deficits within patients. The NIH stroke scale is a stroke severity assessment tool that is biased toward motor behavior, and lacks detailed measurements of specific cognitive functions. Therefore the absence of functionally specific deficits and the presence of larger clusters needed to be confirmed using a diverse battery of behavioral measures.

We investigated the patterns of behavioral deficits in a large cohort of 132 first time symptomatic stroke patients (Corbetta et al., 2015). Patients were assessed for deficits using 44 distinct behavioral measures. We similarly found that the deficits were more widespread within a behavioral domain than previous work on specific deficits has suggested. A principal component analysis (PCA) on language, for example, showed that there was only one main component

underlying language deficits as all of the behavioral measures were highly related. This is in contrast to the classical view that language separates out into production, comprehension and reading deficits. Similarly, for the motor system just one factor for left and one for right limb deficits was identified by PCA, without a distinction between upper and lower extremity or proximal and distal limb function. When the motor deficits were investigated independent of lesions side just one single component was identified. Memory was divided along one of the proposed distinctions, into spatial and verbal memory, and finally, the PCA on attention identified three components (visual field bias, general attention and attention shifting). The lack of differentiation between different types of motor deficits is supported by other studies, which demonstrate that shortly after a stroke distal and proximal deficits as well as upper and lower motor deficits (Beebe & Lang, 2008; Duncan et al., 1994) are highly related.

The different deficits do not necessarily occur in isolation, so a higher order analysis was done by combining all of the behaviors. This resulted in three behavioral components, a cognitive component involving language and verbal memory, a left hemisphere component that contained right limb motor and attention shifting and a right hemisphere component with left limb motor and the visual field bias (a measure of spatial attention). These three components accounted for about 70% of variance across subjects. This supports the notion that, at the group level, the neurological impairments observed following stroke present as a few clusters of behavioral deficits.

Previous studies that identified the more specific classifications of deficits within domains were often done on patients selected for their lesion location or deficit, ignoring the potential presence of other deficits. Moreover, the identification of just a few clusters does not imply that single deficits and the more fine-grained classifications are not present in single

patients, yet across a large cohort of patients, representative of the general stroke population, these differences are relatively insignificant. Therefore we propose an updated framework for describing post-stroke deficits in which a few behavioral clusters of correlated deficits account for the majority of variance across subjects.

1.4 Recovery of behavioral deficits

1.4.1 How do stroke deficits recover?

After having a stroke most patients show some recovery, but many do not fully return to their original levels of functioning. At the group level, the amount and speed of recovery is best predicted by the initial level of behavioral deficit (Byblow, Stinear, Barber, Petoe, & Ackerley, 2015; Cassidy, Lewis, & Gray, 1998; Nys et al., 2005; Pedersen, Stig Jorgensen, Nakayama, Raaschou, & Olsen, 1995). Other consistent predictors of better outcome include younger age, smaller lesion size, and lesion side with left hemispheric lesions showing better upper limb recovery and right hemispheric lesions showing better cognitive recovery (Cheng et al., 2014; Coupar, Pollock, Rowe, Weir, & Langhorne, 2012; Hochstenbach, Otter, & Mulder, 2003; Kertesz & McCabe, 1977; Macciocchi, Diamond, Alves, & Mertz, 1998; Nys et al., 2005; Pedersen et al., 1995; Tilling et al., 2001). All of these factors account for significant degrees of variance explained at the group level. However, the majority of studies on the recovery after stroke are conducted on specific patient groups, focusing on the recovery of a specific domain, not taking into account other deficits that might be present. This makes generalizing results to the general stroke population difficult.

After a stroke the recovery of deficits can be studied as the amount of recovery from the initial deficit or the speed of improvement. Patients with mild initial deficits show better outcomes than patients with more severe deficits (Bonita & Beaglehole, 1988; Coupar et al.,

2012; Kertesz & McCabe, 1977; Kwakkel, Kollen, & Twisk, 2006; Pedersen et al., 1995). For example, motor deficits of most patients recover up to approximately 70% of the difference between their acute deficit and healthy control levels (Coupar et al., 2012; Prabhakaran et al., 2007), an effect that has also been shown in aphasia deficits (Lazar et al., 2010; Wade et al., 1986). This means that someone with a more severe deficits shows more recovery, but also retains a larger deficit than someone starting off with a minor deficit.

There are indications that recovery patterns differ for the different behavioral domains. As time advances recovery tends to decline and the consensus is that most recovery occurs within the first 3 months after symptom onset (e.g., Duncan et al., 1994; Kotila, Waltimo, Niemi, Laaksonen, & Lempinen, 1984; Kreisel, Hennerici, & B auml zner, 2007; Skilbeck, Wade, Hewer, & Wood, 1983; Stone, Patel, Greenwood, & Halligan, 1992b; Wade, Wood, & Hewer, 1985). A few studies suggest that cognitive deficits still show some (albeit smaller and slower) recovery after this 3 month period (eg aphasia: (Kertesz & McCabe, 1977); neglect: (Levine, Warach, Benowitz, & Calvanio, 1986), yet other studies show a faster recovery in these higher cortical deficits (Hier, Mondlock, & Caplan, 1983b). This variation may be due to differences in selection criteria of patients, small group sizes and/or differences in the specific behavioral measures used (Duncan, Lai, & Keighley, 2000) (box 2).

The sizes of samples and the measures used in previous studies on recovery do not allow for clear comparisons between domains and therefore it is unclear which of the identified predictors and moderators of outcome and recovery are domain general and domain specific. Domain general factors have a similar predictive value for all domains, whereas the domain specific factors affect the recovery in specific domains more than others. A more complete evaluation requires a larger cohort of patients with a comprehensive range of behavioral

measures. To elucidate this we investigate the behavioral recovery of language, motor, memory and attention in a large cohort of stroke patients, using measures based on a large range of behavioral measures within each domain in chapter 2.

Box 2. Types of behavioral recovery

The term 'recovery' is usually defined as any improvement in the ability to perform a task. However, this can be separated into restitution and compensation. Restitution implies a restoration of function through potential restoration or reorganization of damaged neural mechanisms. Compensation implies a successful completion of a task through different strategies or neural mechanisms. While this distinction has theoretical merit, in practical terms it is hard to distinguish between restitution and compensation at both the behavioral and neural level.

At the behavioral level a distinction is made between different levels of measuring deficits. Impairment identifies any loss of function, affecting body or mind, referring to the actual problem in body function or structure. Functional limitations refer to difficulties in doing a physical task or activity and, finally, disability refers to the ability of a patient to carry out actions or tasks for functioning in society. Understanding this distinction is important when thinking about the recovery of function and the comparison of behavioral domains. Different measures can assess deficits at different levels, which can lead to variations in results between studies. For example, a patient with a motor deficit causing them unable to make a full reaching movement (a functional limitation) will show this deficit if the kinematics of joint movements are measured (measuring the impairment). However, they might still be able to move an object from point A to point B by using their trunk to compensate, and thus they do not have a disability.

The distinction between disability, functional limitation and impairment are based solely on behavior. Theoretically it could be possible that through reorganization and recruitment of perilesional and secondary brain regions, behavioral functions can be relearnt after a focal stroke. After a larger stroke, when this reorganization is no longer an option, the brain then adapts or compensates through the recruitment of different neural systems. This is a separate distinction of restitution and compensation at the neuronal level, which is hard to prove, and can only be measured using neuroimaging methods. Moreover, behavioral studies in both animal and human studies have shown that restitution of behavioral patterns through neuronal reorganization is unlikely. Patterns of movement, even after minor damage to the motor cortex or the recruitment of secondary brain regions are still abnormal, even if there is no functional limitation (Buma et al., 2016; Friel & Nudo, 1998).

1.4.2 Interhemispheric balance and behavioral recovery

Our framework of syndromes introduced in 1.3, suggesting that deficits are more widespread within a domain and that deficits cluster into a few syndromes, as well as the large incidence of subcortical strokes that damage the white matter, puts more of an emphasis on the connections and interactions between multiple brain regions (see box 1). During recovery this is evident as a recruitment of (related) brain regions to support the impaired function.

The recovery of hemiparesis is paired with shifts and a spread of activation within the ipsi-lesional M1, bilateral activation of M1 and the activation of secondary motor areas (Ward, Brown, Thompson, & Frackowiak, 2003). Best outcome is related to a rebalancing of activity between the ipsi- and contralesional M1, a shift of activation back into the ipsilesional M1 and a refocusing of the initially enlarged region of activation (Cheng et al., 2014; Mäkelä, Lioumis, & Laaksonen, 2015; Rehme, Eickhoff, Rottschy, Fink, & Grefkes, 2012; Ward et al., 2003; J.

Zhang et al., 2014). Recruitment of the ipsilateral (or contralesional) hemisphere is most apparent in severely affected patients (Rehme, Fink, Cramon, & Grefkes, 2011), but the benefits of this pattern are still unclear and may even be related to poor recovery (Loubinoux et al., 2003; Turton, Wroe, Trepte, Fraser, & Lemon, 1996). In a review, Pascual-Leone and colleagues (Pascual-Leone, Amedi, & Fregni, 2005) suggest that initially the increased activation of the unaffected hemisphere is a protective mechanism that may increase inhibitory input on the affected hemisphere. This appears to reduce the demands of the lesioned region, and limits the extension of the lesion. However, persistent over-activation of the contralesional hemisphere is associated with worse outcomes. Similar concepts have been proposed for language, but role of the recruitment of regions in the right hemisphere is as of yet quite unclear (Price & Crinion, 2005).

The initial recruitment of brain regions, predominantly in the unlesioned hemisphere, to support the impaired function and subsequent rebalancing of this activation that is related to better outcomes is also apparent in patients with neglect. Damage to ventral attention regions is thought to cause a functional imbalance between more dorsal attention regions. This initial imbalance between the hemispheres causes a shift of the center of attention or focus into the ipsilesional hemifield, causing neglect of the opposite side. Patients with hemispatial neglect present with hypoactivation in the parietal regions of the lesioned hemisphere, and hyper activation in the undamaged hemisphere. Asymmetrical increases of activation lead to contralateral attention shifts (Szczepanski, Konen, & Kastner, 2010), with stronger activity in patients with more severe neglect (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005). In 1987 Kinsbourne proposed an inter-hemispheric rivalry between the dorsal attention regions in the two hemispheres, which is necessary for the bilateral control of spatial attention (Kinsbourne, 1987).

Activation of one hemisphere is thought to inhibit the other, allowing for controlled attention into either visual field. The often partial recovery of neglect has been related to a rebalancing of task activation (Cassidy, Bruce, & Gray, 2001; Corbetta et al., 2005; Farne et al., 2004; Pizzamiglio et al., 1998; Rengachary, He, Shulman, & Corbetta, 2011).

1.4.3 A systems view on recovery

The classical modular notion of stroke was highly focused on deficits being caused by focal cortical lesions. Multiple large-scale studies, including our study of 132 patients have now shown that only 13-16% of patients have a lesion that is just cortical and the majority of lesions involve the underlying white matter tracts (Corbetta et al., 2015; Kang, Chalela, Ezzeddine, & Warach, 2003; Wessels et al., 2006). Multiple studies have now shown that damage to the corticospinal tract leads to the most severe and worse recovery of motor deficits (Jayaram et al., 2012; Lo, Gitelman, Levy, Hulvershorn, & Parrish, 2010; Schaechter et al., 2009; Stinear, Barber, Petoe, Anwar, & Byblow, 2012; Zhu, Lindenberg, Alexander, & Schlaug, 2010). Similarly, in neglect damage to white matter pathways connecting frontal and temporo-parietal regions leads to severe and persistent impairment (Corbetta et al., 2015; De Schotten et al., 2014; Rengachary et al., 2011; Verdon et al., 2010).

The significance of white matter damage to persistent impairments and the rebalancing of between hemisphere interactions emphasizes the importance of communication between regions for both the production and recovery of behavior. Moreover, task activation studies can be complicated in diverse patient populations, as not all patients might be capable of performing the different behavioral tasks due to their deficits and differences in the ability to perform a task can confound findings. Increased effort in making a movement can for example increase the activation amplitude of motor regions and increase the recruitment of higher order motor as well

as attention regions. Resting state fMRI is a method that allows for the investigation of networks of regions during rest (see box 3). This reveals between functionally related regions though similarities in low frequency fluctuations. This neuroimaging method circumvents these issues present in task activation studies.

Box 3: What is resting state fMRI?

The brain uses up to 20% of the energy of the body, although it weighs only about 2% of the total body weight. Activation by imposing a task on a person causes an increase in brain metabolism of less than 5% (P. T. Fox, Raichle, Mintun, & Dence, 1988), meaning that the brain is essentially always very active even at rest. The majority of brain metabolism is related to neuronal signaling: the re-uptake of glutamate after synaptic release is a highly demanding process that may be partly responsible for this very large metabolic expenditure at rest. Given the amount of energy that the brain expends on maintaining ongoing activity, it is thought that this activity must play an important physiological role (Raichle & Mintun, 2006).

In 1995, Biswal and colleagues (Biswal, Yetkin, Haughton, & Hyde, 1995) showed that frontal regions in the motor cortex displayed temporal correlations of spontaneous fluctuations of the fMRI BOLD signal measured at rest, and that the topography of these slow correlated fluctuations (in the 0.01-0.1 Hz range) was similar to the regions activated during motor tasks. Similar functional connectivity (FC, the inter-regional correlations) has been observed throughout the brain at rest. This method of mapping temporal correlations of the spontaneous BOLD signal has been used to identify multiple sets of functionally connected regions, each forming a brain network (resting state networks) that is related to a specific function, identified based on their similarity with task-activation maps (Smith et al., 2009).

A variety of methods has identified Motor, Visual, Auditory, Dorsal and Ventral Attention, Language, Fronto-parietal, Cingulo-Opercular, and Default Mode networks, that are stable over time in healthy subjects (Damoiseaux et al., 2006; Hacker et al., 2013; Power et al., 2011; Thomas Yeo et al., 2011). The default mode network (DMN) is a network that consists of regions that become *less* active during a task and are more active during rest. This "task negative" network shows a negative correlation (anti-correlation) with the "task positive" networks such as attention and motor function (Raichle et al., 2001).

1.5 Neurophysiology of stroke recovery

1.5.1 Why use resting state fMRI?

Resting state fMRI (box 3) has been used to studies changes in functional connectivity (FC) in multiple patient populations such as stroke, autism, ADHD and schizophrenia (Anderson et al., 2011; Castellanos, 2011; Micheloyannis et al., 2006; Sonuga-Barke & Castellanos, 2007; Uddin et al., 2008). Many of these studies have identified differences, most often decreases, in inter-hemispheric connectivity strength between related regions as compared to healthy controls (Anderson et al., 2011; Carter et al., 2009; He et al., 2007; Jelsone-Swain et al., 2010; Spencer et al., 2003). Another change related to disease states is a decrease in the anti-correlations between the DMN and task positive networks, weakening their (negative) relationship (K. Wang et al., 2007), (Castellanos et al., 2008).

An alternative to resting state fMRI (R-fMRI) is task-based fMRI (T-fMRI), which has frequently been used to map regions related to behavior and investigate mechanisms underlying disorders and brain damage. However, R-fMRI has several advantages over T-fMRI in the study of patient populations.

Task performance influences neuroimaging results. For example, the amplitude of a movement in a motor task influences the magnitude of BOLD signal change (Waldvogel, van Gelderen, Ishii, & Hallett, 1999). This also means that differences in ability to perform a task between patients and controls influence results, even if differences are not due to the condition itself. Moreover, the varied stroke population in which we are interested experiences a wide range of deficits, and not all patients may be able to perform or understand certain tasks. Using R-fMRI removes any confounds caused by differences in ability to perform the task, or differences in effort, and allows for the inclusion of any patient that does not have any contra-indications to T-fMRI, thereby increasing the number of subjects and variety of deficits that can be included in our patient group.

Additionally, task activation paradigms are designed to measure activity related to specific functions. To investigate the brain regions involved in multiple domains, many different tasks would be needed, resulting in a prohibitively long duration in the scanner. With R-fMRI however, a dataset of 10 minutes can provide information about multiple different networks. Furthermore, the relationships among multiple regions within a network and the interactions between regions belonging to different networks, can be taken into account using this technique.

Finally, as discussed, task-driven changes in neuronal activity are relatively small (i.e., ~3-4% change BOLD response over baseline at 3T), requiring averaging across multiple subjects. In contrast, the low-frequency fluctuations of the fMRI signal at rest are larger (5-20%), which allows for the mapping of alterations of temporal correlation between areas at the level of single subjects.

1.5.2 What do we know about functional connectivity after stroke?

The first resting state fMRI study to show effects in brain regions distant to the lesion after a stroke found that focal damage to regions of the frontal, temporal, and parietal cortex (and subcortical white matter), known to cause hemispatial neglect, correlated with strong decrements of inter-hemispheric functional connectivity (FC) in dorsal parietal and frontal regions of the dorsal attention network (He et al., 2007). The decreases in inter-hemispheric FC were correlated with the measured attention deficits. Despite its small sample size, this study demonstrated that stroke causes alteration in functional connectivity. Moreover, it highlighted the importance of inter-hemispheric connectivity, the relevance of this connectivity to behavior, and the interactions of multiple networks.

Multiple studies have now demonstrated the relationship between stroke lesions and alterations in FC (Carter et al., 2009; Ovadia-Caro et al., 2013; Urbin, Hong, Lang, & Carter, 2014; Y. Wang, Chen, Gong, Shen, & Gao, 2010). The importance of the relationship between inter-hemispheric (as opposed to intra-hemispheric) connectivity and behavior has been emphasized in patients with both motor and attention impairments (Carter et al., 2009; Urbin et al., 2014) and confirmed in sensorimotor regions in rats with unilateral strokes (van Meer et al., 2010). In the case of language, disrupted correlations were found between the left and right anterolateral superior temporal cortex and speech comprehension in aphasic patients (Warren, Crinion, Lambon Ralph, & Wise, 2009). In summary, inter-hemispheric abnormalities seem to be a common occurrence in stroke across a number of different behavioral conditions.

Interestingly, Carter et al. showed that spatial attention deficits were specifically predicted by connectivity in the dorsal attention network, whereas motor deficits were predicted by both somato-motor and attention network connectivity (Carter et al., 2009). Similarly,

Dacosta-Aguayo and colleagues showed that multiple networks are involved in the same deficits, finding alterations in 6 out of their 18 identified networks in patients after stroke that were related to cognitive deficits 3 months after stroke (Dacosta-Aguayo et al., 2014). The networks identified included not only regions that have been previously linked to cognition, but also the basal ganglia and visual networks. Wang and colleagues (C. Wang et al., 2014) reported that in recovered chronic stroke patients with motor deficits after subcortical strokes, changes (both increases and decreases) occurred not only in the sensorimotor network, but also in the visual, auditory, default mode and attention networks. Connectivity changes between networks were also identified, between the visual and auditory, the visual and motor, the default mode and fronto-parietal, the auditory and fronto-parietal and the motor and default mode networks. These results suggest that not only the interactions between regions within a network, but also the communication between different networks is important for behavior.

In patients with neglect the decreases in inter-hemispheric connectivity between regions of the dorsal attention network (DAN) are related to the severity of the deficit (Baldassarre et al., 2014; Carter et al., 2010; He et al., 2007). Moreover, damage to the white matter tracts connecting the dorsal and ventral attention regions in the right hemisphere leads to reduced inter-hemispheric correlations (He et al., 2007) and damage to these tracts is also the best predictor of neglect (De Schotten et al., 2014). This suggests that this disconnection between dorsal and ventral attention regions underlies the inter-hemispheric imbalance mentioned previously.

As lesions affect multiple regions and networks through direct cortical as well as white matter damage and the different networks interact with each other, the investigation of changes post stroke needs to take into account changes in connectivity throughout the brain and across multiple networks. Previous work in our lab on stroke and neglect in 84 sub-acute stroke patients

showed widespread reduced inter-hemispheric connectivity between DAN and motor regions, as well as a reduced anti-correlation in the right hemisphere between regions of the DAN and the default mode network (DMN) and increased intra-hemispheric connectivity with the basal ganglia (Baldassarre et al., 2014), again showing that these are multi-network effects. More recent work additionally shows a double dissociation between inter-hemispheric DAN disruptions in neglect and inter-hemispheric motor network disruptions in patients with motor deficits (Baldassarre et al., 2016), suggesting that even after correction for the effect of interactions between behaviors, a specific relationship remains between the deficits and their corresponding networks.

The mechanisms underlying neglect recovery are still largely unknown. A direct correlation with behavioral improvement was only examined in a few small studies (Carter et al., 2010; Corbetta et al., 2005; He et al., 2007), and the effects across multiple networks have not been taken into account.

1.6 Current objectives

We hypothesize that across patients different behavioral domains show similar patterns of recovery over time, but that differences in demographic factors can differentially affect the recovery different domains. In chapter 2 we investigate the similarities and differences in behavioral recovery of multiple behavioral domains in a large, heterogeneous cohort of stroke patients. We use a wide range of behavioral measures to capture the recovery of language, memory, motor and attention deficits. This large dataset allows us to compare the recovery of deficits in a cohort that is representative of the general stroke population. Measures are gathered approximately 2 weeks, 3 months and one year after stroke to track the recovery of the deficits

over time. Moreover, demographic measures are collected in each patient to investigate the influence of these variables on the recovery of each of the behavioral domains.

Previous work (Baldassarre et al., 2014) identified widespread neurophysiological decrements underlying neglect. How these decrements change over time in relation to behavioral recovery is not yet clear. We hypothesize that the changes related to recovery are normalizations of the acute decrements as opposed to reorganization. In chapter 3 we explore these changes in functional connectivity that are related to the improvement of neglect. This relationship between behavioral improvement in neglect and changes in FC is analyzed both in terms of a priori regions and networks known to be abnormal sub-acutely, and in a data driven manner. Moreover, the specificity of the changes to neglect is confirmed through control analyses that remove the effects of other behavioral deficits as well as lesionsize and lag.

Chapter 2: Patterns of behavioral recovery across language, memory, motor and attention deficits after stroke

2.1 Abstract

Strokes can affect different behavioral domains, but most studies of recovery from stroke have focused on a single behavioral domain As a result, it is unclear what features of stroke recovery generalize across domains or are domain-specific.

We measured lesion anatomy with structural MRI and tested behavior in the language, memory, attention and motor domains in a large cohort of stroke patients 2 weeks, 3 months and 12 months post onset. We then examined how recovery and chronic scores in each domain were affected by demographic variables, the magnitude of the acute deficit in that domain, the presence of acute deficits in other behavioral domains, lesion volume and lesion location.

The timecourse of recovery was very similar across domains, with the majority of recovery occurring by 3 months, then plateauing below healthy levels. The best predictor of chronic level of performance in each domain was the severity of initial deficit. However, in individual domains specific variables improved the prediction of chronic scores. Education level predicted chronic language scores, lesion size predicted chronic scores in language and spatial memory domains, while specific subcortical lesion locations added to the prediction of chronic language, motor and attention deficits. Finally, the presence of multiple acute deficits significantly decreased the recovery of attention with a trend for an effect on spatial memory.

We conclude that stroke recovery is affected by both domain-general and domain-specific factors. Domain-specific factors may include those related to compensatory strategies specific to a behavioral domain or to the organization of the associated brain networks as well as specific subcortical regions damaged, while the domain-general component may reflect mechanisms of spontaneous recovery that are routinely active following a stroke.

2.2 Introduction

Strokes can cause many behavioral deficits, the most common being motor (80-85%) and somatosensory deficits (40-50%), aphasia (20-25%), visual deficits (hemianopia/diplopia) (15-20%) and neglect (25-30%) (Appelros et al., 2002; Buxbaum et al., 2004; Rathore et al., 2002; Ringman et al., 2004). Although most people show improvements after stroke, many do not completely recover (Coupar et al., 2012; Hendricks, van Limbeek, Geurts, & Zwarts, 2002; Karnath, Rennig, Johannsen, & Rorden, 2011; Lazar et al., 2010; Prabhakaran et al., 2007; Rengachary et al., 2011). Herein we operationally define *recovery of function* the improvement of impairment in one or multiple domains over time. Understanding the determinants of behavioral recovery is essential for investigating the underlying neuronal mechanisms and for the development of effective treatments and improving treatment outcomes.

In the past, deficits and their recovery have often been investigated in isolation in selected patient groups with a similar deficit or stroke topography. These studies have not allowed a clear identification of those aspects of recovery that are domain specific versus those that generalize across the different behavioral domains. Although most recovery is thought to occur within the first three months post stroke (Duncan et al., 1994; Kotila et al., 1984; Skilbeck et al., 1983; Stone, Patel, Greenwood, & Halligan, 1992b; Wade et al., 1985), variations between domains have been suggested. Several studies of recovery within individual domains have reported that cognitive deficits continue to recover after 3 months post-stroke (eg aphasia: Kertesz & McCabe, 1977; neglect: Levine et al., 1986), but a study by Hier and colleagues (Hier, Mondlock, & Caplan, 1983b) showed the opposite, suggesting instead that recovery of neglect, prosopagnosia and anosagnosia was faster than recovery for motor deficits and hemianopia.

Some factors that may be important for recovery can only be studied using broad, multi-domain assessments of behavior. For example, the presence of a deficit in one domain may affect the recovery of another deficit (Nijboer, Kollen, & Kwakkel, 2014) and deficits of higher cognitive functions influence the length of hospital stay, outpatient care, therapies and functional status at discharge (Galski, Bruno, Zorowitz, & Walker, 1993). Robertson and colleagues (Robertson, Ridgeway, Greenfield, & Parr, 1997) suggested that since learning is central for recovery and attention is essential for learning, attention deficits should impair recovery of other behavioral deficits.

To address the similarities and differences in recovery patterns between domains the current study collected longitudinal data in a large, clinically relevant population of first-time stroke patients. Behavior in multiple domains (motor, attention, spatial memory, verbal memory, language) was collected using a large behavioral battery, allowing for comparisons of the recovery of different domains within the same patients. By *clinically relevant* we mean that the sample is representative of the population in the urban and suburban area of a large US city (St. Louis, MO) as sampled from the group of patients who are admitted with a diagnosis of stroke at the busiest stroke unit in the region (Barnes-Jewish Hospital at Washington University School of Medicine). Patients were prospectively enrolled based on any persistent neurological deficit at discharge, and the sample matched the source population on most demographic, socio-economic, and clinical variables (as previously described in Corbetta et al., 2015). Patients were enrolled independently of stroke topography and severity, allowing for the generalization of results at the population level. As studies have suggested that the majority of recovery occurs within 3 months post-stroke, data was collected at 2 weeks, 3 months and 1 year after stroke. The measures within

each domain were chosen to create a detailed overview of the deficits in each patient and decrease measure-specific noise and bias.

The primary goal of the study was to describe robust patterns of recovery across the behavioral phenotypes to capture changes in behavior over time post-stroke. This is ground knowledge to design novel intervention or monitor the efficacy of current clinical treatments. Robust behavioral phenotypes in different domains of functions (sensory, motor, cognitive) are also essential for correlation with neurological mechanisms of recovery. For instance, in recent work we have shown that behavioral deficits are highly correlated across domains of function, yet the severity of deficits in different domains is correlated with different mechanisms of injury. While motor and sensory (visual) deficits are more strongly predicted by lesion topography than cognitive deficits (memory, attention) (Corbetta et al., 2015); the latter are more strongly predicted by disruption of synchronized activity across multiple networks (Siegel et al., in revision). Therefore, it is possible that the recovery of sensory-motor or cognitive deficits may depend on different mechanisms that have a different temporal trajectory, or more or less influenced by structural or cognitive variables that are related in turn to the neural organization of those functions. For instance, sensory and motor functions may be more hardwired, while cognitive functions may be mediated by more flexible and distributed neural mechanisms. Finally, this work is important for evaluating the influence of variables that have been shown in previous studies to affect recovery, including: 1) demographic variables (e.g. education, age (Kertesz & McCabe, 1977; Pedersen et al., 1995)), 2) magnitude of acute deficit (Duncan, Goldstein, Matchar, Divine, & Feussner, 1992), 3) the presence of deficits in multiple domains (Nijboer et al., 2014) 4) time post-stroke (Duncan et al., 1994; Kotila et al., 1984; Skilbeck et al., 1983; Wade et al., 1985), 5) therapy (Sunderland et al., 1992), and 6) lesion volume and

topography (Lövblad et al., 1997). The weight of these variables on recovery is of considerable clinical interest in light of the growing need of accurate prognosis for treatment and resource planning in an ever more challenging health environment.

2.3 Methods

2.3.1 Subjects

Subjects (n = 172) were prospectively recruited, of whom 132 met post-enrollment inclusion criteria and 103 and 88 subjects returned for the subsequent measurements. Figure 2.1 shows the diagram of enrollment (CONSORT) for this study. All studies were approved by the Washington University Institutional Review Board. This cohort was used in a previous study on sub-acute deficits, not including any longitudinal data (Corbetta et al., 2015).

Inclusion Criteria. (1) Age 18 or greater. No upper age limit. (2) First symptomatic stroke, ischemic or hemorrhagic. (3) Up to two lacunes, clinically silent, less than 15 mm in size on CT scan. (4) Clinical evidence of motor, language, attention, visual, or memory deficits based on neurological examination. (5) Time of enrollment: < 2 weeks from stroke onset. (6) Awake, alert, and capable of participating in research.

Exclusion criteria. (1) Previous stroke based on clinical imaging. (2) Multifocal strokes. (3) Inability to maintain wakefulness in the course of testing. (4) Presence of other neurological, psychiatric or medical conditions that preclude active participation in research and/or may alter the interpretation of the behavioral/imaging studies (e.g., dementia, schizophrenia), or limit life expectancy to less than 1 year (e.g., cancer or congestive heart failure class IV). (5) Report of claustrophobia or metal object in body.

A healthy control group (n = 31) was matched with the study sample for age, gender, and years of education. A larger control group (n = 1,209) was selected from a clinical database (n = 6,260) using the same inclusion/exclusion criteria. Stroke patients and controls provided informed consent according to procedures approved by the Washington University Institutional Review Board.

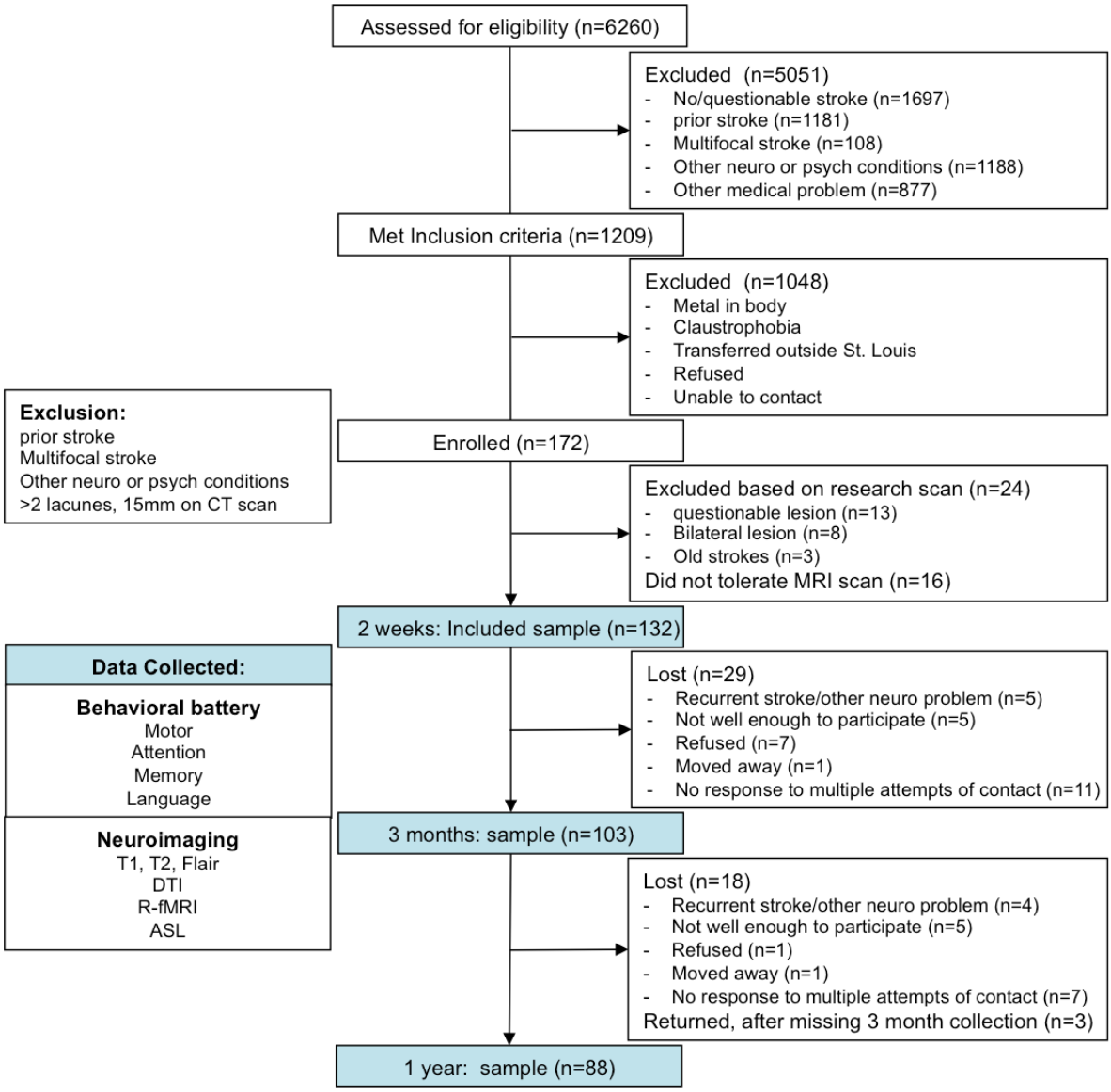

Figure 2.1 Enrollment Flowchart

2.3.2 Behavioral assessment

Subjects were tested approximately two weeks after their stroke, and again at 3 months and 12 months post stroke. These time points were selected based on previous observations that most deficits recover within 3 months, while some studies suggest additional recovery up to 1 year. Data was collected twice in the healthy controls, 3 months apart.

A comprehensive battery of 44 behavioral tests across four behavioral domains, language, memory, motor and attention as well as visual perimetry information were collected (table 2.1, and Corbetta et al., 2015). These domains were chosen to represent a wide range of the most commonly identified deficits in people after a stroke. Within each domain a range of measures was chosen to represent the different components of that domain, e.g. auditory comprehension, speech production, reading both at single word and sentence level for language; proximal/distal upper and lower extremity measures of strength, coordination, dexterity, function for motor including, for instance, separate tests for reaching or grasping; spatial as well as verbal memory, including short- and long-term, encoding, recognition, and retrieval; and, spatial and non spatial aspects of visual attention.

Table 2.1 Behavioral measures

Domain	Test	Score recorded	Function tested
Motor	AROM: Shoulder flexion	L&R Shoulder flexion	Range of motion (ROM)
	AROM: Wrist extension	L&R Wrist extension	
	AROM Lower extremity	L&R Ankle dorsiflection	
	Jaram dynamometer	L&R Grip strength	Strength
	Nine hole peg test	L&R Hand pegs/sec	Dexterity
	ARAT	L&R Total	Dexterity and ROM
	Motricity index	L&R Lower extremity total	Strength
	Timed walk	Index of timed walk + FIM walk item	Walking
	FIM Walk Item		Walking
Language	BDAE: Comprehension	Basic word discrimination	Comprehension
		Commands	
		Complex ideational material	
	BDAE: Expression	Boston naming short form	production, semantic
	BDAE Reading	Oral reading of sentences	comprehension
		Comprehension of oral reading of sentences	
	Experimental measures	Nonword reading	production, phonological
		Stem completion	
	Verbal fluency	Animal naming test	production, semantic
Memory	BVMT	Immediate total recall T-score	Spatial, recall
		Delayed recall T-score	
		Delayed recall percent retained	
		Delayed recognition discrimination index	Spatial, recognition
	HVLT	Immediate total recall T-score	Verbal, recall
		Delayed recall T-score	
		Delayed recall percent retained	
		Delayed recognition discrimination index	Verbal, recognition
	Spatial span	Span forward	Spatial, recall
		Span backward	
Attention	Posner orienting task, reaction time	Visual field effect (left-right)	Visual field
		Overall performance	Average
		Validity effect (valid-invalid)	Shifting
		Disengagement effect [(LI-LV)-RI-RV)]	
	Posner orienting task, accuracy	Visual field effect (left-right)	Visual field
		Overall performance	Average
		Validity effect (valid-invalid)	Shifting
		Disengagement effect [(LI-LV)-RI-RV)]	
	BIT star cancellarion	Center of cancellation	Visual field
	Mesulam unstructured symbol cancellation	Center of cancellation	

2.3.3 Lesions

Lesions were manually segmented using Analyze biomedical imaging software (wwww.mayo.edu) by inspecting all structural images (MP-RAGE, T2 and FLAIR) in atlas space and distinguishing the lesion from healthy tissue, CSF and surrounding vasogenic edema. Each lesion segmentation was independently checked by two neurologists (Alex Carter, MD and MC), and was manually classified as subcortical, cortical, cortical & subcortical, brainstem or cerebellar.

2.3.4 Behavioral data reduction

A principal component analysis (PCA) with oblique rotation was applied to the 2 week behavioral data collected in the stroke patients within each of the domains in order to reduce the number of variables to a smaller number of meaningful components (Corbetta et al., 2015). Oblique rotation was used, because we did not want to force these components to be orthogonal. Components had to satisfy two criteria: (1) the eigenvalues had to be > 1; (2) the percentage of variance accounted for had to be > 10%. This procedure resulted in one component for language, one for motor and two for memory (verbal, spatial). The structure within the attention domain was less clear. After inspection of different results, a three-component solution was chosen. The first component, which included visual field and general attention measures, was used as our attention measure. Therefore, the behavioral recovery analysis was based on five factors: Language, Motor (independent of side), Verbal Memory, Spatial Memory, and Attention.

For motor, a separate PCA analysis was also done in which behavior was coded by left and right limb rather than ipsilesional and contralesional limb, resulting in a two component solution with one factor for left limb deficits and one for right limb deficits. This two factor solution was only used in the following higher order PCA analysis. A higher-order principal

component analysis was conducted on the components that resulted from the within-domain analyses, language, verbal memory, spatial memory, the 3 attention components and the left and right limb motor components. Since the correlations between the resulting components were low, and the results were similar for oblique and orthogonal rotations, we choose to use orthogonal rotations, which are easier to interpret.

The distributions of some of the variables were not normal and could not be made normal through transformation. To ensure this is not influencing our results we compared the correlations between the variables using a Pearson's correlation and a rank order correlation (Spearman's Rho) and we replicated the within domain principal component analyses using rank-order correlation (Spearman's Rho), resulting in similar components.

To ensure comparability, the component scores for subsequent time points and for the age matched controls were generated by normalizing these scores based on the sub-acute values and then re-creating the component scores using the weights generated by the principal component analysis on the 2 week scores. Each of the components, at each of the time-points, was z-scored based on the first measurement of the healthy control group. This made the scores meaningful with 0 being healthy (the mean of the controls) and the measured values being in standard deviations away from this mean. This procedure allowed for comparisons across timepoints and behavioral domains.

2.3.5 Recovery analyses

The amount of recovery depends on the initial deficit. To take this into account a recovery ratio was calculated for each patient for each behavioral domain. The recovery ration is calculated by dividing the total recovery (chronic score – acute score) by the maximum recovery

possible (control average – acute deficit) (Figure 3B). These values were averaged the ratio across patients to determine the recovery ratio for each of the behavioral domains.

Patients with a score 2 standard deviations below the mean of controls were identified as having a deficit, while patients with "no deficit" had scores within 2 standard deviations of healthy controls. For each behavioral factor, we conducted an ANOVA across the three timepoints comparing patients that did vs. did not have a deficit at the sub-acute stage. If the interaction was significant, post-hoc testing was used to test contrasts involving particular timepoints and groups. This analysis tested the hypothesis that recovery in different domains have a similar or different time course, i.e. specifically whether cognitive deficits recover more slowly than sensory motor deficits.

An ANOVA was conducted on the behavior scores in all patients, with the three timepoints and five behavioral domains as independent variables to test our hypothesis that the timecourse of recovery was similar for each of the different behavioral factors. To confirm that the relationship between the different behavioral deficits stayed the same over time, the correlations between the domains for both the acute and 3 month scores as well as change scores were calculated. To further investigate the similarity over time of the relationships between domains, we conducted the higher order principal component analysis on the 3 and 12 months post stroke measurements as well as on the acute timepoint.

2.3.6 Prediction of chronic behavior

Chronic scores were predicted using lesion size, age, education and hours of therapy. A linear regression model with lesion size, age, education and hours of rehabilitation (including physical, occupational, speech) as independent variables was used to predict the 3 or 12 month scores of each of the 5 domains (language, attention, motor, verbal memory and spatial memory).

Each patients' 2 week score for the domain was also included in the model since acute scores have been shown to be excellent predictors of recovery. For each of these predictors the beta weight and its significance in the model was determined to test our hypothesis that different predictors are important for different behavioral variables.

To provide low-dimensional information about lesion location for deficit recovery models we conducted a PCA on lesion locations across all subjects (Corbetta et al., 2015). This was done for all lesions in their respective hemisphere for the prediction of behavioral domains that are scored independent of lesionside (aphasia, verbal and spatial memory) and for all lesions flipped to the left for the behavioral measures that were scored based on lesion side (attention and motor). The loadings on each of the included components for each subject were added to the prediction model that included age, lesionsize, education, therapy and the 2 week score. The number of components was limited to the number of components that explained more than 60% of the variance. If the addition of these components to the model was significant, this suggests that the lesion location is important in the prediction of the outcome for that behavioral domain. For the domains in which the addition was significant the beta values for each lesion component were used to create a weighted image of the components to visualize the lesion locations of importance.

2.3.7 Effects of multiple deficits

We hypothesized that the presence of multiple deficits would negatively influence a patient's recovery. To test this hypothesis, a moderation analysis was used to investigate if (after controlling for age, lesion size and education) the presence of more deficits interacted with the amount of recovery. In a moderation analysis the hypothesis that a variable (the moderator) changes the effect of a predictor(s) on outcome is tested as in an interaction. If the moderator

effect is significant (i.e. interaction), then the moderator variable affects the amount of recovery between the 2 week and chronic time-point. In patients that had a behavioral score for each of the domains (language, spatial memory, verbal memory, visual field attention and motor; N=43), the number of deficits was added as a moderator variable in the regression analysis, allowing us to test the hypothesis that having multiple deficits decreases the amount of recovery.

2.4 Results

Subjects (n = 172) with a first symptomatic stroke anywhere in the brain and clinical evidence of any neurological impairment were prospectively recruited, with n = 132 meeting post-enrollment inclusion. Subjects were tested approximately two weeks after their stroke (sub-acute, M=13.6 days, SD=4.8), and again at 3 months (M=112.0, SD=16.9) and 12 months (M=392.2, SD=52.4). A neurobehavioral battery and structural (T1/T2, Flair), functional (resting state), diffusion, and perfusion magnetic resonance imaging (MRI) scans were collected at each timepoint. This report concentrates on the longitudinal neurobehavioral assessment. Forty patients were excluded because of an inability to tolerate scans, excessive lacunae, artifacts, prior strokes or unidentifiable strokes. Of the final sample of 132 sub-acute patients (mean age 54, standard deviation 11, range 19-83; 71 males; 68 left side lesions), 101 returned for a 3-month data point and 77 returned at 1 year (See table 2.1 for demographics and figure 2.1 for enrollment information).

Table 2.2 Demographics of study sample, controls and source population (CRRG)

Variables	Stroke (n=132)	Controls (n=31)	CRRG (n=2341)
Age (years)	53 ± 10	55 ± 12	61±15 *
Women	61 (46%)	16 (52%)	1133 (48%)
Right handed	121 (92%)	29 (94%)	-

Left hemisphere lesion	68 (52%)	-	948/1725 (55%)
Lesion type			
Ischemic	102 (82%)	-	1778 (76%)
Hemorrhagic	22 (18%)	-	569 (24%
TPA	15 (11%)	-	227/2337 (10%)
Race			*
White	45 (34%)	10 (32%)	1419 (61%)
Black or African American	87 (66%)	20 (65%)	866 (37%)
Other	0 (0%)	1 (3%)	56 (2%)
Years of education	13.2 ± 2.6	13.6 ± 2.6	12.6 ± 2.8*
Risk factors			
Hypertension	92 (70%)	8 (26%)*	1709 (73%)
Diabetes Mellitus	41 (31%)	5 (16%)	462 (20%)*
CAD	11 (8%)	2 (6%)	512 (22%)*
Smoking	62 (47%)	13 (42%)	855 (37%)*
Hours of Therapy	94 ± 143	-	
Lesionsize in cm3	34.6 ± 46.9	-	

*significantly different from stroke sample ($p<0.05$)

Lesion volume varied greatly over patients (ranging from 0.03 cm^3 to 82.97 cm^3, with a mean volume of 10.15 cm^3, standard deviation 13.94 cm^3). Figure 2.2 shows the overlap of lesion topography across patients, with the highest overlap found in subcortical regions.

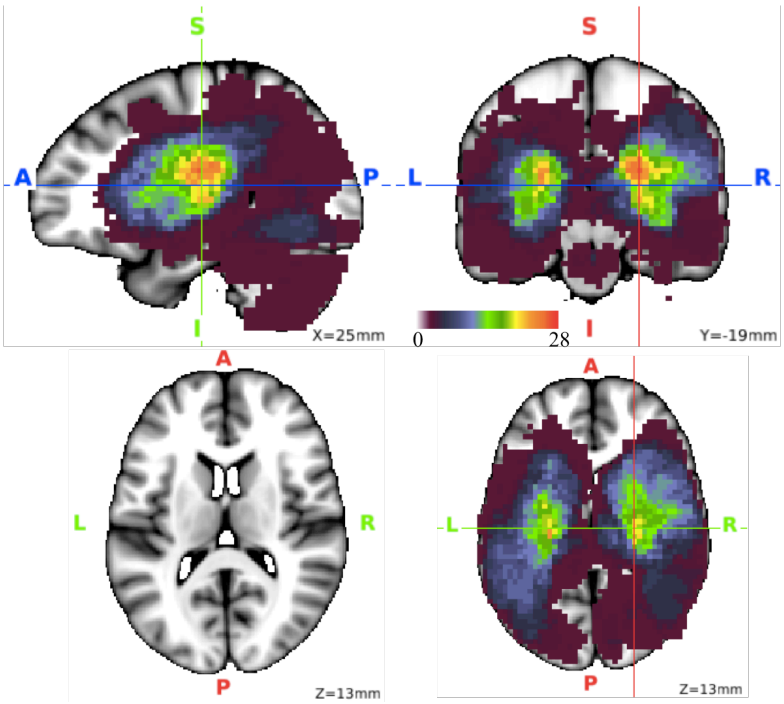

Figure 2.2 Lesion overlap of the sample of 132 stroke patients.
The maximum overlap is 28 lesions and can be seen in sub-cortical white matter and basal ganglia regions.

2.4.1 Demographics and Lesion variables

Within the age matched control group there was a significant correlation between age and education and between age/education and race, i.e. African-American controls were younger and had fewer years of education than Caucasian controls; see Table 2.3 for correlations between demographic variables, therapy and lesion size). In the stroke group African-Americans were less educated, but there was no age difference with White controls. Stroke patients with larger lesions tended to receive more therapy, yet there is no relationship between hours of therapy and race or education. Interestingly, patients varied in the amount of white matter and lacunes, which were correlated ($r=-.362$, $p<0.001$), but did not correlate with lesion size or overall severity.

There were meaningful correlations with overall severity as captured by the NIHSS scores. Patients with more severe deficits had larger lesions and received more therapy and the

NIHSS scores were strongly correlated with language ($r=-0.532$, $p<0.01$), verbal memory ($r=-0.273$, $p<0.01$), spatial memory ($r=-0.539$, $p<0.01$), attention ($r=-0.415$, $p=0.010$, and motor ($r=-0.852$, $p<0.01$).

Robust correlations were found of the demographics with individual domain component scores. Language and memory (spatial in particular) scores were related both to age and education: younger and more educated patients showed better scores both at 2 weeks and 3 months, and were worse in African-American patients.

When considering recovery, there was a strong relationship between acute impairment and amount of improvement (change scores from acute to 3 months; Figure 2.3A), indicating that analyses of recovery must control for this factor. After regressing acute deficits, the only significant correlation occurred between language improvement and both lesion size and education, and between spatial memory improvement and lesion size (Table 2.3).

Finally, the number of lacunes correlated with both language scores at 2 weeks ($r=-0.182$,$p=0.045$) and 3 months ($r=-0.223$,$p=0.028$), but did not correlate with improvement.

Table 2.3 Correlations of demographics and behavioral measures

Controls (n=31)	**Age**	**Education (years)**	**Therapy (hours)**	**Lesion size**	**Lacunae (#)**	**WM Disease**	**Race (ttest)**
Age		0.305*	-	-			t(27)=-3.14**
Education (years)			-	-			t(27)=-3.03**
Stroke (n=132)							
Age		-0.103	0.156	0.064	0.069	0.229**	t(130)=-0.47
Education (years)			-0.010	-0.152	-0.165	-0.006	t(159)=-2.53*
Therapy (hours)				0.476**	0.043	-0.054	t(130)=0.95

Lesion size					-0.102	-0.147	t(130)=0.47
Lacunae (#)						0.362**	t(130)=1.02
WM Disease							t(130)=-0.37
NIHSS							
Total	0.098	-0.048	0.588**	0.588**	-0.070	-0.040	T(105)=0.56
Acute (2 weeks) post stroke							
Language	-0.167	0.173	-0.523**	-0.447**	-0.183*	-0.047	t(122)=-1.61
Verbal Memory	-0.262**	0.305**	-0.277**	-0.125	-0.106	-0.036	t(95)=-1.57
Spatial Memory	-0.298**	0.342**	-0.434**	-0.426**	0.008	-0.078	t(95)=-2.80**
Attention	-0.055	0.161	-0.197*	-0.343**	0.088	0.143	t(99)=-1.50
Motor	-0.111	0.030	-0.531**	-0.419**	0.172	0.094	t(116)=-1.10
3 Months							
Language	-0.153	0.329**	-0.553**	-0.553**	-0.223*	-0.051	t(95)=-2.48**
Verbal Memory	-0.316**	0.250*	-0.295**	-0.178	-0.153	-0.011	t(83)=-1.65
Spatial Memory	-0.173	0.331**	-0.112	-0.092	-0.168	-0.193	t(83)=-2.99**
Attention	-0.188	0.104	-0.411**	-0.418**	-0.002	0.133	t(88)=-1.25
Motor	-0.175	-0.005	-0.555**	-0.286**	0.087	0.051	t(95)=-0.49
Improvement (Acute to 3 months)							
Language	0.133	0.027	0.351**	0.220*	0.116	0.040	t(94)=0.37
Verbal Memory	-0.045	-0.031	0.007	0.059	0.041	0.078	t(74)=0.35
Spatial Memory	0.084	0.036	0.300**	0.455**	-0.149	-0.132	t(74)=1.33
Attention	-0.009	-0.166	0.283*	0.276*	-0.147	-0.129	t(77)=1.19
Motor	0.014	0.084	0.293**	0.181	-0.055	-0.076	t(87)=0.23
Improvement (Acute to 3 months, acute regressed out)							
Language	-0.019	0.283**	-0.158	0.283**	-0.082	-0.007	t(94)=-1.57
Verbal Memory	-0.216	0.089	-0.142	-0.027	-0.009	0.072	t(74)=-0.55

Spatial Memory	-0.064	0.218	0.154	0.235*	-0.188	-0.211	t(74)=-0.74
Attention	-0.208	-0.026	-0.119	-0.087	-0.088	-0.023	t(77)=0.09
Motor	-0.097	0.079	-0.035	-0.031	0.004	-0.030	t(87)=-0.19

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed)

2.4.2 Recovery of behavioral deficits within each domain

The magnitude of recovery showed some differences across domains, but these differences were not significant ($F(4,75)=0.316$, ns). The average recovery ratio was similar for language, spatial memory and attention (0.62, 0.70, 0.70 respectively), but motor recovery was lower, 0.51 (0.58 if the 8 patients with complete hemiparesis are removed) and verbal memory showed even less recovery with an average ratio of 0.38 (Figure 2.3C). When the magnitude of recovery was quantified based on the number of patients who return within the normal range (2SD of healthy controls) we found a similar pattern, with motor showing less recovered patients than spatial memory and attention (figure 2.3D).

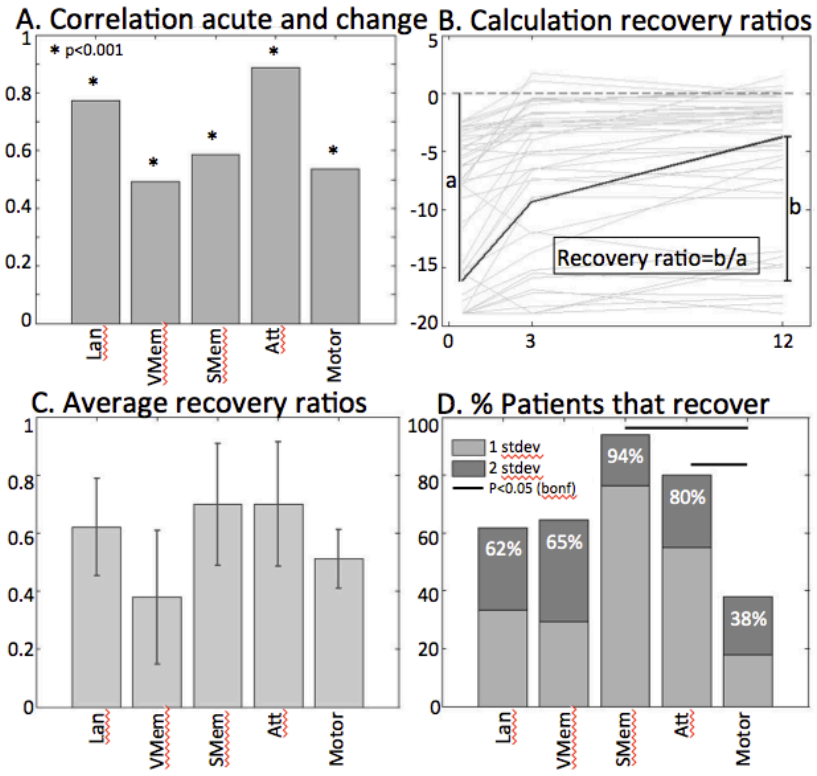

Figure 2.3 Recovery Ratios.
The correlations between acute and change scores (A) are high. The recovery ratio is calculated as change/total possible recovery (B) for each subject and averaged (C). A different measure of recovery is the number of patients with a deficit that recover to normal levels by 1 year (D). Lan: Language, V Mem: Verbal Memory, S Mem: Spatial Memory, Att: Attention.

The timecourse of recovery, however, was similar across domains. For each of the domains there was a significant interaction between patients with and without a deficit over time, due to an increase in the performance of the deficit patients within the first three months towards the level of the no-deficit patients (figure 2.4). Between 3 months and 1 year only patients with language and motor deficits showed significant improvements, but the magnitude of this improvement was small. The differences between the deficit and no deficit groups remained significant for each of the domains at 1 year post stroke (figure 2.4).

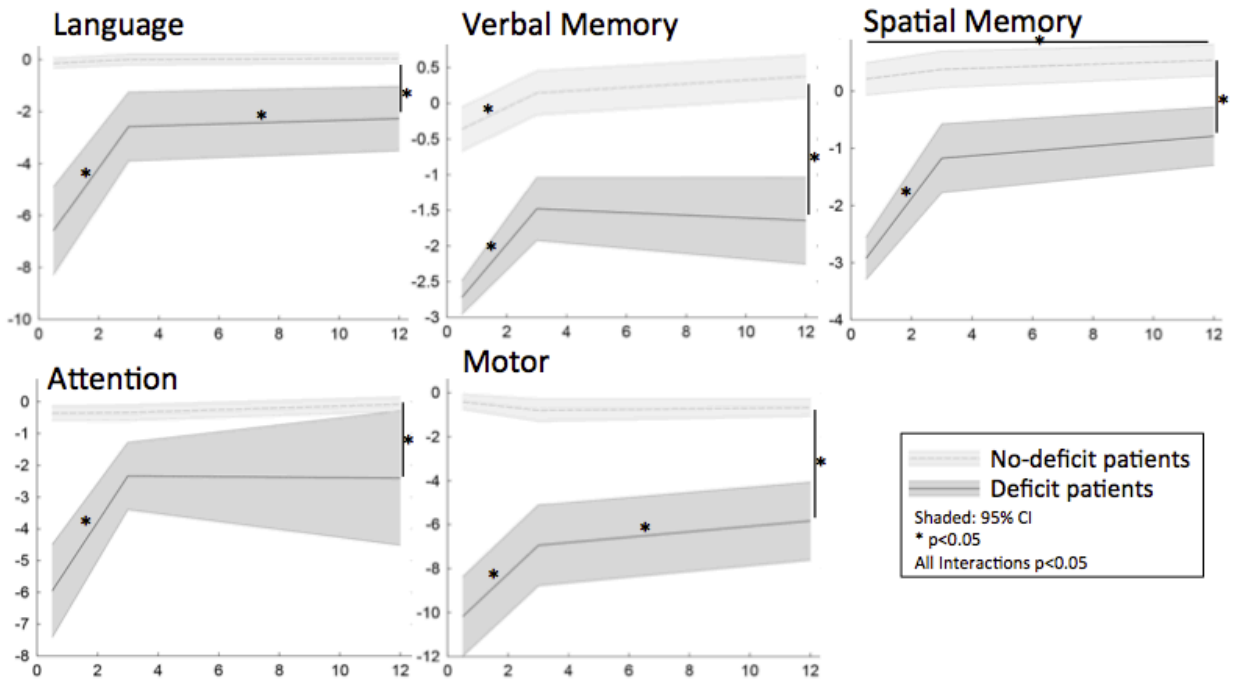

Figure 2.4 Recovery patterns of the behavioral domains.
The recovery over the three timepoints is depicted for patients that did and did not have a deficit 2 weeks post stroke. Interactions between the two groups over time are significant for each domain.

The similarity of the recovery curves across behavioral domains was statistically supported by a repeated measures ANOVA on the behavioral factor scores with time (sub-acute, 3 months, 1 year) and behavioral domain (language, verbal memory, spatial memory, attention, motor) as factors. The ANOVA identified a main effect of time ($p<0.001$), but no interaction between the different domains, indicating that the timecourse and extent of recovery was similar across the whole patient group for the different domains.

A cross-domain correlation analysis was done to explore more subtle differences in the recovery patterns between patients. Two weeks post stroke, several clusters of correlations between domains are evident (Figure 2.5A), namely one involving language, spatial- and verbal memory and one involving spatial memory, motor and attention ($p<0.05$, multiple comparison corrected). At 3 months the first cluster was still present, with correlations between language, verbal and spatial memory, as was the correlation between attention and motor (Figure 2.5B).

The raw change scores (3 months – 2 weeks) correlated for verbal memory and motor as well as spatial memory and attention, suggesting similar change patterns. However, to directly compare the correlation values between the two timepoints, the correlations were Fisher z transformed. The only correlation change that was significant was between language and spatial memory ($p=0.01$, uncorrected). This result was corroborated by correlations of the recovery ratios (improvement/acute severity, which removes the effects of the acute deficit), shown in figure 2.5C, which also were only significant between language and spatial memory ($P<0.05$, multiple comparison corrected). This analysis shows that there are the two behavioral clusters of impairment that recover in tune, one related to language and memory, and one related to motor and attention. While the timecourse is similar, across patients these two clusters were consistent at each time point, as well as in terms of change scores (at least for language and spatial memory).

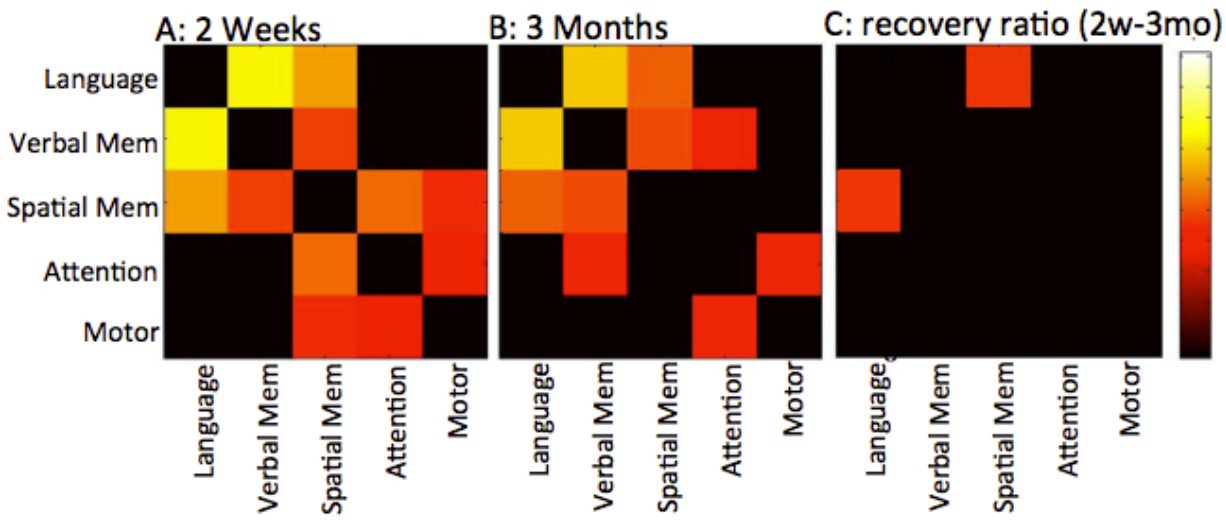

Figure 2.5 Correlations between domains.
The correlations between the domains at 2 weeks (A), 3 months (B) and for the recovery ratio of the recovery between 2 weeks and 3 months (C).

To further support the finding that the relationships between the different domains were consistent over time we applied a second order principal component across the factors at each of

the three time-points. We chose to include a wider range of components, including the two extra attention components as well as the two-component (left and right limb) solution for the motor domain (Corbetta et al., 2015). The relationship between the variables showed similar patterns of covariance among the behavioral domains chronically as was seen acutely (Table 2.4). This result again supports the overall conclusion that there are two/three clusters of behavioral impairment, and that they are maintained as patient recover.

Table 2.4 Higher order PCAs for the different measurement timepoints.

2 weeks	Variance expl: 69%		
Rotated Component Matrix			
	Component		
	1	2	3
Language	.880		
Memory: Verbal	.892		
Memory: Spatial	.583	.528	
Motor: Left Limb		.773	
Motor: Right Limb			.849
Attention: Visual Field		.841	
Attention: Shifting			.693
Attention: Average		.636	.308

3 Months	Variance expl: 65%		
Rotated Component Matrix			
	Component		
	1	2	3
Language	.901		
Memory: Verbal	.859		
Memory: Spatial	.697		
Motor: Left Limb		.825	
Motor: Right Limb			.855
Attention: Visual Field		.743	
Attention: Shifting		-.326	.456
Attention: Average		.644	.490

1 year	Variance expl: 62%		
Rotated Component Matrix			
	Component		
	1	2	3
Language	.897		
Memory: Verbal	.559		.505
Memory: Spatial	.768		
Motor: Left Limb		.726	
Motor: Right Limb			.722
Attention: Visual Field		.648	
Attention: Shifting			.700
Attention: Average		.745	-.326

2.4.3 Prediction of chronic behavior

For each behavioral domain a regression analysis was used to predict the chronic behavioral scores (table 2.5). The predictors included were lesion size, age, education, therapy and the sub-acute behavioral score. Each domain model was significant ($p<0.001$) and explained over 40% of the variance of the 3 month scores (table 2.5). The sub-acute score was the most consistent and strongest predictor in each model ($p<0.001$). Additionally, lesion size and education were significant predictors of chronic language scores and lesion size of spatial memory scores (Table 2.5). Interestingly age and hours of therapy were not significant in any of the models.

Table 2.5 Prediction of 3 month scores

Prediction of 3 Months	**Standardized β**				
Model 1	**Language**	**Verbal Mem**	**Spatial Mem**	**Motor**	**Attention**

Lesion size	-0.196**	0.033	0.232*	0.036	-0.061
Age	-0.023	-0.139	-0.055	-0.044	-0.159
Education (years)	0.182**	0.084	0.157	0.041	-0.009
Therapy (hours)	-0.074	-0.114	0.010	-0.049	-0.081
Sub-Acute score	0.614**	0.710**	0.687**	0.856**	0.580**
Adjusted R^2	**0.689****	**0.637****	**0.457****	**0.767****	**0.417****
Model 2					
Lesion size	0.020	0.053	-0.205	-0.128	0.260
Age	0.007	-0.122	-0.059	-0.037	-0.076
Education (years)	0.168**	0.141	0.203*	0.026	-0.057
Therapy (hours)	-0.061	-0.170	-0.087	-0.163	-0.096
Sub-Acute score	0.425**	0.689**	0.665**	0.773**	0.579**
Lesion PC 1	0.087	0.163*	0.710	0.085	-0.397
Lesion PC 2	-0.257	-0.062	0.485	0.055	-0.250
Lesion PC 3	-0.314**	-0.213	0.002	0.093	0.091
Lesion PC 4	0.066	0.043*	0.475	0.063	-0.250*
Lesion PC 5	-0.075	0.077	-0.119	0.059	-0.072
Lesion PC 6	-0.027	-0.164	-0.138	0.030	-0.060
Lesion PC 7	0.109*	0.062	-0.186	-0.064	0.103
Lesion PC 8	0.098	0.074	0.280	-0.195**	0.142
Lesion PC 9	0.021	-0.084	-0.010		
Lesion PC 10	-0.012	0.191	-0.199		
Lesion PC 11	0.058	0.299*	0.286		
R^2 Change	**0.133****	**0.072**	**0.098**	**0.040***	**0.135***

*P<0.05, **P<0.005

Next, we examined the influence of lesion topography. To provide low-dimensional information about lesion location for deficit recovery models we conducted a PCA on lesion locations across all subjects. Eleven components were identified for lesions independent of lesionside, and eight when all lesions were flipped to the left side (for motor and attention scores which are scored independent of lesion side). Prediction of language recovery improved significantly with addition of the unflipped lesion variable ($P<0.001$), with a significant β for components three and seven (Table 2.5). The weighted lesion image (Figure 2.6) shows that better outcomes are predicted with left anterior cortical and subcortical lesions and worse outcomes with left temporo-parietal-occipital white matter lesions. Lesion location did not add to the models for memory. The model using the flipped lesions were added to the models for predicting motor and attention deficits and were significantly improved prediction for both motor and attention models ($P<0.05$). For motor deficits a significant β was found for the 8^{th} component. The lesions predicted worse outcomes (after the inclusion of sub-acute deficits as a predictor) for patients with subcortical damage. For attention deficits a significant β was found for component 4 and the weighted lesions predicted worse recovery for patients with lateral and posterior white matter damage.

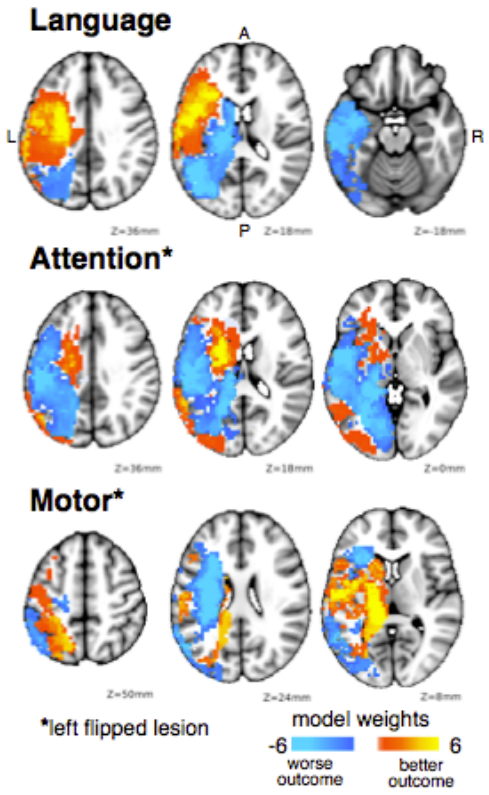

Figure 2.6 Lesion locations significantly adding to the prediction of chronic scores.
Weighted maps of the top 60% lesion PC maps that significantly improve the prediction of chronic behavior above and beyond using age, lesionsize, therapy, education and the 2 week score.

2.4.4 Effects of multiple deficits

Because many patients had multiple deficits (Figure 2.7), we examined whether the recovery of one domain was influenced by deficits in other domains. The effects of education, age, hours of therapy and lesion size (which correlates with number of deficits, r=0.22, p=0.012) were added as covariates of no interest. For each patient, we entered the number of deficits as a moderator variable in a regression analysis that used the sub-acute scores to predict the 3 mo scores. The number of deficits showed a significant negative interaction with attention (t(46)=-2.76, p=0.008) and a marginal negative interaction with spatial memory (t(48)=-1.71, p=0.094), indicating that having multiple deficits negatively influences the recovery of these deficits. There was also a significant main effect of the number of deficits on language (t(48)=-2.52, p=0.015),

indicating that the number of deficits negatively influenced the magnitude of the acute and chronic language deficit, but not the recovery of the language deficit. Interestingly, the presence of multiple deficits only affected the cognitive domains. No interaction effects were seen for motor deficits.

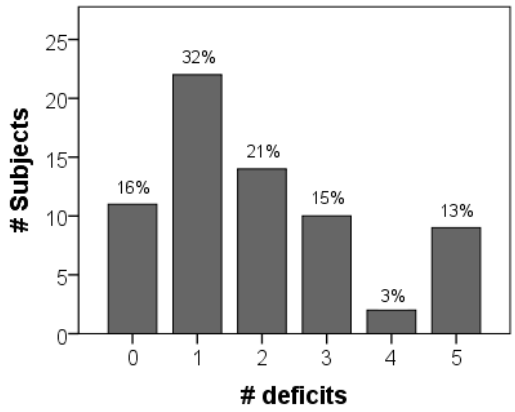

Figure 2.7 Histogram of number of deficits.
Histogram of the number of patients for each number of deficits (> 2 SD below controls) showing that many patients have more than 1 deficit. Only patients that have scores on all domains (n=67).

2.5 Discussion

We investigated the recovery of behavioral deficits in multiple domains during the first year post stroke in a large sample of 132 stroke patients. All domains showed a similar timecourse of recovery with most recovery occurring within the first three months post-stroke. In each domain, chronic scores were best predicted by sub-acute scores. After accounting for this effect, however, domain-specific effects of education, lesion size, and number of other deficits were observed. More years of education predicted higher chronic language scores, larger lesion sizes predicted lower chronic language and spatial memory scores, and more deficits in other domains predicted poorer recovery of attention, and lower acute and chronic language scores.

2.5.1 Recovery patterns

On average patients recover from approximately 70% of their language, spatial memory, and motor deficits, as previously reported for motor and language deficits (Coupar et al., 2012; Lazar et al., 2010; Prabhakaran et al., 2007), but for verbal memory the recovery ratio is only about 38%, yet these differences are not significant. The amount of recovery (change in performance score from acute to 3 months) strongly depends on the initial deficit as evidenced by the high correlation between the sub-acute scores and the change scores. We clearly show that many patients do not fully recover and that most of the recovery occurs within the first 3 months, with only very minor changes after this. Within this large sample the rate and magnitude of recovery is similar across the domains, suggesting that differences found between different studies that focus on specific lesions and/or behavioral deficits could be related to the patient or measure selection. Importantly, our results do not show any differences between the recovery curves of the different domains or the overall pattern of covariance of deficits at the chronic stage as compared to the acute stage.

This similar pattern of recovery across behavioral domains suggests common underlying mechanism. A large part of the initial spontaneous recovery of behavior, purely dependent on time after stroke in the first few weeks (Kwakkel et al., 2006), is driven by the biology which is similar in all strokes (Kwakkel et al., 2006; Warraich & Kleim, 2010). Initially there is a resolution of edema, inflammation and diaschisis accompanied by cell repair (Wieloch & Nikolich, 2006), allowing for normalization of function of regions around and remote to the lesion. In the perilesional area however, neuroplasticity subsequently allows for local changes through neurogenesis, axonal sprouting, dendritic plasticity, angiogenesis and increased excitability (Buma, Kwakkel, & Ramsey, 2013; Carmichael, 2003; Nudo, 2011). These local changes are optimized through synaptogenesis and synaptic strengthening as well as pruning

(long term potentiation and de-potentiation) (T. H. Murphy & Corbett, 2009; Stroemer, Kent, & Hulsebosch, 1995). The exact timelines of these processes are not completely clear as the majority of the studies have been done in mice and rat. In those species these processes are present in the first days to weeks (Ge, Yang, Hsu, Ming, & Song, 2007), which is thought to be comparable to approximately 3 months in humans.

Spontaneous recovery however does not explain all variance (Kwakkel et al., 2006) and enriched environments, training and experience can increase neural plasticity during the first few months post stroke (Biernaskie, 2004; Buma et al., 2013; Dromerick et al., 2015; Krakauer, Carmichael, Corbett, & Wittenberg, 2012; Winship & Murphy, 2009; Zeiler & Krakauer, 2013). As mentioned in the introduction, multiple studies have found some changes after this three month period (Hier, Mondlock, & Caplan, 1983a; Kertesz & McCabe, 1977; Levine et al., 1986). Interestingly, the rate of recovery between 3 and 12 months is not related to the initial recovery rate within the first few months (Cloutman, Newhart, Davis, Heidler-Gary, & Hillis, 2009), supporting the idea that different mechanisms are at play. This later stage of recovery could reflect behavioral adaptations or compensation rather than restitution of the original behavior (Kwakkel, Kollen, & Lindeman, 2004; Nudo, 2011; Zeiler & Krakauer, 2013). These environmental and compensatory mechanisms would likely be domain specific.

We indeed show that in addition to domain-independent recovery, improvement over time of different deficits was influenced by different variables (domain-specific).

2.5.2 Recovery of motor deficits

Motor function relies on a system that precisely projects to the spinal cord motor goals and intentions. It is therefore more hierarchical and more hard-wired than cognitive domains. Accordingly, the initial deficit is a very strong predictor of outcome, and its severity is not

influenced by the presence of other deficits. Moreover, motor deficits tend to be strongly associated with structural damage of motor regions/pathways (Corbetta et al., 2015). In fact the location of structural damage, and degree of damage of the corticospinal tract (Jayaram et al., 2012; Schaechter et al., 2009; Stinear et al., 2012; Carter et al., 2011), more strongly predict motor impairment than functional connectivity of the motor cortex (Carter et al., 2011; Siegel et al., in revision). Here we show for the first time that subcortical lesions including the central white matter, thus corticospinal tract, are associated with weaker motor recovery as compared to cortical lesion (Fig. 2.6).

2.5.3 Aphasia recovery

The language system is less hierarchical than motor, with multiple regions interacting and integrating information. However, in contrast to other cognitive functions in which the location of lesion is not an important predictor, in language the location of the lesion accounts for significant amount of variance (~60%) at the sub-acute stage (Siegel et al., in revision). Here we show that subcortical lesions affecting the white matter in temporoparietal cortex improve the prediction of language recovery.

Interestingly, education is another variable that explains significant variance in the severity of aphasia post-stroke, but also adds to the prediction of outcome when the amount of initial deficit is controlled for with more years of education leading to better outcomes. Higher education leads to better recovery of language and outcome. Connor and colleagues (Connor, Obler, Tocco, Fitzpatrick, & Albert, 2001) found a similar relationship between aphasia severity and education at 4 months post stroke.

The link between education and aphasia severity and its recovery/outcome has several possible explanations. One possibility is related to the concept of ‘cognitive reserve’ (González-

Fernández et al., 2011; Perneczky, Diehl-Schmid, Pohl, Drzezga, & Kurz, 2007). The concept, akin to the concept of 'processing resources', refers to the innate or acquired ability to have higher cognitive resources that can be mobilized toward a task or for recuperating the effects of an injury. Cognitive reserve is supposedly higher in people with higher education (Staff, Murray, Deary, & Whalley, 2004). A larger reserve is thought to let people compensate more effectively by maintaining cognitive efficiency after different forms of grey or white matter damage (Bartrés-Faz & Arenaza-Urquijo, 2011). The neural mechanisms underlying cognitive reserves are unknown, but it has been suggested that they reflect differences in neural efficiency and capacity (Stern, 2006), which in turn could positively influence brain plasticity (reviewed in Nithianantharajah & Hannan, 2009). Another explanation is that education leads to the expansion of language selective representations, which can in turn have more redudancy after insult.

2.5.4 Recovery of memory deficits and neglect

Attention and memory are cognitive domains that involve interactions between widely distributed cortical regions and networks (Mesulam, 1990; Corbetta & Shulman, 2002). In previous work we have shown that the severity of attention, and even more memory deficits, are most strongly dependent on functional interactions between brain regions/networks as measured with resting state fMRI than structural damage (Corbetta et al., 2015; Siegel et al. in revision). Here we show that recovery of attention and spatial memory also depend on 'interactions' as they seem to be uniquely influenced by the number of 'other' deficits. Interestingly, as in prior work, the recovery/outcome of attention depends on the integrity of dorsal white matter regions that contains fiber tracts like the superior longitudinal fasciculus (SLF) and the forceps major (FM), that have both been linked to persistent neglect (Karnath, Rennig, Johannsen, & Rorden,

2011; Lunven et al., 2015). The SLF is the main white matter bundle connecting the parietal to the frontal cortex, whereas the FM connects the bilateral occipital and superior parietal lobules. These white matter tracts connect many different regions that are part of the attention system, suggesting that damage to this region disrupts widespread communication. In our study damage to dorsal and ventral white matter significantly negatively contribute to neglect outcome. In contrast cortical lesions tend to recover better. There was no effect of the lesion type or location on the recovery of memory. Memory is a cognitive function that can be divided according to different classifications (e.g. short and long term, verbal and spatial, declarative and procedural), each requiring the interaction of multiple, widely distributed regions, for processing, storage and maintenance of information, yet there is no well-defined single memory network, making specific lesion locations for both the deficit and recovery quite unclear.

Chapter 3: Normalization of network connectivity in hemi-spatial neglect recovery

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3.1 Abstract

Objective: We recently reported that spatial and non-spatial attention deficits in stroke patients with hemi-spatial neglect are correlated at 2 weeks post-onset with widespread alterations of inter-hemispheric and intra-hemispheric functional connectivity (FC) measured with resting state fMRI (R-fMRI) across multiple brain networks. The mechanisms underlying neglect recovery are largely unknown. In this study we test the hypothesis that recovery of hemi-spatial neglect correlates with a return of network connectivity toward a normal pattern, herein defined as '*network normalization'*.

Methods: We measured attention deficits with a neuropsychological battery, and FC in a large cohort of stroke patients at, on average, 2 weeks (n=99), 3 months (n=77), and 12 (n=64) months post onset. The relationship between behavioral improvement and changes in FC was analyzed both in terms of a priori regions and networks known to be abnormal sub-acutely, and in a data driven manner.

Results: Attention deficit recovery was mostly complete by 3 months, and was significantly correlated with a normalization of abnormal FC across many networks. Improvement of attention deficits, independent of initial severity, was correlated with improvements of previously depressed inter-hemispheric FC across attention, sensory, and motor networks, and a restoration of the normal anti-correlation between dorsal attention/motor regions and default-mode/frontoparietal regions, particularly in the damaged hemisphere.

Interpretation: These results demonstrate that abnormal network connectivity in hemi-spatial neglect is behaviorally relevant. A return toward normal network interactions, and presumably optimal information processing, is therefore a systems level mechanism that is associated with improvements of attention over time after focal injury.

3.2 Introduction

Hemi-spatial neglect is a syndrome affecting approximately 20-30% of stroke patients (Buxbaum et al., 2004; Pedersen, Jørgensen, Nakayama, Raaschou, & Olsen, 1997). Recovery occurs mostly within the first three months post-stroke (Buxbaum et al., 2004; Rengachary et al., 2011). The amount of recovery depends on the severity of the acute deficit (Stone, Patel, & Greenwood, 1992a) and is incomplete in most cases (Rengachary et al., 2011; Ringman et al., 2004).

Anatomically, neglect can be caused by damage to multiple cortical and subcortical regions (He et al., 2007; Mort et al., 2003; Ringman et al., 2004). Neuroimaging studies have related more severe attention deficits in hemi-spatial neglect to a relative imbalance of task-evoked activity between the two hemispheres and a loss of inter-hemispheric correlations (Baldassarre et al., 2014; Carter et al., 2010; Corbetta et al., 2005; Corbetta & Shulman, 2011; He et al., 2007), as well as damage to intra-hemispheric fronto-parietal connections (De Schotten et al., 2014; Verdon et al., 2010). These results support the idea that this syndrome is associated with widespread disruption of cortical activity (Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007), especially in networks related to attention that can manifest abnormal physiology even when structurally intact (reviewed in Corbetta & Shulman, 2011).

In contrast, the mechanisms underlying neglect recovery are largely unknown. Hypothetical mechanisms of recovery include remapping, i.e. a shift of function to neighboring maps; normalization of activity, i.e. a return of the pre-stroke state of activity within/across regions; or reorganization, i.e. a compensatory shift of activity to different regions/networks. Different physiological correlates have been reported in small case series including: normalization of regional cerebral perfusion (Vallar et al., 1988, n=8 patients); shift of activity

back to the damaged hemisphere (Pizzamiglio et al., 1998, n=3); rebalancing of stimulus-evoked activity between left and right hemisphere regions for attention and visual perception (Corbetta et al., 2005, n=11); normalization of depressed inter-hemispheric correlations in the dorsal (DAN) and ventral (VAN) attention networks (He et al., 2007, n=11). Importantly, a direct correlation with behavioral improvement was measured only in some studies (Carter et al., 2010; Corbetta et al., 2005; He et al., 2007)**.**

In a recent large study (Baldassarre et al., 2014, n=84) we confirmed that attention deficits typical of neglect were strongly associated with widespread, multi-network disruption of inter-hemispheric functional connectivity (FC) measured with resting state (R-fMRI). In contrast to previous work(He et al., 2007), we found that the disruption of inter-hemispheric FC did not involve only dorsal and ventral attention regions, but also extended to auditory, motor, and visual networks. In addition, we found that intra-hemispheric attention and motor regions became positively correlated with regions of the fronto-parietal (FPN) and default mode (DMN) networks, which are negatively correlated or uncorrelated in the intact brain. This pattern accounted for over 40% of the variance in behavior-to-FC correlation.

Based on (Baldassarre et al., 2014), we hypothesized that recovery of neglect would be associated with a normalization of the abnormal patterns of network connectivity demonstrated at the sub-acute stage. Normalization of network connectivity, while not excluding other explanations, would be consistent with previous work showing normalization of task-evoked patterns of activation in motor, language, and attention regions (Rehme et al., 2012; Ward et al., 2003), and network theories suggesting that the normal architecture of brain connections, structural and functional, is the best compromise between metabolic demands and computational efficiency (Bullmore & Sporns, 2012).

To test this hypothesis we examined neglect recovery in a large cohort of first time stroke individuals (n=77) with an extensive neuropsychological battery and multiple neuroimaging methods. We defined a behavioral measure of neglect that captured spatial and non-spatial impairments and assessed this measure at, on average, 1-2 weeks, 3, and 12 months post onset. We related behavioral recovery to FC changes in networks that have been found in our prior work to be associated with neglect (Baldassarre et al., 2014). Finally, we conducted a data-driven analysis across all brain regions to show that patterns related to recovery, accounting for large fractions of variance in the behavior-to-FC correlation, correspond to those found sub-acutely.

3.3 Methods

3.3.1 Participants

172 subjects were recruited. All participants provided informed consent with Washington University Institutional Review Board oversight. The inclusion criteria were (1) Clinical diagnosis of stroke; (2) Persistent stroke symptom(s) at hospital discharge; (3) Awake, alert, and able to complete study tasks; (4) Age 18 or older. Exclusion criteria were: (1) Previous stroke; (2) Multifocal stroke; (3) severe psychiatric condition; (4) Dementia; (5) other neurological disorder; (6) Brain injury; (7) Other diagnosis with a life expectancy less than 1 year; (8) Premorbid functional disability as measured by a Modified Rankin score of 2 or higher; (9) Claustrophobia; (10) Implanted metal precluding 3T MRI. 132 met the post-enrollment inclusion criteria (5 could not tolerate scanning, 8 had a bilateral lesion, 12 had no detectable lesion, 11 had incomplete data collection, and 4 for other reasons). Of these 132, 99 patients had a full set of neuro-imaging and attention battery measures collected. 77 of the 99 patients returned for their 3-month data collection and this set of 77 patients is used in the following analyses (Table

3.1). 64 of these patients were retested one-year post stroke. Twenty-two patients with attention and imaging data at the sub-acute stage did not return for their 3 month data collection and therefore were not included in the analyses. There was no difference in attention scores between the patients that did and did not return for their 3 month visit (t(97(=-1.45,p=0.15)) or 1 year visit (t(75)=0.05,p=0.96).

Information about medications was recorded at the time of enrollment, but no attempt was made to control what medications subjects used in the course of the study.

The same behavioral and imaging measures were collected twice, 3 months apart, in 31 age- and education-matched controls.

Table 3.1 Demographics

Variables	Stroke (n=77)	Controls (n=31)	Stroke vs Controls
Age (years)	53 ± 10	55 ± 12	ns
Women	35 (45%)	16 (52%)	ns
Right handed	68 (88%)	29 (94%)	ns
Left hemisphere lesion	39 (51%)	-	-
Lesion type			-
Ischemic	65 (84%)	-	
Hemorrhagic	8 (10%)	-	
Other	4 (5%)	-	
TPA	10 (13%)	-	-
Race			ns
White	24 (31%)	10 (32%)	
Black or African American	53 (69%)	20 (65%)	
Other	0 (0%)	1 (3%)	

Years of education	13.1 ± 2.5	13.6 ± 2.6	ns
Risk factors			
Hypertension	51 (66%)	8 (26%)	p<0.01
Diabetes Mellitus	27 (35%)	5 (16%)	ns
CAD	7 (9%)	2 (6%)	ns
Smoking	40 (52%)	13 (42%)	ns
Depression	5 (6%)	1 (3%)	ns
Measurement (days (range))			
Sub-Acute	13 (6-27)	0	
3 Month	111 (81-181)	96 (66-155)	ns
1 year (n=64)	392 (349-749)	-	

3.3.2 Behavioral testing

Subjects were tested approximately two weeks after their stroke (sub-acute, M=12.8 days, SD=4.49), and again at 3 months (M=111.1, SD=17.5) and 12 months (M=392, SD=52.6). These time points were selected based on previous observations that sensory-motor deficits recover within 3 months, while cognitive deficits take longer up to 1 year. A comprehensive battery of behavioral tests was used to assess motor, memory, attention, language and visual deficits (fully described in Corbetta et al., 2015). Core deficits of hemi-spatial neglect were assessed by the Posner Visual Orienting Task (Posner, 1980) and two cancellation tasks, the Mesulam Unstructured Symbol Cancellation Test (Mesulam, 1985) and the Behavioral Inattention Test (Wilson, Cockburn, & Halligan, 1987). These tests were selected based on their high accuracy in detecting hemi-spatial neglect even at the chronic stage as reported in our previous study (Rengachary, d'Avossa, Sapir, Shulman, & Corbetta, 2009) and are described in more detail in (Baldassarre et al., 2014).

3.3.3 Measures of spatial attention

The Posner task yields 4 measures: (1) Overall Performance (performance averaged for stimuli in both visual fields and both cueing conditions); (2) Visual Field Bias (difference between ipsi- and contra-lesional targets); (3) Validity Effect (difference between valid and invalid targets); and, (4) Disengagement Effect (difference of validity effect between ipsi- and contra-lesional targets). Each measure is computed for both accuracy and reaction time (RT). For the Mesulam and BIT we calculated the center of cancellation (CoC), which corresponds to the lateralized center of mass of hits for stimuli positioned in the contra-lesional and ipsi-lesional side of stimulus array (Rorden & Karnath, 2010).

A principal component analysis was applied to the sub-acute data across the 10 scores to reduce noise and the number of variables (table 3.2, fully described in Corbetta et al (Corbetta et al., 2015)). Since the first component explained the largest component of the variance (29%), and encompassed both a bias in processing lateralized visual stimuli (spatial attention) and an overall impairment in speed and accuracy (non-spatial attention), it was chosen for further analyses. Hereafter Factor 1 will be defined as the Visual Attention Deficit (VAD) as in (Baldassarre et al., 2014).

Table 3.2 PCA on attention measures

Attention IC PCA	**Variance explained: 59%**		
Rotated Component Matrix			
	Component		
	1	2	3
Posner Visual Field effect: RT	.581		
Posner Visual Field effect: Acc	.818		

Posner Validity effect: RT			.743
Posner Validity effect: Acc		.850	
Posner Disengagement effect: RT			.823
Posner Disengagement effect: Acc		-.786	
Posner Average: RT	.542		
Posner Average: Acc	-.760		
Mesulam CoC	.692		-.349
BIT CoC	.403	-.384	-.311
Variance explained (%)	29	16	13
Component Correlations			
2	-0.11		
3	-0.05	0.13	

3.3.4 Functional magnetic resonance imaging (fMRI) scanning and data preprocessing

Scanning was performed on a Siemens 3T Tim-Trio scanner at the Washington University School of Medicine in St. Louis. Each subject was scanned at the sub-acute timepoint, 3 months, and 1 year. Structural scans included: (1) a sagittal MP-RAGE T1-weighted image (2) a transverse turbo spin-echo T2-weighted image and, (3) a sagittal FLAIR (fluid attenuated inversion recovery) (for more detail see (Baldassarre et al., 2014)). 7 functional scans were acquired with a gradient echo EPI sequence (TR=2000 msec, TE=27 msec, 32 contiguous 4 mm slices, 4x4 in-plane resolution, 128 volumes each) for a total acquisition time of ~30 minutes. Resting-state functional MRI scans were obtained while subjects were asked to lie still and fixate a central cross (resting fMRI or R-fMRI). Eye closures were monitored with a video camera.

The fMRI data was preprocessed and motion contaminated frames were removed as in Baldassarre et al ((Baldassarre et al., 2014)).

3.3.5 Lesions

The lesions were manually segmented using Analyze biomedical imaging software (wwww.mayo.edu) by inspecting all structural images (the MP-RAGE, T2 and FLAIR) in atlas space and distinguishing the lesion from healthy tissue, CSF and surrounding vasogenic edema. This was evaluated in all three directions (slices of 2 mm thickness), and was independently double-checked by two neurologists (Alex Carter MD, and MC).

3.3.6 Resting state functional connectivity networks and mapping

169 seed regions of interest (ROIs) were identified as described in (Baldassarre et al., 2014) in a group of healthy controls, separated into 10 networks (Hacker et al., 2013) (see appendix 1 for list of ROIs). Correlations (Pearson r) between the time courses of each of the nodes and all voxels in the rest of the brain were calculated, creating full brain, voxel-wise functional connectivity (FC) maps for each ROI, for each subject, for each of the two sessions. ROIs overlapping with the lesion and lesioned voxels in the voxel-wise maps were excluded from all analyses. The Pearson correlations were Fisher z-transformed, generating z(r) maps, for further analyses.

3.3.7 Functional connectivity - behavior correlations

Based on previous work indicating the importance of a region in posterior parietal cortex, part of the DAN, for the recovery of neglect (He et al., 2007), we first explored the relationship between neglect and FC patterns from a single region of the DAN (right medial IPS or RmIPS) to the rest of the brain, using methods previously employed (Baldassarre et al., 2012)·(Baldassarre et al., 2014). Difference FC maps were created for each subject by

subtracting the 2-weeks maps from the 3-month maps. These maps were subsequently correlated across subjects with the improvement in VAD scores (3 months minus sub-acute). Since behavioral recovery is highly correlated with the degree of sub-acute deficit, the same procedure was repeated using change behavior scores while regressing out the sub-acute deficit scores, examining changes specific to recovery.

Second, to quantify FC recovery effects at the network level, we focused on the two most robust FC correlates of sub-acute attention deficits, namely a decrement of inter-hemispheric FC in DAN, DMN, visual, auditory, and motor networks, and an increase of intra-hemispheric FC between DMN and DAN, motor, visual, and auditory networks. (Baldassarre et al., 2014). Two-factor ANOVAs with Group (N+,N-) and Time (2 weeks, 3 months, 12 months) as factors were conducted on inter-hemispheric FC scores averaged across the homotopic ROI pairs of each network (see Table S1 for ROI list). Similar ANOVAs were conducted on intra-hemispheric FC scores, which consisted of averaged ROI to ROI FC of each DMN ROI vs. each ROI of the other networks.

Finally, to examine the relationship between recovery of attention deficits and FC across the whole brain in a data-driven manner, we employed a procedure introduced in (Baldassarre et al., 2014). A separate analysis was conducted for each hemisphere involving 91 nodes consisting of the nodes belonging to the hemisphere and the nodes falling on the midline. The overarching logic of the analysis was to 1) generate voxel-wise functional connectivity maps for each node for the sub-acute and three-month time-points, which are then subtracted to create change FC maps, 2) compute the correlation across subjects between these maps and behavioral change scores, 3) determine through a data reduction operation with PCA whether these voxel-wise functional connectivity:behavior correlation maps were consistent across nodes, 4) select the

most representative nodes and networks, i.e. those yielding the maps with the highest loadings on the first principal component of the PCA, and 5) display the average functional connectivity:behavior maps from the most representative nodes. The Pearson r-values were transformed into t-scores and then Z-scores over the population. These maps were then thresholded ($|Z|>2.25$, $P<0.05$, cluster-size of 53 voxels) to only retain the statistically significant clusters, accounting for multiple comparisons. This method is explained in greater detail in Baldassarre et al (Baldassarre et al., 2014).

3.3.8 Effects of Lag

Siegel et al (Siegel, Snyder, Ramsey, Shulman, & Corbetta, 2015) developed methods for detecting hemodynamic lags in undamaged tissue within the same vascular distribution as a stroke, and found significant hemodynamic lags in ~30% of sub-acute stroke subjects, which were associated with decrements of FC and with behavioral deficits. However, significant FC:behavior correlations persisted after the effect of lag was removed. Given this prior work, we performed a control analysis to determine if changes of inter-hemispheric FC in the DAN in relation to changes in VAD scores were affected by lags.

For each of the ROIs of the 9 homotopic DAN pairs, the hemodynamic lag was determined as follows: lags in the contralesional hemisphere were assumed to be zero and lags in the ipsilesional hemisphere were defined as the latency of the peak in the cross-correlation between any region and its contralesional homologue. Lags were computed both at 2 weeks and 3 months. For each ROI pair the change in pairwise lag between sub-acute and chronic timepoints was regressed from the change in FC score. The correlation between behavioral improvement (VAD change score) and the average FC residuals across all 9 pairs was calculated.

3.4 Results

3.4.1 Lesion topography

The lesion distribution in the 77 stroke subjects shows the highest overlap subcortically, involving the central white matter and basal ganglia, while cortically the lesions involved mainly the middle cerebral artery distribution (Figure 1A). The mean lesion volume was 20.5 cm^3 (SD±23.4).

Based on the acute (admission) NIH stroke scale scores, the majority of patients (90%) had motor deficits, 21% had aphasia and 17% had hemi-spatial neglect. At the time of our first data collection 7% of the patients were classified as having neglect according to the NIH stroke scale, but our more sensitive neuropsychological battery classified 32% (N=25/77, N+) of the subjects with hemi-spatial neglect at ~2 weeks post stroke, based on a VAD score that was 2 standard deviations below the average score of healthy age matched controls, and 68% (52/77, N-) without neglect.

The lesion distributions for the two groups are shown in Figure 1B (N+: 7 left hemisphere damaged (LHD), 18 right hemisphere damaged (RHD); N-: 32 LHD, 20 RHD). The mean lesion volume of patients with neglect was larger (N+=34.8 cm^3 versus N-=11.3 cm^3, $t(75)=4.28, p<0.001$). For analyses relating behavior to FC analyses, lesion and fMRI maps were flipped in LHD patients so that the right hemisphere was always the damaged hemisphere (Fig.1C).

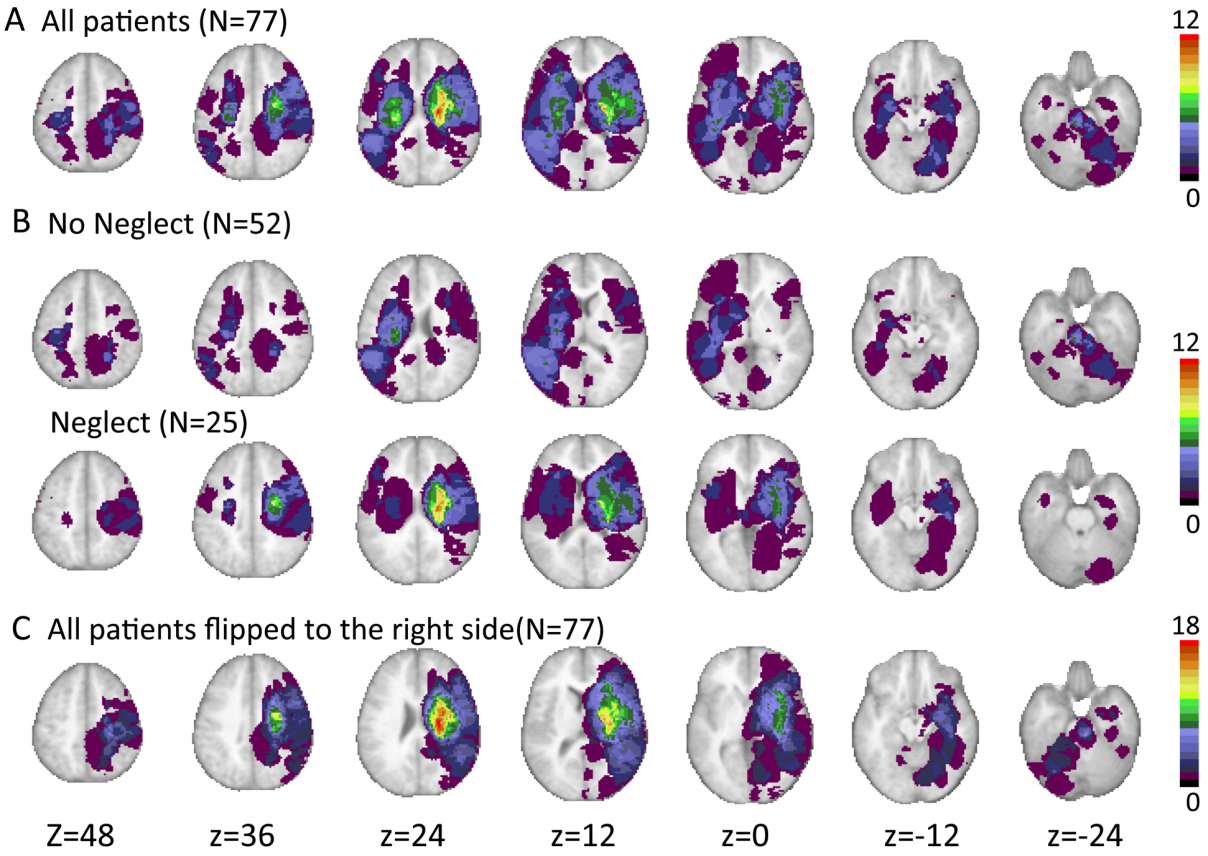

Figure 3.1 Topography of stroke. Lesion overlap image in atlas space for all patients (A), patients without and with neglect (B) and all patients, with lesions flipped to the right side (C). The color scale indicates the number of subjects with lesions at each voxel.

3.4.2 Measures of hemi-spatial neglect and its recovery

The frequency distribution of VAD scores in control and stroke subjects is shown in Figure 2A. The distribution of VAD scores was significantly lower in patients than controls sub-acutely ($t(105)=-3.00$, $p=0.003$), at 3 months ($t(105)=-2.71$, $p=0.008$), and on average got closer to normal at 1-year post stroke ($t(92)=-1.40$, $p=0.165$). There was no correlation between the time of testing post stroke and the severity of neglect (sub-acute: $r=0.06$; $p=0.59$, 3 months: $r=0.124$, $p=0.28$; 1 year: $r=0.054$, $p=0.67$).

The recovery of attention was evidenced by an increase of VAD scores over time (Fig.2A). Based on the 2 SD below control cut-off score, neglect was observed in 25 patients (32%) at ~2 weeks, 14 patients (18%) at ~3 months, and 7 (11%) patients at ~1 year, respectively

(inset Fig.2A). Most patients, however, remained impaired as indexed by VAD scores greater than 1 SD below the control mean (84% at 3 months, and 55% at 12 months).

We compared VAD scores in N+ and N- groups (Fig.2B) using an ANOVA with time (sub-acute, 3 and 12 months) and group (N+, N-) as factors. A significant interaction ($F(2,61)=32.3$, $p<0.001$) indicated recovery in the N+ group. In the first 3 months there was approximately a 59% improvement from the initial deficit ($p<0.001$), but no significant improvement occurred between 3 months and one-year (Fig.2B). N+ maintained significant deficits as compared to the N- group at 12 months ($p=0.002$, Fig.2B). Performance in the healthy control group and N- patients was not significantly different and was stable across time points, indicating good inter-session reliability. There was no effect of having received TPA (n=10) on the recovery of attention deficits ($F(2,61)=0.36$,$p=0.70$).

Finally, we examined whether sub-acute impairment on attention scores and their recovery correlated with acute impairment or recovery of other domains (language, left or right motor function, spatial or verbal memory). At the sub-acute stage, VAD scores correlated with left limb motor ($r=0.51$, $P<0.001$) and spatial memory ($r=0.52$, $p<0.001$) scores (Fig.2C). However, the improvement of VAD scores within the first three months correlated with an improvement in spatial memory ($r=0.47$, $P<0.001$), but not left motor function, language, or verbal memory (Fig.2D). These behavioral results indicate that recovery of attention is more related to recovery of spatial memory than motor or language. This issue is relevant with respect to the functional connectivity correlates of attention recovery, and their specificity, as discussed later on.

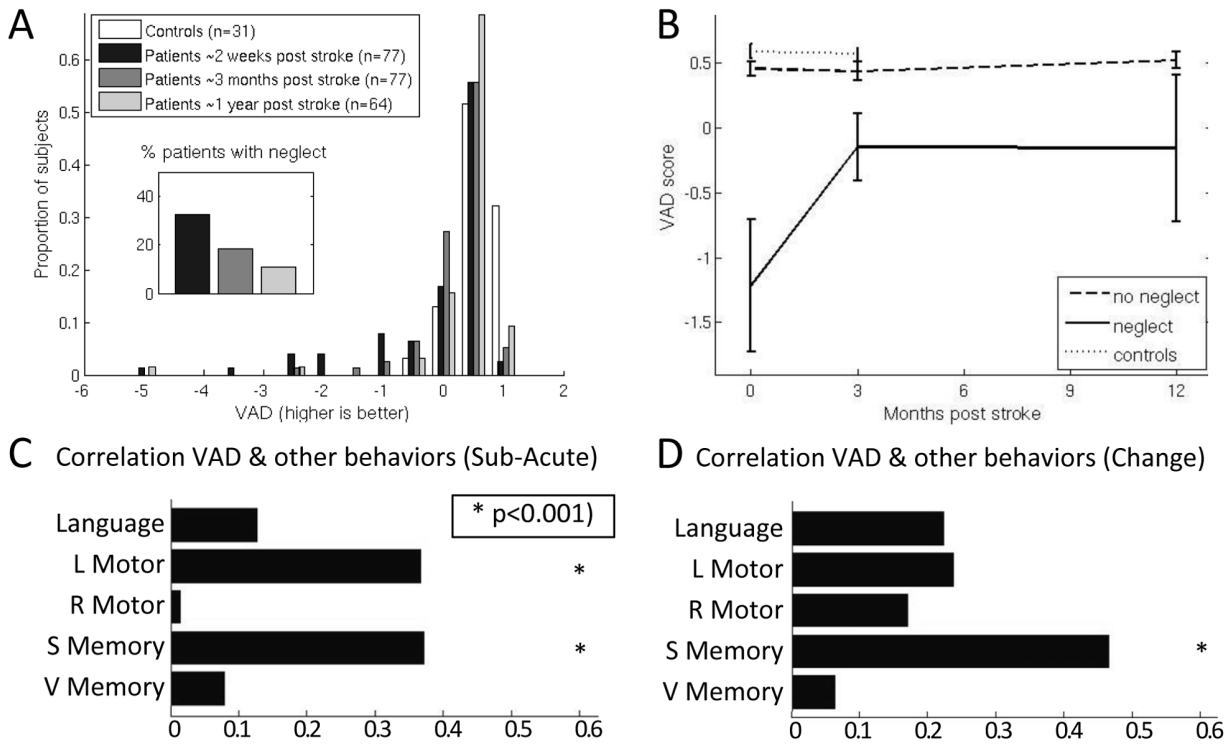

Figure 3.2 Neglect and recovery. The distribution of neglect scores in controls and in patients sub-acutely and 3 months and 1 year post stroke (A). Visual attention deficit (VAD) scores over time for patients with and without sub-acute deficits and controls (B). Correlation of VAD scores with scores in other behavioral domains at the sub-acute timepoint (C). Correlation of the improvement (3 months minus sub-acute) of VAD scores with the improvement of scores in other behavioral domains (D).

3.4.3 Functional connectivity and neglect recovery: R parietal to/from rest of the brain

We performed three different analyses to test the hypothesis that a normalization of the pattern of FC abnormality sub-acutely after stroke (a decrement of inter-hemispheric correlations and abnormal increase of FC within each hemisphere, as seen in (Baldassarre et al., 2014)) was associated with recovery from neglect. The first analysis related neglect recovery to the whole-brain FC of the structurally normal R mIPS (indicated by a star symbol in Fig.3), which has been implicated in the pathophysiology of neglect (Baldassarre et al., 2014; Carter et al., 2010; Corbetta et al., 2005; He et al., 2007).

We confirmed that sub-acutely neglect was associated with widespread decrements of inter-hemispheric FC between R medial intraparietal sulcus (mIPS) and left hemisphere regions of the DAN, visual, auditory, and motor networks (Fig.3B, green/blue regions). As an example the scatter plot indicates that decreases of FC between right and left mIPS were significantly related to VAD (Fig.3A). Moreover, there was a positive correlation between the strength of FC between R mIPS and large swaths of the right hemisphere corresponding to the DMN and FPN (yellow/orange regions), with stronger connectivity corresponding to stronger deficits (Fig.3C). In both cases the effects were stronger in right hemisphere patients.

Figures 3D-F show the relationship between the change (3 months – sub-acute) in FC from R mIPS and the improvement (3 months – sub-acute) of VAD scores. Figure 3E indicates that an increment of inter-hemispheric FC between R mIPS was positively correlated with an improvement of attention (Fig.3D). Similarly a decrement of intra-hemispheric FC also correlated with an improvement of attention (Fig.3F). Notably, the topography of FC:behavior correlation at the sub-acute timepoint is similar to the inverse of the topography of change ($r = -0.78$).

However, these correlations may be biased by the level of initial severity given the severity of attention deficits sub-acutely is strongly related to the degree of improvement from sub-acute to 3 months ($r=-0.89$, $P<0.001$). Hence we re-computed the FC:behavior change maps after regressing out the sub-acute VAD scores. This procedure decreased the strength of the FC:behavior change correlation, but the correlation remained highly significant, both in terms of improvement in inter-hemispheric correlation as well as in a return of the normal negative correlation between right mIPS and the DMN (e.g. supramarginal gyrus)(Figs.3G-I).

Overall, the first set of analyses indicated that the improvement of attention deficits was linked to an increase in inter-hemispheric connectivity across DAN, visual, auditory, and motor networks, and an increase of negative correlation between DAN and DMN/FPN regions. Both results correspond to a normalization of physiological patterns of functional connectivity toward that observed in healthy subjects.

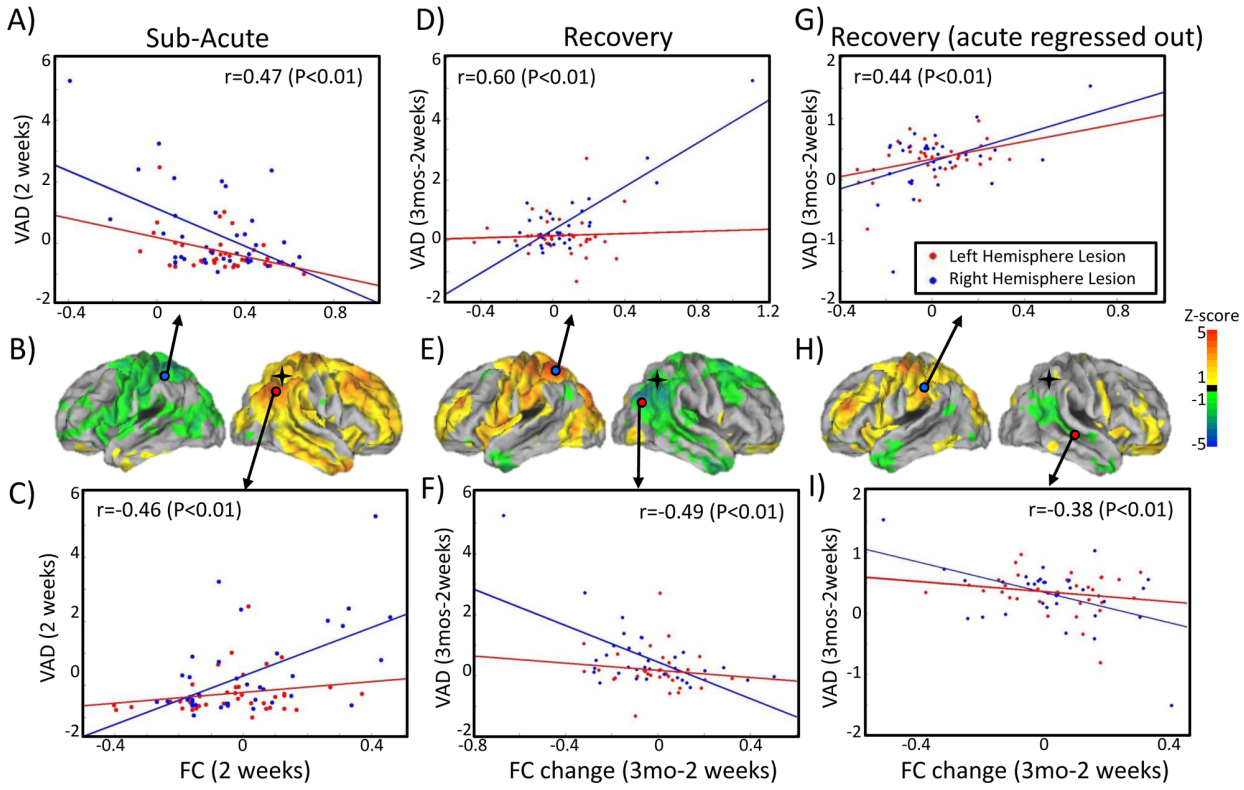

Figure 3.3 Right medial IPS functional connectivity (FC) with the rest of the brain in relation to behavior. FC by behavior maps: sub-acutely post stroke (B), recovery (E) and recovery with sub-acute behavior regressed out (H). Red/yellow indicates a positive correlation and green/blue a negative correlation. Scatter plot of FC versus behavior for an inter-hemispheric region (A, D, G) and intra-hemispheric region (C, F, I) highlights the correlations. Each dot is a patient and blue indicates patients with right hemisphere lesions, red with left hemisphere lesions.

3.4.4 Functional connectivity and neglect recovery: DAN, DMN, and other networks

While the first analysis focused on FC to/from mIPS to the rest of the brain, here we examine the same question focusing on two networks: DAN and DMN. To improve signal-to-

noise, we averaged ROI to ROI correlations across networks, e.g. all inter-hemispheric DAN pairs or DAN to DMN pairs within each hemisphere and we looked at the recovery in N+ and N- groups (Fig. 4). There was a statistically significant interaction between the two groups ($F(2,62)=7.265$, $p<0.001$). Post-hoc tests revealed a decrease in inter-hemispheric DAN connectivity in both groups, but more severely for the N+ group ($p=0.005$), which recovered to the level of the N- group by 3 months. The decrease for both groups however remained below that of the healthy controls ($F(2,93)=5.725$, $p=0.005$)(Fig.4A).

For DAN-DMN connections there was also a significant interaction of time by group ($F(2,62)=5.784$, $p=0.005$ and $F(2,62)=2.940$, $p=0.06$ for the left and right hemisphere respectively), which showed that the negative correlations decreased more strongly in the N+ (as compared to the N-) group ($p=0.001$ and $p=0.007$ respectively) recovering within the first three months to the level of the N- group (Fig.4B-C). FC in the N+ group recovered to the level of the age matched controls in the left hemisphere ($F(2,93)=1.653$, ns), but not the right (damaged) hemisphere ($F(2,93)=6.560$, $p=002$).

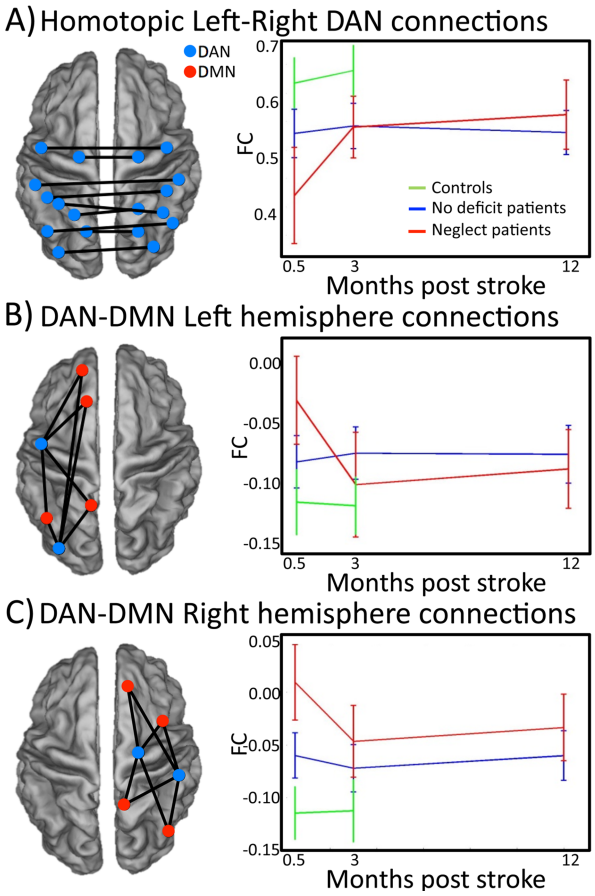

Figure 3.4 DAN and DAN-DMN functional connectivity (FC).
Inter-hemispheric DAN (A), left hemisphere DAN to DMN (B) and right hemisphere DAN to DMN (C) FC over time for the deficit (red) and no deficit (blue) patients and controls (green). The brain figures show a subset of the connections that were averaged in the graphs (blue dots represent DAN ROIs and red dots DMN ROIs).

Given our previous work showing multi-network FC changes associated with attention deficits at the sub-acute stage (Baldassarre et al., 2014), we extended the same analysis to motor, auditory and visual networks (Fig.5A-C). Acute decrements of inter-hemispheric FC in the N+ patients, and improvement within the first three months was robust in the motor and auditory networks, but not in the visual network (Figure 5). Similarly, there was an improvement toward negative correlation with the DMN in motor, auditory, and visual network.

Overall these analyses support at the level of multiple networks that recovery of attention was related to a normalization of inter-hemispheric and intra-hemispheric FC.

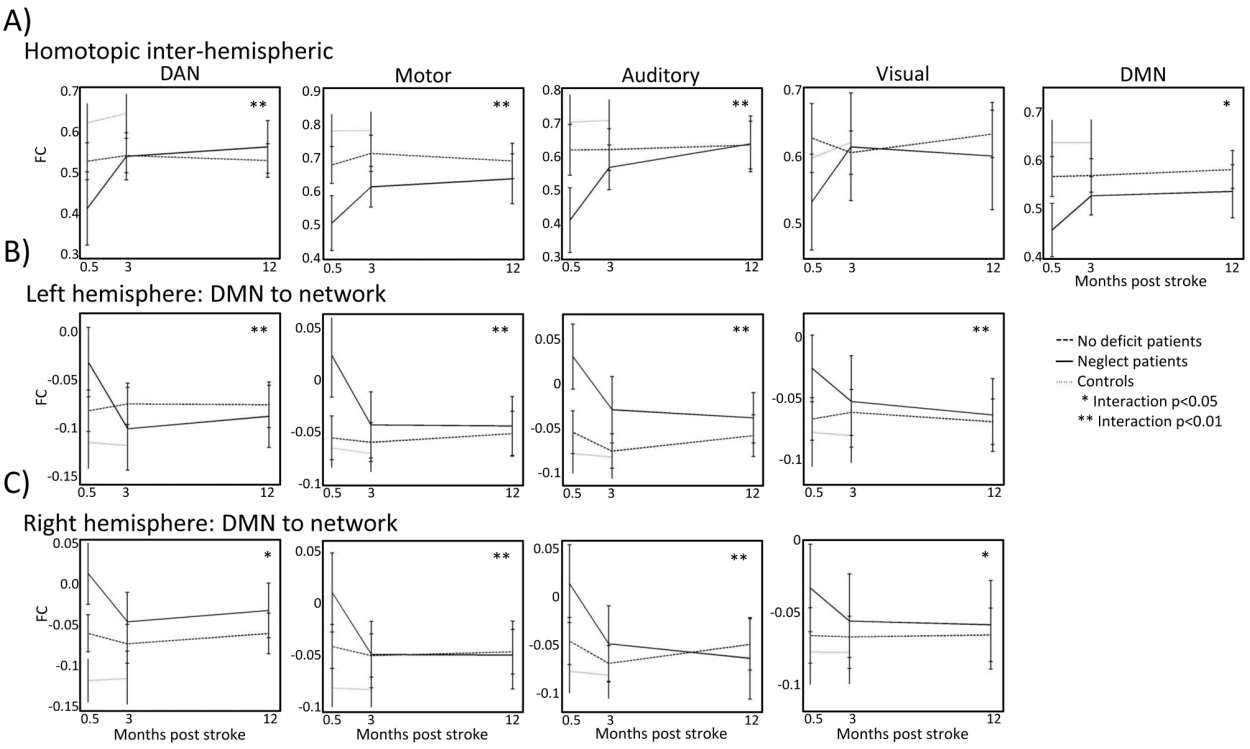

Figure 3.5 Inter- and intra-hemispheric functional connectivity (FC). Homotopic FC (A) for each network and intra-hemispheric FC for the DMN versus other networks in the left (B) and right (C) hemisphere over time for the deficit (dashed line) and no deficit (solid line) patients and controls (dotted line).

3.4.5 Principal component analysis of correlation maps between functional connectivity and neglect recovery

In the third analysis, we employ a data driven approach in which we relate changes in attention performance from 2 weeks to 3 months to changes in FC across the whole set of 169 ROIs. This approach is similar to (Baldassarre et al., 2014), except that FC and behavioral *change* scores are used for the correlation of FC-to-behavior. Voxel-wise maps of FC:behavior correlation for each ROI are summarized by spatial principal component analysis (PCA) to highlight the most consistent maps across ROIs.

Table 3.3 Top 10% ROIs

Left	**network**	**seed**	**x**	**y**	**z**	**Right**	**network**	**seed**	**x**	**y**	**z**
PC1	mn	LdPrCe1	-24	-20	70		Dan	RvIPS	35	-76	23
	dan	LdPrCe	-27	-10	47		vnf	RV3A	26	-90	26

dan	LvPoCe-SMG	-53	-29	37	dan	RpIPS-SPL	20	-67	43
mn	LcPrCe	-42	-17	46	dan	RvIPSd	26	-69	30
dan	LFEF	-19	-8	57	fpn	RIPS	30	-61	39
mn	LSMA1	-10	-12	60	vnf	RLO-RV3A	28	-89	11
mn	LvPoCe	-54	-23	37	dan	RpIPS-SPLd	18	-59	53
mn	LdPoCe	-24	-32	63	dan	RmIPS	28	-49	52
mn	LdmSPL	-7	-44	56	van	RAC	5	-22	40

Left hemisphere PCA: The PCA from left hemisphere ROIs yielded three components that explained respectively 20%, 12%, and 9% of variance across ROIs. The first PC loaded most on ROIs in dorsal parietal and frontal cortex within the DAN and motor network (Figs. 6A, 6B and Table 3.3). The average FC:behavior correlation map from the top 10% nodes showed a widespread positive correlation between changes in inter-hemispheric FC and improvement in VAD scores (yellow/orange). For example, figure 6C shows the correlation between change scores for FC between the top 10% ROIs and a region in the right supramarginal gyrus with VAD change scores. There were also significant negative correlations (green-blue) from the ROIs in DAN and motor network between improvement in VAD and decreases in FC in DMN and FPN regions such as the dorsolateral prefrontal region (DLPFC)(Fig.6D).

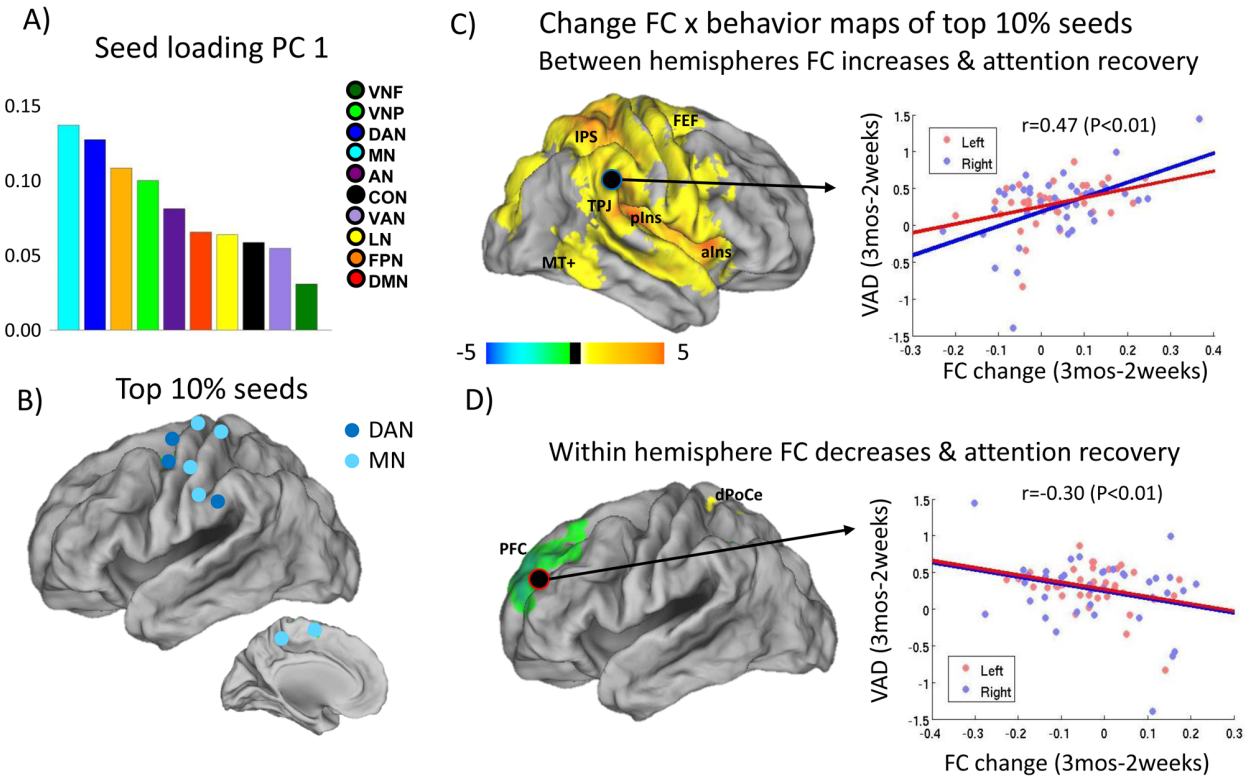

Figure 3.6 Behaviorally relevant functional connectivity (FC) recovery of the left hemisphere. The loadings for each of the 10 networks of the first component of the principal component analysis of voxel-wise FC and behavior change maps of the left hemisphere (A). The voxelwise FC change maps of the top 10% ROIs (depicted in B) are averaged and correlated with the VAD change. The inter-hemispheric FC to VAD change is shown on the left hemisphere (C) and the within hemisphere FC to VAD change is shown on the left hemisphere (D). On the lateral views of the brain red/yellow indicates a positive FC-VAD correlation and green/blue a negative correlation (Z-statistic of Pearson r, thresholded at |Z|>2.25, P<0.05, Monte Carlo corrected). The scatterplots depict the correlation between the average FC change of the top 10% seeds and the black circle and behavioral improvement (C: Supramarginal gyrus, Talairach coordinates: +45 -38 +34; D: PFC, -32 +46 +23). Each dot is a patient and blue indicates patients with right hemisphere lesions, red with left hemisphere lesions. Networks: Networks: VFN = visual foveal representation; VPN = visual peripheral representation;DAN = dorsal attention; MN = motor; AN = auditory; VAN = ventral attention; CON = cingulo-opercular; LN = language;FPN = frontoparietal; DMN = default mode. Labels: FEF, frontal eye fields;IPS, intraparietal sulcus; TPJ, temporal parietal junction; pIns, posterior insula; aIns, anterior insula; MT+, middle temporal complex; PFC, prefrontal cortex; dPoCe, dorsal post central gyrus.

Right hemisphere PCA: The PCA from right hemisphere ROIs yielded three components that explained 19%, 11%, and 11% of variance across ROIs, respectively. As in the left hemisphere, the first PC loaded most on the DAN, but also on auditory and FPN (not shown**).** The top 10% regions were predominantly DAN regions, posteriorly located around the IPS (Table 3.3). The correlation maps from these top 10% regions also showed a strong positive

correlation between improvement in attention deficits and inter-hemispheric FC across large swaths of cortex, and negative correlations within the right hemisphere with posterior DMN regions.

Comparison of sub-acute and change PCA results: Finally, to demonstrate that behaviorally relevant FC changes at 2 weeks normalized during recovery, we compared the top 10% maps from a PCA run on sub-acute FC:behavior maps to the change maps using spatial correlation (after regressing out the sub-acute VAD scores). We found that the sub-acute and change PCA maps (after regressing out the acute scores) were highly correlated: with an r of -0.41 and -0.50 for the maps of the left and right hemisphere respectively (-0.80 and -0.88 sub-acute versus change PCA maps without acute regressed out).

Therefore, the data-driven analysis indicated that recovery of attention deficits correlated with a normalization of inter-hemispheric FC, especially in DAN and motor networks, and a relative decrease of intra-hemispheric FC between DAN/motor and DMN/FPN.

3.4.6 Specificity of network connectivity changes to attention

An important issue is whether these changes in FC are specific to attention or more generally depend on the presence of a lesion or the severity of neurological impairment. To address this concern we performed an analysis in which we correlated changes (3-month-acute) voxel-wise FC to/from right mIPS with changes in motor and language scores derived from a PCA of the neuropsychological battery as in (Corbetta et al., 2015). Figure 7A shows the original voxel-wise correlation with VAD change scores showing strong inter-hemispheric FC increases in sensory-motor and attention networks, and FC decrements with DMN/FPN regions. Figs. 7B-C show FC patterns related to language and motor recovery that appear quite different from attention recovery (Fig.7A). Fig.7D shows FC changes related to attention recovery after

regressing out motor change scores. The pattern albeit slightly decreased is still present. Finally, Fig.7E quantifies these relationships for DAN and DMN ROIs. The strength of FC:behavior correlation, both inter-hemispheric FC increases and intra-hemispheric FC decreases, for attention recovery is not attenuated after regressing out language or motor scores. These analyses confirm the specificity of the reported FC network changes for attention recovery.

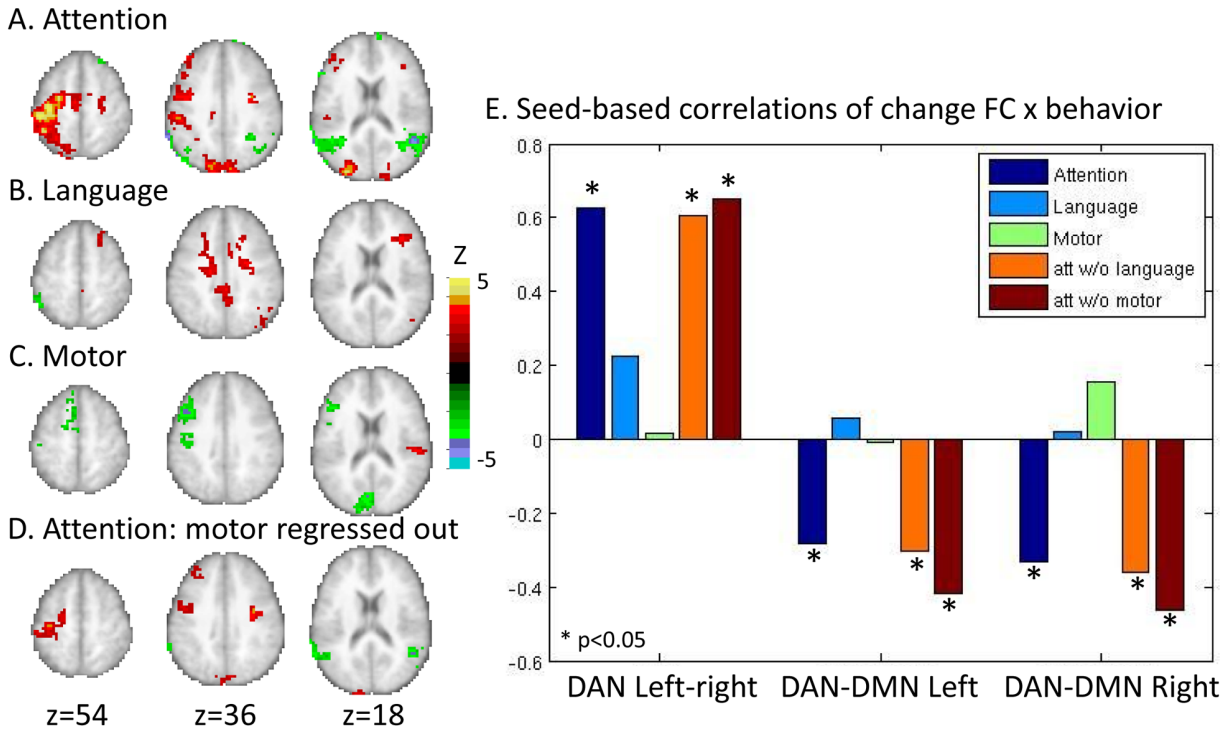

Figure 3.7 R mIPS correlations with recovery of other deficits in patients with right hemisphere lesions. Whole brain functional connectivity improvement correlations of the right medial IPS with behavioral recovery of A. Attention (n=37), B. Language (n=34) and C. Motor (n=34) recovery. In each of these correlations the sub-acute behavioral deficits are regressed out. In D attention recovery is depicted, while regressing out the left limb motor recovery (n=34). E shows the inter-hemispheric dorsal attention network (DAN) and intra-hemispheric DAN to default mode network (DMN) connectivity changes correlated with attention, language and motor improvement as well as attention with language and motor regressed out.

3.4.7 Controls for lag, lesion size, lesion type, and arousal

Prior studies have identified perilesional delays in the resting BOLD signal post-stroke using cross-correlation analysis, i.e. by comparing the latencies of signal time series in the stroke hemisphere with either homologous signal time series in the normal hemisphere or a global

signal computed over the whole brain or gray matter (Amemiya, Kunimatsu, Saito, & Ohtomo, 2014; Lv, 2013). These delays or 'hemodynamic lags' correspond to areas of hypoperfusion and can artificially lower observed FC values (Siegel et al., 2015). Here, we present a limited analysis of the potential effect of hemodynamic lags on the normalization of FC in relation to neglect recovery in nine homotopic pairs of ROIs in the DAN, the network in which we found the strongest effects of recovery ($r=0.63$, $p<0.001$, Fig. 8A). Consistent with the recovery of lag reported in Siegel et al. (Siegel et al., 2015), the lags decreased as the interhemispheric FC recovered ($r=-0.47$, $p<0.001$). However, when the recovery of lag was regressed out of each ROI pair, the inter-hemispheric FC in the DAN ROIs showed a slightly weaker, but still strong correlation with behavioral recovery ($r=0.55$, $p<0.001$, Fig. 8C).

Another possible confound is the volume of the lesion. The volume of stroke in N+ patients was larger than in N- patients. However, we found no relationship between changes in inter-hemispheric FC (DAN) and lesion-size ($r=0.18$, ns). Also regressing out lesion-size from the change in FC only slightly decreased the correlation between FC and behavioral recovery ($r=0.58$, $p<0.001$, Fig. 8D). Moreover, there seems to be no difference in this relationship between FC and behavioral recovery for different lesion types (subcortical, cortical and cortical-subcortical, Fig. 8B). A larger dataset is however needed to quantify this.

Finally, we examined if changes in FC were influenced by the state of vigilance of our patients in the scanner. We used an eye tracker in the scanner in 44 of the patients to determine the percentage of time patients had their eyes open during each resting scan. There was no relationship between the time patients kept their eyes open and homotopic DAN FC (sub-acute: $r=-0.23$, $p=0.11$, 3 months: $r=-0.13$, $p=0.35$) and no difference between the neglect and non-neglect groups on the amount of time they had their eyes open ($t(48)=1.30$,$p=0.197$).

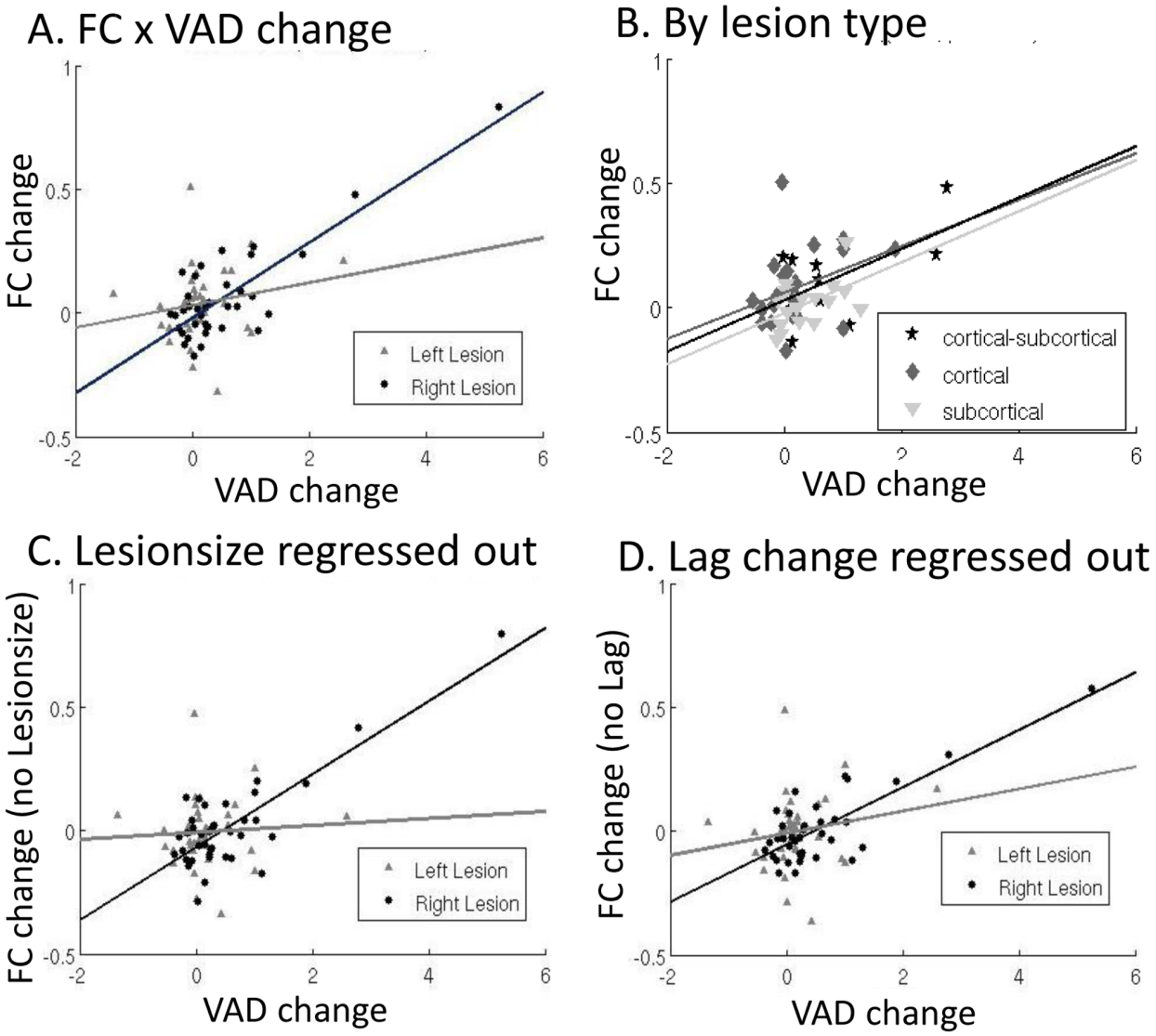

Figure 3.8 Lesion type, Lag and Lesion size. The scatterplots show the correlation between behavior (VAD) change and FC change between sub-acute and 3 months post stroke for the average of the homotopic DAN nodes (A), the correlations of VAD change and FC change separated out by lesion type: subcortical, cortical and cortical-subcortical (B),the correlation between VAD change and FC change when lesion size is regressed out (C) and the correlation between VAD change and FC change with lag change regressed out (D). Each dot is a patient and grey triangles indicate patients with right hemisphere lesions, black circles patients with left hemisphere lesions.

3.5 Discussion

3.5.1 Summary

This study examined network-level correlates of hemi-spatial neglect recovery, the most common cognitive syndrome after right hemisphere stroke. Attention deficits mostly recovered within the first three months post stroke, with little additional improvement between three

months and one year. Correspondingly, we observed changes in FC of structurally normal brain regions also significantly stronger between 2 weeks and 3 months, then plateauing between 3 and 12 months. Attention deficit recovery was significantly correlated with increases in inter-hemispheric FC between regions of the dorsal attention, motor, visual, and auditory networks, and more negative intra-hemispheric FC between dorsal attention/motor and default mode/frontoparietal regions. Notably these changes correspond to a relative normalization by 3 months of the abnormal network FC observed at approximately 2 weeks post-injury. These findings support the behavioral relevance for hemispatial neglect of abnormal network interactions at the sub-acute stage, and indicate that their normalization is associated with recovery of function.

3.5.2 Recovery of attention deficits

The VAD factor loaded on lateralized spatial biases in visual perception and a general decrement in performance consistent with sustained attention impairment. Both features correspond to the most common processing deficits of the hemi-spatial neglect syndrome (Rengachary et al., 2011). Compatible with prior work, performance improved during the first three months post stroke but then plateaued without reaching normal levels (Rengachary et al., 2011; Ringman et al., 2004; Stone, Patel, & Greenwood, 1992a).

Interestingly, while VAD scores sub-acutely correlated with both left motor and spatial memory deficits, consistent with a right hemisphere localization of neglect, changes in VAD scores from 2 weeks to 3 months were significantly correlated with spatial memory deficits, but not motor deficits. Spatial attention and spatial memory are cognitive functions that rely on the integration of information across multiple regions of the brain, and are closely intertwined both behaviorally and neurally. Functionally, attention determines what enters in working memory

(Morey & Bieler, 2012), while information in working memory can bias what is attended (Awh & Jonides, 2001). Neurally, both spatial attention and memory involve distributed networks of frontal-parietal cortical and subcortical regions (Awh & Jonides, 2001; Corbetta, Kincade, & Shulman, 2002). Accordingly, disorders of both functions depend on widespread cortical dysfunction due to structural or functional disconnection (Mesulam, 1990), and their recovery may depend on the restoration of communication across multiple brain regions. In contrast, motor behavior is an output function. Several studies have reported that one of the strongest predictors of motor impairment and recovery is the degree of damage to the corticospinal tract (Jayaram et al., 2012; Schaechter et al., 2009). Interestingly, cortico-spinal damage is a stronger predictor of motor impairment than functional connectivity (Carter et al., 2011). Therefore, while deficits of attention and left limb motor function are correlated sub-acutely, possibly due to the co-localization of related cortical regions in the vascular territory of the most common middle cerebral artery stroke, the recovery of attention and motor function may underlie different mechanisms, with attention more related to functional interactions between distributed brain regions, while motor recovery more related to local structural reorganization.

3.5.3 Functional Connectivity & Attention Recovery

Inter-hemispheric connectivity

Both animals and human stroke studies show correlated decreases in inter-hemispheric functional connectivity (or signal temporal correlation) with motor (Carter et al., 2010; van Meer et al., 2010), and attention deficits (Baldassarre et al., 2014; Carter et al., 2010; He et al., 2007).

Our results show for the first time in a large cohort of human subjects (see van Meer et al., 2010 for a corresponding result in rats) that improvement of inter-hemispheric connectivity over time is associated with behavioral recovery. An improvement of VAD scores from sub-acute to 3

months was correlated with an increase of functional connectivity between inter-hemispheric regions in multiple networks, predominantly the DAN and the motor network, but also auditory and visual regions. Our previous work had showed that hemi-spatial neglect sub-acutely is associated with disrupted inter-hemispheric connectivity in the same networks (Baldassarre et al., 2014). Therefore, the results for both the sub-acute deficit and the recovery of that deficit over time strongly support the behavioral relevance of FC measures.

An improvement of inter-hemispheric FC over time in stroke has been reported in other studies of motor recovery (Golestani, Tymchuk, Demchuk, Goodyear, VISION-2 Study Group, 2012; Xu et al., 2014). For instance, Park et al (Park et al., 2011) observed an improvement of inter-hemispheric FC from 1 to 6 months post stroke in a small group (n=12) of patients by performing a ROI based analysis from the primary motor cortex. They also showed that the degree of acute inter-hemispheric FC impairment correlated with the degree of motor recovery. These studies therefore are also consistent with the notion of normalization of abnormal network interactions in the motor system as a possible mechanisms underlying recovery of function.

Default mode network and DAN

The second pattern of abnormal connectivity associated with the recovery of neglect is a return toward a negative intra-hemispheric coupling between the DMN and the DAN as well as sensory and motor networks. In the healthy brain, regions involved in the processing of 'external' information (e.g. DAN, visual, auditory, motor during visual or auditory processing tasks) are negatively correlated with regions of the DMN, which are instead more involved in the processing of 'internal' information (e.g. memory retrieval, theory of mind, self-referential tasks)(reviewed in Buckner, Andrews-Hanna, & Schacter, 2008). This competitive pattern of task activation is behaviorally relevant. Positive responses in the DAN and negative responses in

the DMN relate to accuracy on a perceptual task, while the reverse pattern holds during memory retrieval (Sestieri, Corbetta, Romani, & Shulman, 2011). Conversely, a failure to suppress DMN activity underlies lapses and deficits in attention (Bonnelle et al., 2011; Weissman, Roberts, Visscher, & Woldorff, 2006). The DAN and DMN are also negatively coupled in the resting state, even after accounting for the effects of global signal regression (M. D. Fox, Zhang, Snyder, & Raichle, 2009), and this coupling is absent in several pathological states. For instance, decreases in segregation between DMN and DAN is found in patients with ADHD (Kessler, Angstadt, Welsh, & Sripada, 2014). Our results show that a recovery of negative coupling between DAN and DMN within each hemisphere (both damaged and normal) is related to the behavioral recovery of neglect. Subjects with more severe inter-hemispheric disruption have less negative or abnormally positive coupling intra-hemispherically.

3.5.4 Behavioral recovery as improvement of network efficiency

Animal and human neuroimaging studies in the last two decades have shown after stroke that performance of motor or language tasks lead to abnormal recruitment and over-activation of cortical regions, often in the undamaged hemisphere, that are not typically present in healthy subjects. This abnormal recruitment typically occurs more strongly in individuals who are more severely impaired (Rehme et al., 2012; Ward et al., 2003). In the course of recovery, activity shifts back to the damaged hemisphere often with a re-mapping of function near the lesion (peri-lesional), especially in patients with better recovery (Ward et al., 2003; Xerri, Zennou-Azogui, Sadlaoud, & Sauvajon, 2014). These dynamic alterations in task-evoked activation must be reconciled with acute alterations and chronic normalization of inter-regional signal temporal correlation reported here.

We propose that observed changes in activity and connectivity reflect a tendency of brain networks toward energy optimization. The brain weighs only 2% of the body weight yet uses about 20% of the total energy (Attwell & Laughlin, 2001). Most energy consumption relates to intrinsic, not task-driven, signaling (Attwell & Laughlin, 2001). Recent theoretical work in network science indicates that the brain's structural and functional architecture is the best energetic compromise for a system that requires both specialized local processing and distributed integration of information (Bullmore & Sporns, 2012).

This architecture renders the system relatively resistant to perturbations (Joyce, Hayasaka, & Laurienti, 2013), but necessarily local and distributed injuries will affect the system processing capacities. While local damage to cortex can be compensated for by highly interconnected neighboring neuronal populations that are part of a network with similar input and output connections (Bullmore & Sporns, 2012), damage to white matter pathways, especially regions in which multiple pathways intersect, will lead to disconnection of wide swaths of cortex and more severe and long lasting deficits (Alstott, Breakspear, Hagmann, Cammoun, & Sporns, 2009; Corbetta et al., 2015). For example, in the case of hemispatial neglect damage to white matter pathways connecting frontal and temporo-parietal regions leads to severe and persistent impairment (Corbetta et al., 2015; De Schotten et al., 2014; Rengachary et al., 2011; Verdon et al., 2010).

A key insight from our work on network abnormalities in stroke is that sub-acutely large parts of cortex show patterns of connectivity that are highly similar, and that similarly correlate with behavioral deficits. For instance, the two characteristic connectivity abnormalities found sub-acutely in hemispatial neglect, i.e. a loss of inter-hemispheric correlation and an abnormally increased correlation between normally segregated networks, is found in over 40% of cortical

regions [10]. In other words, the pattern of resting synchronization across brain regions is highly simplified, i.e. the brain noise variability is decreased. This is also clear from EEG/MEG studies in which the damaged hemisphere typically show slower and less variable brain rhythms (Zappasodi et al., 2014), and EMG studies of muscle synergies, in which the variability of motor patterns during movement is also reduced in stroke (Cheung et al., 2012). Apparently, during task performance, these abnormal and low variability intrinsic brain rhythms give rise to abnormally strong patterns of task activation that are not not only behaviorally, but also metabolically inefficient. To the extent that sub-acute abnormal patterns also include compensatory adjustments, they may reflect an attempt to link regions that are disconnected, either by increasing neural activity upstream of the lesion or by re-routing activity through accessory regions.

Through rehabilitation and possibly neuromodulation (e.g. Grefkes et al., 2010; Sparing et al., 2009) connections and networks may return toward more normal patterns of intrinsic synchronization, which in turn relate to more efficient task patterns of activation. Normalization will result in more efficient energy utilization and increased neural state variability, hence better behavior. Normalization of functional connectivity, as shown here, could be mediated either through undamaged parts of white matter tracts that still connect these regions, or indirectly through regions of the same network (Honey et al., 2009) that share intact structural connections. A similar trend toward normalization of connectivity states has been observed after traumatic brain injury (N. P. Castellanos et al., 2011). In a recent study Lee and colleagues (J. Lee, Lee, Kim, & Kim, 2015) observed a global increase of network efficiency (again measured as a shorter characteristic path length) in the first three months post stroke, and showed that increased efficiency shortly after stroke predicted the amount of motor recovery.

In summary, then, a normalization of the brain's functional architecture toward a healthy state appears to be a property of brain networks after injury that also relates to behavioral recovery.

Chapter 4: Discussion

4.1 Summary

In this thesis we describe for the first time curves of behavioral recovery across multiple domains in a large group of stroke participants who were studied at 2 weeks, 3 months, and 1 year. In contrast to previous reports, but in agreement with others, we show that motor, sensory, and cognitive deficits all tend to maximally improve by 3 months post-stroke. Therefore some aspects of recovery are independent of the specific deficits and underlying neural mechanisms. This therefore represents domain-independent recovery of function. However, we also find that recovery in different domains is differentially influenced by different variables, thus suggesting domain-specific recovery.

The second goal of the thesis was to investigate neurophysiological mechanisms of recovery, specifically examining the recovery of attention deficits after stroke. We show that acute abnormalities in multi-network functional connectivity (FC) MRI, that predict the severity of spatial and non-spatial attention deficits, recover from 2 weeks to 3 months, and plateau afterwards. Importantly, the degree of behavioral recovery is significantly correlated with the changes in FC strongly suggesting that 'normalization' of network abnormalities is one of the mechanisms underlying recovery of function at the systems level.

In the discussion section, we first consider biological mechanisms that could underlie the common recovery (domain independent) observed for different functions, especially from 2 weeks to 3 months (section 4.2). After this initial period subsequent recovery could be driven by the development of compensation strategies and/or development of additional patterns of

activity, which are distinct from the normalization of network abnormalities noted above (section 4.3). Differences in hierarchy and distributions of behavioral domains in the brain, as well as external factors such as prior enrichment and therapy that increase neuroplasticity, could differentially influence the recovery and could also explain some of the variation between subjects over the course of recovery (section 4.4).

The recovery of hemispatial neglect, an attention deficit frequently caused by a stroke, shows a similar pattern of recovery as memory, motor and language, with the majority of recovery occurring within the first three months post stroke. The acute deficit is accompanied by a decrement of inter-hemispheric functional connectivity predominantly between dorsal attention and motor network regions, as well as a decrement in negative correlations between the attention and default mode networks within a hemisphere. The recovery of neglect is related to a return of these decrements towards normal levels, suggesting that normalization and a rebalancing pattern (as opposed to reorganization) is related to better recovery (section 4.5). As the brain has developed to be most efficient in its natural state and the neuroplasticity post stroke is limited, it is reasonable to think that a return to its original state as closely as possible, would be most beneficial. However, when this is no longer possible reorganization and recruitment of other regions could be used as a compensatory strategy.

The acute deficits as well as the recovery of behavioral deficits have been linked to inter-hemispheric imbalances and changes in inter-hemispheric connectivity. How these two are related is, however, not yet clear (section 4.6). We show that the recovery of decrements of this inter-hemispheric connectivity in neglect patients follows a similar recovery pattern as the behavioral recovery, with the majority of the improvement occurring in the first three months

following a stroke. This also suggests a relationship between the changes in connectivity and biological mechanisms, but this needs to be further explored (section 4.7).

4.2 Biological mechanisms of recovery

The similarity between recovery patterns of different behavioral domains we found in chapter 2 suggests common mechanisms of recovery. A large portion of the initial (spontaneous) recovery of behavior is driven by the biological mechanisms underlying recovery after a stroke (Kwakkel et al., 2006). In the first hours to days after stroke the restoration of injured tissue underlies quick functional recovery (Levin, Kleim, & Wolf, 2009). Directly after the initial incident, reperfusion of the penumbra, the regions outside of the core area of the stroke, can assure the survival of (a subset of) these neurons and this is related to initial behavioral improvement (Hillis & Heidler, 2002; Witte, Bidmon, Schiene, Redecker, & Hagemann, 2000). In the following days this is accompanied by a resolution of edema as well as inflammation and diaschisis (Carmichael, Tatsukawa, Katsman, Tsuyuguchi, & Kornblum, 2004; Feeney & Baron, 1986; Ito, Ohno, Nakamura, Suganuma, & Inaba, 1979; Nudo, Plautz, & Frost, 2001). Diaschisis is used as a term for hypometabolism, a low reactivity and depressed functioning of areas remote to the lesion, the recovery of which could be important for functional improvements in this early phase. In contrast, the core area of the stroke (as well as parts of the penumbra affected by apoptosis) is no longer functional. Therefore, subsequent recovery occurs through neuroplasticity mechanisms triggered by the damage, some mechanisms of which are thought to be related to processes present during development (Cramer & Chopp, 2000). Studies on these neuroplasticity mechanisms have shown an increase of inflammatory markers and growth associated proteins (such as BDNF), as well as other changes in gene expression, which promote dendritic outgrowth and sprouting, and diminish growth inhibiting proteins, supporting the formation of

new connections and the migration of neuroblasts to the perilesional cortex (Carmichael, 2012))(Buma et al., 2013; Carmichael, 2006; Zeiler & Krakauer, 2013). This process is then optimized through synaptogenesis and hebbian-type synaptic strengthening (or weakening) through homeostatic plasticity. Moreover, changes in phosphorylation, ion gradients (GABA and glutamate), receptor expression (primarily GABA and NMDA) and other modulatory factors take place and reestablish the pre- and postsynaptic balance of inhibition and excitation (Buma et al., 2013; T. H. Murphy & Corbett, 2009; Nudo et al., 2001; Stroemer et al., 1995). Along with these cellular and molecular changes, angiogenesis takes place forming blood vessels in the perilesional cortex to re-perfuse the tissue.

The timeline of these processes in humans has not been fully clarified. The majority of these studies have been done in animals, and do not directly translate to the human. However, the majority of the mechanisms described above are thought to take place within the first weeks to months after a stroke. A study by Ge and colleagues (Ge et al., 2007) shows that the gene expression patterns in newly generated dentate granule cells in the hippocampus allow for a critical period of plasticity up to 1 to 1.5 months in mice, which is thought to translate to approximately 3 months in humans. Furthermore, remapping has been measured in a similar timeframe. After a lesion to the sensory cortex, the normally highly limb-selective neurons in the perilesional area, become less selective in the processing of sensory input over the first month post stroke, but then become more specific to their newly adopted role during the following weeks (Winship & Murphy, 2009).

The initial biological mechanisms of recovery are independent of the brain regions damaged or the resulting deficits, and this is likely what underlies the similarities we identified in the recovery patterns between different behavioral domains. The timecourse of these

mechanisms are consistent with our finding that the majority of behavioral recovery for memory, attention, motor as well as language occurs within these first three months. Moreover, the high predictive value of deficits measured a few weeks post stroke for chronic deficits (Duncan et al., 1992; Kwakkel, Kollen, van der Grond, & Prevo, 2003) suggests that therapy does not have much of an impact on initial recovery mechanisms (Huang & Krakauer, 2009).

Therapy could have some influence on plasticity mechanisms. The initial months have been shown to be the most sensitive period for learning through therapy, and starting therapy after this period is less effective (Biernaskie, 2004; Maulden, Gassaway, Horn, Smout, & DeJong, 2005; T. H. Murphy & Corbett, 2009; Ottenbacher & Jannell, 1993; Paolucci et al., 2000). Importantly, enriched environments, training and experience increase neural plasticity during the sensitive period of the first few months post stroke (Biernaskie, 2004; Buma et al., 2013; Dromerick et al., 2015; Krakauer et al., 2012; Winship & Murphy, 2009; Zeiler & Krakauer, 2013). Conversely, some studies that show that starting too early (within a few days) could increase histological damage. Clearly more work is needed to elucidate the underlying mechanisms (Dromerick et al., 2015; Krakauer et al., 2012).

4.3 Recovery and compensation

Some recovery can still occur after the first three months after a stroke, which we find for language and motor recovery between three and twelve months after stroke in chapter 2. Cloutman and colleagues (Cloutman et al., 2009) show that the rate of recovery in the first three months is unrelated to the rate of recovery between 3 and 12 months, supporting the idea that different mechanisms are at play. Later recovery could be an adaptation of behaviors through compensation as opposed to a restitution of the original behavior (box 2) (Kwakkel et al., 2004; Nudo et al., 2001; Zeiler & Krakauer, 2013). The term recovery is often used for any behavioral

improvement, ignoring the important difference between restitution and adaptation or compensation. This generalization of the term complicates the comparability and interpretation of results (Levin et al., 2009) and may well explain the large variation in findings across studies. Functional measures that for example evaluate the ability to perform daily tasks typically cannot distinguish between restitution and compensation (box 2). Compensation of a functional impairment, for example by using trunk movements for reaching, enables patients with motor deficits to perform standard stroke research tasks surprisingly well (Cirstea & Levin, 2000).

In standard motor tests, imposed targets can be reached in different ways. Measuring kinematics, which describes details of movements in biomechanical terms, allows for the difference between restitution and compensation to be studied in motor impairments. Kordelaar and others (van Kordelaar, van Wegen, Nijland, Daffertshofer, & Kwakkel, 2013) show that the control over the degrees of freedom of a reaching task improve initially but chronic improvements are likely achieved through motor compensations (Kitago et al., 2012). In support of this, a recent study shows that increased recruitment of secondary motor areas is related to a continuous correction of deviations from the optimal movement pattern (Buma et al., 2016). Restitution versus compensation is harder to distinguish for cognitive deficits, yet a study by Sarno and Levita (Sarno & Levita, 1981) where clinical reports of communication behavior were used, did show improved comprehension of social interactions after the initial 3 months in global aphasics, with less improvement in production, suggesting that chronic language recovery corresponds to compensatory mechanisms using non-verbal communication strategies. While therapy may exert only small influences on the biological mechanisms of recovery, it could have a larger impact on the development and use of compensatory strategies (Huang & Krakauer,

2009). This could be what is supporting the small improvements we find after three months in patients with motor deficits and aphasia (chapter two).

Interestingly, the presence of memory deficits decreases the use of compensation strategies (Wilson, 1996) and thus, more generally, cognitive deficits could influence the ability to learn these strategies (Walker et al., 2004). As chronic recovery is more subtle and therapies are likely to enhance compensation strategies, future work on chronic recovery in larger samples with carefully selected measures of behavior is needed to substantiate these hypotheses.

4.4 Recovery and Cognitive Reserve

Other variables than the ones mentioned thus far, unrelated to the stroke, can affect the recovery after stroke. For instance, the level of education affects the amount of recovery of aphasia deficits post stroke (Chapter 2, Connor et al., 2001; Hillis & Tippett, 2014). Posner and colleagues (Posner et al., 2014) also found that higher education positively influenced neglect recovery, but in our study we failed to replicate this relationship. Interestingly, education has been identified as a protective factor against memory deficits in Alzheimer's disease (Stern, 2006; Stern et al., 1999), as well as against cognitive deficits due to multiple sclerosis (MS) (Bonnet et al., 2006; Sumowski, Chiaravalloti, & DeLuca, 2009) and to traumatic brain injury (Nunnari et al., 2014). This capacity to withstand the cognitive decline, referred to as "cognitive reserve" (Staff et al., 2004), and it is more strongly present in people with a higher education, who hold intellectual occupations that offer cognitive stimulation (Le Carret et al., 2010). A larger reserve is thought to let people compensate more effectively by maintaining cognitive efficiency after different forms of grey or white matter damage (Bartrés-Faz & Arenaza-Urquijo, 2011). Moreover, these protective effects are more prominent in tasks that require higher cognitive functioning such as controlled processes and conceptualization abilities, and less in

tasks that only require simple processing efficiency (Le Carret et al., 2010; Sumowski et al., 2009).

What underlies cognitive reserve is not yet clear. From a systems perspective it could be driven by an increased recruitment of cognitive processes and neural networks, but the related "brain reserve capacity" hypothesis argues it is supported by more fundamental neural differences between people (Nithianantharajah & Hannan, 2009). An enriched environment influences brain development (e.g. cerebral growth, dendritic density, neurogenesis) and has neuroprotective effects which could suggest that cognitive reserve is based on differences in neural efficiency and capacity as well as plasticity (Petrosini et al., 2009; Richards & Deary, 2005; Stern, 2006).

At the network level, Sumowski and colleagues (Sumowski, Wylie, DeLuca, & Chiaravalloti, 2010) show that for similar performance on cognitive tasks, MS patients with a smaller cognitive reserve show increased deactivation of default mode regions (anterior and posterior cingulate cortex) and an increased recruitment of prefrontal regions, suggesting increased effort and a lower cerebral efficiency. Additionally, neural efficiency as well as more efficient parallel information transfer, quantified as a higher global efficiency in the brain, is related to higher intelligence (Li et al., 2009; Neubauer, Grabner, Fink, & Neuper, 2005; van den Heuvel, Stam, Kahn, & Hulshoff Pol, 2009). These results support the notion of efficient communication between brain regions and, with that, efficient integration of information, as being beneficial. Having a higher efficiency or capacity could be associated with less severe cognitive deficits (Ojala-Oksala et al., 2012) and with better recovery of cognitive deficits such as aphasia and neglect after a stroke, which supports our finding on the influence of education on aphasia recovery in chapter 2.

Compared to younger adults, older adults benefit from more distributed processing and recruitment of brain regions, which is likely a compensation strategy (Davis et al., 2009). In people with a larger reserve, a more plastic and efficient capacity to increase recruitment is thought to allow for better information processing (Cabeza, Anderson, Locantore, & McIntosh, 2002; Petrosini et al., 2009). The ability to recruit other regions is, however, constrained by white matter integrity, with decreased integrity leading to worse performance (Davis et al., 2009). With age, white matter disease prevalence increases (chapter 2), which is linked to a decrease in white matter integrity. Already relying on a more distributed system, which could drain the cognitive reserve, could be a factor in the decreased improvement post stroke often seen in patients with older age (Nakayama, Jørgensen, Raaschou, & Olsen, 1994).

4.5 Reorganization or normalization?

Brain efficiency is an essential component of healthy functioning. In chapter 3 we suggest that the brain's healthy functional architecture is the most efficient, and a return as close as possible to that 'normal' architecture results in better outcomes. Many studies have reported an increased recruitment of secondary brain regions post-stroke during motor or cognitive tasks, but it is still not clear if this is beneficial. A return, during recovery, to task activation patterns that are more similar to normal are also related to better outcome (Buma, Lindeman, Ramsey, & Kwakkel, 2010; Hamilton, Chrysikou, & Coslett, 2011; Rehme et al., 2012; Rossini et al., 2007; Rossini, Calautti, Pauri, & Baron, 2003; Ward, 2004). Moreover, the recruitment of regions in stroke and MS patients during task performance, more likely represents overactivation of regions that are normally recruited rather than recruitment of unrelated areas (Rossini et al., 2007; Sweet, Rao, Primeau, Durgerian, & Cohen, 2006).

The preference of normalization over reorganization underscores the limits of plasticity of the adult brain. The local neural plasticity in the peri-lesional regions in the first few months after the stroke can result in local shifts of function within, for example, the motor cortex, as shown in both animal and human studies (Harrison, Silasi, Boyd, & Murphy, 2013; Merzenich et al., 1983; Xerri, Merzenich, Peterson, & Jenkins, 1998), but the limits of local plasticity are still under debate. For example, Buma and others (Buma, Raemaekers, Kwakkel, & Ramsey, 2015) do not find consistent reorganization in patients with upper limb paresis. Moreover, increased recruitment of regions has been suggested to be a transient compensatory strategy rather than actual plasticity (Rossini et al., 2007). In Chapter 3 we report that normalization of functional connectivity patterns is related to the degree of recovery post stroke, both between and within hemispheres. Similar results have been reported in motor recovery after stroke in rats (van Meer et al., 2012) where the integrity and normalization of functional, as well as structural, connectivity was related to behavioral improvement. It appears that since neuroplasticity is limited, a return to the use of original architecture thus leads to the best improvement and outcome after perturbations due to stroke.

4.6 Inter-hemispheric balance and functional connectivity

Inter-hemispheric communication is required for many functions, including the integration of visual information across the two visual fields, speech output (such as naming of visually presented objects), or bi-manual coordination (Paul et al., 2007; Schulte & Müller-Oehring, 2010). The anatomy of the callosal connections involves excitatory glutamatergic connections that project onto inhibitory inter-neurons in the opposite hemisphere, providing a mechanism for cross-inhibition (Bloom & Hynd, 2005). Both animal and human studies have shown that this cross-inhibition can be shifted out of balance due to stroke, measured as

overactivation of the undamaged hemisphere, which in turn causes a decreased activation of the damaged hemisphere in both motor and attention deficits (Corbetta et al., 2005; Mäkelä et al., 2015; Pascual-Leone et al., 2005).

Interhemispheric balance can be modulated through noninvasive neurostimulation methods such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) that induce or apply small electrical currents to modulate brain activity in cortical regions (e.g. Dambeck et al., 2006; Sparing et al., 2009; Takeuchi, Chuma, Matsuo, Watanabe, & Ikoma, 2005). , Howerver, how the interhemispheric balance, or modulation thereof, is related to interhemispheric functional connectivity is not yet clear. Andoh and Zatorre measured interhemispheric functional connectivity between the auditory cortices using fMRI and showed that higher connectivity improved reaction times on an auditory discrimination task (Andoh & Zatorre, 2013). Subsequent continuous theta burst stimulation (cTBS) of the right Heschl's gyrus increased the activation of the contralateral gyrus and this increase again correlated with improved reaction times. Interestingly, the size of the facilitatory effect was related to the baseline interhemispheric FC, suggesting a relationship between activation, connectivity and behavior. But again, the mechanisms underlying this relationship are still unclear and we do not know if distant responses to neural stimulation are due to propagation of neural activity or a compensatory response to adjust for the disruption (Pascual-Leone, Walsh, & Rothwell, 2000).

TMS not only influences brain activity, but can also produce changes in cerebral blood flow (CBF) both locally and distant to the stimulation site (Moisa, Pohmann, Uludağ, & Thielscher, 2010; Paus et al., 1997). CBF can be measured with arterial spin labeling (ASL), an fMRI technique that provides a more quantitative measure of physiology and metabolism than

the fMRI BOLD signal. ASL can also identify functional networks (Jann et al., 2015) and shows an interhemispheric imbalance post stroke with decreases in CBF in the lesioned hemisphere and increases in the unlesioned hemisphere that rebalances with better recovery (Wiest et al., 2014). Moreover, decreases in CBF were related to delays, or hemodynamic lags, of up to 24 seconds measured in the BOLD signal in the lesioned hemisphere of stroke patients (Amemiya, Kunimatsu, Saito, & Ohtomo, 2012).

Hemodynamic time lags could affect the temporal correlations of BOLD fluctuations measured with resting state fMRI. In a study in our lab (Siegel, Snyder, Ramsey, Shulman, & Corbetta, 2015) we demonstrated that there is indeed a relationship between lag, decrements of bloodflow, and behavioral deficits in stroke patients. Even though lags affect FC measures, the correlation between decrements in FC after stroke and behavioral deficits, are robust to lags (Siegel, Snyder, Ramsey, Shulman, & Corbetta, 2015; chapter 3), which also indicates that FC alterations after a stroke are not just driven by hemodynamic changes.

The persistence of decreased functional connectivity after the correction for hemodynamic lag, and the fact that this decrement recover, suggests that it is likely related to alterations of neuronal communication. More work however needs to be done to explore the mechanisms of decrements and recovery thereof, in functional connectivity measures.

4.7 Biological mechanisms of FC Recovery

The recovery of functional connectivity changes shows a pattern similar to behavioral recovery, with the majority of changes occurring within the first 3 months post stroke. This is likely similarly influenced by the biological mechanisms discussed in 4.2. Resolution of edema,

diaschisis, changes in cerebral blood flow and molecular changes are all probable modulators of the BOLD signals around and distant to the lesion.

Task related BOLD signal, a surrogate measure for the mass activation of large numbers of neurons, is strongly affected by the balance of inhibitory and excitatory microcircuits (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). The function of these microcircuits is predominantly exerted by glutamatergic projection neurons and GABAergic interneurons. Microcircuits form nodes, and multiple nodes together form networks at the scale we are investigating with resting state fMRI. As mentioned in the introduction, the brain at rest is responsible for a large part of energy consumption (Fox et al., 1988; Raichle & Mintun, 2006). Moreover, the majority of energy consumption in the brain is related to glutamatergic signaling (Hyder, Patel, Gjedde, & Rothman, 2006). An increase in glutamate release increases the postsynaptic and astrocyte metabolic rate due to activation of the Na^+,K^+-ATPases to maintain the Na^+ gradient, and the conversion of glutamate to glutamine after reuptake (Magistretti & Pellerin, 1999; Raichle, 2010). This increase in metabolic rate causes an increase in the BOLD response (Kapogiannis, Reiter, Willette, & Mattson, 2013). Importantly, glutamate levels, as well as the ratio between glutamate and GABA, correlates with functional connectivity within a network (Kapogiannis et al., 2013).Enhancing $GABA_A$ receptor activity decreases interhemispheric (but not intrahemispheric) FC as measured with EEG in rats (H. Lu et al., 2007). These results suggest that the inhibitory/excitatory balance of these neurotransmitters is significant for the measurement of resting state fluctuations.

After a stroke, intracortical hyperexcitability or disinhibition can be measured in the affected and unaffected hemisphere weeks to months after the stroke, and is thought to promote and facilitate synaptic plasticity (Carmichael, 2003; Liepert, Bauder, Miltner, Taub, & Weiller,

2000; Que, Schiene, Witte, & Zilles, 1999). This disinhibition/facilitation is linked to widespread down-regulation of $GABA_A$ receptors and up-regulation of NMDA (glutamate) receptors (Mittmann, Qü, Zilles, & Luhmann, 1998; Que et al., 1999; Qü, Mittmann, Luhmann, Schleicher, & Zilles, 1998; Schiene et al., 1996). As mentioned above, the GABA/Glutamate balance has been shown to be related to the spontaneous fluctuations in resting state fMRI, and a disruption of the balance is thus likely to change these fluctuations. Additionally, as damage to a single node in a network has widespread effects, local changes in this balance can influence global dynamics such as the correlations of spontaneous fluctuations between remote, but connected regions (Alstott, Breakspear, Hagmann, Cammoun, & Sporns, 2009; Honey & Sporns, 2008; Falcon et al., 2016). Together this suggests that the recovery of the biological mechanisms, including the inhibitory/excitatory balance, could very well be related to the recovery of connectivity within networks that declined in correlation strength initially after the stroke. Future work is needed to directly link these mechanisms and measures.

4.8 Implications and future directions

The results of our research suggest that, clinically, rehabilitation should be emphasized early after stroke. Pharmacological therapeutics such as amphetamines or SSRIs could potentially improve neuroplasticity during (Chollet et al., 2011; Stroemer, Kent, & Hulsebosch, 1998; Walker-Batson, Smith, Curtis, Unwin, & Greenlee, 1995), or could even extend the duration of the sensitive period (K. L. Ng et al., 2015). Neurostimulation studies have shown promising results for improving recovery post stroke (e.g. Brighina et al., 2003; Grefkes et al., 2010; Sparing et al., 2009). TMS and tDCS have local, but also distant, effects that can be measured as changes in functional connectivity (M. D. Fox, Halko, Eldaief, & Pascual-Leone, 2012; Liew, Santarnecchi, Buch, & Cohen, 2014). The mechanisms are not yet clear and

understanding what connectivity changes specifically are related to the recovery of a particular deficit could be an important guide for the targeting of sites to stimulate.

We have shown functional connectivity changes related to the recovery of neglect, and multiple other studies have shown that, similarly, interhemispheric connectivity is related to the recovery of motor deficits. Other work in our lab (Siegel et al, submitted) shows that there are network-specific patterns of FC dysfunction, predominantly interhemispheric, that predict language, memory, motor, attention and visual deficits. There is also a set of regions spread across multiple networks, the decreased interhemispheric FC of which is associated with deficits in multiple domains. This emphasizes the importance of interhemispheric communication for behavior, and suggests that targeting the affected networks could be of use in improving recovery. We discussed the connectivity changes during neglect recovery, but the relationship between the interhemispheric decrements in connectivity in the other domains and recovery still needs to be explored. Moreover, our research warrants further research into the mechanisms underlying general and deficit specific changes in network correlations.

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Appendix

Supplementary Table 3.4 List of 169 ROIs

ROI	Network	Hemisphere	x	y	z	Region	Homotopic pair
1	VNF	L	-25	-93	-2	LFovea-LO	1
2	VNF	L	-33	-86	10	LLO	2
3	VNF	L	-40	-78	-9	LMT	3
4	VNF	R	26	-90	26	RV3A	
5	VNF	R	28	-89	11	RLO-RV3A	2
6	VNF	R	26	-87	-9	Rfovea	1
7	VNF	R	34	-88	-4	RLO	
8	VNF	R	35	-79	0	RLO	
9	VNF	R	27	-84	-14	Rfovea-V4v	
10	VNF	R	42	-80	4	RLOMT	
11	VNF	R	43	-75	-11	RLOMT	3
12	VNF	R	37	-62	-11	RVOIT	
13	VNP	L	-2	-91	8	LV1d-V2d	
14	VNP	L	-13	-93	18	LV3-V3A	2
15	VNP	L	-14	-93	30	LV3A	
16	VNP	L	-23	-56	-2	LPOSd	4
17	VNP	L	-22	-71	6	LV7	
18	VNP	L	-8	-88	-7	LV1v	
19	VNP	L	-11	-74	-6	LVP	1
20	VNP	L	-7	-86	36	LPOSv	3
21	VNP	R	6	-77	11	RV1d	
22	VNP	R	14	-86	8	RV2d	

23	VNP	R	20	-92	18	RV3-V3A	2
24	VNP	R	11	-85	32	RV3-V3A	3
25	VNP	R	18	-76	26	RPOSd	
26	VNP	R	10	-77	-5	RV1v-RV2v	1
27	VNP	R	17	-64	-5	RVP	
28	VNP	R	23	-74	-10	RV4v	
29	VNP	R	20	-50	-3	RPOSv	4
30	DAN	L	-44	0	15	LFO	
31	DAN	L	-49	-5	32	LPrCe	1
32	DAN	L	-19	-8	57	LFEF	2
33	DAN	L	-27	-10	47	LdPrCe	
34	DAN	L	-53	-29	37	LvPoCe-SMG	3
35	DAN	L	-45	-34	45	LdPoCe	4
36	DAN	L	-32	-42	45	LaIPS	
37	DAN	L	-40	-42	-19	LITG	8
38	DAN	L	-22	-53	52	LmIPS	5
39	DAN	L	-31	-80	18	LvIPS	9
40	DAN	L	-43	-65	-2	LMT	6
41	DAN	L	-16	-65	49	LpIPS-SPL	7
42	DAN	R	39	30	12	RIFG	
43	DAN	R	45	-3	34	RPrCe	1
44	DAN	R	23	-8	55	RFEF	2
45	DAN	R	53	-28	36	RvPoCe-SMG	3
46	DAN	R	46	-32	50	RdPoCe	4
47	DAN	R	28	-49	52	RmIPS	5
48	DAN	R	46	-51	-14	RITG	8
49	DAN	R	18	-59	53	RpIPS-SPLd	

50	DAN	R	47	-61	0	RMT	6
51	DAN	R	20	-67	43	RpIPS-SPL	7
52	DAN	R	26	-69	30	RvIPSd	
53	DAN	R	35	-76	23	RvIPS	9
54	MN	M	1	-10	49	SMA	
55	MN	L	-24	-20	70	LdPrCe1	3
56	MN	L	-24	-32	63	LdPoCe	2
57	MN	L	-10	-12	60	LSMA1	
58	MN foot	L	-7	-44	56	LdmSPL	4
59	MN foot	L	-18	-36	55	LdCS	
60	MN	L	-42	-17	46	LcPrCe	
61	MN	L	-32	-25	46	LCS	1
62	MN	L	-12	-20	40	LSMA2	
63	MN	L	-54	-23	37	LvPoCe	8
64	MN	L	-57	-8	21	LvCS	5
65	MN	L	-51	-19	20	LS2	
66	MN	L	-44	-9	15	LmI	
67	MN	L	-31	-14	9	LmI2	6
68	MN	L	14	-57	-19	rcbl	7
69	MN	R	24	-34	60	RdPoCe	2
70	MN	R	11	-46	59	RSPL-preCun	
71	MN	R	22	-18	58	RdPrCe	3
72	MN foot	R	9	-43	53	RmdSPL	4
73	MN	R	10	-33	52	RSMA	
74	MN	R	37	-18	48	RCS	1
75	MN	R	54	-18	37	RvPoCe	8
76	MN	R	56	-2	23	RvCS	5

77	MN	R	31	-13	8	RmI2	6
78	MN	R	-13	-55	-16	lcbl	7
79	AN	L	-30	0	15	LmI3	
80	AN	L	-38	-4	11	LmI	5
81	AN	L	-37	-8	3	LmI	4
82	AN	L	-35	-20	14	LpI	3
83	AN	L	-51	-22	5	LmSTG	2
84	AN	L	-56	-33	16	LSTG1	1
85	AN	L	-29	-34	16	LpI	
86	AN	L	-43	-34	11	LSTG2	
87	AN	R	36	0	12	RmI	5
88	AN	R	38	-6	4	RmI	4
89	AN	R	50	-12	17	RmI	
90	AN	R	59	-19	11	RSTG2	2
91	AN	R	38	-19	12	RpI	3
92	AN	R	34	-24	17	RpI	
93	AN	R	53	-33	18	RSTG1	1
94	CO	M	-1	10	46	dACCmsFC	
95	CO	L	-12	-15	7	LaTha	2
96	CO	L	-33	13	9	LaI	1
97	CO	R	8	3	51	RpreSMA	
98	CO	R	10	-15	8	RaTha	2
99	CO	R	36	16	4	RaIfO	1
100	VAN	L	-33	17	-5	LAI	3
101	VAN	L	-44	10	8	LvIFG	2
102	VAN	L	-10	-32	43	LPC	4
103	VAN	L	-57	-48	32	LSMG	1

104	VAN	R	27	50	23	RaPFC	
105	VAN	R	42	28	1	RIFG-AI	
106	VAN	R	4	18	24	RAC	
107	VAN	R	39	11	21	RvPrCe	
108	VAN	R	46	11	9	RvIFG	2
109	VAN	R	30	8	-5	RAI	3
110	VAN	R	12	5	61	RMFC	
111	VAN	R	5	-22	40	RPC	4
112	VAN	R	52	-46	29	RSMG	1
113	VAN	R	54	-53	11	RSTG	
114	LAN	L	-48	30	-2	LIFG	
115	LAN	L	-44	25	-2	lifg1	1
116	LAN	L	-50	19	9	lifg2	2
117	LAN	L	-45	14	21	lmfg	
118	LAN	L	-7	9	60	lmfc4	
119	LAN	L	-54	-23	-3	lstg1	
120	LAN	L	-56	-33	3	lstg2	
121	LAN	L	-48	-44	3	lstg3	4
122	LAN	L	-52	-54	12	lstg4	3
123	LAN	R	47	25	-4	rifg1	1
124	LAN	R	53	23	7	rifg2	2
125	LAN	R	44	-36	6	rstg2	4
126	LAN	R	61	-43	8	rstg1	3
127	FP	M	0	-29	30	mCing	
128	FP	L	-28	51	15	LaPFC	
129	FP	L	-43	22	34	LdlPFC	3
130	FP	L	-41	3	36	LFC	4

131	FP	L	-51	-51	36	LIPL	5
132	FP	L	-31	-59	42	LIPS	1
133	FP	L	-9	-72	37	LprCu	2
134	FP	R	43	22	34	RdlPFC	3
135	FP	R	39	1	42	RdPrCe	4
136	FP	R	51	-47	42	RIPL	5
137	FP	R	30	-61	39	RIPS	1
138	FP	R	10	-69	39	RprCu	2
139	DMN	M	2	55	9	RmPFC2	
140	DMN	M	-1	44	-2	LAC1	
141	DMN	M	3	43	16	RmPFC1	
142	DMN	M	-4	42	45	LmSFG3	
143	DMN	M	-2	40	27	LmPFC2	
144	DMN	M	-5	31	-4	LAC3	
145	DMN	M	-3	28	55	LmSFG2	
146	DMN	M	4	24	-10	RAC2	
147	DMN	M	0	-32	36	RPC2	
148	DMN	M	0	-65	31	RPreCun	
149	DMN	L	-14	53	13	LMFG2	
150	DMN	L	-9	36	8	LAC2	
151	DMN	L	-19	22	52	LSFG	1
152	DMN	L	-6	16	63	LmSFG1	
153	DMN	L	-37	12	48	LMFG	
154	DMN	L	-41	7	-31	LITG	5
155	DMN	L	-23	-24	-11	Lhip	6
156	DMN	L	-57	-26	-12	LSTS	4
157	DMN	L	-8	-51	29	LpreCunPC	3

158	DMN	L	-41	-62	19	lag	
159	DMN	L	-43	-63	32	LAG	2
160	DMN	L	26	-78	-28	Rcbl	7
161	DMN	R	13	40	40	RSFG2	
162	DMN	R	17	24	51	RSFG	1
163	DMN	R	42	10	-29	RMTG2	5
164	DMN	R	52	-1	-25	RMTG1	
165	DMN	R	24	-20	-13	Rhip	6
166	DMN	R	59	-25	-12	RSTS	4
167	DMN	R	8	-51	29	RPCPreCun	3
168	DMN	R	45	-66	40	RAG	2
169	DMN	R	-25	-77	-33	Lcbl	7

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2008	Stella de Bode, PhD, Wilhelmina Children's Hospital, Utrecht, The Netherlands. *Voxel based morphology in cortical hemispherectomy patients.*
2007	- Erik Aarnoutse, PhD, University Medical Center, Utrecht, The Netherlands. *EEG based Brain Computer Interfacing using working memory.*
2003 – 2010	- Gerry Jager, PhD, Kuan Kho, MD, Erik Aarnoutse, PhD, Nick Ramsey, PhD, University Medical Center, Utrecht, The Netherlands. Summer and part time job as research assistant. Analyzed data, helped organized symposia

Awards

2010 – 2015	- McDonnell Academy Scholar
2014	- Nomination for "Mentor of the year award 2014" by the office of undergraduate research, Washington University, St Louis, MO
2009	- Erasmus Scholarship

Service

2015	- Member of SAGE Young Professionals Board Raising awareness of SAGE among the community age 60 and under by organizing fundraisers, serving as ambassadors in the St. Louis community and promoting SAGE events and programs
2013, 2014	- Organizer of Neuroscience student "Work in Progress" presentations
2013	- Student representative on committee to restructure the Systems Neuroscience course for graduate students, Washington University, St Louis, MO
2012, 2013	- Outgrads Co-President, Washington University, St Louis, MO Organized events and fundraisers, lead the board, worked with other student groups, and mentored undergraduate students
2012	- I-CAN Senator, International graduate students association for Career development And Networking, Washington University, St Louis, MO Organized airport pickups for international students, assisted with event organization
2011	- Outgrads Secretary, Washington University, St Louis, MO Assisted in planning events and fundraisers, coordinated with the rest of the board, took notes
2009	- Mind the brain symposium committee member, Utrecht University, The Netherlands. Assisted in planning the symposium, made the abstract book

Professional development

Spring 2016	- Course Design Institute Workshop on designing an undergraduate course

Fall 2015	- Introduction to the Scholarship of Teaching and Learning Class on developing a project to test teaching effectiveness
Spring 2015	- Seminar on professional development Class on alternative academic and non academic careers
2012-2015	**Workshops** – Developing a Scholarly Approach to Teaching – Peer-Led Team Learning (PLTL): Philosophy and Implementation – Writing a Teaching Philosophy Statement – Structuring an Introductory STEM Course – Problem-Based and Case-Based Learning: Designing Materials – Strategies for Inclusive Teaching – Designing and Facilitating Group Work – Designing Writing Assignments – Teaching a Problem Solving or Recitation Subsection – Teaching a Laboratory Subsection – Leading a Discussion Subsection – Incorporating Active Learning

Publications

Ramsey, L.E., Siegel, J.S., Baldasarre, A., Metcalf, N.V., Zinn, K., Shulman, G.L., Corbetta, M. (submitted). Normalization of network coherence underlies hemi-spatial neglect recovery following stroke. *Submitted*

Siegel, J.S., **Ramsey, L.E.,** Snyder, A.Z., Metcalf, N.V., Chacko. R.V., Weinberger, K., Baldassarre, A., Hacker, C.D., Shulman, G. L., Corbetta, M.. Common and specific disruptions of network connectivity predict impairment in multiple behavioral domains after stroke. *Submitted*

Baldassarre, A., **Ramsey, L.,** Rengachary, J., Zinn, K., Siegel, J. S., Metcalf, Shulman, G. L., Corbetta, M. (2016). Dissociated functional connectivity profiles for motor and attention deficits in acute right-hemisphere stroke. *Brain*

Patel, K., **Ramsey, L.,** Metcalf, N., Shulman, G., and Corbetta, M. (2016). Early Diffusion Evidence of Retrograde Trans-synaptic Degeneration in the Human Visual System. *Neurology*

Siegel, J. S., Snyder, A.Z., **Ramsey, L**., Shulman, G.L., & Corbetta, M. (2015). The effects of hemodynamic lag on functional connectivity and behavior after stroke. *Journal of Cerebral Blood Flow & Metabolism*

Corbetta, M., **Ramsey, L.,** Callejas, A., Baldassare, A., Hacker, C.D., Astafiev, S.V., & Shulman, G.L. (2015). A Common Behavior Clusters and Subcortical Anatomy in Stroke. *Neuron*

Baldassarre, A., **Ramsey, L.,** Hacker, C., Callejas, A., Astafiev, S.V., Metcalf, N.V., & Corbetta, M. (2014). Large-scale changes in network interactions as a physiological signature of spatial neglect. *Brain*

Blankertz, B., Tangermann, M., Vidaurre, C., Fazli, S., Sannelli, C., Haufe, S., Maeder, C., **Ramsey, L.**, Sturm, I., Curio, G., Müller, KR. (2010). The Berlin Brain-Computer Interface: Non-Medical Uses of BCI Technology. *Frontiers in neuroscience*, *4*, 198.

Sommer, I., Cohen-Kettenis, P., van Raalten, T., vander Veer, A., **Ramsey, L. E.,**

Gooren, L., Kahn, R., et al. (2008). Effects of cross-sex hormones on cerebral activation during language and mental rotation: An fMRI study in transsexuals. *European Neuropsychopharmacology*, *18*(3), 215–221.

Poster Presentations

Ramsey, L.E., Baldassarre, A., Shulman, G.L., Corbetta, M. (2014). Importance of task positive and task negative interactions in neglect recovery. *Conference on Resting State/Brain Connectivity 2014*

Ramsey, L. E., Rengachary, J., Strube, M.J., Zinn, K.L., Shulman, G.L., Corbetta, M. (2012).Principle component analysis derived clusters of behavioral deficits caused by stroke. *Neuroscience 2012.*

Callejas, A., **Ramsey, L.E.**, Baldassarre, A., Metcalf, N.V., Rengachary, J., Zinn,

K., Astafiev, S.V., Connor, L.T., Carter, A.R., Shulman, G.L., Corbetta, M. (2012). Lesion distribution and functional outcome for first time stroke in a population representative sample. *Neuroscience 2012.*

Ramsey, L.E., Tangermann, M., Haufe, S., & Blankertz, B. (2009). Practicing fast-decision BCI using a“ goalkeeper” paradigm. *CNS 2009*

De Bode, S., **Ramsey, L.E.,** Bonilha, L., & Mathern, G. (2009). Cortical Athrophy in the Remaining hemisphere Following Hemispherectomy Predicts Motor Performance. *HBM 2009*, 1–1.