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Adapting the concepts of brain and cognitive reserve to post-stroke cognitive deficits: Implications for understanding neglect

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ABSTRACT

Advanced lesion mapping and connectivity analyses are currently the main tools used to understand the mechanisms underlying post-stroke cognitive deficits. However, the factors contributing to pre-stroke architecture of cognitive networks are often ignored, even though they reportedly play a decisive role in the manifestation of cognitive impairment in neurodegeneration. The present review on post-stroke cognitive deficits therefore adopts the concept of brain and cognitive reserve, which was originally developed to account for the individual differences in the course of aging and neurodegenerative diseases. By focusing on spatial neglect, a typical network disorder, it is discussed how individual susceptibility to stroke lesion might explain the reported discrepancies in lesion anatomy, non-spatial deficits and recovery courses. A detailed analysis of the literature reveals that premorbid brain (age, brain atrophy, previous strokes, leukoaraiosis, genetic factors, etc.) and cognitive reserve (IQ, life experience, education, occupation, premorbid cognitive impairment, etc.) greatly impact the brain's capacity for compensation. Furthermore, the interaction between pre-stroke brain/cognitive reserve and the degree of stroke-induced system impairment (e.g., hypoperfusion, lesion load) determines both the extent of neglect symptoms variability and the course of recovery. Premorbid brain/cognitive reserves should thus be considered to: (i) understand the mechanisms of post-stroke cognitive disorders and sufficiently explain their inter-individual variability; (ii) provide a prognosis for cognitive recovery and hence post-stroke dependency; (iii) identify individual targets for cognitive rehabilitation: in the case of reduced brain/cognitive reserve, neglect might occur even with a confined lesion, and non-spatial training of general attentional capacity should represent the main therapeutic target also for treatment of neglect; this might be true also for non-cognitive domains, e.g., motor deficit. This alternative view of how neglect and other cognitive deficits occur and recover promotes discussion about plasticity and recovery to a general rather than a single stroke-based domain, providing more efficiency in recovery research.

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1. Introduction

Stroke continues to be one of the main causes of disability in humans. While the neuroimaging era is associated with a plethora of new data, the technique itself has mainly been used to study isolated brain functions, or is often only applied in one imaging mode, thus restricting our understanding of the causes and consequences of a particular functional deficit. Furthermore, while stroke often leads to cognitive decline or even manifestation of dementia, knowledge about stroke recovery and cognitive reserve are poorly combined and integrated, hindering further development of rehabilitation approaches. As life expectancy increases, cognitive networks are more likely to be compromised before stroke; therefore, clinicians and researchers will be increasingly confronted with more stroke cases that are accompanied by cognitive decline. Until now, neurodegenerative diseases and post-stroke cognitive deficits have been researched and discussed in different frameworks, and while the underlying pathologies are likely to differ, the biological and cognitive mechanisms of brain adaptation to impairment might not. Using spatial neglect as an example, the present review aims to highlight the individual susceptibility to stroke damage by presenting post-stroke cognitive deficits and establish a concept for tailored rehabilitation approaches by discussing (i) the role of premorbid individual characteristics for emerging of post-stroke cognitive deficits, and (ii) the factors influencing neural compensation and hence recovery on the network level. Although this review focuses on the role of brain and cognitive reserve, it is likely one of many factors that contribute to the clinically observed heterogeneity in the recovery from post-stroke deficits.

2. Spatial neglect and its controversial anatomy

Spatial neglect is the common term for deficits in the ability to perceive relevant contralesional stimuli, which cannot be explained by a primary sensory disturbance (Brain, 1941; Critchley, 1949; Heilman, Watson, & Valenstein, 2003). It is evoked by a dysfunction of a large-scale attention network (Mesulam, 1990), rather than by structural damage of specific brain regions (Corbetta & Shulman, 2011). This makes neglect an appropriate model for understanding the emergence and recovery patterns of post-stroke cognitive deficits. Neglect occurs more often and more severely after right hemisphere stroke (Becker & Karnath, 2007; Stone, Halligan, & Greenwood, 1993), and can be observed in any sensory or motor modality, or in distinct spaces related to patient's body or object coordinate (e.g., in the peri- or personal space; ego- or allocentric), though the most clinically-relevant and researched form is visual neglect (Vallar & Bolognini, 2014). The variability of neglect symptoms across patients emphasizes the complexity of the system used to code spatial information, as well as the heterogeneous entity of neglect syndrome (Malhotra & Russell, 2015; Vallar & Bolognini, 2014). This is also reflected in several theories of neglect (Bartolomeo, 2014; Karnath, 2015; Vallar & Bolognini, 2014), which are not intended to be

discussed here, but which, however, hardly explain recovery process from neglect and its variability.

Data on the neuroanatomy of neglect are controversial (Malhotra & Russell, 2015). Structural lesions in the inferior parietal lobe (Mort et al., 2003; Vallar & Perani, 1986), the anterior cingulate (Leibovitch et al., 1998), the temporo-parietal junction or superior temporal cortex (Karnath, Ferber, & Himmelbach, 2001), or the inferior frontal cortex (Husain & Kennard, 1996) in the right hemisphere can each evoke neglect. Neglect is also considered to be evoked by damage to either the long fronto-parietal pathways (Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007; Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomeo, 2008; Shinoura et al., 2009; Thiebaut de Schotten et al., 2011, 2014; Umarova et al., 2010; Urbanski et al., 2008) or the deep temporo-parietal white matter (Samuelsson, Jensen, Ekholm, Naver, & Blomstrand, 1997) connecting the parahippocampal and angular gyri (Bird et al., 2006). The controversies in anatomical correlates of spatial neglect have been linked to the heterogeneity of the behavioral symptoms. Distinct lesions might affect different domains of spatial cognition and can lead to a heterogeneous clinical profile (Azouvi et al., 2002; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010), while some clinical manifestations of neglect might not be detected due to insufficient testing (Bowen, McKenna, & Tallis, 1999; Saj, Verdon, Vocat, & Vuilleumier, 2012; Stone, Halligan, Marshall, & Greenwood, 1998). Another reason for the discrepancies in lesion anatomy might be the time point at which neglect is assessed: Since neglect might completely recover soon after stroke (Cassidy, Lewis, & Gray, 1998; Khurshid et al., 2012; Stone, Patel, Greenwood, & Halligan, 1992; Umarova et al., 2016), lesion anatomy during distinct stroke phases can differ significantly. The data, however, remain to be inconclusive even taking into account the heterogeneity of neglect. For example, egocentric neglect is reportedly associated with perisylvian lesions, while allocentric deficit is linked to more posterior lesions of the angular, middle temporal, and middle occipital gyri (Chechlacz, Rotshtein, & Humphreys, 2012). At the same time, hypoperfusion of temporal regions has been reported to lead to allo- and of parietal lesions to egocentric neglect (Hillis et al., 2005; Shirani et al., 2009).

Spatial extinction represents another type of spatial deficit, which is characterized by the failure to respond to a contralesional stimulus presented simultaneously with an ipsilesional one. Whether extinction is a 'mild' form of neglect or another kind of attentional deficit is still an open question. Some data have shown that these syndromes are dissociable (Hillis et al., 2006; Vallar, Rusconi, Bignamini, Geminiani, & Perani, 1994), also due to the distinct functional state of the attention network (Umarova et al., 2011). On the other hand, extinction has also been described as part of the neglect syndrome, especially when the lesions are clustered in the inferior parietal lobe (Posner et al., 1984; Vallar et al., 1994; Rees et al., 2000; Vuilleumier and Rafal, 2000). Anatomically, extinction can be caused by hypoperfusion and subsequent lesion to the right temporo-parietal junction and temporal cortex (Chechlacz et al., 2013; Karnath, Himmelbach, & Küker, 2003; Ticini, de Haan, Klose, Nagele, & Karnath, 2010), as well as to the occipital (Hillis et al., 2006) and inferior parietal cortex (Vossel et al., 2011). Though a few studies were able to

dissociate neglect and extinction phenomena anatomically (Chechlacz et al., 2013; Vossel et al., 2011), the lesion anatomy of neglect and extinction shows an overlap.

About one third of neglect patients demonstrate persistent deficit (Campbell & Oxbury, 1976; Cassidy et al., 1998; Samuelsson et al., 1997). The literature on lesion anatomy underlying neglect persistence or recovery is also inconclusive. For example, damage to the temporal (Karnath, Rennig, Johannsen, & Rorden, 2011; Saj et al., 2012) or fronto-parietal (Farnè et al., 2004) regions was reported to predict a poorer recovery from neglect; post-stroke atrophy of ipsilesional white matter (Lunven et al., 2015; Samuelsson et al., 1997) was also linked to persisting neglect. At the same time, patients with comparable lesion size and anatomy might differ in their recovery pattern, while the latter is determined by functional connectivity within the preserved network (Umarova et al., 2016). Therefore, it is unclear whether lesion anatomy alone possesses enough power to predict neglect occurrence and recovery, or whether an individual's characteristics and size of the lesion (Peers et al., 2005) also have to be taken into account. In line with the latter, Cherney and Halper (2001) reported no influence of lesion anatomy on further recovery of neglect (Cherney & Halper, 2001). A recent study showed that the locus of damage only plays a minor role in contributing to the variance of attention deficits (Corbetta et al., 2015).

3. Adapting the concepts of cognitive and brain reserve for heterogeneity of neglect anatomy and recovery

How discrepancies in anatomy of neglect and its recovery can be explained? Studies performed before the 'neuroimaging era' mainly analyzed clinical factors and lacked the methodological power to comprehensively evaluate lesion anatomy. In turn, advanced neuroimaging studies did not consider the individual's capacity to respond to and recover from the lesion. This can be partly explained by the necessity for large sample data in order to control for many possible confounding factors, a feat which is hardly achievable in advanced neuroimaging studies.

In comparison to the other functional systems that are commonly damaged in stroke, such as the more 'centered' to functional nodes motor and language systems, spatial attention is heavily reliant on the intactness and effectiveness of the entire cognitive network (Corbetta & Shulman, 2002; Mesulam, 1981). Therefore, to explain the anatomy of and recovery from neglect, it is not only the damaged part of the network that should be considered, but also the spared part, which determines how and to what extent the lesion could be compensated. This might represent a more favorable alternative to the existing approaches that are based purely on static interpretation of mapped lesions.

The inter-individual variability in response to brain damage is captured by concepts of brain and cognitive reserve. These concepts were recently developed to elucidate the compensatory mechanisms underlying aging and dementia, and to account for the frequent discrepancy between the degree of brain pathology versus functional deficit in a given patient (for Review see Barulli & Stern, 2013). Though the concepts of brain and cognitive reserve were proposed as independent models, in the present review we will consider them together as factors determining pre-stroke network architecture and its effectiveness. The neural applications of these concepts for stroke are represented by (i) brain and cognitive reserve, (ii) severity of lesion (intrinsic challenge), while their interaction determines (iii) neural compensation (Fig. 1). Brain and cognitive reserves represent the neural 'hardware' and 'software' that respectively compensate for stroke damage. For neurodegeneration, brain reserve is defined by pre-morbid brain size (e.g., total intracranial volume), the number of neurons and other quantitative parameters, or genetic factors such as APOE (Barulli & Stern, 2013). For stroke patients, the premorbid (pre-stroke) brain reserve might consist of (i) developmental and genetic factors with e.g., total intracranial volume and APOE as proxies; (ii) changes related to normal aging; (iii) the extent of pre-stroke brain pathology with e.g., previous strokes, brain atrophy, leukoaraiosis as proxies. Though these factors correlate with each other (higher age is associated with both more severe brain atrophy and leukoaraiosis), their manifestation varies significantly across patients. Nowadays, there is clear evidence for a relevance of brain reserve in the occurrence and recovery from neglect. Large sample data has shown that spatial neglect is more common in older stroke patients (Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1997; Ringman, Saver, Woolson, Clarke, & Adams, 2004) or those with extreme hemoglobin level (Gottesman, Bahrainwala, Wityk, & Hillis, 2010; Luvizutto et al., 2014), and that this association seems to be independent of infarct size and stroke severity (Gottesman et al., 2008). Diffuse cortical brain atrophy (Levine, Warach, Benowitz, & Calvanio, 1986) or leukoaraiosis (Bahrainwala, Hillis, Dearborn, & Gottesman, 2014) are additional factors strongly associated with the occurrence and severity of neglect, which constrain the brain capacity to compensate for stroke damage (Fig. 1). Most of studies in neglect controlled only for demographic age, which insufficiently reflects brain reserve due to the high variability in individual anatomical features, age-related brain changes and co-morbidities.

Cognitive reserve is defined as a function of lifetime intellectual activities and other environmental factors (e.g., occupational-educational history, crystallized intelligence, number of intellectually stimulating leisure activities, socio-economic status etc.), which shape network efficiency, processing capacity and flexibility (Barulli & Stern, 2013). Cognitive reserve modulates the cognitive effects of pathology and normal aging (Barulli & Stern, 2013; Vemuri et al., 2012, 2011). In stroke research, cognitive reserve can be assessed as education years, education degree level, vocabulary, and questionnaires on occupational or status attainment. Future studies should explore if crystalized and fluid intelligence assessment are also appropriate at least in the chronic stroke phase. Anosognosia — a syndrome highly associated with neglect (Buxbaum et al., 2004; Starkstein, Fedoroff, Price, Leiguarda, & Robinson, 1992; Vallar & Bolognini, 2014; Vossel et al., 2012) — occurs more often in patients who are cognitively-impaired before stroke (Appelros, Karlsson, Seiger, & Nydevik, 2003). Besides one study showing a lack of association between the level of pre-stroke cognition and the

Degree of recovery

⇑

Neural compensation:
- Structural reorganisation
- Functional reorganisation

⇑

Presence / severity of initial
neglect

Brain and cognitive reserves: ⟷ Severity of network
Different susceptibiltiy to lesion   impairment by stroke

Premorbid brain reserve:
- developmental/genetic factors
  (e.g. brain size*, APOE*)
- age-related changes (e.g. age [1])
- pre-stroke brain pathology
  (e.g. brain atrophy [2]/ leukoareosis [3],
  previous stroke *)

- Hypoperfusion [4]
- Lesion size [5]
- Lesion anatomy: localisation [6],
  disruption of functional [7]/
  structural connectivity [8]
- Presence of hemianopia [9]

Premorbid cogntive reserve:
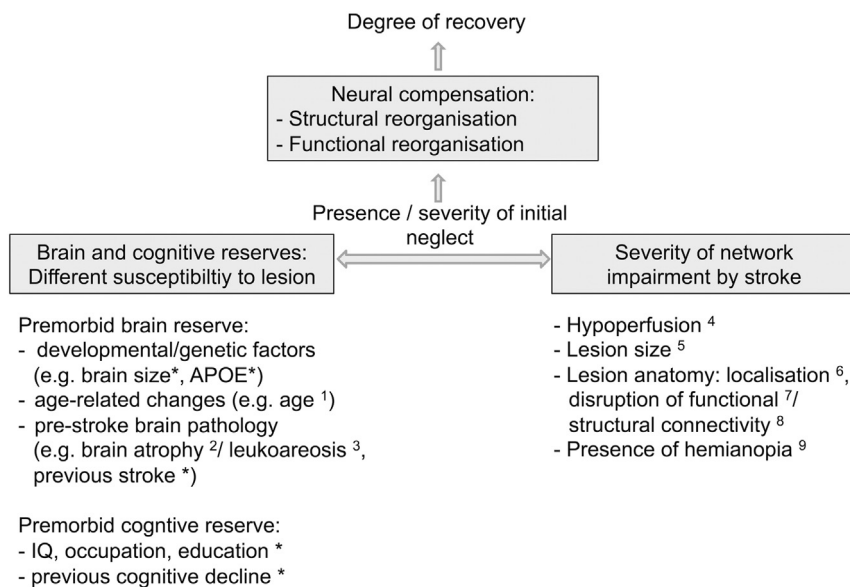- IQ, occupation, education *
- previous cognitive decline *

Fig. 1 – Schematic representation of the brain/cognitive reserve concept in the context of neglect. Brain and cognitive reserves might explain the individual susceptibility of each patient to stroke lesion. The interaction between lesion factors and brain and cognitive reserves further determines whether neglect will occur and how it will recover. This concept could also be applied to other post-stroke cognitive deficits. 1 – (Gottesman et al., 2008; Pedersen et al., 1997; Ringman et al., 2004); 2 – (Levine et al., 1986); 3 – (Bahrainwala et al., 2014); 4 – (Hillis et al., 2000; Khurshid et al., 2012); 5 – (Hier et al., 1983; Karnath, Fruhmann Berger, Kuker, & Rorden, 2004; Levine et al., 1986); 6 – (Farnè et al., 2004; Karnath et al., 2011; Saj et al., 2012); 7 – (Baldassarre et al., 2014); 8 – (Corbetta et al., 2015; Lunven et al., 2015; Samuelsson et al., 1997; Thiebaut de Schotten et al., 2014; Umarova et al., 2014); 9 – (Hier et al., 1983; Karnath et al., 2011; Samuelsson et al., 1997). * – data from other post-stroke cognitive deficits (for references please see main text).

occurrence of neglect (Appelros et al., 2003), cognitive reserve has unfortunately not been investigated in the context of spatial neglect.

Importantly, brain and cognitive reserve might interact, since function impacts the structure and vice versa (Budisavljevic et al., 2015; Draganski et al., 2004; Thiebaut de Schotten et al., 2011; Zatorre, Fields, & Johansen-Berg, 2012). For stroke patients, this multicollinearity might be even more complex: subjects with higher cognitive reserve tend to lead a healthy life style and a better management of vascular risk factors, and hence will show better brain reserve (less severe brain atrophy, less severe leukoaraiosis, etc.). Therefore, the consideration of proxies of cognitive reserve might provide more insight into causal-end-effect relations in stroke research. Moreover, cognitive reserve is easier to measure in the routine clinical practice and large stroke trials than its neurophysiological underpinnings such as altered functional connectivity (Marques et al., 2016; Santarnecchi, Rossi, & Rossi, 2015) or its reorganization (Eavani et al., 2016), gray matter volume or its metabolism (Arenaza-Urquijo et al., 2013) or noradrenergic activity (Robertson, 2014).

Factors influencing the severity of lesion in context of spatial neglect, or severity of network impairment, are in contrast well investigated. This is determined not only by lesion location but also size. Large lesions more often lead to neglect and compromise further recovery (Hier, Mondlock, & Caplan, 1983; Karnath et al., 2011, 2004; Levine et al., 1986; Smith, Clithero, Rorden, & Karnath, 2013); the same applies to lesions associated with hemianopia (Hier et al., 1983;

Samuelsson et al., 1997) probably by restricted neural compensation due to reduced sensory input. There is a great influence of other ischemic factors besides lesion ones (e.g., initial mismatch size, timepoint of recanalization, incomplete cortical necrosis) that influence neglect occurrence and outcome (Hillis, Barker, Beauchamp, Gordon, & Wityk, 2000; Leibovitch et al., 1998; Weiller et al., 1993). Therefore, the individual severity of network impairment by stroke is difficult to assess, but it is reflected by the initial pronouncement of neglect symptoms, which can sufficiently predict further recovery (Cassidy et al., 1998; Karnath et al., 2011; Samuelsson et al., 1997; Stone et al., 1992).

Neural compensation refers to situations where neuropathology compromises primary task-related networks and hence requires the recruitment of additional, compensatory networks to accomplish the task (Barulli & Stern, 2013). At the system level, compensatory brain responses contributing to stroke recovery include activation in secondary areas that are normally connected to the injured zones through a distributed network, a shift in interhemispheric lateralization toward the contralesional hemisphere, and shifts in representational maps surrounding the infarcted zone (Cramer, 2008). The recruitment of these compensatory strategies depends on properties and intactness of its operators – cortical centers and their connectivity, – and therefore on brain and cognitive reserve. For example, age (Ward, Swayne, & Newton, 2008; Ziegler, Ridgway, Dahnke, & Gaser, 2014) and behavioral experience (Draganski et al., 2004; Granert et al., 2011) influence cortical anatomy and function, whereas anatomical

features of cortical centers predict network output (Amunts et al., 1999, 2004). Similarly, white matter microstructure depends on age (Giorgio et al., 2010) and behavior (Sexton et al., 2016); and the inter-subject variability in white matter anatomy (Burgel et al., 2006) impacts behavioral performance in healthy subjects (Thiebaut de Schotten et al., 2011; Bender, Prindle, Brandmaier, & Raz, 2016) and stroke patients (Forkel et al., 2014). Altogether, applying the concept of brain/cognitive reserve allows generalization of factors influencing stroke recovery, and improves our mechanistic understanding of many single biomarkers. Factors benefitting network efficiency/capacity — e.g., by stronger inter-connectivity within it or by higher cortical excitability/density — facilitate recovery. And vice versa: worse connectivity within networks (e.g., leukoaraiosis) or damage to secondary cortical centers (e.g., by previous stroke) constrains the recovery potential. It is to emphasize that the weight of brain/cognitive reserve on stroke recovery depends on the functional domain: varying from very high for large-scale distributed networks underlying cognitive functions (e.g., spatial attention) to very low for localized networks (e.g., motor system).

Lesion load also determines the compensational strategies: a small lesion of the association cortex might be well compensated by perilesional cortex (Umarova et al., 2016), but would require a shift in interhemispheric lateralization or recruitment of secondary functional centers if the primary motor cortex would suffer a stroke (Ward, Brown, Thompson, & Frackowiak, 2003a, 2003b). In many cases, the larger the injury or greater the deficits, the more compensatory events are needed (Cramer, 2008). Therefore, the network capacity for neural compensation is a product of the interaction between premorbid brain and cognitive reserves, and the severity of stroke-induced network impairment (Fig. 1). The network's capacity to compensate is often reflected by severity of initial deficit. This actually explains why the severity of initial neglect (Cassidy et al., 1998; Karnath et al., 2011; Samuelsson et al., 1997; Stone et al., 1992), or overall stroke severity (Gottesman et al., 2008), can each be a strong predictor for neglect outcome. Thus, a stroke lesion could be uncritical *per se* without evoking neglect, if damage only occurs to single functional node of the spatial network, as other functional centers or perilesional cortex compensate the lesion. This explains, why damage restricted to the temporo-parietal junction only, which is essential for spatial processing (Corbetta & Shulman, 2002; Karnath & Dieterich, 2006), does not lead to neglect (Smith et al., 2013). Lesions encompassing all or most components of the network lead to profound neglect that transcends the mass effect of the larger lesion (Mesulam, 1981), and this occurs independent from brain and cognitive reserves. Lesions with intermediate size and localization might not lead to any kind of spatial deficit in individuals with high brain and cognitive reserves (e.g., young patients without previous stroke history), whereas they could provoke neglect or extinction in others (e.g., patients with accelerated neurodegeneration). Therefore, besides age, the brain and cognitive reserves are to be considered. In cases of critical lesions and insufficient brain and cognitive reserves, satisfactory post-stroke network efficiency is not achievable (Barulli & Stern, 2013); this is reflected by residual spatial deficits, even in clinically-recovered neglect (Bonato, 2015).

Poor interaction between brain/cognitive reserve and lesion factors (Fig. 1) might explain why in some neglect patients the network reorganization does not occur (Umarova et al., 2016) or with other words, why the undamaged part of the specific network might not compensate. Similarly, the severity of network impairment might explain the distinct role of the contralesional hemisphere (shift in hemispheric lateralization) in stroke recovery (Bestmann et al., 2010; Biernaskie, Szymanska, Windle, & Corbett, 2005; Blank, Bird, Turkheimer, & Wise, 2003; Crinion & Price, 2005; Johansen-Berg et al., 2002; Nishimura et al., 2007; Saur et al., 2006). Overall, evidence suggests that brain and cognitive reserves influence neglect occurrence and outcome. Furthermore, by considering initial neglect severity as a reflection of the individual's response to stroke damage, spontaneous recovery from neglect might be predictable (Fig. 1).

If all these assumptions are correct, then neglect might emerge without stroke but just due to the reduction of the brain and cognitive reserve. This is partly the case: whereas young adults show a strong attentional leftward bias (Bowers & Heilman, 1980; McCourt & Jewell, 1999; Voyer, Voyer, & Tramonte, 2012), normal aging is associated with its suppression or even a reversed rightward bias (i.e., behavior similar to spatial neglect) (Benwell, Thut, Grant, & Harvey, 2014; Failla, Sheppard, & Bradshaw, 2003; Fujii, Fukatsu, Yamadori, & Kimura, 1995; Schmitz & Peigneux, 2011). This is thought to result from age-related reduction of resources and dominance for attentional processing in the right hemisphere (Jewell & McCourt, 2000) or with other words decline in brain reserve. The role of brain and cognitive reserve is also partly confirmed by neglect occurring in neurodegenerative diseases (Andrade et al., 2012; Bublak, Redel, & Finke, 2006; Ishiai et al., 2000; Silveri, Ciccarelli, & Cappa, 2011; Venneri, Pentore, Cotticelli, & Della Sala, 1998), whereas damage to different neural substrates can produce different types of neglect (D'Anna et al., 2016; Silveri et al., 2011). The next question is, whether neglect is continuously worsening in stroke patients over years due to the continuous reduction of the brain and cognitive reserve resulting from aging-related neurodegeneration? Unfortunately there are currently no studies on the time course of neglect over more than two years post-stroke. A limited number of studies reported deterioration in some neglect tests in the subacute (Farnè et al., 2004) or chronic (Cherney & Halper, 2001; Halligan & Marshall, 1991; Stone et al., 1992) stroke phase, though without explicitly discussing this point.

4. Non-spatial deficits in neglect

Neglect has been also shown to be associated with non-lateralized deficits in spatial processing, such as non-lateralized deficits in spatial working memory (Malhotra et al., 2005; Wansard et al., 2014) with effects on visual search (Husain et al., 2001; Wojciulik, Husain, Clarke, & Driver, 2001), sustaining attention to spatial locations (Malhotra, Coulthard, & Husain, 2009), and abnormal temporal dynamics of visual attention (Husain, Shapiro, Martin, & Kennard, 1997). Besides deficient spatial processing, non-spatial deficits can also arise in neglect patients. These

include hypo-arousal and reduced alertness (Heilman, Schwartz, & Watson, 1978; Robertson, Mattingley, Rorden, & Driver, 1998), deficit of selective attention (Cassidy et al., 1998), impaired temporal resolution to transient events (Battelli et al., 2001, 2003), loss of attentional capacity (Robertson, 2001), impairment of general cognitive function (assessed by Mini-Mental State Examination), and poor performances in episodic memory, working memory/calculation, and constructional praxis, even after controlling for lesion volume, age, and education (Lee et al., 2008). Conversely, Farnè et al. (2004) did not find differences in sustained and divided attention between patients with and without neglect.

Non-spatial cognitive deficits may interact with spatial deficits and play an important role in determining the range, severity and duration of neglect (Vallar & Bolognini, 2014). Two underlying mechanisms are discussed in the literature. The first connects neglect to a fundamental loss of attentional capacity that is not confined to one region of space (Robertson, 2001) and hence induces further cognitive impairment; it is argued that non-spatially lateralized loss of attentional capacity is required to coexist with the spatial bias for the disorder to persist in a clinically significant way. The second explains the non-spatial deficit in neglect by damage to common attentional centers e.g., the fronto-parietal network (Corbetta & Shulman, 2011; Husain & Rorden, 2003), which provides both spatial and non-spatial processing (Duncan, 2013). According to the concept of brain and cognitive reserves, both explanations are possible (Fig. 2). Patients with
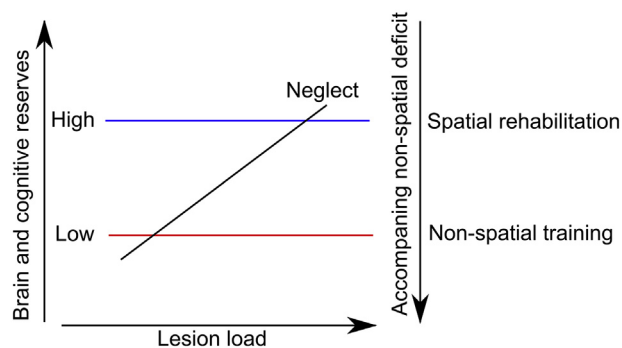

Fig. 2 — **Predicting how brain/cognitive reserves might influence the presence of spatial neglect and accompanying non-spatial deficits. Patients with sufficient brain and cognitive reserves are assumed to have suffered from a large, critically-located lesion in order to present with neglect. Patients with reduced neural reserves are predicted to present with neglect even in cases of restricted lesions, and should demonstrate pronounced non-spatial cognitive deficits, which at least in part of a premorbid origin. Such patients would not benefit from spatial rehabilitation; whereas non-spatial training of modalities such as alertness and sustained attention (Robertson, 2001) should play a decisive role here. This principle could also be applied to other post-stroke cognitive deficits: Training of elementary mental operations might be an important unspecific promoter to improve recovery of complex stroke-induced cognitive deficits in patients with reduced brain/cognitive reserve.**

sufficient brain and cognitive reserves but severe neglect — e.g., a young stroke patient with a subtotal infarct in the middle cerebral artery territory — will present with a non-spatial deficit due to damage to the common centers for spatial attention and other cognitive functions (Husain & Rorden, 2003). Neglect amelioration would be probably achieved by intensive training of spatial, lateralized functions. In contrast, older stroke patients or those with accelerated neurodegeneration (e.g., brain atrophy, leukoaraiosis) with seemingly uncritical lesion load can still suffer from neglect and will present with fundamental loss of attentional capacity (Robertson, 2001). This spatial imbalance would not benefit from spatial rehabilitation, but rather from training of attentional capacity, e.g., of alertness (Robertson et al., 1998; Sturm, Thimm, Kust, Karbe, & Fink, 2006; Thimm, Fink, Kust, Karbe, & Sturm, 2006) and sustained attention. Such patients might also benefit from pharmacological intervention (Gorgoraptis et al., 2012; Singh-Curry, Malhotra, Farmer, & Husain, 2011; Vossel, Kukolja, Thimm, Thiel, & Fink, 2010).

Application of the brain and cognitive reserve concept also allows another possible explanation for the association between non-spatial deficits and neglect. If neglect is more likely to occur in patients with reduced premorbid brain and cognitive reserves, it is possible that non-spatial deficits are not induced by stroke *per se*, but are rather premorbidly acquired or exacerbated by stroke. Although future studies with large-scale cognitive assessments are required to validate these assumptions, an individually-tailored approach to rehabilitation might improve stroke outcome and reduce disability in daily-life activities better than those therapies that do not take patients' neural reserves and ability to compensate into account.

Though neglect was shown to be associated with worse stroke outcome (Buxbaum et al., 2004; Denes, Semenza, Stoppa, & Lis, 1982; Jehkonen, Laihosalo, & Kettunen, 2006), the model used in these studies did not consider for lesion load or brain/cognitive reserve besides age, all of which can negatively influence stroke outcome (Leśniak, Bak, Czepiel, Seniów, & Członkowska, 2008). These studies also did not include the assessment of other cognitive deficits. In line with the point, rapid recovery from initial neglect did not directly improve the poor outcome (Jehkonen et al., 2000). Moreover, neglect only in combination with increased age predicted best the poor functional outcome (Jehkonen et al., 2000). Comprehensive analysis of demographic and co-morbid factors in 602 stroke patients showed no independent influence of neglect on admission and discharge Barthel Index, duration of rehabilitation in hospital, mortality, or rate of discharge from hospital for independent living (Pedersen et al., 1997). Thus, it is the interaction between restricted brain/cognitive reserves and lesion load rather than neglect *per se* that likely induces poor stroke outcome.

5.   Brain and cognitive reserves in other stroke-induced cognitive deficits

The concept of brain and cognitive reserve can explain the occurrence and recovery of other stroke-induced cognitive deficits. They are shown to be negatively influenced by

reduced brain reserve including older age (Jaillard, Grand, Le Bas, & Hommel, 2010; Klimkowicz-Mrowiec, Dziedzic, Słowik, & Szczudlik, 2006; Narasimhalu et al., 2009; Nys et al., 2005; Zhou et al., 2005), previous stroke (Mok et al., 2004; Narasimhalu et al., 2009; Pendlebury & Rothwell, 2009; Srikanth, Quinn, Donnan, Saling, & Thrift, 2006; Troncoso et al., 2008; Zhou et al., 2005), presence of Alzheimer's disease pathology (Troncoso et al., 2008) and APOE4 (Ballard et al., 2004; Wagle et al., 2009), brain atrophy and white-matter hyperintensities (Burton et al., 2003; Jokinen et al., 2005; McMurtray, Liao, Haider, Licht, & Mendez, 2007; Mok et al., 2004; Pendlebury & Rothwell, 2009; Sachdev et al., 2007; Stebbins et al., 2008; Wen et al., 2004) and diabetes mellitus (Klimkowicz-Mrowiec et al., 2006; Nys et al., 2005). Even for aphasia, which emerge from a dysfunction of more 'centered' network, the brain reserve is to be considered: For example, age (Engelter et al., 2006) and an intact contrale-sional language network (Forkel et al., 2014) have been suggested to explain partly the strong variance in language recovery among stroke patients (Lazar, Speizer, Festa, Krakauer, & Marshall, 2008). Cognitive decline and disability progression in multiple sclerosis also have been shown to be modulated by brain reserve measured as intracranial volume (Sumowski et al., 2014, 2016). Similarly, reduced cognitive reserve — such as a low level of education (Jaillard et al., 2010; Ojala-Oksala et al., 2012; Zhou et al., 2005) and pre-stroke cognitive decline (Mok et al., 2004; Nys et al., 2005; Srikanth et al., 2006) — can predict cognitive deficits induced by stroke. More severe stroke impairment characterized by larger (Nys et al., 2007), multiple (Saczynski et al., 2009) lesions and stronger initial stroke deficits (Jaillard et al., 2010; Mok et al., 2004) are also predictors for poorer stroke-induced cognitive deficits, also by constraining neural compensation (see Fig. 1).

All discussed issues are relevant for effective rehabilitation, i.e., to match the right patients with the right training approach (Cramer et al., 2011). Restricted brain/cognitive reserve might constrain effect of not only cognitive training but also rehabilitation on non-cognitive domains, e.g., motor function (Mullick, Subramanian, & Levin, 2015), since also the latter is based on learning of the new strategies and recruiting of collateral networks. Training of elementary mental operations might be an important unspecific promoter to improve recovery of complex cognitive (Manly, Hawkins, Evans, Woldt, & Robertson, 2002) and non-cognitive functions through cross-modal network interaction. Moreover, there are data on transition from post-stroke independence to dependence in the chronic stroke phase (Ullberg, Zia, Petersson, & Norrving, 2015). It is unknown if it is, at least partly, caused by the natural reduction of the brain/cognitive reserve and might be prevented by specific training. Future studies should investigate this issue to improve the long-term stroke outcome and to prevent the deterioration of post-stroke disability.

In summary, there is sufficient evidence in the literature to suggest that factors providing information on brain (e.g., brain volume, leukoaraiosis etc.) and cognitive (e.g., education years, vocabulary etc.) reserves, as well as the severity of stroke impairment (e.g., initial NIHSS-score, lesion volume etc.), should be reported and considered in addition to comprehensive lesion mapping of stroke-induced deficits. Future studies are required to determine how exactly neural compensation should be predicted after stroke, i.e., whether a cognitive test battery or a simpler scoring system for de-mographic and lifespan activities should be implemented. This question is essential, since without early cognitive training, post-stroke cognitive deficits might restrict the effectiveness of rehabilitation, also due to interaction with other domains including motor and language, and in turn compromise stroke outcome.

6. Conclusion

This review applied the concept of brain and cognitive re-serves in the context of neglect in an attempt to explain the inter-individual symptoms and lesion variability observed in stroke-induced cognitive disorders. This alternative view of how neglect and other cognitive deficits occur and recover provides several advantages. First, it elucidates different pat-terns of recovery, which warrant a finer evaluation of each patient's brain and cognitive reserves after stroke so that therapy can be individually tailored and potential outcome can be predicted. Second, it explains why certain types of therapeutic manipulation of the attention network improve other network functions (Robertson et al., 1998), and provides potential starting points for new rehabilitation approaches based on individual cognitive architecture. Finally, it pro-motes discussion about plasticity and recovery to a general rather than a single stroke-based domain, providing more efficiency in recovery research.

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