Dissecting and alleviating post-stroke fatigue: Cognitive phenotype, brain disconnectome mapping and non-invasive brain stimulation

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GENERAL SUMMARY

The overarching aim of this thesis has been to contribute to a better understanding of fatigue in the chronic phase after stroke. Although the acknowledgment of fatigue and the debilitating consequences associated with this condition has been on the rise for the last two decades, much is still unknown regarding underlying mechanisms. Moreover, treatment options are few and sparsely documented. Subtle cognitive impairments have been hypothesized to play a role in fatigue etiology, as have brain perturbations caused by the stroke lesion. Still, the literature is characterized by inconsistent findings, and further documentation of the detailed relationship between subjective fatigue, cognition, and neuronal underpinnings using sensitive measures is needed.

In three separate empirical papers, the present thesis examines chronic phase post-stroke fatigue at different levels, using a mix of methods and novel approaches. Starting with the cognitive and behavioral correlates of fatigue, we performed a detailed examination of the relationship between self-reported, general, subjective fatigue and cognitive performance using a well-documented attentional paradigm. Subjective fatigue was associated with a slowing of responses throughout the duration of the 20 min task session, and the effect was most pronounced in the most cognitively demanding condition, suggesting that fatigue entails an increased vulnerability for performance deterioration when the attentional system is put under sustained pressure. The effect was not found for depression, suggesting that this type of sustained tasks may be particularly sensitive to fatigue. In an effort to pinpoint the specific mechanisms driving the observed differences in response times, we fitted a computational drift diffusion model to the response time data. Results suggested that the interaction between time on task and fatigue was best explained by the parameter comprising sensory encoding and motor responses.

The search for brain perturbations associated with post-stroke fatigue is ongoing. Accumulating evidence highlights the role of network structure- and function for a range of symptoms, as illustrated by the observation that lesions affecting large white matter pathways or densely connected hubs may yield more severe symptoms. The effect of a lesion may thus be determined, at least in part, by the disconnectivity it causes in implicated networks and degree of preserved network function. In recognition of this, we applied a novel approach to

study the brain correlates of fatigue, by indirectly estimating the white matter pathway disconnection caused by the lesion, thus capturing not only the immediate damage caused by the stroke lesions but also distal effects. The results provided no evidence for a simple association between structural disconnectivity and fatigue, but revealed associations between fatigue, depression and sleep quality. Together, the findings supports that chronic phase PSS is a complex condition that is not simply explained by lesion characteristics such as extent and distribution of structural brain disconnection.

While there is currently little documentation on efficient treatment options for fatigue after stroke, preliminary evidence suggests beneficial effects of non-invasive brain stimulation. In a sham-controlled, randomized trial, we therefore evaluated the effect of repeated transcranial direct current stimulation (tDCS) combined with computerized cognitive training. Results revealed no added effect of tDCS. In recognition of the close association of fatigue and depression, we recorded symptoms at five consecutive time points during the intervention, and adopted a network approach to assess individual symptom centrality across time. Fatigue items demonstrated overall high centrality compared to depression items, suggesting that the impact of fatigue is of importance for the general symptom constellation. Also, patients withdrawing from the study had higher baseline fatigue scores and younger age than the patients completing, underscoring the need of individual adjustments of treatment protocols for this patient group.

Together, the results from Paper I – III suggest that subjective fatigue is associated with a time-dependent reduction in processing efficiency during sustained attentional effort, but do not provide evidence for a simple association between lesion characteristics, degree of structural disconnection and fatigue in the chronic stroke phase. tDCS did not demonstrate beneficial effects on self-reports of fatigue or depression. Future studies should aim to generalize the findings to a broader spectrum of the stroke patient population, both in terms of stroke severity and functional outcome.

LIST OF PAPERS

1. Ulrichsen, K. M., Alnæs, D., Kolskår, K. K., Richard, G., Sanders, A. M., Dørum, E. S., Ihle-Hansen, H., Pedersen, M. L., Tornås, S., Nordvik, J. E. & Westlye, L. T. (2020). Dissecting the cognitive phenotype of post-stroke fatigue using computerized assessment and computational modeling of sustained attention. *European Journal of Neuroscience*, *52*(7), 3828-3845. https://doi.org/10.1111/ejn.14861

2. Ulrichsen, K. M., Kolskår, K. K., Richard, G., Alnæs, D., Dørum, E. S., Sanders, A. M., Tornås, S., Sanchez, J. M., Engvig, A., Ihle-Hansen, H., de Schotten, M. T., Nordvik, J. E. & Westlye, L. T. (2021). Structural brain disconnectivity mapping of post-stroke fatigue. *NeuroImage: Clinical*, 102635. https://doi.org/10.1016/j.nicl.2021.102635

3. Ulrichsen, K.M., Kolskår, K.K., Richard, G., Pedersen, M. L., Alnæs, D., Dørum, E.S., Sanders, A.M., Tornås, S., Maglanoc, L. A., Engvig, A., Ihle-Hansen, H., Nordvik, J.E., Westlye, L.T. (2021). No effect of tDCS on fatigue and depression in chronic stroke patients: a randomized sham-controlled trial combining tDCS with computerized cognitive training. *Preprint available at MedRxiv* https://doi.org/10.1101/2021.06.22.21258133

ABBREVIATIONS

ANT	Attention Network Test
CCT	Computerized Cognitive Training
FSS	Fatigue Severity Scale
hDDM	Hierarchical Drift Diffusion Model
MRI	Magnetic Resonance Imaging
NIHSS	National Institutes of Health Stroke Scale
PHQ-9	Patient Health Questionnaire
PSD	Post-Stroke Depression
PSF	Post-Stroke Fatigue
RT	Response Time
tDCS	Transcranial Direct Current Stimulation
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
VSLM	Voxel-Based Symptom Lesion Mapping

INTRODUCTION

BACKGROUND

Fatigue, the feeling of being overly tired, worn out, devoid of energy and aversive to effort, is familiar to most of us. In its healthy form, transient fatigue provides a protective reaction to stress and high energy consumption, guiding us towards rest and energy restoration. Simultaneously, fatigue constitutes a hallmark symptom in a range of medical conditions. Here, in its pathological form, fatigue can be excessive and persistent, unresponsive to rest, and negatively affecting life in many aspects (Annoni, Staub, Bogousslavsky, & Brioschi, 2008). This is the type of fatigue commonly experienced after stroke, referred to as post-stroke fatigue (PSF). Karl Gustafsen, a 77 years old stroke patient suffering from PSF, describes his experience with fatigue like this:

"In the aftermath of the stroke, my greatest challenge seems to be this endless quantity of fatigue. It can be overpowering at times. Fatigue resulting from a stroke is recognized as a different species from normal fatigue. It's not just the physical sort you feel after, say, a hard mountain climb, nor the mental weariness you might feel after a long day at work. Post-stroke fatigue is more like a double whammy, hitting you broadside both mentally and physically to produce a bone-tiredness that chases you at every turn and is impossible to escape from, except in brief intervals" (Gustafson, 2019, p. 23).

Although fatigue is a fundamentally subjective experience, implying that we could find as many definitions of fatigue as there are sufferers, Gustafson's account paints a vivid picture of fatigue from a first-hand perspective that resonates well with the commonly used descriptions of post-stroke fatigue in the literature. And it touches on a central aspect of post-stroke fatigue, namely that it separates from normal tiredness by being disproportionate to efforts and difficult to relieve: it can be triggered by seemingly trivial activities, creating unpredictable and frustrating conditions for rebuilding life after stroke.

While recent years has offered an increased awareness of post-stroke fatigue in the clinic and a growing body of post-stroke fatigue research, our understanding of fatigue has not developed proportionally to efforts (Kuppuswamy, 2017). One of the major challenges in

research on post-stroke fatigue may be attributable to the nature of the phenomenon itself - as an unspecific and subjective symptom with low diagnostic specificity and aberrant definitions, fatigue presents as a challenging object for empirical research (DeLuca, 2005). For the individual patient, fatigue can be particularly difficult to cope with due to the invisibleness of the difficulties, leading to concerns about the legitimacy of the experience and challenges with explaining their condition to others (Röding, Lindström, Malm, & Öhman, 2003). Attempts to treat or alleviate post-stroke fatigue has largely fallen short, and a recent Cochrane report concluded that we do not yet have sufficient empirical support for any treatment (Wu, Kutlubaev, et al., 2015). Yet, its significance to patients can hardly be understated. Around 40 percent of stroke patients listed fatigue as the worst, or one of the worst, symptoms after stroke (Ingles, Eskes, & Phillips, 1999), and stroke care surveys have identified fatigue, emotional and cognitive problems amongst the main unmet needs in stroke survivors in the chronic phase (McKevitt et al., 2010; Walsh, Galvin, Loughnane, Macey, & Horgan, 2015).

The observation that fatigue plays a prominent role in the late/chronic stroke phase has important implications. Fatigue does not appear to follow a predictable trajectory of improvement over time, and a recent meta-analysis suggests increasing rates of fatigue with increasing time since stroke (Toby B. Cumming et al., 2018). Moreover, fatigue may present as the only remaining stroke complication in patients with nearly fully recovered strokes (Bogousslavsky, 2003; Staub & Bogousslavsky, 2001a). In this respect, fatigue represents for many a major obstacle for going back to life as it were, as the early and excessive exhaustion interferes with engaging in professional, social or leisure activities. Taken together, this conveys a sense of urgency to the work of advancing the current understanding of post-stroke fatigue, its constituents and correlates, and identification of efficient preventive or treatment approaches.

This thesis aims at contributing evidence to further our understanding of what post-stroke fatigue is and how it can be alleviated. Three papers are included, addressing fatigue in the chronic stroke phase at different levels: Paper I examines how fatigue manifests at the behavioral/cognitive level during a sustained attentional task, Paper II investigates the brain neurological substrate of fatigue and Paper III evaluates the effects of noninvasive brain stimulation combined with cognitive training on symptoms of fatigue and depression in a randomized controlled design. The thesis is organized in three main parts: 1) an introductory

section, where key concepts, current knowledge and knowledge gaps are discussed in relation to the three papers comprising the thesis, 2) a section presenting the paper in terms of aims, hypotheses, methods and results, and 3) a discussion of the thesis' contribution to the field, including methodological and ethical considerations, limitations, and future directions.

STROKE AND FATIGUE IN A HISTORICAL CONTEXT

Stroke is characterized by inadequate blood supply to the brain, causing brain cells to die from lack of oxygen and nutrients. It can be of ischemic or hemorrhagic origin, and represents a leading cause of deaths and disability worldwide (Donkor, 2018; Feigin, Norrving, & Mensah, 2017; Johnson et al., 2019). On a global scale, the population growth, increased life expectancy and increased prevalence of risk factors are likely to contribute to a rise in stroke prevalence (Di Carlo, 2009; Feigin et al., 2014; Feigin et al., 2016). Although recent years have offered major improvements in acute stroke care and survival rates (Lackland et al., 2014; Walsh et al., 2015), stroke was among the main causes disability in 2013, accounting for 4.5 percent of Disability-Adjusted Life Years (DALYs) (Feigin et al., 2017). Adding to the clinical and human burden of stroke, the economic costs associated with treatment, rehabilitation and informal care are substantial (Di Carlo, 2009; Rajsic et al., 2019). For most stroke survivors, having a stroke constitutes a life changing experience, and depending on stroke severity, some may need life-long care. Persistent deficits after stroke can manifest in a multitude of domains, including cognitive, motoric, language/speech, emotional and sensory-motoric functions (P. W. Duncan, Goldstein, Matchar, Divine, & Feussner, 1992; Hankey, Jamrozik, Broadhurst, Forbes, & Anderson, 2002; Leegaard, 1983). Among the long term consequences of stroke, post-stroke fatigue is among the most frequently reported (Walsh et al., 2015) and least understood (De Doncker, Dantzer, Ormstad, & Kuppuswamy, 2018).

While fatigue in association with other neurological diseases such as multiple sclerosis and Parkinson's disease has been widely recognized and extensively researched (de Groot, Phillips, & Eskes, 2003; Staub & Bogousslavsky, 2001a), the acknowledgement of post-stroke fatigue as an independent and frequent stroke sequela is relatively new. PSF was not even mentioned in the 1996 first edition of the handbook "Stroke: A practical guideline to management" (DeLuca, 2005). Fatigue after stroke was first addressed in an academic setting by Leegaard (1983), within the framework of "diffuse cerebral symptoms" together with other emotional and cognitive symptoms such as reduced memory, impaired attention and emotional lability. In the following decades, post-stroke fatigue was little researched and

generally considered to be a constituent of post-stroke depression (PSD) (Ponchel, Bombois, Bordet, & Hénon, 2015). As fatigue is a common symptom of depression, and the majority of depressed patients also experienced fatigue (P. N. Stein, Sliwinski, Gordon, & Hibbard, 1996), this was the dominant view until converging evidence of cases of post-stroke fatigue frequently appearing independent of depression (Ingles et al., 1999). In the coming years, numerous observations of patients suffering from fatigue in the absence of depression or other significant impairments, sparked interest in post-stroke fatigue as a specific syndrome (Bogousslavsky, 2003; Ingles et al., 1999).

EXTENT AND IMPLICATIONS

Prevalence

Despite a general consensus that post-stroke fatigue is prevalent in the stroke population, prevalence rates are highly variably, with estimates ranging from 35% to 92% (F. Duncan, Wu, & Mead, 2012). The discrepancies are explained in part by the lacking consensus on how to define fatigue, the use of different scales and different cut-off values, as well as heterogeneity in study designs and samples, where patients are assessed in different stages of recovery (Acciarresi, Bogousslavsky, & Paciaroni, 2014; Wu, Mead, Macleod, & Chalder, 2015). Moreover, variation in stroke type, stroke severity, age of included stroke survivors and number of comorbidities may affect estimates of prevalence rates (Ponchel et al., 2015).

Course of fatigue

The relationship between fatigue severity and time since stroke is encumbered with uncertainty, with studies reporting both increasing (Schepers, Visser-Meily, Ketelaar, & Lindeman, 2006), decreasing (Christensen et al., 2008) and stable (van Eijsden, van de Port, Visser-Meily, & Kwakkel, 2012) levels of fatigue with time. Notably, a recent individual participant meta-analysis including >2000 stroke patients assessed with the Fatigue Severity Scale (FSS), suggested greater fatigue with increasing time since stroke (Toby B. Cumming et al., 2018). Summarizing five longitudinal studies, Wu, Mead, et al. (2015) revealed that two thirds of patients with fatigue at early assessments (within ~three months after stroke onset) also reported fatigue in the chronic phase, while between 12 to 58% of the patients *not* experiencing early fatigue, had developed fatigue in the chronic phase. These observations led Wu, Mead, et al. (2015) to suggest three different temporal courses of fatigue; persistent fatigue, recovered fatigue and late onset fatigue.

Although early fatigue has been consistently identified as a predictor for late fatigue (Lerdal & Gay, 2013; Snaphaan, Van der Werf, & de Leeuw, 2011), the fact that fatigue can also initially emerge during the chronic phase suggests that there may be several etiologies and mediating factors following the acute stage (De Doncker et al., 2018). One conceptual model by Wu, Mead, et al. (2015) is in line with these observations, drawing a distinction between early and late fatigue. Here, they suggest that while early fatigue is predominantly determined by stroke lesion characteristics and biological factors associated with the stroke, late fatigue may be more strongly affected by behavioral and psychosocial factors, although residual neurological deficits and disability may perpetuate late post-stroke fatigue both directly and indirectly, through their effect on affective factors. However, studies have identified associations between stroke lesion characteristics and fatigue at 15 and 18 months post stroke onset (Snaphaan et al., 2011; Wai Kwong Tang et al., 2014), suggesting that stroke related brain perturbations may mediate fatigue in the chronic phase as well, although the mechanisms of such mediation are still largely unknown. I will elaborate on this subject in the section on PSF and lesion characteristics below.

A related account of early versus late fatigue has implicated an acute immune response and the secretion of inflammatory cytokines in the genesis of early fatigue (Ormstad, Aass, Amthor, Lund-Sørensen, & Sandvik, 2011, 2012; Wen, Weymann, Wood, & Wang, 2018). While acute phase cytokines and other blood components predicted fatigue at 6 and 12 months post stroke onset, no such associations were found for fatigue at 18 months since stroke (Ormstad et al., 2011), suggesting different pathways mediating early and late fatigue.

Implications

A growing body of research has related post-stroke fatigue to a range of negative outcomes. Fatigue after stroke can prevent social participation and rehabilitation adherence (Glader, Stegmayr, & Asplund, 2002; Nadarajah & Goh, 2015), and has been identified as an independent contributor to disability (Mandliya et al., 2016) as well as a predictor of increased mortality (Glader et al., 2002). The detrimental outcomes of persistent fatigue have also been demonstrated in a long term follow up study where fatigue and depression were identified as the major contributing factors to reduced quality of life in young stroke survivors (Naess, Waje-Andreassen, Thomassen, Nyland, & Myhr, 2006). On a related note, fatigue tends to be rated as a more severe symptom in patients with lower levels of physical or

cognitive disability (Van Zandvoort, Kappelle, Algra, & De Haan, 1998), possibly reflecting that fatigue constitutes and becomes a more salient symptom in patients with overall better recovery and more subtle disabilities, or that otherwise well-recovered patients have higher expectancies of things to return to normal and face higher demands from the environment (de Groot et al., 2003; Staub & Bogousslavsky, 2001a).

MEASUREMENT, DEFINITIONS AND MODELS

The literature on fatigue in general is characterized by a lack of consensus on terminology, conceptual frameworks and a vast number of different measurement instruments, and the PSF field is no exception (Kuppuswamy, 2017; Manjaly et al., 2019; Skogestad, Kirkevold, Indredavik, Gay, & Lerdal, 2019). In the following section, I provide a brief overview of frequently used measurement scales, definitions and models.

Measurements

A systematic review by G. Mead et al. (2007) identified no less than 52 fatigue scales applied in the literature, among which none were developed for post-stroke fatigue specifically. Based on an evaluation of measurement validity in relation to PSF, Mead et al. (2007) recommended the following four scales for post-stroke fatigue assessment: Fatigue Assessment Scale (FAS), Profile of Mood States (POMS-Fatigue), Multidimensional Fatigue Symptom Inventory (MFSI-General) and the vitality subscale of the SF-36v2 (McNair, Lorr, & Droppleman, 1971; Michielsen, De Vries, Van Heck, Van de Vijver, & Sijtsma, 2004; K. D. Stein, Martin, Hann, & Jacobsen, 1998; Ware Jr & Sherbourne, 1992). Other reviews (Lauren B Krupp, Nicholas G LaRocca, Joanne Muir-Nash, & Alfred D Steinberg, 1989) have identified the Fatigue Severity Scale (FSS) among the most commonly used measure for post-stroke fatigue (Toby B Cumming, Packer, Kramer, & English, 2016; Lerdal et al., 2009). The FSS is also recommended by the American Heart Association (AHA) for assessing fatigue after stroke (Hinkle et al., 2017).

Definitions and models

The subjective nature of fatigue implies that the patient´s self-reported experience is the primary basis for definitions and measurement (De Doncker et al., 2018). Commonly applied definitions in the literature are "*fatigue is a feeling of lack of energy, weariness, and aversion to effort*" (G. Mead et al., 2007), and "*decrease or loss of abilities associated with a heightened sensation of physical or mental strain, even without conspicuous effort, an*

overwhelming feeling of exhaustion, which leads to inability or difficulty to sustain even routine activities and which is commonly expressed verbally as a loss of drive" (Staub & Bogousslavsky, 2001a, p. 76). Other definitions found in the literature include:

"A feeling of physical tiredness and lack of energy that is described as pathological, abnormal, excessive, chronic, persistent or problematic"	(de Groot et al., 2003)
"A feeling of weariness, tiredness, and lack of energy that is pathologic and chronic»	(Choi-Kwon & Kim, 2011)
"A subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities" (Commonly used definition of fatigue in multiple sclerosis)	(Haselkorn, Balsdon Richer, & Fry Welch, 2005)
"A subjective experience of extreme and persistent tiredness, weakness or exhaustion after stroke, which can present itself mentally, physically or both and is unrelated to previous exertion levels"	(Zedlitz et al., 2012)
"Over the past month, there has been at least a 2 week period when patient has experienced fatigue, a lack of energy, or an increased need to rest every day or nearly every day. And this fatigue has led to difficulty taking part in everyday activities" (Case definition for community-dwelling patients)	(Lynch et al., 2007)

Fatigue has also been defined from a more mechanistic perspective, proposing that "*pathological fatigue is, thus, be best understood as an amplified sense of normal (physiological) fatigue that can be induced by changes in one or more variables regulating work output. Fatigue could develop during a disease because of dissociation between the level of internal input (motivational and limbic) and that of perceived exertion from applied effort*" (Chaudhuri & Behan, 2004, p. 979).

A recent theoretical development incorporates the acute immunological response with a mechanistic understanding of fatigue in the chronic stage (Kuppuswamy, Rothwell, & Ward, 2015). The authors speculate that the early proinflammatory environment may depress motor cortex excitability, and that these changes are irreversible in some patients, possibly

dependent on genotypes. The authors further suggest that such motor deficits coupled with alterations in sensory processing and poor sensory attenuation give rise to fatigue through an increase in "estimated action cost" or effort (De Doncker et al., 2018; Kuppuswamy et al., 2015).

As fatigue is considered a complex, multidimensional phenomenon, most theoretical accounts take on a biopsychosocial approach. Lerdal et al. (2009) focus on how fatigue is experienced, and propose a model consisting of three components; fatigue antecedents, experiences and effects. The suggested antecedents are personal factors, pre-stroke fatigue, stroke characteristics, biomarkers, and chronic diseases, while the component of experience also incorporates other concomitants of stroke, like depression, anxiety and sleep disturbance. Also according to the biopsychosocial framework, a model by Ormstad and Eilertsen (2015) propose that early fatigue is related to immune response and kynurenine pathway activation, but simultaneously emphasizes the importance of acknowledging fatigue in the late phase as a means of facilitating adaptive coping and thus decrease the risk of developing depression. Underscoring the complexity of post-stroke fatigue and the probability of numerous mechanisms in play, studies have identified sleep problems (Naess, Lunde, Brogger, & Waje-Andreassen, 2012), anxiety (Toby B. Cumming et al., 2018; Wu, Barugh, Macleod, & Mead, 2014), pain (Naess et al., 2012; Wai Kwong Tang et al., 2014), various medications (Chen & Marsh, 2018), lack of social support (K. M. Michael, Allen, & Macko, 2006), aphasia (Glader et al., 2002; Staub & Bogousslavsky, 2001b), reduced physical function (Lerdal et al., 2011; Aarnes, Stubberud, & Lerdal, 2020) and depression (Ponchel et al., 2015; Wu et al., 2014) to be associated with fatigue. Yet, causality has been hard to establish, and for many of the mentioned factors, the existence of a bidirectional relationship is likely.

As evident from the above definitions, post-stroke fatigue can manifest in the psychological and physical domains, and the notion of an increased weariness and sense of effort is central to several definitions. Regarding the mental aspect of the fatigue experience, there are several frameworks emphasizing the role of subtle cognitive deficits, particularly within attention and processing speed (Bushnik et al., 2015; Birgitta Johansson & Ronnback, 2014; Birgitta Johansson & Rönnbäck, 2012). The coping hypothesis (Van Zomeren, Brouwer, & Deelman, 1984; Van Zomeren & Van den Burg, 1985) originally developed in relation to patients with traumatic brain injury, in brief proposes that subtle cognitive impairments require

compensatory effort to maintain performance, which leads to the subjective feeling of fatigue. Evidence from imaging studies have provided some support to this framework by showing that, compared to healthy controls, individuals with TBI display increased brain network activity when performing attentional tasks (Kim et al., 2012; Kohl, Wylie, Genova, Hillary, & Deluca, 2009). Yet, the question of how or whether brain lesion characteristics in stroke relate to fatigue in the chronic phase, remains open. Below, I elaborate on the association between stroke lesions, cognitive deficits and fatigue.

STROKE LESIONS AND FATIGUE

Although the brain perturbations caused by the cerebral infarct is assumed to be a precipitating event in the development of post-stroke fatigue, the relationship between stroke lesion characteristics and fatigue etiology remains elusive (Paciaroni & Acciarresi, 2019). Observations of fatigue being more prevalent in the aftermath of minor strokes compared to transient ischemic attacks (TIA)(Naess et al., 2012; Winward, Sackley, Metha, & Rothwell, 2009) suggest that the cerebral infarction is of importance. Moreover, fatigue after stroke is described as qualitatively different than normal tiredness or pre-stroke fatigue by stroke survivors (Flinn & Stube, 2010; Thomas, Gamlin, De Simoni, Mullis, & Mant, 2019), and the fact that fatigue is a hallmark symptom in a range of neurological diseases and acquired brain injuries, also speaks of a central origin (Chaudhuri & Behan, 2004).

The findings on the relationship between fatigue and lesion characteristics are partly conflicting and largely inconclusive. One study identified basal ganglia infarcts as predictors of fatigue (Wai Kwong Tang et al., 2010), and caudate infarcts have been found to be more frequent in patients with fatigue (W. K. Tang et al., 2013). Moreover, Wai Kwong Tang et al. (2014) observed an increased risk of non-remitting post-stroke fatigue at 15 months post-stroke in patients with subcortical white matter infarcts, whereas Snaphaan et al. (2011) found higher risk of fatigue at 15 months post-stroke in patients with infratentorial lesion. Regarding the latter, brain stem and thalamic strokes have been associated with post-stroke fatigue (Mutai, Furukawa, Houri, Suzuki, & Hanihara, 2017), as have basilar artery infarctions (Naess, Nyland, Thomassen, Aarseth, & Myhr, 2005). It has been hypothesized that disruptions to the reticular activation system and associated subtle attentional deficits may contribute to PSF (Staub & Bogousslavsky, 2001b) and that disconnection between insula and the anterior cingulate cortex or frontal lobe, caused by right insula damage, may cause impaired energy or drive (Manes, Paradiso, & Robinson, 1999). Yet, the clinical

generalizability of these findings remains unclear, as several studies report no significant association between stroke location- or type, and fatigue (Appelros, 2006; Ingles et al., 1999; Kutlubaev et al., 2013; G. E. Mead et al., 2011; Ormstad et al., 2011; Radman et al., 2012; Schepers et al., 2006).

The lack of consistency with regards to the brain correlates of post-stroke fatigue may be partly attributable to varying times of measurement and differences in how lesion characteristics are defined and specified. Moreover, although lesion-based localization studies have produced indispensable insights in the relationship between brain and behavior, there is an increasing awareness of its inherent limitations. One of the key concerns stems from the clinical observation that lesions in different locations can give rise to the same clinical symptoms (Corbetta et al., 2015; Fox, 2018; Vuilleumier, 2013), through processes like e.g. diaschisis (where focal injury causes remote neurophysiological changes in distant regions) (Carrera & Tononi, 2014; von Monakow, 1914) and disconnection (Geschwind, 1974). Moreover, accumulating neuroimaging evidence suggest that many symptoms are related to complex brain networks in anatomically distant but interconnected regions (Lim & Kang, 2015), and that lesions affecting densely connected hubs or white matter pathways may be associated with more severe symptoms (Fox, 2018), implying that even smaller lesions may have large implications if localized in such areas. Following this logic, certain clinical symptoms in the aftermath of stroke, such as fatigue, may be mediated not primarily by the localization or size of the focal lesion, but rather by the functional neuroanatomy of the implicated networks and degree of preserved network function (Bartolomeo & de Schotten, 2016; de Schotten, Foulon, & Nachev, 2020; Lim & Kang, 2015).

Methods including connectivity-based measures, capturing network perturbations beyond the focal lesion, may therefore provide both a theoretically and clinically relevant tool for studying associations between lesion impact and specific symptoms after stroke. Newer advances/developments now allow for indirect estimations of individual lesions' effect on global brain connectivity (Foulon et al., 2018). Such lesion-network mapping approaches has been applied to the study of a variety of brain disorders (Darby, Joutsa, & Fox, 2019; Ferguson et al., 2019; van den Heuvel & Sporns, 2019), and recent work suggest improved predictive value with inclusion of implicated network projections (de Schotten et al., 2020; Griffis, Metcalf, Corbetta, & Shulman, 2019). Yet, this approach had not yet been applied to study post-stroke fatigue. In Paper II, we therefore investigate whether an indirectly estimated

maps of structural disconnection add insight on the relationship between lesion-related brain disconnectivity and fatigue beyond what is detectable by conventional lesion measures.

COGNITIVE IMPAIRMENTS AND FATIGUE

Long-term cognitive impairments are frequent following stroke (Mahon et al., 2017; Schaapsmeerders et al., 2013) and have been hypothesized to contribute to fatigue after acquired brain injuries (Birgitta Johansson & Ronnback, 2014; Ponsford et al., 2012). Problems with attention and memory are common complaints in otherwise well-recovered patients with PSF (Birgitta Johansson & Rönnbäck, 2012; Koopman et al., 2009), and many report increased fatigue when engaging in tasks requiring mental effort, referred to as mental fatigue (Birgitta Johansson & Ronnback, 2014). Still, the accumulated evidence on associations between post-stroke fatigue and objective cognitive correlates is divergent.

A recent review paper including 11 studies on post-stroke fatigue and cognition concluded that there are currently no convincing evidence of a significant association between global cognitive status and fatigue after stroke, but suggestive evidence of an association between attention, processing speed, memory and fatigue (Lagogianni, Thomas, & Lincoln, 2018), mirroring a previous review from Ponchel et al. (2015). Also, studies reporting no association between PSF and cognition tend to use rather coarse measures of general cognitive function, such as the Mini-Mental State Examination (MMSE; (Folstein, Folstein, & McHugh, 1975; Kutlubaev et al., 2013; van Eijsden et al., 2012), which may not be sufficiently sensitive to individual differences in less severe end of the clinical spectrum (Holtzer, Shuman, Mahoney, Lipton, & Verghese, 2010; Snaphaan et al., 2011).

It has been speculated that cases of post-stroke fatigue may be associated with subtle attentional impairments that is not readily revealed by standard neuropsychological assessments (Bogousslavsky, 2003), and that tests putting stronger demands on processing speed and attentional function *over time* may be more appropriate for detecting mental fatigue and its cognitive correlates (Holtzer et al., 2010; Birgitta Johansson & Rönnbäck, 2012; Jonasson, Levin, Renfors, Strandberg, & Johansson, 2018). Moreover, assuming that a key clinical characteristic of mental/cognitive fatigue is "*decreased performance during acute but sustained mental effort*" (DeLuca, 2005), temporal analyses/monitoring of performance may provide information that is not revealed by sum scores.

As revealed by a review on cognitive correlates (Lagogianni et al., 2018), the majority of significant correlations between self-reported fatigue and cognitive function were identified using mental fatigue sub-scales, and not general scales such as the FSS. Although the former may be more sensitive for the mental aspect of fatigue, it is plausible that reported correlations were higher because the items in mental fatigue scales also reflect subjective cognitive complaints rather than general fatigue (i.e. "I had trouble concentrating" (attention), "I have been forgetful" (memory), and "My thinking has been slowed down" (processing speed). The significant correlations may thus in part reflect an association between subjective and objective measures of cognitive impairments, rather than a relationship between general fatigue and cognition. In line with this, it has been suggested that for the purpose of evaluating the association between cognitive function and fatigue, general measures of fatigue should be included (Lagogianni et al., 2018).

In Paper I we therefore investigated the association between subjective general fatigue, attentional function and mental fatigue as defined above ("decreased performance during sustained effort") using the Attention Network Test (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002). The ANT is a widely used experimental paradigm, combining a cued reaction time task (Posner, 1980) with a flanker task (Eriksen & Eriksen, 1974), allowing for parsing of attentional components. Moreover, because the tasks involves 288 trials and lasts for 20 minutes, the effects of sustained effort can be evaluated. Furthering our understanding of the relationship between subjective fatigue, mental fatigability and attentional function is imperative, as these putatively connected constructs represent common obstacles to almost recovered stroke survivors hoping to return to previous activities and everyday life (Birgitta Johansson & Rönnbäck, 2012).

HOW CAN POST-STROKE FATIGUE BE ALLEVIATED?

Despite the growing acknowledgement of post-stroke fatigue as a distressing and prevalent problem after stroke, there is still uncertainty about how it can best be managed and alleviated. A randomized controlled trial demonstrated that a 12-week cognitive therapy intervention alleviated fatigue, with best effects being obtained when augmenting therapy with graded activity training (A. M. Zedlitz, Rietveld, Geurts, & Fasotti, 2012). However, the authors point to several study limitations such as lack of sham/control conditions, implying that the generalizability of the findings is uncertain. Mindfulness-based interventions have also shown some promise for alleviating fatigue in patients with MS and acquired brain

injuries (B. Johansson, Bjuhr, & Rönnbäck, 2012; Ulrichsen et al., 2016). Still, a 2015 Cochrane review comprising 12 intervention studies concluded that the evidence of the included treatments' efficacy was insufficient (Wu, Kutlubaev, et al., 2015). Following this, a pilot RCT has demonstrated beneficial effects of cognitive behavioral therapy (CBT) compared to treatment as usual (Nguyen et al., 2019), and a phase II trial has shown promising effects of modafinil with regards to fatigue and quality of life (Bivard et al., 2017). Due to the putative association between post-stroke fatigue and specific cognitive deficits, cognitive rehabilitation has been put forward as potentially relevant intervention for this patient group (Aarnes et al., 2020). Recently, a clinical trial revealed evidence supporting beneficial effects of a single session of tDCS in mildly impaired stroke patients suffering from high fatigue (De Doncker, Ondobaka, & Kuppuswamy, 2021). Together with positive effects from tDCS fatigue studies in other patient populations, this may suggest that tDCS has potential to relieve post-stroke fatigue.

tDCS

The interest in non-invasive brain stimulation techniques has grown significantly in the past 20 years (Fregni et al., 2015). tDCS represents one of the most frequently applied and extensively researched neuromodulatory techniques (Brunoni et al., 2012). It is typically administered via a battery-driven direct current stimulator with two electrodes (anodal and cathodal), whose location on the scalp is decided according to the brain functions of interest (Stagg & Nitsche, 2011). While the specific mechanisms by which tDCS modulate behavior are still unclear and reliable neurophysiological effects have been difficult to establish (Horvath, Forte, & Carter, 2015), the main mechanism of action is generally assumed to be altered cortical excitability induced by subthreshold modulation of neuronal membrane potential (Purpura & McMurtry, 1965; Woods et al., 2016). When coupled with relevant actions or tasks targeting the behavior one wish to modulate, altered cortical excitability may facilitate synaptic plasticity through LTP-like effects (Au et al., 2016; Woods et al., 2016).

Due to its assumed neuromodulatory properties, tDCS has been evaluated as a therapeutic intervention in a range of disorders, including but not limited to, Alzheimer's disease, chronic pain, depression and stroke recovery within motor and cognitive domains (Paulo Sergio Boggio et al., 2012; DaSilva et al., 2012; Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010; L. Valiengo et al., 2016; L. C. L. Valiengo et al., 2017). There is evidence suggesting that tDCS can boost the effects of behavioral interventions like language treatment for aphasia

(Fridriksson, Richardson, Baker, & Rorden, 2011) and cognitive training (Au et al., 2016; Jo et al., 2009; Martin, Liu, Alonzo, Green, & Loo, 2014), but the generalizability of such findings is unclear. Moreover, several studies have reported beneficial effects on fatigue after tDCS in patients with multiple sclerosis (Chalah et al., 2020; Charvet et al., 2018; Ferrucci et al., 2014), and the aforementioned study by De Doncker, Ondobaka, and Kuppuswamy (2020) found improvement of fatigue in stroke patients after a single session of anodal tDCS. While such preliminary findings are promising, it remains to be confirmed whether the fatigue-reducing effects of repeated tDCS seen in multiple sclerosis patients can be generalized to chronic stroke samples. This question is addressed in *Paper III*, where the effects of tDCS in combination with computerized cognitive training is evaluated with regards to self-reported symptoms of fatigue and depression.

Computerized cognitive training

Based on the general and emerging principle of the plastic brain, that is, the brain's ability to change in response to experience, the number of studies attempting to restore or improve cognitive functions through systematic training has been growing rapidly (Shipstead, Redick, & Engle, 2012). CCT is one on several types of cognitive training, typically consisting of repeated, structured sessions of various computerized tasks. The basic assumption is that repeated practice of tasks targeting specific cognitive abilities can lead to improved cognitive functioning bearing real-life implications (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008; Sternberg, 2008). The latter is typically the main goal, and is inherently relying on far-transfer effects, where improvement in performance on trained tasks will generalize to outcomes that are dissimilar to the trained tasks and ultimately every day functioning.

The identification of working memory as a central component of the cognitive system with a close relationship to higher cognition has motivated the development of training programs specifically targeting working memory functioning, with the hypothesis that working memory improvement may generate broader cognitive benefits (Klingberg et al., 2005; Morrison & Chein, 2011; Shipstead et al., 2012). While early findings were highly encouraging, suggesting that a fixed number of practices could produce increases in fluid intelligence (Jaeggi et al., 2008) and decrease symptoms of ADHD (Klingberg et al., 2005), a growing number of subsequent studies have failed to replicate the initial, promising effects (Redick, 2019). Specifically, the generalizability of practice effects beyond the specific training context (far-transfer effects) has been subject to much controversy and problematic to

establish. Several meta-analyses conclude that training effects are predominantly found in near-transfer tasks (tasks that are similar to the trained tasks), while evidence in support of generalized far-transfer benefits is weak to non-existent (Melby-Lervåg, Redick, & Hulme, 2016; Sala & Gobet, 2019). Yet, other meta-analyses have reported evidence for far transfer-effects, albeit smaller than near-transfer effects (Karbach & Verhaeghen, 2014) or evidence of effects under specific circumstances and for certain patient groups (Hill et al., 2017; Weicker, Villringer, & Thöne-Otto, 2016).

Summary

Accumulating evidence suggests that fatigue continues to impose a significant burden on stroke survivors' quality of life in years after stroke onset. However, current understanding of underlying mechanisms remain elusive, and effective treatment options are still not identified. It has been speculated that subtle cognitive deficits, particularly within attentional functions, may play a role in PSF etiology. Still, the literature on the relationship between fatigue and cognition remains largely inconclusive, possibly due to the use of screening measures with low sensitivity to subtle deficits and fatigue.

Among the biological correlates of post-stroke fatigue, stroke lesion characteristics have been most frequently studied. However, the predictive value of conventional lesion characteristics such as location, size or type, have remained unclear. Connectome-based approaches such as indirectly estimating the extended structural network disconnectivity implied by the lesion have not yet been applied to target post-stroke fatigue, and may have the potential to reveal new knowledge on the association with brain perturbations and fatigue.

Regarding treatment of post-stroke fatigue, the need for efficient interventions is widely recognized. Studies on fatigue in other neurological populations suggest that tDCS may have the potential to alleviate post-stroke fatigue. Coupled with computerized cognitive training, tDCS may be particularly efficient considering the hypothesized association between fatigue and cognitive impairments, but the effects and acceptability of repeated tDCS on post-stroke fatigue should be evaluated in randomized controlled trials.

MAIN RESEARCH OBJECTIVES AND HYPOTHESIS

PAPER I

Post-stroke fatigue is a prevalent and persistent symptom among stroke patients, and the current lack of a mechanistic understanding of its pathophysiology has impeded the development of targeted rehabilitation programs. Cognitive difficulties are common among stroke patients with post-stroke fatigue, but studies using conventional neuropsychological assessments have yielded divergent findings on the cognitive signatures related to post-stroke fatigue. In contrast to standard neuropsychological assessment, computerized assessment of sustained attention may be more sensitive to cognitive manifestation of fatigue.

Hence, the main objectives of Paper I was to characterize the relationship between subjectively reported fatigue and attentional function as measured by the ANT, and to investigate whether and how fatigue manifest in performance during sustained mental effort. The ANT was chosen as it is a widely used and well documented paradigm, enabling parsing of different attentional networks while simultaneously allowing for evaluating time-effects on performance. Based on previous literature on fatigue in other populations (Holtzer et al., 2010; Pauletti et al., 2017), we hypothesized that subjective fatigue would be associated primarily with executive network efficiency, and that subjective fatigue would interact with time-on-task, resulting in reduced performance after sustained effort for patients with high fatigue. A second aim was to evaluate whether a computational approach using drift diffusion modeling (DDM) of the behavioral data could elaborate the understanding of the hypothesized relationship between subjective fatigue and sustained performance. DDMs applied to fast two-choice decision tasks provide estimates of the cognitive processes assumed to underlie observed behavior (Roger Ratcliff & McKoon, 2008). In an exploratory analysis, we fitted a hierarchical drift diffusion model to the ANT behavioral data, and tested for associations between model parameters and subjective fatigue. Due to the exploratory approach, no specific hypotheses were defined.

PAPER II

Brain perturbations caused by the stroke lesion are assumed to be precipitating events in post-stroke fatigue etiology, but the specific predictive value of key lesion characteristics such as location and neuroanatomical distribution is still uncertain (De Doncker et al., 2018). The brain is increasingly conceptualized as a complex, highly interconnected network, implying that abrupt changes to key neural pathways can spark cascade effects by altering connectivity in remote cortical areas (Fox, 2018; Rehme & Grefkes, 2013). In this context, even small, focal lesions can cause connectome-wide perturbations if occuring in densely connected areas. Recent advances within neuroimaging have resulted in remarkable roadmaps of brains' connectivity, collectively coined the brain connectome, and such templates derived from normative samples have enabled the indirect estimation of disconnection caused by individual lesions (Salvalaggio, De Filippo De Grazia, Zorzi, Thiebaut de Schotten, & Corbetta, 2020). In support of a (dis)connectivity approach, recent work suggest that lesions affecting large white matter pathways cause a greater number of symptoms (Corbetta et al., 2015), as do lesions affecting highly connected hubs (Warren et al., 2014). Such lesion-network mapping approach has been applied to the study of a variety of brain disorders (Darby et al., 2019; Ferguson et al., 2019; van den Heuvel & Sporns, 2019), and may provide a more sensitive measure to capture the brain perturbations associated with fatigue.

In light of the considerable inconstancy in the existing research literature examining the relationship between lesion characteristics and fatigue, the main aim of this study was to investigate the added explanatory value of a structural disconnectivity approach compared to conventional lesion-symptom mapping. Because no previous studies have examined post-stroke fatigue by a disconnectivity approach, we had an agnostic view regarding involvement of specific brain networks and conducted a whole-brain analysis. However, based on recent work suggesting improved predictive value with inclusion of network projections (de Schotten et al., 2020; Griffis et al., 2019), we hypothesized that the disconnectivity based approach would exhibit higher sensitivity to fatigue than conventional measures of lesion characteristics.

PAPER III

Despite a growing awareness of post-stroke fatigue in research and the clinic, few treatment options exist for fatigue. Simultaneously, fatigue and emotional distress rank high among patients' reports of unmet needs in life after stroke, underscoring the importance of identifying effective treatments. There are studies suggesting that non-invasive brain stimulation techniques such as tDCS have may have the potential to alleviate fatigue and depression in other patient groups, but the acceptability and effects of repeated tDCS for post-stroke fatigue in chronic stroke patients need to be further explored. Moreover, due to the assumed link between subtle cognitive impairments and mental fatigue, cognitive training may prove beneficial for patients with post-stroke fatigue. The aim of this study was to evaluate the added effect of tDCS combined with cognitive training with regards to alleviate fatigue and depression. 74 chronic stroke patients were included in a randomized sham-controlled design, where tDCS or sham stimulation were administered simultaneously with computerized cognitive training. We hypothesized that patients receiving real stimulation would display larger reductions in fatigue and depression symptoms than patients receiving sham.

In recognition of the strong association and clinical overlap between fatigue and depression, we used an exploratory network-approach to map the relationship between individual fatigue- and depression symptoms at baseline and across five time points. Repeated measures of symptom severity also provide relevant information on stability and fluctuations in individual symptoms over time. Due to the exploratory approach assumed, no specific hypotheses were formulated for the network analyses.

RESEARCH QUESTIONS

PAPER I

Is subjective fatigue associated with attentional network efficiency as measured by the ANT, and is subjective fatigue associated with mental fatigability conceptualized as reduced performance with sustained mental effort? Can the use of a computational approach (hDDM) expand our understanding of fatigue-related differences in performance?

PAPER II

Does applying a structural disconnectivity approach add to our understanding of the neuronal underpinnings of post-stroke fatigue in the chronic stroke phase beyond what is revealed by conventional lesion characteristics?

PAPER III

Can tDCS combined with computerized cognitive training alleviate symptoms of fatigue and depression in chronic stroke patients? Is degree of fatigue associated with training gain and the probability of completing the intervention? How do individual symptoms of depression and fatigue fluctuate over time, and how do symptoms vary in terms of network centrality?

MATERIAL AND METHODS

DESIGN AND GENERAL SETTING

This thesis is part of the StrokeMRI study (Beck et al., 2021; Dørum et al., 2020; Kolskaar et al., 2020; Richard, Petersen, et al., 2020; Sanders et al., 2021), a collaborative research project with an overarching goal to identify determinants of stroke rehabilitation and recovery as well as successful ageing and brain health. For this purpose, both healthy control participants and stroke patients were included. A central part of the project was to evaluate the clinical feasibility of combined tDCS and computerized cognitive training with regards to improvement of cognitive function in particular. In this respect, the assessment of tDCS' effects on post-stroke fatigue and depression presented in Paper III should be regarded pre-specified, but exploratory endpoints.

PARTICIPANTS

Healthy Control group

Healthy control group participants were recruited through newspaper advertisements, word-of-mouth and online social media. Of the 500 persons responding, approximately 400 persons were deemed eligible for inclusion after a telephone screening interview. A final sample of 346 healthy controls completed a comprehensive test protocol, including a battery of cognitive assessments, self-reports of mental distress, multimodal MRI and blood sampling. General inclusion criteria were age > 18 with no known diagnoses of neurological or psychiatric disease, no previous strokes or other acquired brain injuries. Persons taking medications with significant effect on central nervous system functioning were also excluded. As with the stroke patients, MRI-contraindications were a criterion for exclusion.

Patient Sample

Stoke survivors in a chronic phase (Paper I – III) were recruited from the stroke unit at Oslo University hospital (OUS) and the Geriatric Department at Diakonhjemmet Hospital. Suitable participants were identified by the hospital staff, and invitation letters were sent to approximately 900 patients admitted with acute stroke between 2013-2016, of which

approximately 250 responded to decline or to receive more information. Following an initial telephone screening, 77 patients were deemed eligible and scheduled for inclusion. Paper II included an additional subsample of 18 patients recruited within 14 days of hospital admittance. These patients participated in an affiliated stroke-MRI sub-study (not the RCT), and the data presented in Paper II were collected from follow-up tests conducted at minimum three months post stroke.

We included patients aged 18 or older, with clinically documented stroke of ischemic or hemorrhagic etiology. Exclusion criteria included contraindications for MRI (i.e. metal implants, claustrophobia, pregnancy), other neurological conditions diagnosed prior to the stroke, severe mental illness and drug abuse.

Table 1 presents sample descriptive information for each paper, while Figure 1 describes the study protocol for patients:

Table 1

	Paper I	Paper II	Paper III
Patients (N)	53	84	74 baseline/ 54 complete*
Months since stroke	25 (6 – 45)	22 (3 – 45)	25 (6 – 45)
Age, years (mean(SD))	69.0 (7.43)	65.8 (12.6)	69.1 (7.3)
Age range, years	47 - 81	24 – 87	47 - 81
Males/Females (count)	38/15	60/24	40/14
Healthy controls (count)	NA	155 (age/sex-matched)	NA
Design	Cross sectional	Cross sectional	RCT/Cross sectional

*Table data reported on completing patients

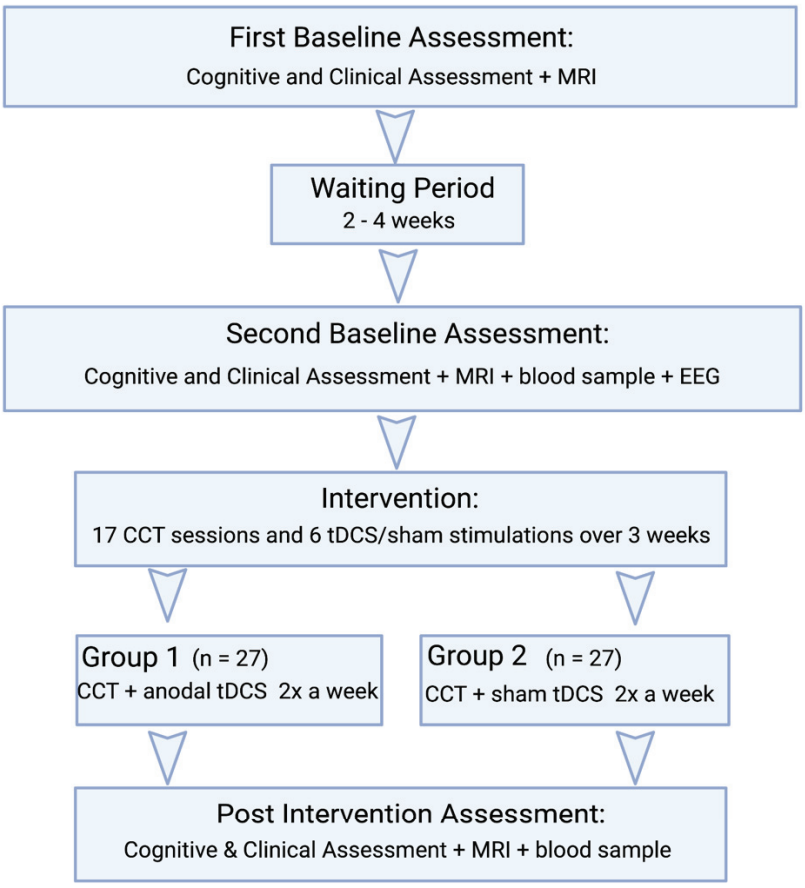

Fig. 1. Flow chart of study protocol and timeline from baseline to post-assessments.

SELF-REPORT SCALES AND COGNITIVE ASSESSMENTS

All self-report and cognitive data included in the present study were collected using validated and standardized neuropsychological tests and questionnaires.

Fatigue Severity Scale

FSS is a one-dimensional, 9-item scale, originally developed to assess fatigue in patients with multiple sclerosis and lupus (L. B. Krupp, N. G. LaRocca, J. Muir-Nash, & A. D. Steinberg, 1989). In the later years it has been extensively used in other neurological conditions, and it is currently one of the most frequently used self-report measures to assess fatigue severity after stroke (Lerdal et al., 2011; Whitehead, 2009). A recent psychometric study concluded that FSS is reliable and valid for measuring fatigue in stroke patients, but has limited specificity for differentiating stroke-related fatigue from fatigue in other populations (Ozyemisci-

Taskiran, Batur, Yuksel, Cengiz, & Karatas, 2019). Although FSS was designed to assess *the impact of fatigue* in daily life on specific types of functioning (Krupp et al., 1989), it is now primarily used as a unidimensional measure of *fatigue severity* (Dittner, Wessely, & Brown, 2004). While this may represent a limitation of the scale, applying a widely used scale facilitates comparison with previous studies, as well as synthesizing and communication of results. Moreover, a review including 18 fatigue scales concluded that FSS was among the three measures that demonstrated good psychometric properties, as well as an ability to detect change in fatigue over time (Whitehead, 2009). The latter is considered important, as we in Paper III reported fatigue measures at five consecutive time points. Different cut off values for clinically significant fatigue are reported in the literature. Commonly used values are ≥ 4 (L. B. Krupp et al., 1989; Nadarajah & Goh, 2015; Schepers et al., 2006; Wai Kwong Tang et al., 2010) or ≥ 5 (Kjeverud et al., 2020; Lerdal, Wahl, Rustoen, Hanestad, & Moum, 2005; Naess et al., 2012).

Patient Health Questionnaire for depression

Symptoms of depression were measured by The Patient Health Questionnaire 9 (PHQ-9; (Kroenke, Spitzer, & Williams, 2001). PHQ-9 is a nine-item self-report scale, based on the DSM-IV criteria for depression. Items are scored from 0-3, reflecting presence of symptoms (0 - not at all, 3 – nearly every day). The PHQ-9 has proven a reliable and valid measure of depression and depression severity in the general population and in stroke patients (Beard, Hsu, Rifkin, Busch, & Björgvinsson, 2016; Williams et al., 2005), where a cut off value of 10 has demonstrated good sensitivity and specificity for major depression (Williams et al., 2005).

Other measures

Information on sleep quality was collected by Pittsburg Sleep Quality Index (PSQI; Buysse, Reynolds Iii, Monk, Berman, & Kupfer, 1989) and subjective cognitive, perceptive and motoric problems assessed by the Cognitive Failures Questionnaire (CFQ; Broadbent, Cooper, FitzGerald, & Parkes, 1982).

Cognitive assessments

General cognitive abilities were assessed by the subtests “Vocabulary” and “Matrix Reasoning” from Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI II; Wechsler, 2011). Screening for cognitive impairment was done by The Montreal Cognitive

Assessment (MoCA; Nasreddine et al., 2005) and the Mini-Mental State Examination (MMSE; Folstein et al., 1975). The ability to inhibit cognitive interference was assessed by D-KEFS color-word interference test (Delis, Kaplan, & Kramer, 2001) and the California Verbal Learning Test (CVLT; Delis, 2000) was used as a measure of episodic verbal learning and memory. A complete overview of measures included in the StrokeMRI protocol but not presented in the present work, can be found in Richard, Kolskår, et al. (2020).

The Attention Network Test (ANT)

In Paper I, we analyze and report behavioral data collected with the ANT (Fan et al., 2002), a widely used computerized test of attentional function. In the ANT, a cued response time (RT) task (Posner, 1980) is combined with the Erikson flanker test (Eriksen & Eriksen, 1974) into one experimental paradigm, allowing for parsing of three different components of attention, assumed to be largely independent from each other (Fan et al., 2002). Briefly, these are an executive control component, based on RT change associated with the introduction of a cognitive conflict (the details of the test are illustrated in Figure 2, as presented in Paper I), an alerting component, based on RT change accompanying a temporal cue/warning signal that the stimulus *is about to occur* and reflecting vigilance*,* and an orienting component, based on change in RT resulting from getting a cue on *where* the stimulus will occur, thus providing information about how efficiently the individual selects and orients towards sensory information (Posner & Petersen, 1990).

We applied a conventional version of the ANT, as previously described (Fan et al., 2002). Figure 2 depicts the details of the task. Briefly, participants were instructed to keep their gaze towards a fixation cross presented for 400, 800, 1200 or 1600 milli seconds. Immediately succeeding the fixation cross, and prior to the target stimulus, one out of four cues would appear for 100 milliseconds; a spatial cue (temporal and spatial cue), a center cue (temporal cue only), a double cue (temporal cue only), or no cue. Then, the task stimulus of five arrows was presented for 1700 milliseconds, and the participant was instructed to decide whether the middle arrow (target arrow) was pointed left or right. Responses were executed by pressing the right or left mouse button. Participants were encouraged to make responses *as quickly and as accurately* as possible.

The full paradigm consisted of a practice block of 24 trials followed by three rounds of 96 trials each (corresponding to 288 trials in total). Each round lasted approximately 6 minutes and participants were encouraged to take a short break (maximum 2 minutes) between each round. E-prime software (Psychology Software Tools, Pittsburgh, PA) was used for setting up the experiment and collecting the responses.

Figure 2 shows details of the ANT conditions

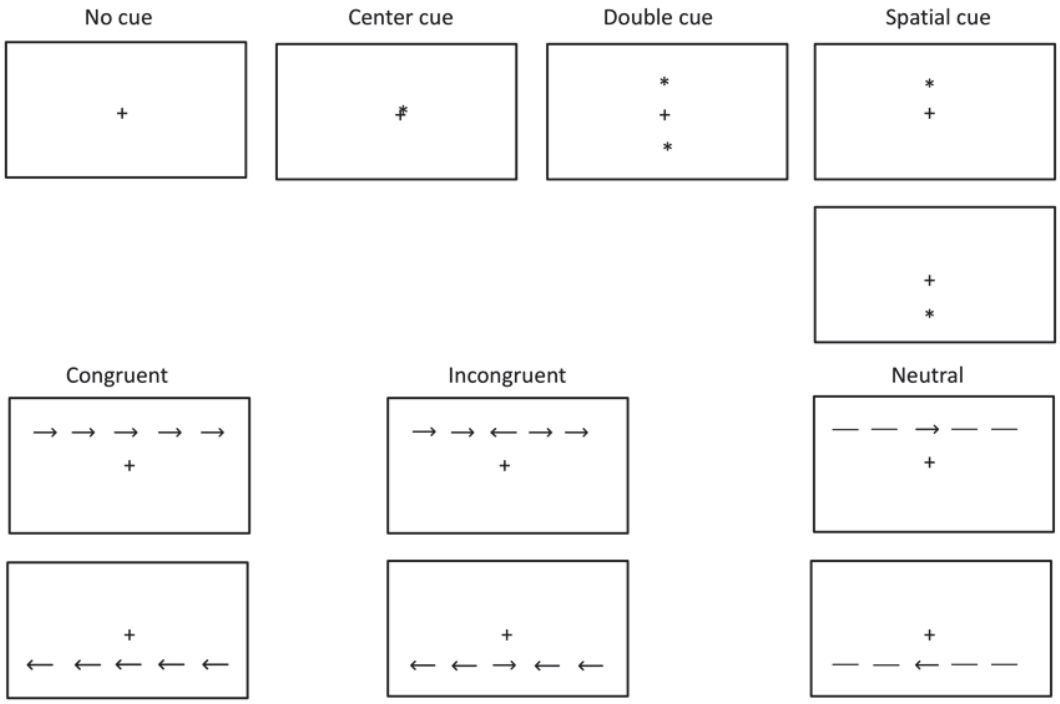

Fig. 2. A schematic representation of the ANT cue and flanker conditions. Adapted from Paper I (Ulrichsen et al., 2020).

Individual network scores were computed using the following definition based on median RTs:

Executive control = (RT incongruent – RT congruent)/RT congruent

Alerting = (RT no cue – RT center cue)/RT center cue

Orienting = (RT center cue – RT spatial cue)/RT spatial cue

NEUROIMAGING

MRI acquisition

All participants were scanned on a 3T GE 750 Discovery MRI scanner at Oslo University Hospital. A 32-channel head coil was used, with paddings applied to minimize head motion. The full protocol included structural (T1, FLAIR), functional (resting-state and task-based fMRI) and diffusion data. Only data from T1-weighted and FLAIR are presented in this thesis, used for lesion demarcation as presented in Paper II. T1-weighted images were acquired using a 3D IR-prepared FSPGR (BRAVO), with scan time 4:43 and the following parameter specifications: TR: 8.16 ms; TE: 3.18 ms; TI: 450 ms; FA: 12°; voxel size: 1 × 1 × 1 mm; slices: 188; FOV: 256 × 256, 188 sagittal slices. Corresponding parameters for FLAIR were TR: 8000 ms; TE: 127 ms, TI: 2240; voxel size: 1 × 1 × 1 mm).

Lesion delineation

Lesions were semi-automatically delineated in native space, using the Clusterize-Toolbox (De Haan, Clas, Juenger, Wilke, & Karnath, 2015) running under MATLAB (MathWorks, 2018). Trained personnel (a radiographer and a physician) traced lesions based on visible damage and hyperintensities on FLAIR images, and guided by neuroradiological descriptions. Using a linear transformation with 6 degrees of freedom, FLAIR images were registered with the high-resolution T1 images. T1 images were subsequently registered to MNI152 standard space by linear affine transformations (with 12 degrees of freedom). Native-to-standard transformation matrices (nearest neighbor interpolation) were applied to register the binarized lesion masks to standard space.

Figure 3 shows a probabilistic representation of stroke location across all patients (n=84).

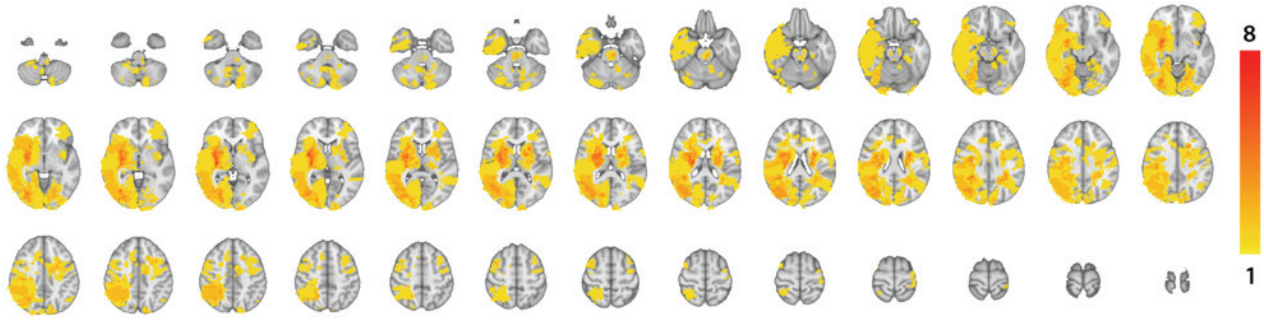

Fig. 3. Adapted from Paper II. Heatmap displaying lesion overlap across stroke patients by 70 slices (2 mm thickness) from z(voxel) = 1 to z = 70.

Structural Disconnectome maps

Disconnectome maps were calculated using an automated tractography-based procedure, described in detail elsewhere (Foulon et al., 2018) and implemented in the *BCBtoolkit* (Brain Connectivity Behaviour Toolkit (BCBtoolkit)). Here, full-brain tractography data from 170 healthy individuals (7T data, derived from the Human Connectome Project) serves as a training set used to track fibers passing through individual lesions. The probability of lesion-related disconnection (ranging from 0 to 100%) can then be presented in individual disconnectome maps. In Paper II, we also computed individual summary measures of total disconnection severity, by a) calculating mean voxel intensity across the disconnectome map, and b) summarizing the total number of voxels with >50% probability of disconnection (corresponding to intensity of >.5).

Figure 4 shows a probabilistic representation of the neuroanatomical distribution of estimated white matter disconnection across all patients.

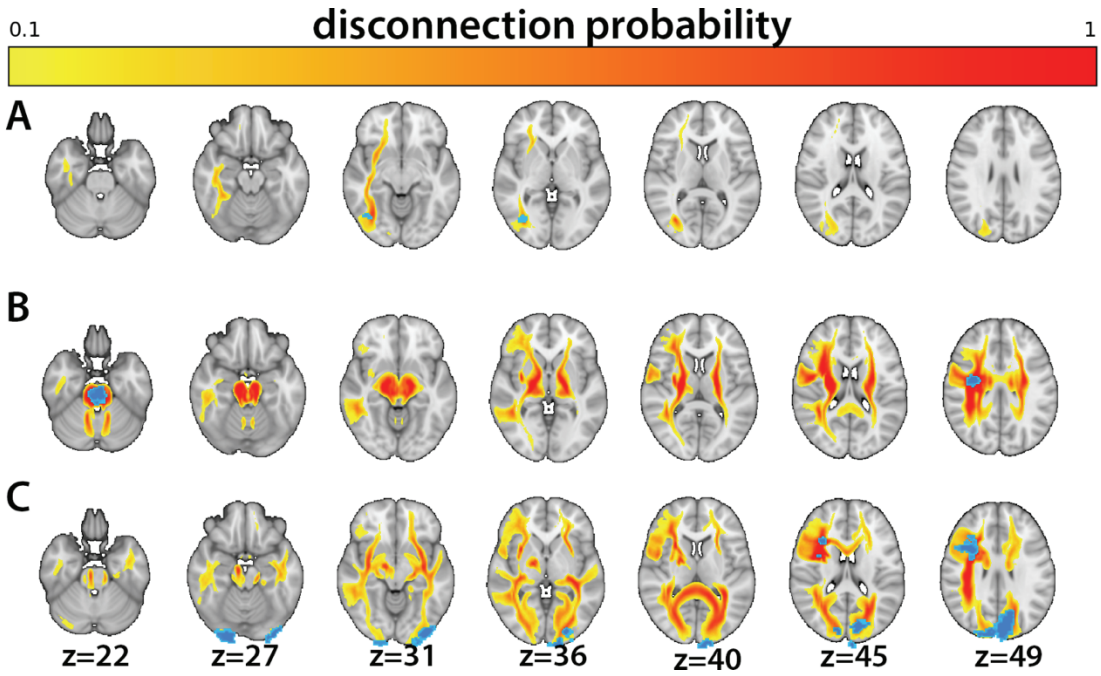

Fig. 4. Adapted from Paper II. Individual lesions (blue) and associated disconnectome maps (yellow–red). Probability for disconnection ranges from 10 (yellow) to 100 (red). Patient **A**: right cerebral white matter lesion, Patient **B:** brain stem lesion, Patient **C:** left and right cerebral cortex and white matter lesions.

INTERVENTION PROTOCOL

Randomization and blinding

An in-house Matlab script was used to randomize participants into the experimental conditions (sham vs active), while ensuring balanced numbers of participants between the groups. Both patients and we who administered the stimulation were blinded to the experimental condition throughout the experiment, as well as during initial data analyses.

tDCS

Each session of stimulation lasted for 20 minutes (administered during the first 20 minutes of Cogmed training), whereof 120 seconds were ramp-up and 30 seconds fade-out. Sham stimulation was provided using the fade in – short stimulation – fade out approach (Ambrus et al., 2012). The short stimulation following fade in/ramp-up lasted for 40 seconds, thus providing a tingling sensation, before fade out in accordance with factory settings. To minimize risks of adverse effects, active stimulation was set to 1 mA. We used a direct current stimulator (neuroConn DC plus, Germany) with 5x7 cm rubber pads to deliver the stimulation. Rubber pads were covered in high-conducting gel to keep impedance below 20 kΩ. The anodal electrode was placed at the left dorsolateral prefrontal cortex (F3) and the cathodal electrode at right occipital/cerebellum (O2). As previously described, the intervention was created and conducted as a collaborative effort between different PhD projects, where the primary goal was to evaluate the potential effects of tDCS in combination with cognitive training on cognitive function.

Decisions on study settings such as electrode placement was motivated first and foremost by previous literature on tDCS and cognition. Yet, there are several randomized controlled studies (Chalah, Riachi, et al., 2017; Charvet et al., 2018) and case reports (Ayache, Lefaucheur, & Chalah, 2017; Chalah, Lefaucheur, & Ayache, 2017) reporting beneficial fatigue effects of repeated anodal tDCS to the left DLPFC in MS patients. With regards to depression, the left DLPFC is a frequent target area for anodal tDCS (Bennabi & Haffen, 2018; Paulo S. Boggio et al., 2008), and associations between depression after stroke and left DLPFC connectivity or damage (Egorova et al., 2017; Grajny et al., 2016) may suggest positive effects of stimulation to this region (Egorova et al., 2017). Together, these

observations suggest a sufficient rationale for assessing the potential of fatigue- and depression effects of tDCS to this region in stroke patients.

Computerized cognitive training (Cogmed)

Computerized cognitive training was administered by Cogmed QM (Cogmed Systems AB, Stockholm, Sweden), a commercially available working memory training system. Cogmed was originally developed by Klingberg et al. (2005), and has been applied in a variety of patient groups suffering from impaired working memory, including stroke patients (Björkdahl, Åkerlund, Svensson, & Esbjörnsson, 2013; Nyberg et al., 2018; van de Ven, Murre, Veltman, & Schmand, 2016). The training program is available online, and can be practiced from home, requiring only a computer with internet connection and speakers. It consists of 10 different training tasks, targeting visuospatial and verbal working memory, where each session includes 8 of the 10 tasks and lasts around 45 minutes. Level of difficulty is adjusted according to performance, meaning that the tasks get increasingly challenging as performance improves.

The original Cogmed QM protocol consists of 25 training sessions, often carried out over the course of five weeks. In the present study, due to practicality and feasibility concerns, we included 17 of the 25 training sessions spanning a period of three to four weeks, corresponding to approximately five training sessions per week. The training sessions with simultaneous tDCS or sham stimulation were carried out at Oslo University Hospital (two days a week, yielding a total of 6 stimulation sessions), while the remaining sessions were completed at home.

STATISTICAL ANALYSES

A variety of different statistical procedures were used in Paper I-III, and will therefore be presented independently for each paper. If not stated otherwise, statistical analyses have been conducted using R version 4.0.3 (R core team, 2020).

Paper I

In line with previous reports (Chang, Pesce, Chiang, Kuo, & Fong, 2015; Westlye, Grydeland, Walhovd, & Fjell, 2011) response times <200 milliseconds (2% of responses) were removed

from analyses, assumed to reflect fast guesses. Participants with over 50% incorrect responses within the respective flanker conditions were discarded from analyses. This applied to one participant.

Associations between RT, subjective fatigue and time on task

To model the association between subjective fatigue (standardized FSS scores), time on task (trial number 1 – 288) and RT, we estimated linear mixed-effects models using the nlme package in R (Pinheiro, Bates, DebRoy, Sarkar, & Team, 2007). To identify the best fitting model, we started with a maximal model, in line with recommendations from Barr, Levy, Scheepers, and Tily (2013). Here, random slopes for FSS*time were included at subject level, together with random intercepts and the following fixed effects/covariates: FSS*time, PHQ scores, age, flanker condition, sex, stroke topography, lesion volume, TOAST classification for stroke etiology and NIHSS scores. As the initial model did not converge, we removed fixed effects sequentially until attaining convergence. We started with dropping NIHSS scores, due to the low variability in the distribution of scores (mean = 1.4, median = 1 and SD = 1.2). TOAST scores were then discarded, based on a high number of "not specified/unknown" cases, and PHQ scores were removed due to high correlations with FSS.

After identifying the most complex converging model, we formally tested whether random slopes should be included by comparing model fit between model with/without random slopes using the ANOVA function in R, and this procedure supported the inclusion of random slopes. As a final step in model refinement, independent variables with no significant predictive value were removed (lesion load and location), and this improved model fit marginally. To obtain an indication of FSS effect size, we estimated the final model with and without FSS scores, and compared models by ANOVA as described above. FSS models performed significantly better in terms of model fit ($p < .001$). Importantly, we re-ran the same analyses with PHQ scores substituted for FSS scores to assess whether potential effects were specific for fatigue or common for symptoms of depression. Details of model selection can be found in Supplementary Material, Paper I. Further, to test whether effects were different between flanker conditions, models were estimated separately for incongruent, congruent and neutral flankers, respectively.

In a follow-up analyses investigating whether effects of sustained effort interacted with PSF status, the above described models were re-run with dichotomized FSS scores (mean FSS

score >= or < 4 (L. B. Krupp et al., 1989; Nadarajah & Goh, 2015; Schepers et al., 2006) instead of FSS continuous scores. Of note, these group models (PSF/no PSF) were run without inclusion of random slopes to secure convergence.

Associations between ANT network scores and subjective fatigue

ANT network scores were computed according to a previous definition (Westlye et al., 2011) and as described in detail in the introduction. We estimated linear models for each attentional network to test for associations with FSS, covarying for age and sex.

Hierarchical drift diffusion modeling

To further investigate the relationship between subjective fatigue and specific cognitive processes underlying RT differences in ANT, we conducted an exploratory analysis fitting a hierarchical drift diffusion model (hDDM) to the RT data. Computational approaches such as the DDM have been applied to decompose data from fast two-choice decision tasks in a range of clinical disorders (White, Ratcliff, Vasey, & McKoon, 2010), providing a theoretical framework to understand cognitive processes and a psychometric tool to disentangle the specific processes hypothesized to underlie observed behavior. A significant advantage with the DDM is that it extracts more information from the behavioral data and both mean RT, RT distributions and accuracy are accounted for in the same model (Roger Ratcliff, Thapar, & McKoon, 2003). Briefly, the original model postulates four parameters (R. Ratcliff, 1978). drift rate (v): the rate or speed of information accumulation, assumed to reflect processing efficiency, non-decision time (t): a "non-cognitive" parameter, accounting for time needed to encode the stimulus and execute a response, decision threshold (a): reflecting the amount of evidence needed to make a decision, and the starting point (z), describing bias toward a response option (Roger Ratcliff & McKoon, 2008).

hDDM modelling was performed in the python toolbox HDDM (Wiecki, Sofer, & Frank, 2013), with starting points as predefined in the toolbox, and mildly informative priors. Data was accuracy coded (errors = 0, correct = 1). For more detailed model specifications, see methods section Paper I. To identify the model best explaining the data, we estimated and compared a variety of different cognitively plausible models, where parameter fixations were guided by theoretical assumptions and previous practice in the literature (Roger Ratcliff, Smith, & McKoon, 2015; Roger Ratcliff et al., 2003).

To evaluate where the interaction between time on task (trial 1- 288) and FSS should be localized (in which parameter), we first fitted a model where all three parameters (a, t and v) were allowed to vary by this interaction term. Using a systematic approach, the following nine simple models were estimated and compared in terms of which parameter fixations yielded best model fit: a) Main effect of time on t, v or a, b) main effect of FSS on t, v or a, and c) interaction effect between FSS*time on trial on either t, v or a. Model comparison by model fit indicated that the interaction between FSS and time on trial should be placed in t, non-decision time.

Model fit was evaluated by comparing of deviance information criteria (DIC) values from respective models. The DIC provides an estimate of a model's fit relative to other models, where lower values indicate better support (François & Laval, 2011). Additionally, for the models including individually estimated regressors, posterior predictive checks (PPC) were conducted to evaluate how the model succeeded in reproducing distributions from the observed data (Wiecki, 2016). For each parameters' estimated posterior distribution, 500 samples were randomly drawn from the estimated posterior distribution, and these simulated datasets were then compared with observed data, providing an estimate of fit and uncertainty in the model. Table 2, Paper I, provides an overview of different models tested and associated DIC values. The best model in terms of model fit and convergence allowed non-decision time to vary across warning cue conditions, and drift rate to vary between flanker conditions while keeping boundary separation constant.

Paper II

For analyses of structural disconnectome maps and binarized lesion masks, we used the randomise tool within FSL (Smith et al., 2004; Woolrich et al., 2009) to conduct permutation-based inference. Associations between FSS scores and disconnectome/lesions masks were evaluated in separate models within the framework of the general linear model (GLM), where linear effects of FSS were tested voxel-wise. In addition, we re-estimated the model with a) a dichotomized fatigue-variable (FSS score of ≥/< 4, corresponding to commonly used clinical cutoff value (Nadarajah & Goh, 2015; Schepers et al., 2006), and b) the upper tertile of FSS

scores contrasted with the lowest tertile, motivated by the possibility that more extreme scores might demonstrate increased sensitivity to brain correlates associated with fatigue.

Two different procedures were used to control for depression: a) excluding patients fulfilling the criteria for clinical depression (≥ 10 on PHQ, n = 74 remaining), and b) including normalized PHQ-and FSS scores in the same model. 5000 permutations were performed for each contrast. Applying threshold free cluster enhancement (TFCE; Smith & Nichols, 2009) to correct for multiple testing, results were considered significant at $p<.05$. For transparency, we also plotted distributions of the uncorrected t-values from the main models, as shown in Supplementary Material, Paper II.

Follow-up analyses were conducted in R, version 3.4.0 (R core team, 2020) to explore whether sensitivity could be increased by creating simple summary measures, and to quantify the evidence for an absent association if results were indicative of such. Simple disconnection measures were computed for each patient by a) calculating the mean voxel intensity across the total disconnectome map, and b) summarizing the number of voxels with a probability of disconnection larger than 50%.

Using the BayesFactor package (Morey, Rouder, Jamil, & Morey, 2015) we then computed linear correlations between these disconnection measures, FSS and PHQ. We further tested for associations between fatigue and more clinical, stroke-related characteristics (lesion location, as defined in four categories – left/right hemisphere, both hemispheres or cerebellum/brain stem, TOAST classification of ischemic stroke, months since stroke onset, lesion volume (defined as number of voxels in the lesion mask), and stroke severity (NIHSS score at hospital discharge used as a proxy for clinical severity). We estimated linear models with FSS scores as dependent variable, while controlling for age, sex and depression scores. To allow for model comparison by Bayes Factor, clinical stroke variables were added subsequently, and the lmBF function was used to compute Bayes Factors for model comparison against the null (intercept only) model.

Paper III

We used Bayesian hypothesis testing to assess the effects of tDCS on fatigue and depression, and to quantify evidence supporting the alternative and null hypothesis. Mixed effects regression models were created in the Stan computational framework (http://mc-stan.org/), using the brms package (Bürkner, 2017). Mixed models were estimated separately for FSS and PHQ, entering FSS or PHQ as dependent variables, and time (1-5), tDCS group (sham or active), tDCS group * time, sex and age as fixed factors, with participant as random factor. All variables were standardized prior to analysis. Models were run using 4 chains (8000 iterations each), of which the first 4000 were discarded as burn-in. We applied normal priors with means of 0 and standard deviations of 1.

Baseline group differences between completing (n=50) and withdrawing (n=19) patients were assessed by t-tests for independent samples. In post-hoc analyses testing for specific effects of fatigue on study adherence, we estimated logistic regression models using completing/withdrawing status as dependent variable, and fatigue status, PHQ scores, sex and age as independent variables. Fatigue status was defined as either ≥ 5 or ≥ 4 on FSS. Since both 5 and 4 are commonly used cutoff values in the literature, we chose to report both for transparency.

Cogmed individual training gain was quantified following the approach by Kolskaar et al. (2020), estimating the effect of repeated training by running linear models with task performance as dependent variable, and session number as independent variable. The models were estimated separately for each Cogmed subtask, yielding one beta-estimate (slope) per task for each individual, reflecting individual performance change across sessions/time. Testing for multivariate outliers, we used the mvoutliers package in R and the aq.plot function (Filzmoser & Gschwandtner, 2018). The subtasks “hidden objects” and “digits” displayed a high number of outliers relative to the remaining tests and were discarded from further analyses. Association between fatigue and training gain were then assessed by estimating linear models for each task, using the estimated beta slope as dependent variable, and baseline FSS score, age and sex as independent variables. To test whether effects were specific for fatigue or common to depression, we re-ran the same models with PHQ as independent variable instead of FSS.

As an additional test of baseline associations between fatigue/depression and measures of cognitive functions at baseline, we estimated Bayes factors for correlations between score on FSS or PHQ, neuropsychological test performance (MoCA, WASI, CVLT, Stroop), and a subjective measure of cognitive failures (CFQ).

To get an estimate of the time-dependent variability of the individual FSS and PHQ items, we estimated the coefficient of variation value (CV) for each item on FSS and PHQ across time point 1 to 5, resulting in one CV value per item for each person. Because FSS and PHQ have different scale properties, direct comparisons of CV values across scales are not meaningful, but the CV value still offers relevant information about the relative variability of individual items within each scale.

To explore the centrality of individual symptoms and symptom-level associations, we estimated networks based on Spearman's rank order correlation matrixes using the qgraph package in R (Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012). Two baseline (n = 74) networks were estimated: one with FSS sum score and individual PHQ items (investigating associations between specific depressive symptoms and general fatigue severity), and one with all individual items from both scales. The sum-FSS network was EBICglasso regularized (tuning parameter 0.15), while the all-item network was based on full correlations without regularization, because of stability issues due to the high number of parameters relative to sample size. PHQ item # 9 displayed a highly skewed distribution (mean = 0.08) and was thus discarded from all-item networks. All-item networks were then estimated for all time points (1-5) and plotted according to their loadings principal component analyses (PCA) component loadings, enabling visual comparison of network structure across time. In the temporal networks, only completing patients (n=50) were included. Of note, the low number of observations implies that this (PCA)-feature of node-placement should be regarded an exploratory means of visualizing the data, and does not allow for conclusions on dimensionality. Network stability was evaluated using case-dropping bootstrap in the bootnet package (Epskamp, Borsboom, & Fried, 2018). Stability was acceptable for the regularized network and good for the unregularized networks, but see methods and results section Paper III for details.

To evaluate the relative centrality of the included nodes (items) in the network, we estimated strength centrality, which represents the sum of all edge weights directly connected to a

particular node (Bringmann et al., 2019). Strength is thus a coarse, but stable, measure of centrality (Fried, Epskamp, Nesse, Tuerlinckx, & Borsboom, 2016) and it the most commonly evaluated centrality measure in networks on psychological constructs (Malgaroli, Calderon, & Bonanno, 2021). To obtain an estimate of the individual nodes' aggregated centrality across time, we followed the approach by Malgaroli et al. (2021), ranking each node (from 1-17) according to strength centrality at each time point, before calculating across-time mean of these temporal rankings. We used Spearman correlations to test whether item centrality (mean ranking across time) was associated with symptom severity (mean item score across time).

RESEARCH ETHICS

All data presented in this thesis were collected from a study approved by the Regional Committee for Medical and Health Research Ethics (South-East Norway, 2014/694; 2015/1282), and by the data protection regulation Oslo University Hospital (Personvernombudet OUS). All participants provided oral and written consent prior to participation, and received a compensation by a 500 NOK gift card.

As the study protocol was quite extensive, we strived to convey a realistic picture of the labor-intensity associated with participation during the first consultation, and emphasized the right to withdraw consent and leave the study at any point. The study spanned over a period of 6 or more weeks, and we had regular conversations with the patients about their experience with the repeated assessments and training. In cases where participation was deemed to be too time consuming, demanding or tiring, the patient was thanked for her/his contribution and received the compensation as agreed, without completing the protocol (n=19).

Low intensity tDCS administered by conventional protocols is considered safe (Woods et al., 2016). Reported side effects or adverse events are typically non-existent or mild (Antal et al., 2017; Bikson et al., 2016). Yet, typical sensations of itching, pinching or burning can be uncomfortable, and we monitored adverse events by the end of each session. One patient experienced discomfort resulting in a decision to quit the study. Although there are no known side effects of undergoing MRI, the assessments can be uncomfortable. Lying still in the scanner for about an hour can be particularly challenging for people with claustrophobia, so all volunteers were screened for claustrophobia and discouraged from participating if such issues were revealed.

MR images from both stroke patients and healthy control participants were evaluated by a trained neuroradiologist. Incidental findings warranting further investigation were followed up by informing participants and conveying information to relevant instances, in most cases the general practitioner, in line with participant consent. The same procedure was followed for all relevant health related information collected during the study (although not presented here), such as blood pressure and blood test results.

SUMMARY OF PAPERS

Abstract Paper I

Post-stroke fatigue is prevalent among stroke patients, but its mechanisms are poorly understood. Many patients with post-stroke fatigue experience cognitive difficulties, but studies aiming to identify cognitive correlates of post-stroke fatigue have been largely inconclusive.

With the aim of characterizing the relationship between subjective fatigue and attentional function, we collected behavioral data using ANT and self-reported fatigue scores using FSS from 53 stroke patients. In order to evaluate the utility and added value of computational modeling for delineating specific underpinnings of RT distributions, we fitted a hierarchical drift diffusion model (hDDM) to the ANT data.

Results revealed a relationship between fatigue and RT distributions. Specifically, there was a positive interaction between FSS score and elapsed time on RT. Group analyses suggested that patients without post-stroke fatigue increased speed during the course of the session, while patients with post-stroke fatigue did not. In line with the conventional analyses based on observed RT, the best fitting hDD model identified an interaction between elapsed time and fatigue on non-decision time, suggesting an increase in time needed for stimulus encoding and response execution rather than cognitive information processing and evidence accumulation.

The results demonstrate the significance of considering the sustained nature of effort when defining the cognitive phenotype of post-stroke fatigue, intuitively indicating that the cognitive phenotype of fatigue entails an increased vulnerability to sustained effort, and suggest that the use of computational approaches offers a further characterization of specific processes underlying behavioral differences.

Abstract Paper II

Stroke patients commonly suffer from post-stroke fatigue. Despite a general consensus that brain perturbations constitute a precipitating event in the multifactorial etiology of post-stroke fatigue, the specific predictive value of conventional lesion characteristics such as size and localization remains unclear.

The current study represents a novel approach to assess the neural correlates of post-stroke fatigue in chronic stroke patients. While previous research has focused primarily on lesion location or size, with mixed or inconclusive results, we targeted the extended structural network implicated by the lesion, and evaluated the added explanatory value of a structural disconnectivity approach with regards to the brain correlates of post-stroke fatigue.

To this end, we estimated individual structural brain disconnectome maps in 84 stroke survivors in the chronic phase (≥3 months post stroke) using information about lesion location and normative white matter pathways obtained from 170 healthy individuals. Post-stroke fatigue was measured by the FSS. Voxel wise analyses using non-parametric permutation-based inference were conducted on disconnectome maps to estimate regional effects of disconnectivity. Associations between post-stroke fatigue and global disconnectivity and clinical lesion characteristics were tested by linear models, and we estimated Bayes factor to quantify the evidence for the null and alternative hypotheses, respectively.

The results revealed no significant associations between post-stroke fatigue and disconnectome measures or lesion characteristics, with moderate evidence in favor of the null hypothesis. These results suggest that symptoms of post-stroke fatigue among chronic stroke patients are not simply explained by lesion characteristics or the extent and distribution of structural brain disconnectome, and are discussed in light of methodological considerations.

Abstract Paper III

Fatigue and emotional distress rank high among self-reported unmet needs in stroke survivors. Currently, few treatment options exist for post stroke fatigue, a condition frequently associated with depression. Non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) have shown promise in alleviating fatigue and depression in other patient populations, but the acceptability and effects of repeated stimulation for chronic phase stroke survivors are not established.

Here, we used a randomized sham-controlled design to evaluate the added effect of tDCS combined with computerized cognitive training to alleviate symptoms of fatigue and depression. 77 patients were enrolled at baseline (mean time since stroke = 26 months) and 54 patients completed the intervention. Self-report measures of fatigue and depression were collected at five consecutive timepoints, spanning a period of two months.

While fatigue and depression severity were reduced during the course of the intervention, Bayesian analyses provided evidence for no added effect of tDCS. Lower baseline symptoms of fatigue and depression were associated with higher improvement rate in select tasks, and study withdrawal was higher in patients with more severe fatigue and younger age. Time-resolved analyses of individual symptoms by a network-approach suggested overall higher centrality of fatigue symptoms (except item 1 and 2) than depression symptoms.

In conclusion, the results reveal no effect of tDCS on fatigue or depression, but support the notion of fatigue as a significant stroke sequela with possible implications for treatment adherence and response.

DISCUSSION

A main goal of this thesis was to increase our understanding of post-stroke fatigue in terms of behavioral and cognitive correlates, neural underpinnings and treatment. Data were collected from a range of modalities, including self-report measures, behavioral data, cognitive and neuropsychological assessments and MRI data. In the following, the results from Paper I-III will be discussed in light of existing knowledge and relevant theories.

Linking subjective fatigue, mental fatigability and attentional impairment by tracking sustained performance in the ANT

An accurate characterization of the different aspects of fatigue may elaborate our understanding and inform selection and development of tailored treatments (Manjaly et al., 2019). In Paper I, we present results from linear mixed models on ANT data suggesting a significant interaction between subjective fatigue and time-on-task on response times, meaning that high fatigue was associated with a stronger slowing of responses throughout the paradigm, particularly in the most demanding (incongruent) condition. While several studies have reported no correlation between cognitive impairments and fatigue (Kutlubaev et al., 2013; Schepers et al., 2006; van Eijsden et al., 2012), stroke patients suffering from fatigue often report increased fatigue with sustained mental effort and attentional difficulties, and in this respect the current findings may represent a step towards bridging the gap between subjective experience and more objective behavioral measures. Interestingly, when estimating the main effect of time separately for high vs. low fatigue patients, patients with low fatigue demonstrated a significant decrease in RTs over time (i.e. faster responses) in the incongruent condition, in contrast to patients with high fatigue, who showed no such changes in RT. Our results thus mirror reports from studies on patients with traumatic brain injuries (TBI) linking sustained effort and cognitive function to fatigue, by demonstrating improved performance after repeated practice for healthy controls, but not for TBI patients with fatigue (Birgitta Johansson & Rönnbäck, 2015; Skau, Bunketorp-Käll, Kuhn, & Johansson, 2019).

The observed negative interaction between subjective fatigue and sustained attentional effort may be interpreted as a manifestation of fatigue/fatigability, an expression of an underlying cognitive impairment (such as subtle attentional difficulties), or both (Tommasin et al., 2020).

Whether fatigability constitutes a distinct phenomenon or should rather be conceptualized as an aspect of cognitive impairment, is still debated (Tommasin et al., 2020). However, few studies, including Paper I in this thesis, are designed to make such causal inference.

We discuss this matter in further detail in Paper I, and provide a speculative theoretical context of van Zomerens coping hypothesis (Van Zomeren et al., 1984), which postulates that subtle cognitive deficits associated with brain injury may be temporarily masked by compensatory mechanisms and increased effort. However, compensation and effort increase have a cost, namely increased fatigue, which over time results in deteriorating performance. Interestingly, the strongest effect was identified in the most cognitively demanding condition (incongruent flanker, conflict resolution), and the effect was time dependent, providing support to the notion of effort as a key feature of fatigue. As described by Kahneman (Kahneman, 1973), attention is a limited capacity. Following this, we can speculate that if patients with high fatigue and subtle attentional impairments have to invest more effort to maintain performance, this may be unproblematic in low demanding tasks, but as task complexity and mental load increases, as in the conflict condition, performance deteriorates (Van Zandvoort et al., 1998).

Evidence from imaging studies provide some empirical support to the interpretational framework emphasizing the notion of effort. A fMRI study on mental fatigue in patients with TBI revealed increased activation over time in patients performing a cognitive task in the scanner, in contrast to healthy controls demonstrating a subsequent reduction in activation (Kohl et al., 2009). Yet, the lack of subjective fatigue measures constituted an important limitation in this study. A more recent study on TBI patients reported similar results, observing thalamus and caudate deactivation over time in healthy controls but not in patients (Berginström et al., 2018). It´s speculated that altered recruitment of brain regions in response to sustained attentional tasks reflect increased cerebral “effort” in the patients, which in turn might manifest as subjective fatigue. A relevant prospect for future stroke studies could be integrating functional MRI or other functional brain imaging measures with self-reported fatigue and sustained attentional tasks like the ANT, to investigate whether the fatigue-related response time patterns revealed in Paper I are accompanied with specific patterns of activation in the brain.

By fitting a computational drift diffusion model to the ANT data, we were able to further parse the response time patterns into specific sub-processes and assess associations with fatigue. The best fitting model indicated an interaction between time on task and subjective fatigue on non-decision time, the parameter encompassing stimulus encoding and motor response execution (Roger Ratcliff & Smith, 2010). This particular finding thus suggests that the observed differences in response time distributions between fatigued and non-fatigued patients may be explained, at least in part, by non-cognitive mechanisms, and ties well with the mechanistic model of fatigue as a symptom reflecting sensorimotor deficits (Kuppuswamy et al., 2015). In further support of this hypothesis, a study from 2021 demonstrated that higher fatigue was associated with reduced pre-movement facilitation and a slowing of response times (De Doncker, Brown, & Kuppuswamy, 2021). It should be noted that while our model demonstrated adequate convergence, the error rate in the data was low. Because parameters are estimated based on distributions of both accuracy and response times, the low error rate could have implications for the validity of the results. In addition, ANT is not a commonly applied paradigm in hDDM modelling, and all though a recent study demonstrated encouraging results for hDDM modelling of ANT data devoid of errors (O'Callaghan et al., 2017), the results should be replicated in samples with higher error rates.

In accordance with previous studies on post-stroke fatigue (Kutlubaev et al., 2013; Naess & Nyland, 2013; Schepers et al., 2006; van Eijsden et al., 2012), we found no associations between post-stroke fatigue and cognitive functions measured by global screening tools (MMSE in Paper I, or MoCA in Paper II-III) or more specific tests such as the Stroop Color Word Interference test (Delis et al., 2001), the California Verbal Learning Test (CVLT-II; Delis, 2000) or WASI (WASI-II; Wechsler, 2011) in Paper III. Nor did the results support any main effect of FSS on response times in the ANT. A relationship with subjective fatigue was only revealed when putting the attentional system under sustained pressure, underscoring the relevance of accounting for the effect of time and task difficulty when examining manifestations of fatigue in a cognitive/neuropsychological context.

Fatigue and depression

Among the range of concomitant experiences associated with post-stroke fatigue, depression is the most consistently reported (Ponchel et al., 2015; Wu et al., 2014). Despite the close association, it is now generally recognized that post-stroke fatigue can manifest independently of depression (Schepers et al., 2006; van der Werf, van den Broek, Anten, & Bleijenberg,

2001). This is supported by the results we report in Paper III, where all patients scoring above the clinical cutoff for depression reported fatigue, while only a third of the patients experiencing moderate or severe fatigue reported depressive symptoms above cut off. It has been suggested that the overlapping symptoms together with the disparity of prevalence, may hint of both common origins as well as independent mediators of fatigue (De Doncker et al., 2018).

Gaining more insight in the relationship between fatigue and depression by using self-reports alone has inherent limitations. While contrasting fatigue with depression was never a main aim for the present thesis, we include depression scores in the majority of analyses conducted on fatigue, hereunder analyses on ANT data, MRI data, cognitive training and brain stimulation. This offers an opportunity to identify common or unique mechanisms and correlates within the different modes of measurement.

In Paper I, the identified association between self-reported fatigue and response time distributions in the ANT, was not found for depression. This observation lends further support the notion of fatigue as a partly separate phenomenon from depression, and suggests that fatigue, but not depression, entails an increased vulnerability to sustained effort in cognitively demanding attentional task.

Studies addressing the relationship between post-stroke fatigue and depression across time have primarily assessed patients with longer time intervals (e.g. three or six months), using fatigue scale sum scores or binary diagnosis status as outcome measures (Douven et al., 2017; F. Duncan et al., 2015; Kjeverud et al., 2020). While sum scores provides relevant, clinical information about overall symptom load and prevalence, it does not offer insight into which symptoms are more pronounced or how specific symptoms covary. It is conceivable that certain depressive symptoms are more strongly related to fatigue severity, and similarly, that certain aspects of fatigue are more associated with overall depression. Moreover, symptoms do not manifest randomly - some symptoms co-occur more frequently than others (Hofmann, Curtiss, & McNally, 2016), but the ways in which they co-occur vary substantially, resulting in heterogeneity in the clinical manifestations. Taken together, this supports the intuitive notion that a sole focus on total sum scores, attaching equal weight to all symptoms, may not convey the full picture when investigating the relationship between fatigue and depression.

The network analyses framework offers a tool to move beyond these problems, conceptualizing diagnoses as interconnected networks of symptoms and their interactions (Boschloo et al., 2015; Malgaroli et al., 2021). Networks are increasingly used to address the heterogeneity of various conditions, while also probing etiological underpinnings (Borsboom & Cramer, 2013), as illustrated by the notion that highly influential symptoms and related edges may have a larger impact on disease trajectories and outcome (Hofmann et al., 2016). In addition, network approaches appear well suited to deal with comorbidities and overlapping clinical conditions, because rather than aiming to remove or disentangle nonspecific symptoms occurring in multiple diagnoses, such symptoms are conceptualized as important bridges that will affect other symptoms in the network if activated (Hofmann et al., 2016). Thus, investigating repeated measures of post-stroke fatigue and depressive symptom associations by a network approach, may further inform hypotheses about the putative reciprocal relationship between the two conditions, with possible implications for treatment approach.

On this backdrop, we investigated the relationship between repeated measures of self-reported individual symptoms of fatigue and depression using a network-based approach. Results are presented in Paper III, and suggested higher centrality of fatigue items then depression items (with exception of FSS item 1 and 2). As a means of visualizing change and stability in network structure and item associations across time, network nodes from the temporal networks were plotted according to their PCA loadings. It should be noted that the sample size is too small to allow for explicit interpretation of PCA results, so this analyses feature should be considered explorative. However, strength centrality measures for network estimated on full Spearman correlations demonstrated acceptable stability, and the centrality plots thus provide a reliable indication of centrality for the individual items.

Overall, results suggested high centrality of FSS items relative to PHQ items. The item displaying highest ranked centrality across time was FSS item #9 (“Fatigue interferes with my work, family, or social life”). Although the applied design does not enable causal inference, the overall relative importance of fatigue items suggested by the network estimations may be seen as support to the hypothesis that fatigue after stroke exacerbates the risk of depression (Ormstad & Eilertsen, 2015). Following this line of interpretation, the high centrality of FSS item #9 may indicate that fatigue restraining social and professional activities is particularly

stressful and predisposes for increases in respective symptoms. The relevance of this hypothesis could be evaluated in longitudinal studies designed to disentangle the causal relationship between symptoms. Provided that FSS item #9 has significant impact on the symptom network, interventions aimed at limiting the negative impact of fatigue on the social and professional domain could potentially alleviate both fatigue- and depressive symptoms. In addition, FSS item #9 was identified among the most stable items across time points (as reflected by low coefficient of variation value relative to other FSS items), possibly reflecting that the impact of fatigue in terms of social and professional obligations is a more stable trait than e.g. fatigue in relation to exercise.

Structural disconnectivity mapping of post-stroke fatigue

In Paper II, we adopted a novel approach to the study of the lesion-related neural underpinnings of fatigue in chronic stroke patients. Results from permutation testing revealed no association between fatigue and individual disconnectome maps, reflecting the structural, distal effects of focal lesions, nor between fatigue and binarized lesion maps, reflecting volume and location. Results from the same analyses conducted with PHQ scores mirrored results from the fatigue models, with no significant effects identified for depression. Moreover, results from linear models including conventional clinical stroke characteristics such as TOAST, lesion location (coarsely defined as either left/right hemisphere, both hemispheres or cerebellum/brainstem) or months since stroke did not support an association with fatigue or depression. Importantly, Bayesian comparisons of models with stroke characteristics (including global disconnectivity measures) versus null models revealed that all models with stroke characteristics provided moderate support of no lesion-related effects on fatigue and depression.

A strength of the current study is the use of Bayesian analyses, providing a quantitative estimate of the probability of no association between global measures of disconnectivity and fatigue, which is not attainable using conventional null-hypothesis significance testing (Keysers, Gazzola, & Wagenmakers, 2020). Although several methodological limitations have to be taken into account when interpretating the findings, the moderate evidence for no association between global disconnectivity and fatigue may suggest support for the view that fatigue in the chronic phase is associated primarily with other factors, and that lesion related brain perturbations have a lesser impact at this stage. According to a review by Wu, Mead, et

al. (2015), studies reporting significant associations between fatigue and lesion characteristics were generally conducted shortly after stroke onset, whereas studies finding no associations tended to measure fatigue at a later stage. In the current study, the mean time since stroke onset was 22 months. Considering that the characteristics of brain perturbations, stroke sequela and the relationship between them change over time through recovery and compensation (Fornito, Zalesky, & Breakspear, 2015; Fox, 2018), the temporal aspect may be particularly relevant. Future studies may be able to delineate the dynamics in the associations between brain perturbations and fatigue as a function of time since stroke incidence.

In the discussion section, Paper II, methodological considerations and limitations are discussed in detail. A key concern relates to one of the main cautionary notes involving sample size and related power to detect effects. Although a sample size of n = 84 is in line with common practice in MRI stroke studies (see e.g. a review by Nickel and Thomalla (2017) finding that sample sized in studies assessing the relationship between PSD and lesion location using VLSM analyses varied from 24 – 55), studies with even larger samples will allow for stronger conclusions, and reduce the probability both for false positives and negatives (see e.g. Westlye, Alnæs, van der Meer, Kaufmann, & Andreassen, 2019). VLSM analyses are fundamentally restricted by the variability of lesions represented in the sample. Regarding the present results, this represent a fundamental limitation particularly for analyses on focal/binarized lesion maps, as the spatial scope of the analyses was limited by lack of whole brain representation. For example, there was a higher prevalence of right hemispheric strokes than left hemispheric strokes, and prefrontal cortex was minimally affected. As a consequence, the sample displayed low numbers of lesioned voxel overlap in the binarized lesion maps. However, due to this particular concern, the use of disconnectome maps may me particularly relevant in smaller samples, as the disconnectivity measures represent information about common disruptions across spatially distant lesions (Griffis et al., 2019).

On another note, the psychological construct one aims to understand in terms of properties of the brain will always be inherently dependent on how the construct is operationalized and measured. In terms of fatigue, it has been shown that frequently used scales correlate only moderately, load on different factors (A. Zedlitz, Van, Van, Geurts, & Fasotti, 2016) and display low content overlap (Skogestad et al., 2019). Thus, a person may be considered as fatigued by one scale, but not by the other. Although this constitutes a limitation in all research relying on some quantification of psychological constructs, it may be particularly

relevant for subjective and often fluctuating phenomena such as mental health and fatigue and warrants caution before formulating strong statements about the existence or absence of specific relationships.

Lastly and importantly, our approach did not allow for inference about functional (dis)connectivity. Aberrant functional connectivity has been implicated in fatigue in relation to TBI (Nordin et al., 2016; Ramage, Tate, New, Lewis, & Robin, 2019; Schönberger et al., 2017) and multiple sclerosis (Høgestøl et al., 2019). Investigating whether the present results (no association revealed between subjective fatigue and structural brain connectivity) replicate with functional disconnectivity measures could thus be a relevant prospect for future studies. Moreover, provided that the behavioral pattern we observed during sustained ANT performance is a valid cognitive phenotype of fatigue, functional connectivity measures could also be integrated with the approach applied in Paper I, to explore whether the fatigue-related differences in response time distributions (ANT-task) manifest in brain activation.

tDCS combined with computerized cognitive training: No added effect of tDCS

Results from the intervention study presented in Paper III revealed no added beneficial effect of repeated tDCS with regards to symptoms of fatigue or depression. Although sample size was moderate, the Bayes Factor evidence for the null hypothesis provided strong evidence (BF_{01} >10) for no tDCS effect (no interaction between time and experimental condition on symptom severity). These results thus contrast previously referred tDCS studies on patients with MS, reporting beneficial effects of tDCS stimulation on fatigue (Chalah et al., 2020; Charvet et al., 2018; Ferrucci et al., 2014), and the recent study on tDCS for fatigue in stroke patients (De Doncker, Ondobaka, et al., 2021).

Direct comparison of results between studies is complicated by heterogeneity in patient samples and differences in tDCS protocols (regarding stimulation frequency, electrode montage, current amperage and number of sessions). For example, De Doncker, Ondobaka, et al. (2021) applied two 20 minute sessions of 2 mA stimulation bilaterally to the motor cortices, with 10 minutes break between sessions, thus differing from our design in both current amperage, electrode design, duration and number of sessions. This implies that while we can say with a certain confidence that fatigue was not reduced by the tDCS administered by the current design, other setups targeting other areas may still prove effective.

Also, the existence of lesions may be a complicating factor in tDCS stroke studies. It is conceivable that treatment response may interact with individual characteristics such as lesion location or size, as illustrated by Saiote et al. (2014), reporting no group effects of tDCS in MS patients, but a correlation between treatment response and lesion load in the left frontal cortex. Discerning associations between treatment response and stroke characteristics may be a relevant target for future well-powered studies.

The observation that patients withdrawing from the study (n=19) had significantly higher fatigue scores than the patients completing the study corroborates the notion that fatigue can be a hinderance to compliance with rehabilitation programs (K. Michael, 2002). Because the majority of the patients withdrew during the double-baseline phase, prior to the intervention, we cannot infer that the intervention per se was intolerable to patients with high fatigue. Still, many put forward the anticipated labor-intensity of the intervention as a reason for withdrawing, suggesting that effective interventions for patients with fatigue need to be adjusted according to the individuals' energy, time and resources. On a related note, the patients who completed the intervention reported a significant reduction in symptoms from pre- to post assessments. This reduction was not related to tDCS, however, and because we did not have any control arm for the cognitive training, we cannot disentangle the positive effects from placebo and other unmeasured variables.

METHODOLOGICAL CONSIDERATIONS

Representativeness and selection bias

Several methodological dilemmas are associated with recruiting and including of participants. Stroke survivors comprise a highly heterogeneous group, in terms of stroke and lesion characteristics and severity, level of functioning, comorbidity and age. Criteria for inclusion will affect the quality and variability of the data, as well as the generalizability of the results.

As the study protocol was rather extensive, with 17 meetings scheduled at Oslo University Hospital in addition to 10 home-based training sessions, patients with more disabling symptoms and severe fatigue may have been prevented from participating. Patients with significant aphasia or neglect would also be excluded due to difficulties perceiving test instructions and training content displayed on computer screens. The relatively low NIHSS

scores in the sample (all patients scored below 7 at the time of hospital discharge) confirm that the included patients suffered relatively mild strokes, and attrition analyses in Paper III revealed that fatigue scores were higher in patients who withdrew from the study, than in the patients who completed the intervention. If the patient sample turns out to be highly selected and significantly different than the patient population in general, this may compromise the generalizability of the findings and limit transfer value to a clinical setting. Yet, as reported in Paper II, we observed significant differences between patients and age-and sex-matched matched healthy controls on self-reported symptoms of fatigue and depression, as well as in cognitive functioning, suggesting that patients in the current sample were experiencing symptoms of mental distress and cognitive impairments beyond what could be explained by age or sex alone. Moreover, fatigue severity was comparable to what have been reported in other chronic phase stroke studies (Choi-Kwon, Han, Kwon, & Kim, 2005; Toby B. Cumming et al., 2018; Valko, Bassetti, Bloch, Held, & Baumann, 2008) as were levels of depression (Dajpratham et al., 2020). However, we cannot exclude the possibility that inclusion of more severely impaired patients could reveal associations not detectable in the current sample, and sampling a broader spectrum of the stroke patient population in regards to symptoms (i.e. aphasia, neglect, motor dysfunction etc.) would likely increase the generalizability.

Sample size

Achieving a sufficient sample size is a frequent challenge in clinical trials, and our study is no exception. According to Ferreira and colleagues (2019), clinical stroke trials have problematically low recruitment yields, in some studies down to four (Koh, Lin, Jeng, Huang, & Hsieh, 2017) or eight (Talelli et al., 2012) percent. With 74 patients included out of 900 letters sent, our recruitment yield is low, but comparable to similar studies. Our sample size can be considered modest. To what extent this poses a threat to the validity of the results, depends in part on the research question asked, as well as applied models and methods. In this thesis, the sample size represents a limitation especially concerning MRI analyses, and we cannot exclude the possibility that relevant associations between lesion locations and clinical symptoms were missed due to a lack of statistical power, specifically related to VLSM analyses and the subsequent lack of whole brain representation coupled with low lesion overlap.

Lack of information on relevant variables

As previously described, post-stroke fatigue has been associated with a great number of risk factors, and many of them are not covered in the current work, implying that we have limited grounds to make statements about etiology. For example, pre-stroke fatigue have been reported to predict post-stroke fatigue in the chronic phase (Choi-Kwon, Choi, Kwon, Kang, & Kim, 2007; Lerdal et al., 2009), as have pain (Naess et al., 2012; Wai Kwong Tang et al., 2014), lack of social support (K. M. Michael et al., 2006), anxiety (Toby B. Cumming et al., 2018; Wu et al., 2014) and use of various medications (Chen & Marsh, 2018). Stroke patients frequently take a range of medications, of which many can cause fatigue. Current data on medication use was based on self-report only, resulting in incomplete reports for several patients. In addition, the combination of a moderate sample size and individual medication plans with regards to type of medication dosage and regime implies that a meaningful synthesizing of medication protocols and associated statistical tests on these data would not be very reliable. Medication was therefore not included in the analyses. Paper II explicitly states that medication status constitutes an important possible confounder.

Aphasia has also been hypothesized to contribute to (mental) fatigue (Staub & Bogousslavsky, 2001b), and patients with speech impairments have been reported to experience more fatigue two years after stroke than patients without such deficits (Glader et al., 2002). Yet, while we did not administer any formal tests of aphasic deficits, none of the included patients demonstrated or reported significant difficulties with language comprehension or production.

Considerations on the design of the intervention

Designing and initiating an intervention study without infinite time and resources at hand involves balancing of competing priorities. Pragmatic concerns will often conflict with best practice, and one have to balance what is practically feasible with what is methodologically ideal. The current study is no exception in this respect, and the design of the intervention part of the StrokeMRI project (tDCS combined with CCT, presented in Paper III) comprises both strengths and limitations. First, the double-blind randomized sham-controlled design represents a considerable strength, in that it enables direct evaluation of a stimulation effect compared to sham. However, all patients received CCT, and the lack of an active control group condition for cognitive training implies that we were not able to disentangle effects of the computerized training from other factors such as placebo, regression towards the mean or

positive effects of meeting with research staff on a regular basis. While the inclusion of an active control CCT control group would represent a considerable strength in this respect, this was not practically feasible for the current study. Consequently, we did not aim to identify effects of CCT per se, but rather the added effect of tDCS when combined with cognitive training.

Regarding the design and extent of the intervention, the applied setup with 17 training sessions trainings and six stimulations does not allow for direct comparison with other studies using different protocols. There are currently little consensus in the literature on how to implement tDCS interventions in order to optimize effects (Marquez, van Vliet, McElduff, Lagopoulos, & Parsons, 2015), and on a general note concerning stroke rehabilitation, more (in terms of intensity or frequency) is not always better (Cassidy & Cramer, 2017). While some studies suggest increased effect of stimulation with higher amplitude or higher number of sessions (Charvet et al., 2018), we aimed to minimize the chances of adverse effects by limiting stimulation to 1 mA. Related to number of sessions, the choice of six tDCS sessions was partly motivated by feasibility concerns, as increasing the number of sessions would significantly prolong the study period and require substantially more resources in terms of research staff and effort from participants. A related concern was limiting the scope of the intervention to avoid patient drop-out because participation got too demanding or time consuming. Moreover, the current setup with 17 training sessions administered over approximately three weeks was also in part motivated by the fact that mean hospitalization time in Norwegian rehabilitation hospitals (spesialisthelsetjenesten) ranges between 8 and 22 days, depending on the conditions' complexity and institution (public vs private) (Myrli, 2020). An intervention length of around three weeks might thus increase the applicability/transfer value to clinical practice.

Measurement/operationalization of fatigue

Lack of consistency in measurement and diagnostics of post-stroke fatigue represents a major challenge in the field (Skogestad et al., 2019). It contributes to heterogeneity in results and impedes communication and synthesizing of findings across studies (A. Zedlitz et al., 2016). The highly subjective nature of fatigue, and the fact that it is common to a range of illnesses and conditions while simultaneously constituting a normal reaction to stress and strain, implicates that it is difficult to operationalize and disentangle specific types of fatigue, post-

stroke fatigue included. Currently, the most frequently used measure of post-stroke fatigue is the FSS, which is also the measure adopted in the present work. While the FSS has several previously described beneficial properties, whereof the widespread use of the scale is one of them, it is not developed for post-stroke fatigue specifically. Moreover, FSS primarily taps into fatigue interference (six items concern fatigue interference, while the remaining three items concerns general fatigue severity), despite its common application as a one-dimensional measure of fatigue severity. This implies that there are several dimensions of the post-stroke fatigue experience not being captured by the FSS, such as diurnal variations (Birgitta Johansson & Rönnbäck, 2012), recovery time and management strategies (Skogestad et al., 2019), and it can thus be considered a rather coarse measure of a complex phenomenon. A recent review on measures used to quantify post-stroke fatigue revealed low content overlap between the various scales (Skogestad et al., 2019), exacerbating challenges with generalizability and synthesizing of results across studies. As such, development of stroke-specific fatigue measures and greater consensus on definitions and measurements appears an important step in developing the field further, and future studies could benefit from including a more detailed characterization of the fatigue experience.

On a final note regarding the FSS, item #1 an #2 are sometimes disregarded in favor of an abbreviated version (FSS7), as studies have revealed reduced reliability and discriminative properties when including these specific items (A. Zedlitz et al., 2016) as well as impaired potential to detect change across time (Lerdal & Kottorp, 2011). While such observations correspond to the results presented in Paper III, where #1 and #2 were found to have overall low centrality as compared to the respective FSS items, the full FSS scale was nonetheless used in the papers comprising this thesis in an attempt to cover a more comprehensive part of the fatigue spectrum and comply with the most commonly used application. Moreover, the inclusion of other, domain-specific measures of fatigue such as e.g. the mental fatigue scale (MFS; Birgitta Johansson & Ronnback, 2014) could provide a richer description of the phenomenon, and reveal details of the relationship between fatigue and behavioral measures (such as the ANT) not detected by FSS.

Lack of prospective registration

Guidelines for preregistration of clinical trials were developed following the WHO's *Joint*

statement on public disclosure of results from clinical trials, and joined by the Research Council of Norway in 2017 (RCN, 2020). Preregistration is an important tool for reducing bias and facilitate transparency in clinical research involving human subjects, and most scientific journals now require trial ID for publication. When the StrokeMRI project was initiated in 2012-2013, preregistration was both intended and initialized, but due to practical circumstances the registration was unfortunately never completed. While the study is now retrospectively registered, preregistration prior to data collection should be a priority for future research as it fulfills a range of purposes and benefits both the research community and patients.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

The overarching aim of this thesis has been to contribute to a better understanding of the symptoms and mechanisms of fatigue in the chronic phase after stroke. Beyond the above discussed methodological considerations, we used various and novel approaches to discern the correlates of fatigue at different levels. Briefly summarized, Paper I suggested that subjective fatigue is associated with an increased vulnerability to sustained attentional effort despite no apparent associations with baseline cognitive performance, and that this effect is specific for fatigue in contrast to depression. Paper II demonstrated that chronic phase fatigue could not be explained by neither conventional lesion characteristics nor by the extent and distribution of structural disconnection in our sample, while Paper III provided evidence for no added effect of tDCS combined with cognitive training with regards to fatigue or depression, and found more severe symptoms to be associated with less favorable outcomes in terms of attendance and training gain.

The considerable heterogeneity characterizing the stroke patient population calls for personalized treatment. Coupled with the multifactorial etiology of post-stroke fatigue, a “one size fits all” approach to treatment seems unrealistic, and different subgroups of patients are likely to benefit from different treatments (Barker-Collo, Feigin, & Dudley, 2007). Accurately defined subgroups in future studies could strengthen claims and contribute to identifying the most appropriate interventions for specific groups.

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RESEARCH REPORT

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Dissecting the cognitive phenotype of post-stroke fatigue using computerized assessment and computational modeling of sustained attention

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Abstract

Post-stroke fatigue (PSF) is prevalent among stroke patients, but its mechanisms are poorly understood. Many patients with PSF experience cognitive difficulties, but studies aiming to identify cognitive correlates of PSF have been largely inconclusive. With the aim of characterizing the relationship between subjective fatigue and attentional function, we collected behavioral data using the attention network test (ANT) and self-reported fatigue scores using the fatigue severity scale (FSS) from 53 stroke patients. In order to evaluate the utility and added value of computational modeling for delineating specific underpinnings of response time (RT) distributions, we fitted a hierarchical drift diffusion model (hDDM) to the ANT data. Results revealed a relationship between fatigue and RT distributions. Specifically, there was a positive interaction between FSS score and elapsed time on RT. Group analyses suggested that patients without PSF increased speed during the course of the session, while patients with PSF did not. In line with the conventional analyses based on observed RT, the best fitting hDD model identified an interaction between elapsed time and fatigue on non-decision time, suggesting an increase in time needed for stimulus encoding and response execution rather than cognitive information processing and evidence accumulation. These novel results demonstrate the significance of considering the sustained nature of effort when defining the cognitive phenotype of PSF, intuitively indicating that the cognitive phenotype of fatigue entails an increased vulnerability to sustained effort, and suggest that the use of computational approaches offers a further characterization of specific processes underlying behavioral differences.

Abbreviations: ANT, attention network test; CI, confidence interval; DIC, deviance information criteria; FSS, Fatigue Severity Scale; hDDM, hierarchical drift diffusion model; MCMC, Markov chain Monte Carlo; MMSE, Mini-Mental Status Examination; NIHSS, National Institutes of Health stroke scale; PHQ-9, Patient Health Questionnaire; PPC, posterior predictive checks; PSF, post-stroke fatigue; RT, reaction time; *SD*, standard deviation; TOAST, Trial of ORG 10,172 in Acute Stroke Treatment.

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KEYWORDS

attention networks, cognitive fatigue, computational modeling, reaction time, rehabilitation, stroke sequela

1 | INTRODUCTION

Post-stroke fatigue (PSF) is a common complaint among stroke survivors, with an estimated prevalence ranging between 25% and 85% (Cumming, Packer, Kramer, & English, 2016). The symptom burden is often pervasive and persistent (Duncan, Wu, & Mead, 2012; Schepers, Visser-Meily, Ketelaar, & Lindeman, 2006; van der Werf, van den Broek, Anten, & Bleijenberg, 2001) and associated with poorer outcome after rehabilitation, higher mortality (Michael, 2002; Naess, Lunde, Brogger, & Waje-Andreassen, 2012) and increased probability of institutionalization (Glader, Stegmayr, & Asplund, 2002). Post-stroke fatigue has been defined as a highly prioritized future research topic by stroke survivors, family members and healthcare professionals (Pollock, St George, Fenton, & Firkins, 2012).

Although a universally accepted definition is lacking (Deluca, 2005), PSF is generally conceptualized as the feeling of debilitating tiredness and loss of energy (Stulemeijer, Fasotti, & Bleijenberg, 2005). Moreover, many patients suffering from PSF experience cognitive difficulties such as problems concentrating (Johansson & Rönnbäck, 2012; Koopman et al., 2009) and report increased fatigue when engaging in cognitively demanding activities over time, often referred to as mental or cognitive fatigue (Johansson & Ronnback, 2014). To date, identifying robust and objective cognitive correlates of PSF has proven difficult, and the literature has failed to confirm or refute an association between self-reported fatigue and cognitive function (Lagogianni, Thomas, & Lincoln, 2018). However, this may partly be due to the use of multifactorial neuropsychological tests, with varying or low cognitive specificity and which do not account for the temporal aspects during the course of a test session (Holtzer, Shuman, Mahoney, Lipton, & Verghese, 2010). In line with this, many of the studies failing to identify an association use rather general measures of cognitive function such as the Mini-Mental State Examination (MMSE; (Folstein, Folstein, & McHugh, 1975); van Eijsden, van de Port, Visser-Meily, & Kwakkel, 2012; Kutlubaev et al., 2013) and a recent review on factors associated with PSF concluded that although the evidence does not support a link between *general* cognitive function and PSF, there may be an association between attentional functioning, processing speed and fatigue (Pihlaja, Uimonen, Mustanoja, Tatlisumak, & Poutiainen, 2014; Ponchel, Bombois, Bordet, & Hénon, 2015).

With the assumption that a critical characteristic of cognitive fatigue is the failure to maintain or sustain cognitive effort over time, monitoring performance *over time* should increase sensitivity to cognitive manifestations of fatigue (Holtzer et al., 2010) and would also be closer in line with the conceptual definition of cognitive fatigue as "decreased performance during acute but sustained mental effort" (Deluca, 2005). Accordingly, the attentional network task (ANT; (Fan, McCandliss, Sommer, Raz, & Posner, 2002)) appears to be appropriate for examining the relationship between self-reported fatigue and attentional function over time in stroke patients. ANT combines a flanker test (Eriksen & Eriksen, 1974), and a cued reaction time task (Posner, 1980) in a computerized behavioral paradigm requiring sustained attention over time. The full version lasts for about 20 min, where accuracy and response times (RT) are tracked over time in 288 trials with varying cognitive demands. The ANT allows for estimation of individual-level attention network scores such as the alerting, orienting and executive components, defined as relative differences in average RTs between different flanker and cue conditions (Fan et al., 2002).

ANT has been applied in studies of fatigue and attention in other neurological patient groups, such as Parkinson's disease, where fatigue was associated with reduced efficiency in the executive attentional network (Pauletti et al., 2017) and chronic fatigue syndrome, associated with higher RT in the most cognitively demanding condition (Togo, Lange, Natelson, & Quigley, 2015).

Although representing a widely applied and valuable contribution to theories on attentional function, analytical approaches based on mean RTs are vulnerable to trade-offs between speed and accuracy which are not accounted for in the model (Miller & Ulrich, 2013), and they do not provide information about which underlying mechanisms give rise to observed RT differences. In contrast, computational approaches such as the drift diffusion models (DDM; (Ratcliff, 1978)) simultaneously model the full distribution of RTs and accuracies to estimate parameters reflecting specific theoretical cognitive constituents of the decision process. DDMs are frequently

applied to simple and speeded decision-making tasks (Ratcliff & McKoon, 2008; Ratcliff, Smith, Brown, & McKoon, 2016), offering both a theoretical framework to understand basic cognitive processes, and a psychometric tool to translate behavioral data into subcomponents of cognitive processing (Ratcliff & McKoon, 2008). DDMs conceptualize decision-making as a noisy process where information is accumulated over time, continuing until a decision threshold is reached and a response is initiated (Ratcliff & McKoon, 2008). Four parameters are postulated in the original model (Ratcliff, 1978): *drift rate* (v), describing the rate or the speed of information accumulation, reflecting processing efficiency; *non-decision time* (t) representing time needed for stimulus encoding and response execution; *decision boundary separation* (a) indicating how much evidence is needed before a decision is made; and the *starting point* (z), reflecting any bias toward one of the two responses (Ratcliff & McKoon, 2008). The parameters have been validated in various experimental paradigms (Lerche & Voss, 2017; Voss, Rothermund, & Voss, 2004).

Applying computational models such as the DDM in clinical research may allow for a dissection of specific cognitive processes underlying observed group and individual differences in RT patterns. For example, assessing young and older subjects with a signal detection task, Ratcliff, Thapar, and McKoon (2001) found that the prolonged RTs often observed in older individuals were not explained by slower drift rates but rather longer non-decision times and higher decision thresholds, which provided a relevant adjustment to the long-held notion of a general slowing in cognitive aging (Brinley, 1965; Salthouse, 1985). In the context of stroke patients and PSF, such computational approaches may provide a valuable, supplementary tool to expand our understanding of cognitive function beyond conventional methods of neuropsychological assessment and statistical analysis.

In sum, a large number of stroke patients suffer from PSF, and many experience cognitive difficulties and cognitive fatigue. Attentional deficits may be particularly involved. The ANT paradigm allows us to determine whether and how subjective fatigue manifests cognitively during prolonged effort, and assess associations between subjective fatigue and efficiency of the attentional networks. With the aim of characterizing the relationship between subjective fatigue and attentional function, we collected behavioral data using the ANT and self-reported symptoms of fatigue using the fatigue severity scale (FSS; (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) from 53 chronic stroke patients (>6 months since hospital admission). We hypothesized that self-reported symptoms of fatigue as measured by the fatigue severity scale (FSS; (Krupp et al., 1989) would interact with time on task, manifesting in an increase in RT for patients with high fatigue levels relative to patients with low levels of fatigue. Further, we expected to find a negative association between fatigue and executive network functioning, in line with previously mentioned literature. Main analyses were conducted with FSS score as a continuous predictor, and follow-up sensitivity analyses were conducted with PSF group (high/low PSF) as a factor predictor, or separately for patients with high/low PSF to assess manifestation of group differences. Lastly, evaluating whether DDM modeling can elaborate our understanding further by characterizing the specific cognitive processes underlying observed differences in RT patterns, we performed an exploratory analysis where we fitted a hDDM to the ANT behavioral data and tested for associations between the model parameters (drift rate (v), non-decision time (t) and boundary separation (a)) and fatigue (FSS) score. To account for the temporal aspects of task performance, we specifically tested for interactions between FSS, trial number and performance. In line with our first hypothesis, we hypothesized that any associations between subjective fatigue and model parameters will interact with time, with increasing associations between fatigue and model parameters with more sustained performance.

2 | MATERIALS AND METHODS

2.1 | Sample

Stroke patients who had been previously admitted with acute stroke to the Stroke Unit, Oslo University Hospital, or the Geriatric Department, Diakonhjemmet Hospital, between 2013 and 2016, were invited by letter. Patients had to be in a chronic phase, defined as minimum 6 months post-stroke, with no other severe neurological, psychiatric or neurodevelopmental conditions. Among the approximately 900 invitation letters, 250 patients responded to decline or obtain more information. Seventy-seven were interested and eligible for inclusion and provided informed consent. Nineteen of the 77 patients withdrew during the course of the study and before the data for the current paper were collected. Four additional patients were excluded because of medical conditions. One patient was excluded due to behavioral criteria for the ANT (see below), resulting in a final sample of $n = 53$ stroke patients.

Table 1 summarizes relevant demographic and clinical information of the patient group, and Figure 1 shows the age distribution. This work was part of an intervention study on cognitive rehabilitation after stroke with a double baseline, randomized controlled design (see (Kolskaar et al., 2019) for more details, including a description of overall study design). All data for the current study were collected from the baseline assessments prior to the intervention, starting 6–45 months after the acute stroke.

Mini-Mental Status Examination scores < 24 may indicate cognitive impairment and warrant further examination (Strobel & Engedal, 2008). One patient scored below 24, but further neuropsychological assessments done by a clinical psychologist indicated that cognitive function was sufficient for participation and that the inclusion criteria were not violated. The study was approved by the Regional Committee for Medical and Health Research Ethics, south-east Norway. All participants provided their written informed consent prior to inclusion.

TABLE 1 Sample characteristics

Current demographic and clinical information	Mean	*SD*	Min	Max
Age	69.00	7.43	47	81
Males/females (count)	38/15	–	–	–
Education in years	14.56	3.65	9	30
FSS	3.53	1.46	1.11	6.77
PHQ-9	4.79	3.61	1	14
MMSE	28.22	1.68	22	30
Stroke-related information				
NIHSS at hospital discharge	1.14	1.23	0	6
Months since stroke	25.59	9.40	6.00	45.00
TOAST classification for ischemic stroke[a]	Large artery artherosclerosis (19)			
	Small vessel occlusion (18)			
	Cardioembolism (6)			
	Other known/not known (10)			
Stroke location	Right Hemisphere (20)			
	Left Hemisphere (18)			
	Brainstem/cerebellum (7)			
	Both Hemispheres (5)			
	Not specified (3)			

[a]All but one patient suffered ischemic stroke.

2.2 | FSS

Fatigue was measured by the FSS (Krupp et al., 1989), which is a one-dimensional, 9-item self-report scale, and one of the most frequently used measures to assess fatigue after stroke and other neurological conditions (Cumming et al., 2016; Lerdal et al., 2009; Whitehead, 2009). The nine items are statements about impact of fatigue on different areas of daily life, and responses are given on a nine-point Likert scale reflecting degree of agreement (minimum mean score 1, maximum mean score 7). A review of 22 fatigue measures concluded that FSS was among the three scales that demonstrated good psychometric properties, as well as sensitivity to change in fatigue over time (Whitehead, 2009). Figure 1 shows the distribution of mean FSS scores by sex. Average FSS score was 3.53 (SD = 1.46), and 35% of the patients reported mean FSS > 4, which is a commonly adapted threshold for clinical fatigue in stroke studies (Krupp et al., 1989; Schepers et al., 2006; Tang et al., 2010). Table S1 shows the mean scores per item for patients with- and without PSF according to this cutoff value, offering a more detailed characterization of fatigue complaints in the sample. The PSF group scored significantly higher on all items.

2.3 | PHQ-9

Depressive symptoms were measured by the self-report scale Patient Health Questionnaire (PHQ-9; Spitzer, Kroenke, Williams, & Patient Health Questionnaire Primary Care Study, 1999). PHQ-9 consists of nine items based on the DSM-IV criteria for depression. These are scored 0–3, providing severity scores ranging from 0 to 27. Briefly, sum scores of 5, 10, 15 and 20 represent mild, moderate, moderately severe and severe symptom levels. Average PHQ score in the patient sample was 4.79.

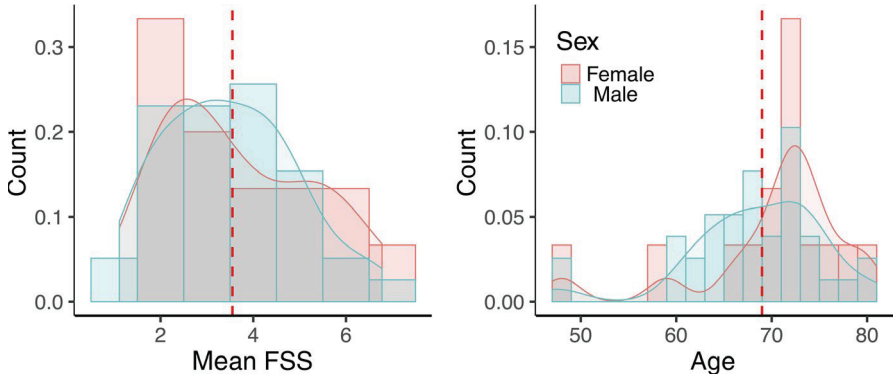

FIGURE 1 Distribution of mean FSS scores by gender and distribution of age by gender. Red line denotes the mean [Colour figure can be viewed at wileyonlinelibrary.com]

2.4 | Attention network test

A conventional version of the ANT was applied, as previously described (Fan et al., 2002). In the ANT, accuracy and response times (RT) are tracked over time in trials with varying cognitive demands in a computerized paradigm. By combining a flanker test (Eriksen & Eriksen, 1974), and a cued reaction time task (Posner, 1980), the ANT estimates network scores as relative differences in mean RTs between different flanker and cue conditions (Fan et al., 2002). Figure 2 depicts the details of the task.

Briefly, participants were instructed to direct their gaze at fixation cross that was presented with a duration of 400, 800, 1,200 or 1,600 milliseconds. Immediately following the fixation cross, one out of four cue conditions would appear for 100 milliseconds; no cue, a center cue (temporal cue only), a double cue (temporal cue only), or a spatial cue (temporal *and* spatial cue), alerting the attention toward the stimulus about to appear. Then, five small arrows or lines were presented for 1,700 milliseconds, and the task was to, as quickly and correctly as possible, decide whether the middle arrow (target arrow) was pointed left or right. Participants responded by pressing the left or the right mouse button. The four flanker arrows/lines surrounding the middle, target arrow could point in either the same direction (congruent flankers) or the opposite (incongruent flankers) direction as the middle, target arrow, or they could simply be lines without direction, constituting neutral flankers. The flanker arrows/lines represent the different stimulus conditions associated with different cognitive demands, where incongruent flankers typically result in the highest error rates and RTs (Westlye, Grydeland, Walhovd, & Fjell, 2010).

Starting with a practice run of 24 trials, the full test consisted of 288 trials, divided into three rounds (96 trials per round), lasting about 20 min. Participants were instructed to take a short break between rounds. For setting up the experiment and collecting responses, E-prime software (Psychology Software Tools, Pittsburg, PA) was applied.

2.5 | Statistical analyses

Statistical analyses were performed using R version 3.4.0 (2017-04-21; R Core Team, 2017) and the python toolbox HDDM (Wiecki, Sofer, & Frank, 2013). Figures were produced using the ggplot2 package (Wickham, 2009).

2.5.1 | Outlier exclusion and data cleaning

Trials with RT < 200 ms, thought to reflect fast guesses, were removed from the analysis, in line with previous ANT reports (Chang, Pesce, Chiang, Kuo, & Fong, 2015; Westlye et al., 2010). 2% of the responses were removed due to this criterion. Participants having more than 50% incorrect responses within any of the flanker conditions were discarded. One participant was removed due to this criterion.

2.5.2 | Associations between FSS, time and RT

In order to characterize the relationship between subjective fatigue (FSS_z), time (trial 1–288) and RT, we applied linear mixed-effects models using the lme function from the nlme package in R (Pinheiro, Bates, DebRoy, & Sarkar, 2013). Following the recommendations from Barr, Levy, Scheepers, and Tily (2013), we started with a maximal model, including by-subject random slopes for FSS_z * time at the subject level, in addition to random

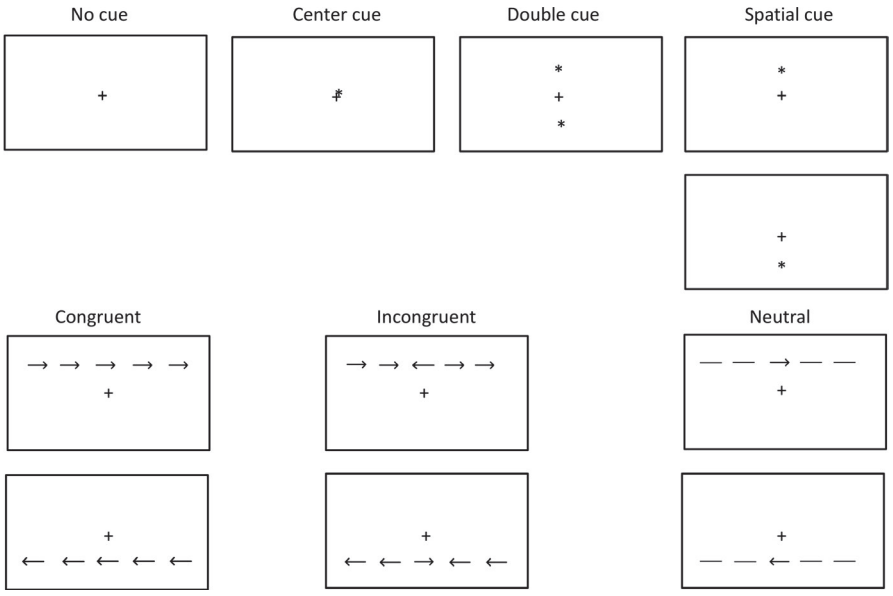

FIGURE 2 A schematic representation of the ANT cue and flanker conditions

intercepts, and all fixed effects or covariates of potential interest. These were *z*-normalized FSS scores × time, age, sex, flanker condition, stroke topography (left or right hemisphere, brainstem/cerebellum), lesion volume (defined by number of voxels affected), TOAST classification for stroke etiology (large artery artherosclerosis, small vessel occlusion, cardioembolism or "other known or unknown factors"), NIHSS scores and z-normalized PHQ scores. Non-converging models were dealt with by sequentially simplifying the fixed effect structure until reaching convergence. The full model did not converge, and we dropped NIHSS, on the basis that the variability in NIHSS scores was small (mean = 11.4, median = 1, *SD* = 1.23), reflecting the fairly highly functioning patient sample. Next, we removed TOAST classification of stroke etiology, due to a large number of cases in the "not specified/unknown" category, and then excluded PHQ scores because of high correlations with FSS.

The most complex converging model was specified as follows: lme (RT ~ FSS_z * time + age + sex + flanker + lesion volume + lesion location, random = 1 + FSS_z * time|id, data = data, method = "REML"). As a formal test of whether random slope effects were warranted, we used the ANOVA function in R to compare model fit between this model and a similar model without a random slope term, and results indicated that random slopes should be included. To further refine the model, we tested whether removing independent variables that did not provide predictive value improved model fit. Model fit improved marginally by removing lesion volume and lesion location. As an indication of FSS effect size, we compared the final model with a model that did not include FSS score. Model formulae and notes on model selection are provided in Table S2.

Assessing whether PSF status (PSF defined by mean FSS score > 4, in line with common practice (Krupp et al., 1989; Schepers et al., 2006)) interacted with the effect of time/trial number, we reran the above-specified regression model with PSF status included in the model instead of FSS score as a continuous measure. Additionally, to test whether effects varied between flanker conditions, we estimated the full regression model separately for each flanker condition. In these follow-up models, random slopes were not estimated in order to secure convergence. To explore whether the relationship between time, fatigue and performance manifested differently according to PSF status, we repeated the above-described within-flanker linear mixed-effects models within patients with PSF and patients without PSF.

Importantly, to test whether potential effects were specific for fatigue or could be explained by depressive symptoms, the full linear mixed-effects model was repeated with PHQ instead of FSS, keeping all other model specifications constant.

In all analyses, the time variable refers to trial number (1–288).

2.5.3 | Associations between conventional ANT network scores and FSS

Based on a previous definition (Westlye et al., 2010), we computed the conventional ANT network scores orienting, alerting and executive control network based on median RTs:

$$\text{Executive control} = (\text{RT incongruent} - \text{RT congruent})/\text{RT congruent}$$

$$\text{Alerting} = (\text{RT no cue} - \text{RT center cue})/\text{RT center cue}$$

$$\text{Orienting} = (\text{RT center cue} - \text{RT spatial cue})/\text{RT spatial cue}$$

To assess the association between estimated attentional networks and subjective fatigue, we ran a linear model for each attentional network and tested for main effects of FSS, covarying for age and sex. We then estimated change in network efficiency over time (network slope) for each network and fitted this to a linear model adding FSS, age and sex as predictors to test for interactions between attentional networks, time and FSS. Network slopes were created in two steps: First, we ran linear models for each patient within each flanker and cue condition separately, predicting RT by trial number. Then, change in network efficiency/network slope was calculated for each patient by subtracting the betas from the first models in the same way as outlined above, that is:

$$\text{Executive slope} = (\text{beta incongruent} - \text{beta congruent})$$

Following the same procedure as in the RT models above, we reran the network analyses replacing FSS with PSF status as independent variable, to investigate whether attentional networks were differently affected by time dependent on PSF status.

As an additional test of potential associations between subjective fatigue and stroke-related variables, we estimated the correlations between FSS score, NIHSS score, lesion volume and months since stroke, respectively.

2.5.4 | Hierarchical drift diffusion modeling

Cleaned RT and accuracy data were submitted to hierarchical drift diffusion modeling by use of the python toolbox HDDM (Wiecki et al., 2013). HDDM uses hierarchical Bayesian parameter estimation, which provides enhanced statistical power and allows for estimation of both individual and group parameters simultaneously (Wiecki et al., 2013). We applied mildly informative priors and starting points as predefined in the toolbox (Wiecki et al., 2013). We did not estimate any bias in starting point. The data were accuracy-coded (accurate responses = 1, erroneous responses = 0). In addition to the data cleaning described above, an outlier mixture model

included in the HDDM was applied, which assumes that a fixed proportion (5%) of trials are outliers that come from a uniform distribution not generated by a diffusion process (Wiecki et al., 2013). A mixed-effects model allowing for some outliers has been shown to provide a better fit in likelihood models than models not allowing for any outliers at all (Wiecki et al., 2013).

2.5.5 | Model selection/ defining parameters

When parametrizing the hDDM, we tested different cognitively plausible models to identify the model that best explained data, guided by the theoretical assumption that *drift rate (v)* should be allowed to vary as a function of stimulus difficulty condition (Ratcliff, Smith, & McKoon, 2015). Further, *decision threshold (a)* was assumed to be constant across stimulus conditions, following the logic that if *a* varies with stimulus conditions, the participant would have to first identify the condition, before adjusting threshold and then start accumulating information from the stimulus, a sequence of events that does not seem plausible (Thapar, Ratcliff, & McKoon, 2003). *Non-decision time (t,* stimulus encoding and motor responses) was not expected to be affected by flanker condition, given that the visual stimuli were highly similar across flanker conditions and motor responses were simple and identical across conditions (simple button press).

Building on the above-mentioned assumptions, we estimated different models and tested which combination of parameter fixations provided the best model fit. See Table 2 for an overview of models tested.

Variability estimates were included in the preliminary models, but were discarded as they failed to converge adequately and slightly worsened model fit. Variability parameters are often estimated poorly, and less complex models may improve estimates of the parameters of interest (Lerche & Voss, 2016). To evaluate in which parameter the interaction between time and FSS should be localized, we estimated a

TABLE 2 Parameter fixations and model fits (DIC) for various hDDM regression models

Model		Samples	DIC
(a ~ warningcue)	A1	1,500	−15,424
(t ~ warningcue)	A2	1,500	**−15,717**
(v ~ warningcue)	A3	1,500	−15,169
([v ~ flanker + time * FSS, t ~ time * FSS + warningtype, a ~ FSS * time], group_only = True)	B1	12,000	−16,608
(a ~ time)	C1	1,500	−14.356
(t ~ time)	C2	1,500	**−14.448**
(v ~ time)	C3	1,500	−14.219
(a ~ FSS)	D1	1,500	−14.109
(t ~ FSS)	D2	1,500	**−14.110**
(v ~ FSS)	D3	1,500	−14.109
(a ~ FSS:time)	E1	1,500	−14.353
(t ~ FSS:time)	E2	1,500	**−14.454**
(v ~ FSS:time)	E3	1,500	−14.222
(['v ~ flanker, t ~ warningtype, a ~ FSS * time], group_only = True)	F1	6,000	−16,590
([v ~ flanker, t ~ time * FSS + warningcue], group_only = True)	F2	6,000	**−16,602**
([v ~ flanker + time * FSS, t ~ warningtype], group_only = True)	F3	6,000	−16,575
([v ~ flanker, t ~ time * FSS + warningcue], group_only = False)	G1	6,000	−17,648
([v ~ flanker, t ~ time * FSS + warningcue], group_only = False)	G2	12,000	−17,648
([v ~ flanker, t ~ time * FSS + warningcue], group_only = True)	**H1**	**12,000**	**−16,602**

Note: DIC, deviance information criterion, where lower values indicate a better model fit. DIC values in bold indicate the combination of parameter fixation that provided the best fit for each model comparison (model comparisons between same letter models (i.e., A1–A3).

regression model where all three parameters (*a*, *t* and *v*) were allowed to vary by the interaction term. To further explore which parameter fixations provided the best model fit, we ran nine simple models with (a) the main effect of time on either *a*, *t* or *v*; (b) the main effect of FSS on either *a*, *t* or *v*; and (c) the FSS*time interaction on *a*, *t* or *v* separately. Finally, we estimated the best model with individual regressors and group only regressors.

Model fit was assessed by comparing the deviance information criteria (relative DIC values) between models. In Bayesian analyses, the DIC provides an estimation of fit of the model to the data, where lower DIC values indicate that the model has better support (François & Laval, 2011). In models where individual regressors were estimated, we simulated data from the respective models and performed posterior predictive checks (PPC) to evaluate whether the model was able to reproduce central patterns in the observed data (Wiecki, 2016). 500 data sets were simulated by drawing 500 samples for each parameter from the estimated posterior distribution. The simulations thus capture the uncertainty in the estimated model and allow for comparisons with the observed data.

Final choice of model was based on a combination of model fit and convergence (see below).

2.5.6 | Estimating the posterior distributions and assessing convergence (model diagnostics)

We used a Bayesian framework and Markov chain Monte Carlo sampling (MCMC) to estimate the posterior distributions (Kruschke, 2014). In the preliminary models, when testing and comparing parameter fixations, models were estimated on 1,500 or 6,000 samples. The final model was run on 12,000 samples. To improve convergence, the 4,000 first samples were discarded, and thinning was set to 2 (keeping only every second sample).

A valid model should demonstrate convergence of the MCMC chains (Wiecki, 2016). Convergence was assessed by plotting and visually inspecting traces and autocorrelation plots for each estimated parameter. As a more formal test of convergence, the Gelman–Rubin statistics (R^; (Gelman & Rubin, 1992) were calculated. These values should be close to 1 and not exceed 1.1 if the chains have converged successfully, that is, if the samples of the different chains are similar (Wiecki et al., 2013).

2.5.7 | Hypothesis testing within the hDDM

Effects of task and cue conditions, as well as the effects of time and fatigue status, were determined by Bayesian hypothesis testing, by assessing the degree of overlap between posterior distributions. If less than 5 percent of the posterior distributions of two parameters overlap, the difference is said to be credible, or an effect is credibly different than null when at least 95 percent of the posterior distribution does not contain zero.

3 | RESULTS

3.1 | ANT behavioral results

Table 3 shows mean RT and error rates for each flanker condition. Two-tailed, one-sample *t* tests revealed significant differences in RT between incongruent and congruent condition, $M = 111$, CI = 101–122, $t(52) = 20$, $p < .001$, between incongruent and neutral condition, $M = 124$, CI = 112–136, $t(52) = 20$, $p < .001$ and between congruent and neutral condition, $M = 12$, CI = 3.7, $t(52) = 3.6$, $p < .001$.

There was no significant association between FSS and mean RT across ($r = .09$, $p = .48$) or within conditions (incongruent flanker: $r = .05$, $p = .67$, congruent flanker: $r = .11$, $p = .47$, neutral flanker: $r = .12$, $p = .37$). There was no association between FSS and error rate ($r = -.09$, $p = .48$).

3.2 | Associations between FSS, time and RT

Table 4 shows the summary statistics from a linear mixed-effects model testing for associations between RT and FSS, time, sex, age and flanker condition for all conditions simultaneously. The model including FSS score performed significantly better than the model not including FSS score as indicated by ANOVA model comparison, supporting the predictive value of FSS (L.ratio(1) = 19.09, $p < .001$, see also Table S2).

The model presented in Table 4 was also run with lesion volume and lesion location as independent variables to control for effects related to lesion characteristics. As both volume and location displayed low predictive value and did not improve model fit, they were not included in the final analyses. Results from the linear mixed model including lesion volume and lesion location are presented in Table S3.

TABLE 3 Error rates and mean RTs by flanker condition

	Mean RT in ms			
Flanker	**Total (*SD*)**	**Error (*SD*)**	**Accurate (*SD*)**	**Accuracy (%)**
Congruent	668 (187)	841 (329)	667 (185)	99.2
Incongruent	773 (199)	645 (300)	776 (195)	97.7
Neutral	655 (180)	713 (245)	654 (179)	99.1

TABLE 4 Linear mixed-effects models for whole sample, all flanker conditions

	t	Beta	CI	*p*
Intercept	0.63	109.49	(−229.4, 448.5)	.526
FSS_z	0.37	7.02	(−29.9, 43.6)	.298
Time	−1.03	−0.03	(−0.09, 0.03)	.870
Time:FSS	2.65	0.07	(0.02, 0.14)	.008
Sex	0.04	1.92	(−77.34, 81.2)	.962
Age	3.34	8.15	(3.37, 12.93)	.001*
Incongruent flanker	40.5	111.52	(106.14, 116.93)	<.000*
Neutral flanker	−4.31	−11.78	(−17.15, −6.43)	<.000*

**p*-Values that remained significant after Bonferroni correcting for multiple comparisons.

TABLE 5 Linear mixed-effects models by flanker stimulus, one model per condition

	Neutral			Incongruent			Congruent		
	Beta	*t*	*p*	Beta	*t*	*p*	Beta	*t*	*p*
FSS	8.31	0.50	.614	−1.21	−0.06	.949	13.67	0.78	.472
Time	−0.03	−1.68	.091	−0.05	−2.27	.023	−0.00	−0.26	.791
Time:FSS	0.09	4.22	<.001*	0.10	4.16	<.001*	0.04	2.08	.037
Sex	−4.78	−0.13	.896	0.14	0.00	.997	2.06	0.05	.958
Age	8.22	3.71	<.001*	8.42	3.26	.002*	7.95	2.08	.037

**p*-Values that remained significant after Bonferroni correcting for multiple comparisons.

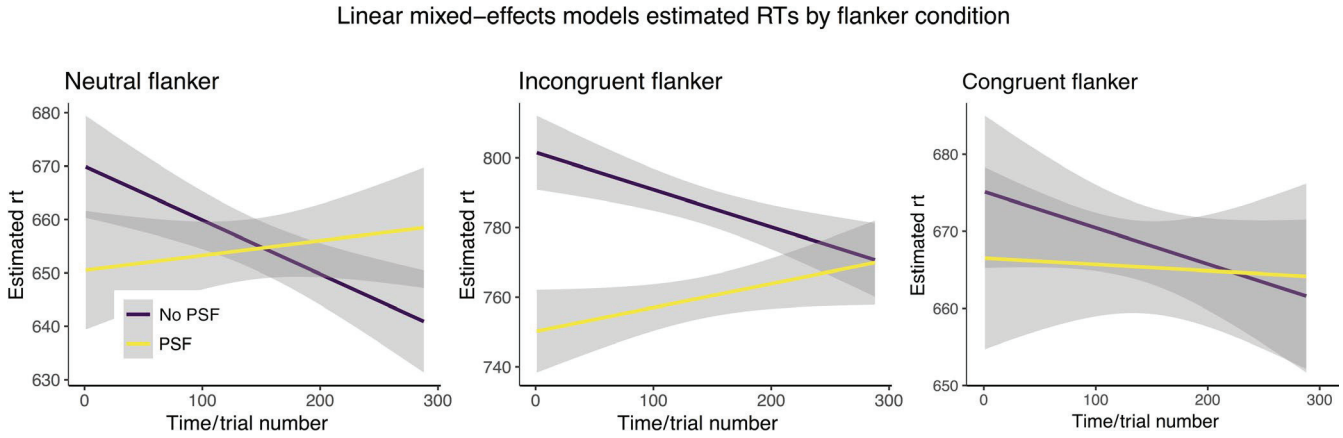

FIGURE 3 Estimated RT from linear mixed-effects models plotted by PSF status [Colour figure can be viewed at wileyonlinelibrary.com]

Table 5 presents summary statistics for models estimated for each flanker condition separately, estimating the effect of FSS score, time (trial number) and the interaction effect between time and FSS. Figure 3 shows the estimated RT (output from Table 5) plotted by group (PSF vs. non-PSF patients, based on mean FSS score ≥ 4). Briefly, after Bonferroni correction for multiple comparisons (corrected alpha 0.5/8 = .006), the interaction between time and FSS was significant in the neutral and incongruent condition, as was the association between age and RT, indicating that age was associated with increased RT across conditions. There was no significant main effect of FSS on RT in any condition.

Corresponding linear mixed model with group (PSF status) instead of FSS score revealed similar associations with the various independent factors as presented in Table 4, except for identifying a negative main effect of time ($\beta = -0.05$, $SE = .01$, $t = -3.31$, $p < .001$). The interaction effect between PSF status and time was comparable to that of FSS score and time, albeit smaller ($\beta = 0.06$, $SE = .01$, $t = 2.27$, $p = .022$), and only nominally significant. All results from the model with PSF status as predictor are presented in Table S4.

Mixed-effects models with PHQ score included instead of FSS did not indicate significant interaction effects between depressive symptoms and time on RT in any flanker condition.

Table 6 shows summary statistics from linear mixed models estimating the main effect of sustained performance (time) on RT in the various flanker conditions, conducted separately for patients with and without PSF. In this model, that included only trial number (time) and not FSS score as predictor, the results suggested that patients without PSF demonstrated more speeded RTs in the incongruent condition during the course of the experiment, while patients with PSF did not show any significant changes in RT in any condition.

3.3 | Associations between FSS and other clinical measures

There was no correlation between FSS score and months since stroke ($r = .00$, $p = .97$), between FSS score and lesion volume, indicated by number of voxels affected ($r = -.14$, $p = .30$) or FSS score and stroke severity, indicated by NIHSS score ($r = .10$, $p = .46$). FSS score was positively correlated with PHQ score ($r = .47$, $p < .001$).

3.4 | Associations between ANT network scores and FSS

One-sample t tests revealed significant group-level network score effects for executive control network ($M = 0.18$, CI = 0.17–0.20, $t = 21.57$, $p < .001$), orienting network ($M = 0.06$, CI = 0.05–0.08, $t = 11.27$, $p < .001$) and alerting network ($M = 0.04$, CI = 0.03–0.06, $t = 7.47$, $p < .001$). Table 7 shows summary statistics from linear models estimating the associations between ANT network scores and FSS. Whereas the analyses revealed a nominally significant negative association between FSS and the executive network score ($t = -2.23$, $p = .03$) and a negative effect of age on the alerting network ($t = -2.17$, $p = .03$), no associations remained significant after correction for multiple comparisons.

Table 8 shows linear models testing associations between ANT network efficiency change over time (network slope) and FSS score, age and sex. Results suggested a (nominally) significant association between executive slope (network efficiency change over time, where positive score indicate efficiency) and FSS ($t = 2.24$, $p = .029$). No associations remained significant after correction for multiple comparisons. See Figure 4 for network slopes plotted against FSS scores. Follow-up linear models with PSF status as predictor instead of FSS did not support a significant main effect of PSF status ($t = -0.73$, $p = .466$) on executive network slope.

3.5 | hDDM regression models

The best fitting model that showed adequate convergence allowed *drift rate (v)* to vary across flanker conditions, *non-decision time (t)* to vary across warning cue conditions and time while *boundary separation (a)* was kept constant ("v ~ flanker," "t ~ warningcue +time"). In this group-level model, no Gelman–Rubin statistics (R-hat values) were > 1.1, and chains and autocorrelations confirmed adequate convergence for all parameters.

A less restricted model where all parameters were allowed to vary by the FSS*time interaction term generated a slightly better model fit (DIC value −16,608 vs. −16,602), but worse convergence in terms of (R-har values > 1.1), chains and autocorrelations. This model was therefore discarded as not sufficiently valid. Estimations of the best fitting model ("v ~ flanker," "t ~ warningcue + time") on the individual level produced the best fit in terms of DIC values, but posterior predictive checks indicated that the models did not sufficiently reproduce observed patterns in the data and the standard deviations for t:FSS and t_time:FSS showed suboptimal convergence.

TABLE 6 Linear mixed-effects models estimating RT by time for PSF/non-PSF patients separately

	Neutral			Incongruent			Congruent		
	Beta	***t***	***p***	**Beta**	***t***	***p***	**Beta**	***t***	***p***
Non-PSF patients									
Time	−0.06	−2.17	.029	−0.10	−3.22	.001*	−0.01	−0.55	.575
Sex	34.1	0.66	.509	10.9	0.18	.854	26.5	0.48	.632
Age	10.1	2.90	.007	8.96	2.21	.035	8.90	2.39	.024
PSF patients									
Time	−0.00	−0.12	.377	0.00	0.18	.851	0.00	0.17	.859
Sex	−47.4	−0.76	.454	−9.77	−0.13	.897	−25.7	−0.38	.707
Age	7.86	2.26	.036	8.36	1.99	.062	8.17	2.15	.045

*p-Values that remained significant after Bonferroni correcting for multiple comparisons.

3.6 | Effect of time and FSS on *t*, non-decision time

Figure 5 shows the posterior distributions for non-decision time, t. hDDM provided support for a negative main effect of time (P(t_time < 0) = 0.98) on non-decision time, indicating that time needed for stimulus encoding and response execution decreased during the course of the test. hDDM did not identify a main effect of FSS on non-decision time (P(t_FSS > 0) = 0.77). In contrast, the model provided evidence for a positive interaction effect between time on task and FSS on non-decision time (P(t_time:FSS > 0) = 1.00), suggesting that the association between FSS and non-decision time increased during the course of the experiment, so that patients with high levels of fatigue were more negatively affected by time on task (resulting in higher non-decision times), than patients low on fatigue. The interaction effect is small, but robust (posterior distribution not overlapping the null, model displaying good convergence), and it is in the opposite direction of the main effect of time when FSS is not accounted for.

TABLE 7 Linear regression models by ANT network

	Orienting		Alerting		Executive	
	t	*p*	*t*	*p*	*t*	*p*
FSS	0.57	.567	−1.03	.305	−2.23	.030*
Age	1.10	.276	−2.17	.034	−1.18	.243
Sex	1.66	.103	−0.41	.681	−0.03	.975

*Nominally significant *p*-values.

TABLE 8 Linear regression models by ANT network slope

	Executive		Alerting		Orienting	
	t	*p*	*t*	*p*	*t*	*p*
FSS	2.24	.029*	0.18	.85	0.55	.580
Age	0.832	.409	−0.54	.587	1.44	.156
Sex	−0.98	.332	0.697	.489	0.27	.787

Note: Higher network values indicate lower relative network efficiency.

*Nominally significant *p*-values.

3.7 | Effect of warning cue on *t*, non-decision time

Figure 6 (left) shows the posterior probability plot for non-decision time (*t*) as a function of warning cue (intercept: center cue). Non-decision time was lowest for cue conditions "up" and "down". "No cue" resulted in the highest non-decision time out of all cue conditions. Thus, model evidence suggests that the presence of cues facilitated the process of stimulus encoding and response execution, and most efficiently so when the cues provided both temporal and spatial information ("up" and "down").

3.8 | Effect of flanker conditions on drift rate

Figure 6(right) shows the posterior probability plot for the drift rate (*v*) estimated by flanker condition (intercept: congruent condition). The model provided strong evidence supporting that drift rate was lower in the incongruent condition compared to both congruent and neutral condition (P(v_Incongruent < v_Congruent) = 1.0, and P(v_Incongruent < v_Neutral) = 1.0), suggesting lower rates of evidence accumulation in the cognitively most demanding condition (incongruent flanker with cognitive conflict). Drift rate was highest in the neutral condition (P(v_Neutral > v_Congruent) = 1.0, P(v_Neutral > v_Incongruent) = 1.0).

4 | DISCUSSION

Post-stroke fatigue is a common and debilitating symptom in stroke patients, yet its mechanisms are poorly understood. Many patients suffering from PSF report increased fatigue

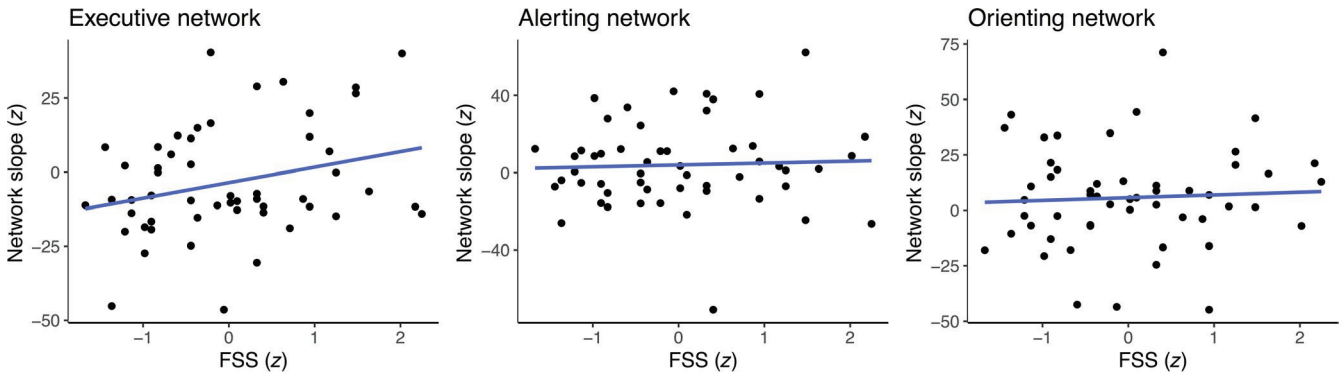

FIGURE 4 Estimated attention network slopes plotted against *z*-normalized FSS scores [Colour figure can be viewed at wileyonlinelibrary.com]

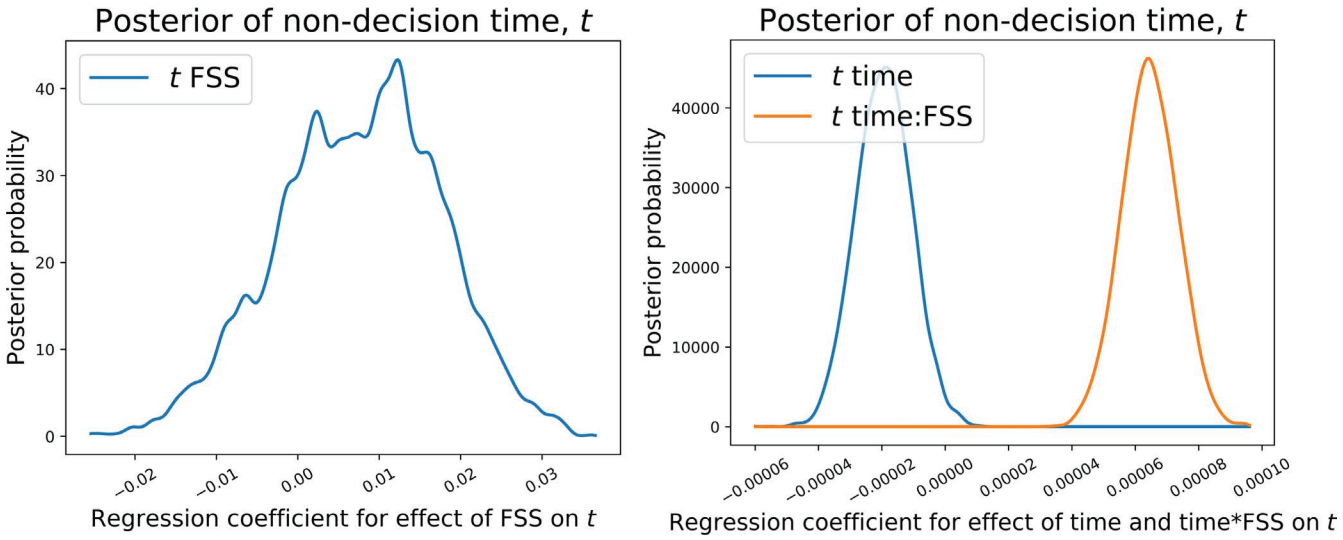

FIGURE 5 Posterior distributions of non-decision times (t) as a function of FSS score (left), and as a function of (a) time and (b) the interaction between FSS score and time (right). hDDM provided no evidence in support of a main effect of FSS, but indicated a negative main effect of time ((P(t_time < 0) = 0.98), and a small, but robust ((P(t_FSS*time > 0) = 1.0) positive interaction effect between FSS and time on non-decision time (t; neither of the distributions in the right plot overlap the null) [Colour figure can be viewed at wileyonlinelibrary.com]

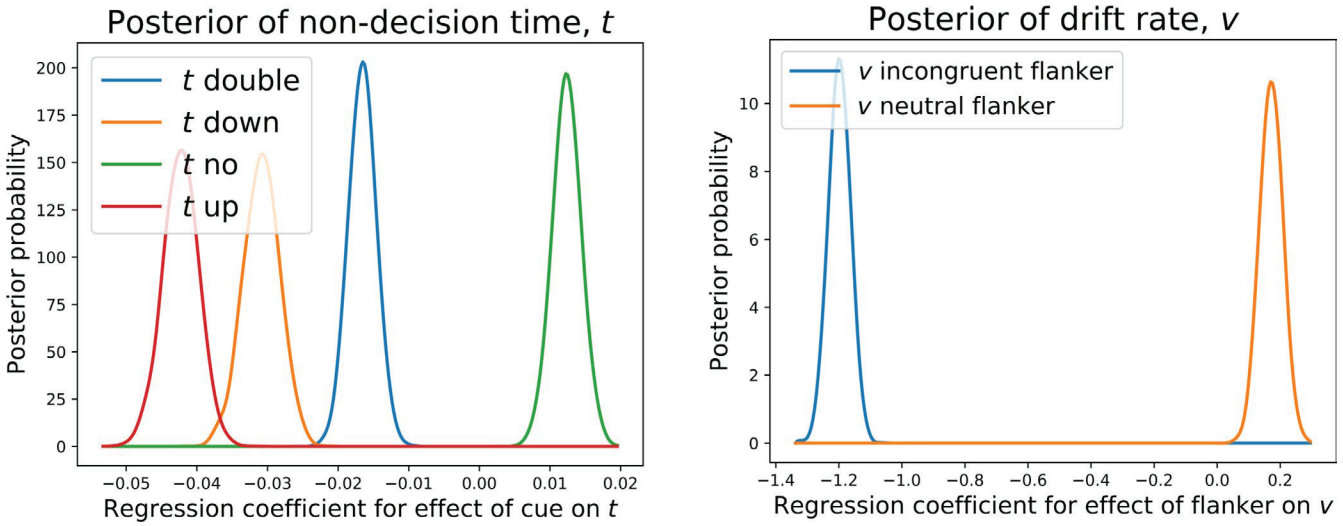

FIGURE 6 Posterior distributions of non-decision time (left) and drift rate (right). Drift rate posteriors (right plot) for incongruent and neutral flanker conditions are plotted relative to the intercept (congruent flanker condition). Incongruent drift rate is lower than both congruent and neutral drift rate, and the distributions are not overlapping. In the left plot showing non-decision time, posteriors probability distributions for different warning cue conditions are plotted relative to the intercept (center cue) [Colour figure can be viewed at wileyonlinelibrary.com]

and cognitive difficulties when engaging in cognitive tasks, but previous studies have largely failed to establish robust associations between subjective fatigue and cognitive performance. The scarcity of evidence may be due to the use of instruments lacking cognitive sensitivity and specificity, and tests that do not account for the effect of time on task.

In the current study, we aimed to characterize the relationship between subjective fatigue and attentional function, taking duration of effort into account. To this end, we collected behavioral data using ANT and self-reported fatigue using FSS from 53 chronic stroke patients. First, we tested the assumption that FSS scores would interact negatively with time on task, manifesting in a performance decline for patients with high fatigue relative to patients with low fatigue. Results from linear mixed models provided support for this hypothesis, identifying significant interactions between FSS score and time on RT in the neutral and incongruent flanker conditions. In these whole sample models, no significant main effects of time or FSS were identified. Interestingly, when examining the main effect of time separately for patients with and without PSF, results revealed that non-PSF patients significantly improved

RTs over time in the most cognitively demanding condition, while the PSF group did not demonstrate significant improvement.

These findings underscore the relevance of taking time on task into account and measure sustained performance when addressing fatigue. Because the study design does not allow causal inference, the observed interaction between subjective fatigue and RT may be either a manifestation of fatigue, a cause of fatigue (i.e., that attentional difficulties give rise to fatigue), or both. Providing a speculative theoretical context, the coping hypothesis (Van Zomeren, Brouwer, & Deelman, 1984; Van Zomeren & Van den Burg, 1985) offers one explanatory framework for the observed interaction. Originally articulated in relation to traumatic brain injury patients, this view suggests that the chronic effort needed to compensate for subtle, cognitive deficiencies gives rise to secondary symptoms, hereunder fatigue. Hence, subtle cognitive deficits associated with stroke may be temporarily disguised by a compensating and temporary increase in cognitive effort. However, this compensation comes with the cost of increased feeling of fatigue, in particular during sustained effort. In line with this, the current interaction between time on task and fatigue may be understood as a result of increased cognitive effort, producing increased tiredness over time, resulting in suboptimal performance. The concept of "cognitive compensation" also ties well with evidence from the split sample analysis indicating that non-PSF patients' performance benefitted from practice (sustained performance) in the most cognitively demanding condition, while the PSF group did not improve with practice. This may reflect a weakening of learning effects due to cognitive compensation costs as described above, or, alternatively, a failure to benefit from practice due to increasing fatigue.

The interaction between FSS and time can also be mediated by motivation, with high levels of fatigue leading to reduced motivation and suboptimal performance. Accordingly, the role of motivation is implied by the high scores on the FSS item reflecting reduced motivation when feeling fatigued.

Regardless of the specific theoretical account, the results can be understood as lending support to Holtzers definition of cognitive fatigue as "an executive failure to monitor and optimize performance over acute but sustained cognitive effort resulting in performance that is lower and more variable than the individual´s optimal ability" (Holtzer et al., 2010, p. 123).

It should be noted that the interaction between time on task, self-reported fatigue and RT did not change when depressive symptoms were added to the model. Moreover, when testing the model with PHQ score on the interaction term instead of FSS, we did not find any interaction effects between depressive symptoms and time. These results suggest that although fatigue and depression are overlapping and correlated clinical phenomena, the specific characteristics of fatigue may be more strongly associated with sustained attentional performance during the course of a demanding cognitive task.

Results did not reveal any significant association between stroke location/laterality or lesion volume and outcome variables (RT or FSS), suggesting that, in this sample, lesion location and volume are not strong predictors of subjective fatigue or attentional function as measured by ANT. Whereas the lack of a robust relationship between lesion location/lesion volume and FSS score is in line with previous reports (Choi-Kwon, Han, Kwon, & Kim, 2005; Mead et al., 2011), the literature is not conclusive, and right hemispheric lesions are frequently associated with attentional dysfunction and neglect (Robertson, Ridgeway, Greenfield, & Parr, 1997; Spaccavento et al., 2019; Vallar & Perani, 1986). The current lack of predictive value of stroke location highlights the complex etiology of attentional function in chronic stroke patients. However, we cannot rule out that different operationalizations of attentional dysfunction or alternative categorizations of lesion location could reveal stronger associations.

Our hypothesis that FSS scores would be associated with overall reduced executive network efficiency was not supported, and no associations between fatigue and attentional networks remained after correcting for multiple comparisons. This finding does not support previous studies on fatigue in neurological conditions, linking fatigue to reduced efficiency of the ANT executive network (Holtzer et al., 2010; Togo et al., 2015). There was, however, a nominally significant association between change in executive network efficiency over time (network slope) and fatigue, indicating that patients with higher levels of fatigue exhibited a larger decline in executive network efficiency with sustained effort than patients reporting lower levels of fatigue. Although these findings did not remain after corrections for multiple comparisons, they may suggest that subjective fatigue is less associated with reduced executive attention per se, and more with an increased susceptibility to distractors when the attentive system is put under sustained pressure.

Suggestive FSS network effects were only observed in the executive network. It is unclear whether the lack of alerting and orienting network effects reflects that subjective fatigue is related to executive attention exclusively, or rather reflects psychometric properties of the ANT networks. A psychometric evaluation of the ANT networks based on 15 previous studies (MacLeod et al., 2010) reported that the power to identify significant effects varied across networks, while network reliability was consistently highest for executive network effects, and low to medium for alerting and orienting network effects.

Because traditional analyses based on observed data alone do not allow for any inference regarding the specific cognitive processes that may underpin differences in RT, we performed an exploratory analysis where we fitted a hierarchical drift diffusion model (hDDM) to the ANT behavioral data.

This computational dissection of the ANT data indicated that the interaction between fatigue and time on RT was best explained by non-decision time, and not the speed of evidence accumulation (drift rate) or response style (boundary separation). hDDM revealed no main effect of FSS on any of the model parameters, but provided evidence of an interaction between time and FSS on non-decision time, indicating increasing effects of FSS during the course of the experiment. In this respect, the results concurred with the linear mixed-effects models on RT data, suggesting stronger associations between fatigue and hDDM parameters with more sustained performance, and indicate that hDDM is sensitive to fatigue in a cognitive context when explicitly modeling the interactions with time.

Non-decision time (t) comprises both sensory encoding and motor response output (Ratcliff & Smith, 2010). The fact that model evidence was stronger for the models where the interaction between FSS and time was estimated on non-decision time, rather than on drift rate or boundary separation, indicates that fatigue may be specifically associated with non-decision aspects of the response process, such as stimulus encoding or response execution rather than with the speed or efficiency of the evidence accumulation or with the decision threshold (i.e., how much information is required before making a decision). Previous studies have reported higher non-decision times in older compared to younger individuals (Ratcliff et al., 2001), and in this respect, patients reporting high fatigue are responding more like elderly individuals, but only after sustained exertion.

It is also interesting to note that the negative main effect of time (in non-decision time) suggested by the current model is in line with previous drift diffusion research on practice effects, identifying a reduction in the non-decision component across trials (Dutilh, Vandekerckhove, Tuerlinckx, & Wagenmakers, 2009). In this context, the current positive interaction between time and fatigue on non-decision time may be understood as fatigue counteracting the otherwise beneficial effects of practice.

This ties well with results from the linear mixed-effects models, suggesting that patients with PSF did not improve performance over time, in contrast to patients without PSF who got faster with during the course of the session. However, this effect was found in the incongruent condition, defined by flankers, while in the reported hDDM results, non-decision time primarily accounts for variance introduced by cues. One explanation could be that responses in the incongruent condition require an inhibition of the dominant motor response after the decision is made and that the identified interaction between fatigue and time on non-decision time is driven by a stronger slowing of these inhibitory responses in patients with higher levels of fatigue.

Research aiming to delineate the nervous system pathophysiology of PSF may further inform hypotheses about this apparent link between non-decision time and fatigue. Applying transcranial magnetic stimulation (TMS), a previous study (Kuppuswamy, Clark, Turner, Rothwell, & Ward, 2014) reported higher motor thresholds in stroke patients with high fatigue and suggested that patients with PSF experience diminished excitability of motor pathways, regarding both corticospinal outputs and facilitatory inputs. In this respect, the current observation of an interaction between time and fatigue on non-decision time might reflect altered neuronal excitability. However, how such neurophysiological mechanisms would translate into the subjective perception of fatigue remains unclear. Here, the perception of effort might be central, in the sense that subjective fatigue may manifest when volitional motor cortex input does not longer produce the expected output due to reduced excitability (Kuppuswamy et al., 2014).

These explorative results based on computational modeling provide a novel account of the specific cognitive underpinnings of PSF. When the task context is appropriate, DDM parameters can be interpreted directly (Froehlich et al., 2016) and thus provide insight into the modular and temporal evolution of the decision process. Decision boundary separation (a) adjusts the trade-off between speed and accuracy (Pedersen, Frank, & Biele, 2017). Large estimates of (a) are typically interpreted as indicative of a conservative decision style, associated with higher RTs but more accurate responses (Pedersen et al., 2017). Larger estimates of drift rate (v) are typically interpreted as more efficient information processing and are expected to vary by "the quality of the information extracted from the stimulus" (Ratcliff & McKoon, 2008, p. 3), implying that experimental conditions varying in difficulty should produce different drift rates (Ratcliff & McKoon, 2008). In line with this, and in agreement with previous studies estimating the effect of stimulus difficulty on drift rate (Voss et al., 2004), hDDM identified a credible effect of flanker type on drift rate, with the more cognitively demanding incongruent condition resulting in the lowest drift rate, while neutral flankers yielded the highest drift rate.

To sum, results from linear mixed-effects models suggested that subjective fatigue interacts with time on task, possibly counteracting practice effects, in particular in the most cognitively demanding incongruent flanker condition. Group analyses revealed that patients without PSF improved performance over time in the incongruent condition, while the PSF group did not. Additionally, higher FSS scores were associated with declining efficiency in the executive network over time. However, the effect was small and was not associated with PSF status. Lastly, hDDM modeling identified an interaction between fatigue scores and time on non-decision time.

Some limitations should be considered when interpreting the results of the current study. In line with most clinical studies, the study design does not allow for causal inference. Still,

the findings may pave the way for future clinical or experimental studies examining possible causal mechanisms and subsequent interventions. Moreover, as subjective fatigue can manifest as both a normal and a pathological phenomenon, and no universally accepted definition or criteria of PSF exists, we adopted an explorative approach, aiming to characterize the relationship between subjective fatigue and sustained attentional performance by a continuous measure symptom scale. While our main objective was not to identify case–control differences between stroke patients and healthy controls, but rather to characterize the cognitive correlates of post-stroke fatigue using computational modeling of response patters, future studies adding a healthy control group may provide stronger interpretations regarding the clinical sensitivity of the computational behavioral parameters.

The distribution of NIHSS scores indicates that the current patients were sampled from a relatively healthy part of the full population of stroke patients. It is possible that a higher fatigue symptom burden on the group level could reveal associations that were not expressed in this relatively well-functioning patient sample. Reported fatigue levels are, however, comparable with what has been reported in other studies (Wang, Wang, Wang, & Chen, 2014) and higher than what is reported in healthy control samples (Valko, Bassetti, Bloch, Held, & Baumann, 2008). Further studies are needed to test the generalizability of the findings to different and more severely affected patient samples.

Although the classical version of ANT (Fan et al., 2002) appears to be a suitable paradigm to target cognitive aspects of PSF, as performance requires sustained attentional and executive resources (Holtzer et al., 2010), other versions of the test, like the ANT-I Vigilance task (Roca, Castro, López-Ramón, & Lupiánez, 2011), could offer a more comprehensive account of relevant, associated processes like vigilance. It should also be noted that the error rate in the sample was low. This might have implications for the validity of the results from hDDM model, because the model estimates parameters based on distributions of both RT and accuracy and assumes different RT distributions for correct versus erroneous responses. Moreover, ANT is not frequently applied in hDDM modeling and may not be ideal for such due to existence of flankers and cues. However, our model displayed adequate convergence, and a recent hDDM study reported encouraging results for ANT data with no error responses (O'Callaghan et al., 2017).

In conclusion, the current study represents a novel approach to assess the cognitive phenotype of fatigue in stroke patients. The results indicate a relationship between the subjective experience of fatigue and response time distributions from a sustained attention task and demonstrate the significance of considering the sustained nature of the task when targeting fatigue in a neuropsychological context, intuitively indicating that the cognitive phenotype of fatigue entails an increased vulnerability to sustained effort. It is encouraging that the evidence suggests a link between self-reported fatigue and performance in a computerized, standardized paradigm, as it may contribute to bridging the gap between subjective experience and behavioral performance in this complex and prevalent stroke sequela. The explorative application of an advanced computational model on the temporal evolution of response times enabled the possibility to parse the observed response time patterns into specific cognitive processes. In general, the use of computational approaches in the neuropsychological workup may offer a dissection of the specific cognitive processes underlying observed behavioral differences, with clinical relevance.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

KMU conceived the study, collected the data, analyzed the data and wrote the manuscript. DA was involved in the design of the work, data analysis and interpretation, and critical revision of the paper. KK, GR and AMS were involved in data collection and quality control and contributed to drafting the paper, ESD was involved in data collection and contributed to drafting the paper. HIH was involved in interpreting of results and critical revision of the paper. MLP was involved in data analysis, interpreting of result and critical revision of the paper. ST was involved in interpretation of results and critical revision of the paper. JEN was involved in data collection and critical revision of manuscript. LTW was involved in conception of the study, interpretation of results and critical revision of manuscript.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data can be supplied from the corresponding authors on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Supplementary Material

Supplementary Table 1
FSS item score per group (PSF and no PSF)

	Patients with fatigue			Patients without fatigue			Group difference**	
FSS item*	Mean	Median	SD	Mean	Median	SD	t	p
#1	6.0	6	1.2	3.7	3	1.7	-5.6	<.001
#2	4.3	5	1.5	2.1	2	1.4	-5.2	<.001
#3	5.0	5	1.9	2.2	2	1.1	-8.6	<.001
#4	5.3	5	1.6	3.5	3	1.1	-4.9	<.001
#5	4.9	4.5	1.2	2.0	2	1.1	-6.2	<.001
#6	5.0	5	1.5	2.0	2	0.9	-8.3	<.001
#7	4.8	5	1.7	2.6	2	1.5	-5.0	<.001
#8	5.5	5.5	1.3	2.2	2	1.2	-9.1	<.001
#9	4.7	5	1.5	2.1	2	1.4	-6.0	<.001

*Items in the Fatigue Severity Scale, English (US) version
1. My motivation is lower when I am fatigued
2. Exercise brings on my fatigue
3. I am easily fatigued
4. Fatigue interferes with my physical functioning
5. Fatigue causes frequent problems for me
6. My fatigue prevents sustained physical functioning
7. Fatigue interferes with carrying out certain duties and responsibilities
8. Fatigue is among my three most disabling symptoms
9. Fatigue interferes with my work, family, or social life.
** Group differences tested by unpaired t-tests.

Supplementary Table 2

Overview of lme model selection and formulae of key models

Linear mixed effects models	Model notes	AIC	Anova comparisons
lme(rt ~ time * FSS_z + PHQ_z + Sex + Age + Flanker + lesionVoxels + topography + NIHSS + stroke_type, random =~1+time*FSS_z |id, data=data, method="REML")	**1a**. Full model with random slopes and random intercepts. Did not converge		
lme(rt ~ time * FSS_z + Sex + Age + Flanker + lesionVoxels + topography + random =~1+time*FSS_z|id, data=data, method="REML")	**1b**. Reduced number of fixed effects. Model converges. Results are **reported in supplementary Table 3**	175589	
lme(rt ~ time * FSS_z + Sex + Age + Flanker + lesionVolume + topography + random =~1 |id, data=data, method="REML")	**1c**. Same as above, but random intercept only. Model 1b displayed better fit by anova comparison	175673	anova(1b, 1c) p<.0001.
lme(rt ~ time * FSS_z + Sex + Age + Flanker + lesionVoxels + topography + random =~1+time*FSS_z|id, data=data, method="ML")	2a. Same as (**1b**), but "ML" for comparison of fixed effects	175637	
lme(rt ~ time * FSS_z + Sex + Age + Flanker + lesionVoxels + random =~1+time*FSS_z|id, data=data, method="ML")	2b. Removed lesion location (no significant predictive value). Improved fit marginally, no significant difference	175631	anova(2a, 2b) p=.937
lme(rt ~ time * FSS_z + Sex + Age + Flanker + random =~1+time*FSS_z|id, data=data, method="ML")	2c. Removed lesion volume (no significant predictive value). Improved fit marginally, but no significant difference	175635	anova(2a, 2c) p=.794
lme(rt ~ time * FSS_z + Sex + Age + Flanker + random =~1+time*FSS_z|id, data=data, method="REML")	2d. Same model as 2c, but "REML". This is the model **Reported in Table 4**	175604	
lme(rt ~ time + Sex + Age + Flanker + random =~1|id, data=data, method="ML")	2e. "Null model" without FSS for measure of FSS effect size	189261	
lme(rt ~ time * FSS_z + Sex + Age + Flanker + random =~1|id, data=data, method="ML")	2f. Similar to 2e, but with FSS as predictor.	189295	anova(2e, 2f) p<.001
Formulae for various models reported in text.			
lme(rt ~ time * PSF Status + Sex + Age + Flanker + lesionVoxels + topography + random =~1+FSS_z |id, data=data, method="REML")	**3a.** Predicting RT from the interaction between PSF status and time, instead of continuous		

	fatigue score and time. **Reported in text.**
lme(rt ~ time * FSS_z + Sex + Age + lesionVoxels + topography + random =~1id, data=data[incongruent flanker only], method="REML")	**4a** Model testing interaction between FSS score and time on RT. Repeated for each flanker condition **Reported in Table 5**

Supplementary Table 3

Linear mixed effects model for whole sample, all flanker conditions, full model

	t	*Beta*	*CI*	*p*
Intercept	0.51	100.59	(-282.4,483.59)	.606
FSS_z	0.16	3.30	(-35.99,42.6)	.300
Time	-1.03	-0.03	(-0.09,0.03)	.870
Time:FSS	2.64	0.07	(0.02,0.14)	.008
Sex	0.09	3.99	(-81.39,89.37)	.927
Age	3.08	8.136	(2.97,13.3)	.003*
LesionVoxels	-0.19	-0.00	(-0.04,0.03)	.849
Left Hemisphere	0.14	6.41	(-80.55,93.38)	.885
Brainstem/cerebellum	0.66	40.86	(-79.12,160.86)	.508
Both Hemispheres	0.27	18.44	(-114.18,151.07)	.786
Incongruent flanker	40.5	111.529	(106.13,116.92)	<.000*
Neutral flanker	-4.31	-11.79	(-17.15,-6.43)	<.000*

Supplementary Table 4

Linear mixed effects model for whole sample, all flanker conditions

	t	*Beta*	*CI*	*p*
Intercept	0.47	87.19	(-270.7, 445.1)	.633
PSF status	0.50	19.45	(-56.0, 94.9)	.616
Time	-3.31	-.05	(-0.09, -0.02)	<.000*
Time:PSF status	2.27	0.06	(0.01, 0.12)	.023
Sex	0.03	1.31	(-78.2, 80.9)	.974
Age	3.31	8.37	(3.43, 13.33)	.001*
Incongruent flanker	40.2	111.47	(106.04, 116.91)	<.000*
Neutral flanker	-4.36	-12.01	(-17.42, -6.62)	<.000*

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Structural brain disconnectivity mapping of post-stroke fatigue

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ABSTRACT

Stroke patients commonly suffer from post stroke fatigue (PSF). Despite a general consensus that brain perturbations constitute a precipitating event in the multifactorial etiology of PSF, the specific predictive value of conventional lesion characteristics such as size and localization remains unclear. The current study represents a novel approach to assess the neural correlates of PSF in chronic stroke patients. While previous research has focused primarily on lesion location or size, with mixed or inconclusive results, we targeted the extended structural network implicated by the lesion, and evaluated the added explanatory value of a structural disconnectivity approach with regards to the brain correlates of PSF. To this end, we estimated individual structural brain disconnectome maps in 84 S survivors in the chronic phase (≥3 months post stroke) using information about lesion location and normative white matter pathways obtained from 170 healthy individuals. PSF was measured by the Fatigue Severity Scale (FSS). Voxel wise analyses using non-parametric permutation-based inference were conducted on disconnectome maps to estimate regional effects of disconnectivity. Associations between PSF and global disconnectivity and clinical lesion characteristics were tested by linear models, and we estimated Bayes factor to quantify the evidence for the null and alternative hypotheses, respectively. The results revealed no significant associations between PSF and disconnectome measures or lesion characteristics, with moderate evidence in favor of the null hypothesis. These results suggest that symptoms of post-stroke fatigue among chronic stroke patients are not simply explained by lesion characteristics or the extent and distribution of structural brain disconnectome, and are discussed in light of methodological considerations.

1. Introduction

Between 25 and 85 percent of stroke survivors experience post stroke fatigue (PSF) (Cumming, Packer, Kramer, & English, 2016), described as an excessive and debilitative tiredness that can be unrelated to strain and not ameliorated by rest (UK Stroke Association, 2020; de Groot, Phillips, & Eskes, 2003). Persistent PSF can be highly distressing, negatively impacting quality of life (de Bruijn et al., 2015; Naess, Waje-Andreassen, Thomassen, Nyland, & Myhr, 2006) and preventing social participation and attendance to rehabilitation programs (Nadarajah & Goh, 2015). PSF is associated with both poor functional outcome and increased mortality (Glader, Stegmayr, & Asplund, 2002), and a recent

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meta-analysis revealed that the prevalence increases with time since stroke (Cumming et al., 2018). Early detection, prevention and treatment of fatigue might thus have positive effects on the overall outcome of stroke rehabilitation and quality of life. As such, identification of risk factors is important to facilitate detection and individual tailoring of rehabilitation programs.

PSF is considered a multifactorial condition with a complex etiology (Choi-Kwon & Kim, 2011). Among the most commonly reported risk factors are depression (Ponchel, Bombois, Bordet, & Hénon, 2015; Wu, Barugh, Macleod, & Mead, 2014), reduced physical function (Lerdal et al., 2011; Aarnes, Stubberud, & Lerdal, 2019), anxiety (Cumming et al., 2018; Wu et al., 2014), various medications (Chen & Marsh, 2018), pain and sleep disturbances (Naess, Lunde, Brogger, & Waje-Andreassen, 2012). While PSF is generally conceptualized as an independent condition, the clinical overlap with depression is substantial (Cumming et al., 2018), and the nature of the relationship between fatigue and depression has been debated. The use of advanced brain imaging to detect the brain correlates of the two clinical syndromes may facilitate our understanding of the phenomena through identification of both common and specific brain mechanisms (Høgestøl et al., 2019).

Despite a general consensus that the lesion and the associated brain perturbations following the stroke constitute causal factors for PSF, little is known about the predictive value of key lesion characteristics such as extent and neuroanatomical distribution. Fatigue is more prevalent following a minor stroke compared to a transient ischemic attack (TIA) (Naess et al., 2012; Winward, Sackley, Metha, & Rothwell, 2009), suggesting that the vascular lesion itself is of importance with regards to fatigue. Further, stroke survivors describe the fatigue experienced after stroke as qualitatively different than fatigue before stroke or normal tiredness (Thomas, Gamlin, De Simoni, Mullis, & Mant, 2019). Lastly, fatigue is a common sequela or symptom in several neurological conditions, i.e. traumatic brain injury, multiple sclerosis and post-poliomyelitis, jointly referred to as "central fatigue" (Chaudhuri & Behan, 2000, 2004).

Studies examining associations between lesion characteristics and fatigue in stroke survivors have generated mixed findings. In line with the hypothesis of fatigue caused by nervous system disruptions (Chaudhuri & Behan, 2000, 2004), basal ganglia infarcts have been identified as predictors of fatigue (Tang et al., 2010) and caudate infarcts were more frequent in patients with, than without, PSF (Tang et al., 2013). Further, infratentorial infarcts have been associated with increased risk of fatigue (Snaphaan, Van der Werf, & de Leeuw, 2011), as have right hemisphere lesions, brainstem and thalamic lesions (Mutai, Furukawa, Houri, Suzuki, & Hanihara, 2017). Subcortical white matter lesions have been associated with PSF 15 months post-stroke (Tang et al., 2014), but the generalizability of these findings is unclear (Snaphaan et al., 2011). In short, the relationship between fatigue and lesion location remains unresolved (De Doncker, Dantzer, Ormstad, & Kuppuswamy, 2018), and several studies find no significant associations between lesion characteristics and fatigue (Choi-Kwon et al., 2005; Ingles et al., 1999; Mead et al., 2011).

It is conceivable that clinical symptoms following a stroke are not mediated primarily by the localization of the lesion, but rather by the functional neuroanatomy of the extended brain networks that are affected by the lesion and degree of preserved network function (Bartolomeo and Thiebaut de Schotten, 2016; Nordin et al., 2016; Thiebaut de Schotten et al., 2020). Neuroimaging suggests that many psychiatric and neurologic symptoms are related to complex brain networks of anatomically distant but connected regions (Fox, 2018) that are vulnerable to injuries in a range of locations. Through processes like diaschisis (remote neurophysiological changes or dysfunctions of a distant region caused by a focal injury (Carrera & Tononi, 2014; von Monakow, 1914)), disconnection (Geschwind, 1974) and transneuronal degeneration (Cowan, 1970), stroke lesions may affect brain function and behavior in ways not readily predicted by the location or size of the damaged tissue. For example, functional network disturbances have been observed between remotely connected cortical areas in both the unaffected and affected hemisphere (Rehme & Grefkes, 2013), and abrupted connectivity may cause impairments that are functionally similar to tissue necrosis (Bonilha et al., 2014), like when a patient suffers severe Brocas aphasia without any damage to Brocas area (Fridriksson et al., 2007). Probing the extended brain network characteristics involved in a lesion and its associations with outcome may therefore provide theoretically and clinically relevant information of the functional neuroanatomy of specific symptoms post stroke and other brain disorders.

Recent large-scale collaborative neuroimaging efforts have resulted in remarkable advances in the characterization of the human brain "connectome" and "disconnectome" (Thiebaut de Schotten et al., 2020), providing highly valuable roadmaps for studies attempting to link symptoms, lesions and brain networks. Notably, normative samples enable indirect estimations of structural and functional disconnection, by which individual lesions from clinical structural imaging can be embedded onto a template of functional or structural connections derived from healthy subjects, and the lesions' effect on the global connectome is estimated by tracking the connections passing through the lesion (Salvalaggio et al., 2020). A key advantage of atlas based tractography methods is that they do not require costly and specialized imaging sequences beyond those routinely collected in the clinic (Boes et al., 2015), thus offering a versatile tool for clinical-neuroanatomical predictions in studies on brain lesions (Salvalaggio et al., 2020). While functional and structural (dis)connectivity are intimately connected, there are evidence suggesting that a lesion's impact on functional connectivity is primarily determined by how the lesion affects the structural connectome (Griffis et al., 2019), and indirect measures of structural disconnection have been found to perform significantly better than indirect measures of functional disconnection in predicting behavior (Salvalaggio et al., 2020).

By date, the relationship between PSF and stroke lesions has not been evaluated using a structural disconnectome approach, but a recent study on fatigue in multiple sclerosis (MS) revealed associations between structural network disconnection and subjective fatigue severity beyond what was explained by conventional MRI measures (Fuchs et al., 2019). With regards to the inconsistent findings on the relationship between stroke lesions and PSF, targeting structural network disconnections in addition to lesion characteristics may thus have the potential to advance our understanding on the relationship between brain perturbations and fatigue beyond what is revealed by traditional lesion-symptom mapping.

To evaluate the added explanatory value of a disconnectivity based approach with regards to the brain correlates of PSF, we quantified lesion disconnectivity indirectly using information about normative white matter pathways in the healthy population to estimate individual structural disconnection (disconnectome) maps in 84 S survivors in the chronic phase. The maps were created by a tractography-based procedure (Foulon et al., 2018) yielding voxel-wise probability of structural disconnection of white matter tracts (Salvalaggio et al., 2020).

Associations between disconnectome maps and PSF (assessed by the Fatigue Severity Scale (FSS)), were examined using permutation testing. Due to the substantial overlap and interaction between fatigue and depression and the possibility of common mechanisms across these conditions, all voxel-wise analyses were done with a) fatigue scores, b) depression scores (measured using the Pittsburg Health Questionnaire (PHQ-9) (Spitzer et al., 1999) fatigue and depression scores combined. The above described disconnectome based analyses were repeated on the binarized lesion maps, reflecting a traditional voxel-based lesion symptom mapping (VSLM) approach (Bates et al., 2003). In addition, we estimated the global disconnectivity for each patient, and tested for correlations with FSS, using Bayes factor to quantify evidence for the null hypothesis. Finally, in agreement with a more traditional, clinical approach, we applied linear models to test for associations between PSF and stroke related factors such as stroke location (right hemisphere, left hemisphere, brainstem, cerebellum, or both hemispheres), months since

stroke, stroke severity (using National Institute of Health Stroke Scale (NIHSS; Lyden et al., 2009) score at discharge as a proxy for clinical severity) and etiology as defined by the stroke subtype classification system Trial of Org 10,172 in Acute Stroke Treatment (TOAST; Adams et al., 1993).

Due to a lack of previous studies applying a disconnectivity approach to PSF, we remained agnostic about the specific brain networks involved and performed a whole-brain analysis. Based on recent work demonstrating the benefits of targeting network projections of a lesion (Griffis et al., 2019; Thiebaut de Schotten et al., 2020), and the notion that many psychiatric and neurological conditions correspond more closely to brain networks than specific regions (Fox, 2018), we expected the disconnectivity based approach to demonstrate higher sensitivity to PSF than conventional lesion-related approaches.

2. Materials and methods

2.1. Study participants

Table 1 summarizes demographic and clinical information for the patient sample and the healthy control group.

2.1.1. Healthy control group

Healthy individuals > 18 years were recruited through newspaper ads, word-of-mouth and social media (Dørum et al., 2020; Richard et al., 2018). Exclusion criteria for healthy controls included a history of stroke, neurological or psychiatric disease, medications with significant effects on central nervous system function and MR contraindications.

Healthy controls and stroke patients were matched on age and sex, using *MatchIt* in R (Stuart, King, Imai, & Ho, 2011) and the default method *nearest*. Applying a ratio of 2:1 (two controls selected for each patient), healthy participants were collected from a pool of 341 controls (age 24–92), resulting in an age- and sex matched control group of 155 individuals (mean age = 64.7, SD = 12.3, 44 females).

2.1.2. Patients

We recruited 84 S patients from the Geriatric Department, Diakonhjemmet Hospital, the Stroke Unit, Oslo University Hospital and Bærum Hospital. A subsample of the patients (n = 66) participated in a longitudinal intervention study examining the effects of cognitive training and tDCS on cognitive function (see Kolskaar et al. (2020) for details). All data reported in the current study were collected prior to the intervention. Criteria were ischemic or hemorrhagic stroke in a chronic phase defined as ≥ 3 months since admission, age above 18 years, no MRI contraindications and no other known, severe neurological conditions prior to the stroke. While aphasia was not a formal exclusion criterion and was not assessed explicitly, no patients reported or revealed severe speech or language impairments. All participants provided informed consent prior to enrollment. The study was approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway.

Table 1

Sample characteristics	Patients (n = 84)		Control group (n = 155)		t (p)	BF**
Demographic and clinical information	Mean (SD)	Min-Max	Mean (SD)	Min-Max		
Age	65.8 (12.6)	24–87	64.7 (12.3)	24–92	1.0 (0.279)	0.16
Males/females (count)	60/24		111/44			
Education in years	14.5 (3.4)	7–30	15.7 (3.3)	6–25	0.6 (0.513)	0.6
FSS	3.9 (1.5)	1–7	2.9 (1.3)	1–6	−3.9 (<0.001)	1911
PHQ-9	5.0 (4.5)	0–21	3.2 (3.0)	0–15	−3.2 (0.001)	30
Montreal cognitive assessment (MoCA)	26.3 (2.4)	19–30	27.4 (1.7)	22–30	3.0 (0.002)	171
Stroke related patient information						
NIHSS at hospital discharge	1.1 (1.2)	0–6				
TOAST classification for ischemic stroke*	Large artery artherosclerosis (26) Small vessel occlusion (26) Cardioembolism (13) Other determined etiology (6) Undetermined etiology (13)					
Lesion location	Brainstem/cerebellum (17) Left Hemisphere (26) Right Hemisphere (34) Both Hemispheres (6)					
Months since stroke	22.0 (11.9)	3–45				

*all but one patient suffered ischemic stroke
**BF = Bayes factor.
Both frequentist and Bayesian statistics are reported, in line with current pragmatic recommendations (Keysers et al., 2020).

3. Clinical measures

Stroke subtype was classified by the Trial of Org 10,172 in Acute Stroke Treatment (TOAST; (Adams et al., 1993), and clinical assessment of stroke severity was indexed by the National Institute of Health Stroke Scale (NIHSS) at hospital discharge.

Subjective fatigue was measured by the Fatigue Severity Scale (FSS) (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989), which is a self-report scale consisting of 9 statements about impact of fatigue on daily life. Degree of agreement is indicated on a seven-point Likert scale (lowest possible total score 7, highest score 63). FSS is one of the most frequently used instruments for measuring fatigue in neurological conditions (Cumming et al., 2016) and has demonstrated reasonable psychometric qualities (Whitehead, 2009). A commonly adapted threshold for clinical fatigue is a mean score of >= 4 (total score >= 36) (Krupp et al., 1989; Nadarajah & Goh, 2015; Schepers, Visser-Meily, Ketelaar, & Lindeman, 2006), where a higher score is suggested to indicate a moderate to high impact of fatigue (Schepers et al., 2006).

Depressive symptoms were measured by the depression module of the PHQ-9, in which occurrence of depressive symptoms corresponding to the DSM-IV criteria is rated on a 9-item Likert scale. Scores range from 0 (not at all) to 3 (nearly every day), yielding a minimum score of zero and a maximum score of 27. A cutoff score of ≥ 10 has demonstrated acceptable sensitivity and specificity for depression (Kroenke et al., 2001). Cognition was measured by Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), and sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989).

4. MRI acquisition

Patients were scanned at Oslo University Hospital on a 3 T GE 750 Discovery MRI scanner with a 32-channel head coil. We collected structural (T1w, FLAIR), functional (resting-state and task-based fMRI) and diffusion MRI data. For lesion demarcation used in the present analysis T1-weighted images were collected using a 3D IR-prepared FSPGR (BRAVO) sequence (TR: 8.16 ms; TE: 3.18 ms; TI: 450 ms; FA: 12°; voxel size: 1 × 1 × 1 mm; slices: 188; FOV: 256 × 256, 188 sagittal slices), and T2-FLAIR with the following parameters: TR: 8000 ms; TE: 127 ms, TI: 2240; voxel size: 1 × 1 × 1 mm).

5. Lesion demarcation

Lesions were demarcated in native space, using the Clusterize toolbox (de Haan et al., 2015) with SPM8 running under Matlab R2013b

(The Mathworks, Inc., Natick, MA). Lesions were traced by trained personnel (a physician and a radiographer), based on hyperintensities and visible damage on FLAIR images, and guided by independent neuroradiological descriptions of dMRI/FLAIR images (see Dørum et al. (2020) for details). The binarized lesion masks were registered to MNI space using nearest neighbor interpolation, using the transformation parameters obtained using the T1w data. To register the FLAIR images to the T1 images, we applied a linear transformation with 6 degrees of freedom. T1 images were registered to MNI152 space by linear affine transformation with 12 degrees of freedom. Fig. 1 displays a probabilistic map of lesion overlap across patients.

5.0.1. Disconnectome maps

To calculate the disconnectome maps we used an automated tractography-based procedure (Foulon et al., 2018) implemented in the *BCBtoolkit disconnectome maps* (Brain Connectivity Behaviour Toolkit (BCBtoolkit)). Briefly, a training set based on full-brain tractography data obtained from a normative group of 170 individuals from the Human Connectome Project 7 T data (HCP 7 T) was used to track fibers passing through each lesion. Using affine and diffeomorphic deformations (Avants et al., 2011; Klein et al., 2009), each patients MNI 152 space lesions were registered to each controls native space, and used as seed for the tractography in Trackvis (Wang et al., 2007). Subsequently, the tractography was transformed to visitation maps, binarized and registered to MNI152 space, before a percentage overlap map was produced by summarizing each point in the normalized healthy subject visitation maps. The resulting disconnectome maps indicate a voxel-wise probability of lesion-related disconnection ranging from 0 to 100%. We computed two simple summary measures of disconnection severity, defined for each patient as a) mean voxel intensity across the individual disconnectome map and b) number of voxels within the individual disconnectome map with intensity > 0.5 (reflecting 50% probability of disconnection).

5.1. Statistical analysis

Voxel wise analyses on disconnectome maps and binarized lesions (VLSM) were done by non-parametric permutation-based inference as implemented in the FSL randomise tool (Winkler et al., 2014). The statistical tests subsequently described were repeated in separate models for disconnectome maps and binarized lesions alike. Within the framework of the general linear model (GLM), linear effects of fatigue and depression (indicated by total score on FSS and PHQ, respectively) were tested in separate models, covarying for age and sex. To comply with a more common clinical definition of PSF, we re-ran the model on dichotomized fatigue variables defined as either a) a mean FSS score of ≥ 4, consistent with the common cut off value, or b) the upper tertile of FSS total score (contrasted with the lowest tertile), reflecting the possibility that more extreme scores demonstrate increased sensitivity to fatigue related brain correlates. We estimated models controlling for depression in two different ways, first by excluding patients scoring above clinical threshold on PHQ (remaining $n = 74$), and second, by including z-normalized summary scores from both FSS and PHQ in the same model. One additional model tested the effect of fatigue and depression combined, applying the total of the z-normalized sum scores (zPHQ + zFSS) as predictor. For each contrast, 5000 permutations were performed. Results were thresholded by threshold free cluster enhancement (TFCE, Smith and Nichols (2009)) and considered significant at $p < 0.05$, two tailed, corrected for multiple comparisons using permutation testing. One patient suffered a very large stroke and constituted an outlier in terms of number of affected voxels (~8 SDs above the mean). Main analyses were therefore repeated with this patient excluded.

Subsequent statistical analyses were performed using R version 3.4.0 (R Core Team, 2017). In a follow-up analysis aiming to increase sensitivity to clinical measures and evaluate the relationship between global disconnectivity and fatigue, we computed two disconnection severity measures, defined for each patient as a) mean voxel intensity across the individual disconnectome map and b) number of voxels within the individual disconnectome map with intensity > 0.5 (reflecting 50% probability), and correlated these with FSS and PHQ-9. To quantify the evidence in favor of the null and alternative hypothesis, we applied Bayes factor hypothesis testing, in line with current recommendations (Keysers et al., 2020). We applied the BayesFactor package (Morey et al., 2015) with default priors. For transparency, key analyses were run with different priors.

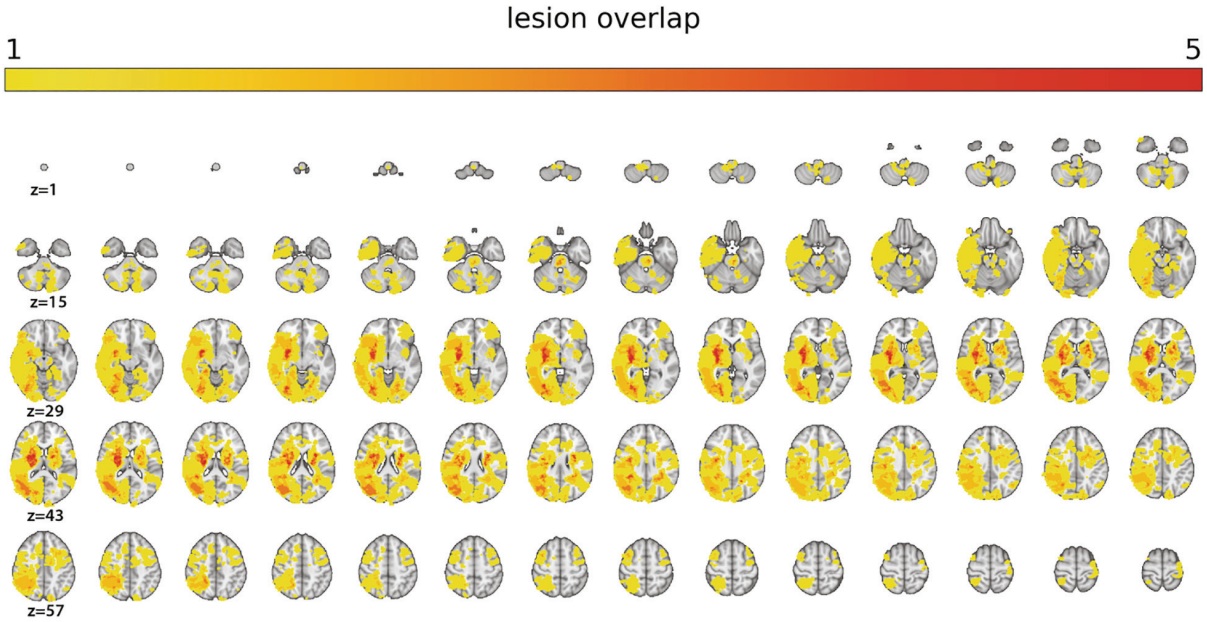

Fig. 1. Heatmap displaying lesion overlap across stroke patients by 70 slices (2 mm thickness) from z(voxel) = 1 to z = 70. Maximal overlap was 8, but for illustration purposes, the color scale saturates at 5.

To test for associations with clinical, stroke-related characteristics (TOAST classification, months since stroke, lesion volume and lesion location), we applied linear models with FSS score as dependent variable, controlling for age and depressive symptoms. Lesion location was clustered by four categories – right or left hemisphere, both hemispheres or brainstem/cerebellum. Stroke variables were added subsequently, allowing for model comparison by Bayes factor for each added variable. We applied the lmBF function from the BayesFactor package to compute Bayes factors. As an additional test of the added predictive value of global disconnectivity measures compared to clinical stroke characteristics, we also estimated the models with mean voxel intensity across the individual disconnectome map and number of voxels within the individual disconnectome map with intensity > 0.5.

6. Results

6.0.1. Fatigue and depression in the stroke sample compared to healthy controls

Fig. 2 shows the distributions of FSS and PHQ score in each group. 48 percent of the stroke patients reported clinically significant fatigue (mean FSS > 4), compared to 23 percent of the control participants. Severe fatigue (mean FSS > 6) was reported by 9 percent of the patients and 1 percent of the healthy controls. A two-tailed, two sample *t*-test (ttestBF in BayesFactor, with default Cauchy prior) provided compelling evidence (Bayes Factor: BF) > 150) for higher total FSS scores in the patient group (mean $= 35$) compared to healthy controls (mean $= 26$, median posterior $\delta = -8.5$, 95% credible interval (CI) $= [-11–-5]$), relative to the null hypothesis. Stroke patients (mean $= 5.0$) also reported higher levels of depression symptoms on the PHQ than controls (mean $= 3.2$). 18 percent of the patients scored 10 or higher, indicating clinical depression, compared to 2.4 percent of the controls. The corresponding Bayes factor provided strong evidence for a group difference in PHQ sum score (BF $= 20$, 95% CI $= [-2.5–-0.5]$).

6.0.2. Fatigue associations in patient sample

Among patients, Bayes factor estimation for linear correlations provided strong evidence (BF > 150) for a positive association between FSS and PHQ (median posterior $\delta = 0.71$, 95% CI $= [0.59–0.80]$), suggesting more depressive symptoms with increasing fatigue. The substantial association persisted when re-estimating the correlation after excluding the fatigue-item ("feeling tired or having little energy") from the PHQ scale (median posterior $\delta = 0.61$, 95% CI $= [0.46–0.73]$). There was only anecdotal support for an association between FSS and age (BF $= 1.20$, median posterior $\delta =$ -0.18, 95% CI $= [-0.38–0.02]$). Mean global PSQI score was 6.8 (SD $= 3.6$), with 51 patients (60%) scoring > 5, indicating poor sleep quality in a majority of patients. Global PSQI correlated moderately with FSS score (BF > 150, median posterior $\delta = 0.49$, 95% CI $= [0.31–0.64]$), and strongly with PHQ score (BF > 150, median posterior $\delta = 0.61$, 95% CI $= [0.47–0.73]$).

7. Permutation based analyses on disconnectome maps and lesions

Fig. 3 shows a selection of stroke lesions and the associated disconnectome maps, for illustrative purposes.

Permutation testing revealed no significant associations between the disconnectome maps and the clinical measures (FSS, PHQ-9, FSS/PHQ combined), or of fatigue status defined by either a) mean FSS score of ≥ 4, or b) by the lowest vs highest FSS tertile. Controlling for depression by a) excluding patients with depression from the analysis or b) including PHQ scores in the model revealed similar results.

Similarly, permutation tests on binarized lesion maps (voxel-based lesion symptom mapping) revealed no significant associations with the clinical measures (fatigue, depression or fatigue/depression combined, or on group defined by fatigue status (mean FSS score ≥ 4). Due to the considerable reduction in sample size when including only the lowest and highest FSS tertile (n $= 56$), we did not repeat this analysis on the binarized lesion maps. For transparency, the distributions of the uncorrected t-values across the brain from the models testing for associations with either disconnectome or lesion maps are depicted in Supplementary Fig. 1, and the corresponding number of uncorrected voxels with $p < 0.05$ are reported in Supplementary Table 1.

7.1. Associations between global summary measures of disconnectivity and clinical measures

Both measures of global disconnectivity (mean value in disconnectome map and number of voxels with disconnection probability $> 50\%$) were strongly correlated with lesion size (posterior mean $= 0.74$, BF > 150 and median posterior $\delta = 0.68$, BF > 150, respectively). Global disconnectivity (mean value in disconnectome map) was not correlated with FSS (median posterior $\delta = 0.03$) or PHQ (median posterior $\delta = 0.03$). Bayesian correlations (using default priors) provided moderate evidence (BF $= 0.26$) for these null effects, relative to H1 (positive associations between disconnectivity measures and FSS/PHQ). This indication of a null effect was mirrored in correlations between the

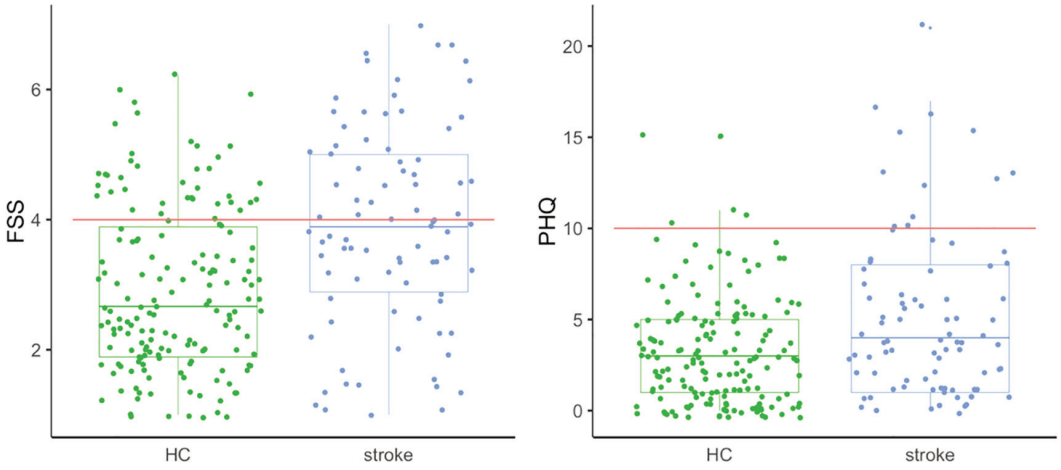

Fig. 2. Distributions and group differences in FSS and PHQ for healthy controls (HC) and stroke patients. Red line denotes cut off value for clinically significant symptom load. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

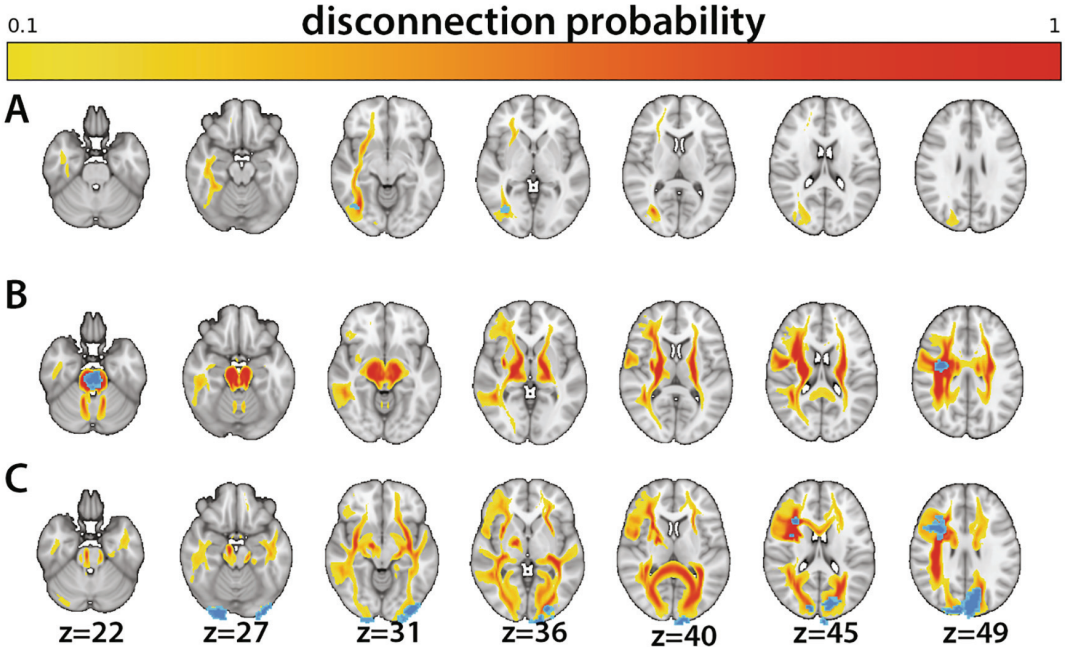

Fig. 3. Individual lesions (blue) and associated disconnectome maps (yellow–red). Probability for disconnection ranges from 10 (yellow) to 100 (red). Patient **A**: right cerebral white matter lesion, Patient **B:** brain stem lesion, Patient **C:** left and right cerebral cortex and white matter lesions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

alternative measure of disconnectivity (number of voxels with disconnection probability > 50%) and FSS (median posterior $\delta = 0.05$, BF = 0.29), and PHQ (median posterior $\delta = 0.02$, BF = 0.26). For transparency, Bayes factors of the main correlations estimated on different priors are reported in Supplementary Table 2, while Supplementary Table 3 reports the correlations after removing the most extreme outlier in terms of lesion size.

7.2. Associations between clinical stroke-related characteristics and FSS

Linear models (lmBF) corrected for age and depressive symptoms did not provide evidence for associations between FSS scores and lesion location (brainstem/cerebellum, left or right hemisphere or both hemispheres), lesion volume, months since stroke or TOAST stroke classification (see Supplementary Table 4 for model comparisons and associated Bayes factors). No stroke related variable, including global disconnectivity, demonstrated Bayes factors > 1, indicating low predictive value for all. Specifically, all extended models with stroke lesion variables displayed Bayes factors below 0.33 when compared to the simpler null model, suggesting moderate evidence of no effect of stroke lesion characteristics.

8. Discussion

Fatigue following stroke is common and represents a significant clinical burden. Stroke sequelae reflect both cell death at the site of the lesion, as well as structural and functional alterations in extended brain networks. Brain network dysfunction, directly or indirectly related to the stroke lesion, is a putative mechanism underlying PSF pathophysiology. Previous studies have primarily assessed lesion characteristics such as volume or location, and the added explanatory value of probing the extended brain network connections with the lesion has been unclear. To this end, we calculated structural disconnectome maps for 84 patients in the chronic phase and used permutation testing to evaluate the association between PSF symptoms and regional network disconnection.

Permutation testing revealed no significant associations between symptoms of fatigue and disconnectome maps, or between fatigue and binarized lesion maps (VLSM). We found no support for our hypothesis that a disconnectivity approach by disconnectome maps would add predictive value of fatigue beyond conventional lesion analyses. In line with this, Bayes factor estimations on correlations between disconnectivity summary measures and FSS score provided moderate evidence for the null hypothesis (no association) relative to the alternative hypothesis (association between fatigue and disconnectivity). However, results are not decisive, and alternative explanations of the absent effects must be considered.

The lack of added predictive value from the disconnectivity measures when compared to more traditional lesion characteristics is in general agreement with recent studies (Hope et al., 2018; Salvalaggio et al., 2020) reporting similar predictive value for models including (dis)connectivity measures compared to models with lesion information only. The lack of robust associations between disconnectome maps and the clinical measures has several likely explanations. It has been suggested that the information provided in the disconnectome maps is largely embedded in the binarized lesion masks (Hope et al., 2018; Salvalaggio et al., 2020), implying that the two representations of lesion related pathology convey overlapping variance. Indeed, the correlation between lesion volume and global disconnectivity, operationalized as the average voxel value across the disconnectome map or the number of voxels with probability of disconnection > 50%, was relatively strong, intuitively supporting that larger lesions project to a larger proportion of the brain.

Alternatively, it may be that disconnectome maps and lesion masks convey similar information primarily when the sample is large and lesion diversity sufficiently high to capture the variance embedded in the disconnectome maps (Griffis et al., 2019). This could imply that in many real-life situations where large samples are not always realistic/feasible, such as in clinical stroke populations, disconnectome maps may provide relevant, complementary and unique information. In agreement with this, a recent study revealed that structural disconnectome maps explained a larger proportion of the variance in core functional connectivity disruptions than did focal lesions, and displayed significant correlations with behavior (Griffis et al., 2019), thus facilitating the

understanding of individual differences in outcome. Moreover, higher accuracy in cognitive and mobility prediction for models including disconnection metrics than models based on lesion volume has been reported (Kuceyeski et al., 2016).

A key assumption underlying our analyses is that the indirectly calculated disconnectome maps provide a realistic estimate of structural network disconnection and that these disconnections have functional effects. As depicted in Fig. 3, the degree of estimated tract disconnection can be extensive, even for smaller lesions. While such lesion to brain network mapping supports the notion that lesions in hub-like regions project to and implicates an extended set of brain regions and networks (Colizza et al., 2006; Van Den Heuvel & Sporns, 2011), the tractography process used to build the normative training set has several inherent limitations and errors can be introduced in any stage of the tracking process (Schilling et al., 2019). Noise and artefacts in the image acquisition, difficulties establishing fiber orientation (Jeurissen et al., 2019) and choices regarding the tracking algorithm and parameters such as stop criteria and curvature threshold (Knösche et al., 2015; Schilling et al., 2019), are among the commonly recognized pitfalls. Consequently, the reconstructed pathways based on diffusion tractography may not necessarily reflect true structural connections, and to which degree disconnectome maps reflect biological disconnections is still debated (Salvalaggio et al., 2020), warranting caution when interpreting tractography results without supporting converging evidence (Jeurissen et al., 2019). These limitations are not specific for the currently employed algorithm, and further work is needed to overcome general limitation of biological accuracy and validity of diffusion based tractography. On a related note, different approaches for disconnectome mapping may reveal different associations with clinical measures, which should be pursued in future validation studies.

The added value of disconnectome maps in brain-behavior mapping also depends on the reliability, validity and functional neuroanatomy of the included clinical and behavioral measures. For example, primary motor dysfunctions, which may require simpler operationalizations and measurements than more complex cognitive symptoms, are more strongly associated with focal damage, while other behaviors, like verbal associative memory, may be more strongly predicted by extended network function (Griffis et al., 2019; Siegel et al., 2016). The lack of significant associations between brain characteristics and behavioral measures in the current study may therefore be partly related to the properties and measurement of PSF. Although fatigue is painfully tangible for the individual patient, it is unspecific and difficult to operationalize, and the lack of "gold standard" measures of subjective fatigue has been characterized as one of the major obstacles to PSF research (Nadarajah & Goh, 2015). In the current study, we applied the FSS as a general measure of fatigue interference and severity. As FSS is the most widely used fatigue measure in stroke research (Cumming et al., 2016), reporting FSS scores facilitates communication and synthesizing of results across studies. Still, FSS constitutes a rather coarse measure of a complex phenomenon, and does not provide information on other relevant aspects of PSF such as diurnal fluctuations and fatigue subtypes. It is conceivable that more finely grained measures of i.e. fatigue subtypes could reveal associations not detected by the FSS.

Mimicking the results from the disconnectome approach, linear regressions testing for associations between FSS and lesion characteristics (volume and location) revealed no significant associations. This is in agreement with several previous studies (Choi-Kwon et al., 2005; Ingles et al., 1999; Mead et al., 2011). Still, the literature is inconclusive, and some suggest significant associations between PSF and lesion characteristics (Snaphaan et al., 2011; Tang et al., 2014, 2010). The inconsistency between studies may be attributable to differences in how lesion site is defined and reported, as well as time since stroke and clinical characteristics and severity of the sample. Studies that do not report significant associations between fatigue and lesion characteristics tend to define lesion location broadly (Wu et al., 2015), such as posterior/anterior circulation or left/right hemisphere, while studies reporting significant associations often apply a more detailed account of lesion site (e.g. which specific structures are affected) and are conducted within the first few months after stroke. The temporal aspect may be of particular importance, considering that the character of stroke sequelae and associated brain correlates change over time through processes of recovery and compensation (Fornito et al., 2015; Fox, 2018). In the present study, fatigue was measured on average 22 months post stroke. The absence of identified stroke lesion effects may thus suggest that lesion characteristics play a less critical role in the chronic phase (Aarnes et al., 2020).

In addition to the general limitations related to the interpretation of imaging-based measures of brain connectivity listed above, the results should be interpreted in light of the following caveats. First, the recruited patients suffered mild strokes and were drawn from a highly functioning part of the stroke population, as the extent and type of assessments prevented the more disabled patients from participating (e.g. severe aphasia, paralysis, severe neglect). This limits generalizability of results, and we cannot exclude the possibility that including more severely fatigued patients would reveal associations not detected in the current study. However, even in this sample of fairly high functioning stroke patients, levels of fatigue were significantly higher than in the healthy control group, and comparable to fatigue levels reported in other samples of chronic stroke patients (Choi-Kwon et al., 2005; Valko et al., 2008). Moreover, fatigue correlated highly with depression and moderately with sleep quality, in line with previous reports (Choi-Kwon et al., 2005; Park et al., 2009; van de Port et al., 2007), intuitively indicating that FSS scores reflect a relevant clinical phenotype.

Second, related to the complex and multifactorial nature of PSF, the design of the current study does not allow for an extensive account of all factors potentially involved in fatigue etiology. Unmeasured factors like pain (Naess et al., 2012; Tang et al., 2014), pre-stroke fatigue (Choi-Kwon et al., 2005; Duncan et al., 2014), social support (Michael, Allen, & Macko, 2006) and specific cognitive impairments like memory problems and reduced processing speed (Pihlaja et al., 2014; Ulrichsen et al., 2020) have been associated with PSF, as have the use of various medications (Chen & Marsh, 2018) (see e.g. Aarnes et al. (2020) for an updated review on PSF related factors). While the aim of this paper was to evaluate the added explanatory value of a structural disconnectome approach with regards to subjective fatigue, rather than providing an extensive mapping of associated factors and comorbidities, the number of potential confounders constitutes a principal constraint to the understanding of PSF etiology in our sample.

Third, VSLM analyses are inherently contingent on and restricted by the variability of the patients' lesion locations, as a lesion site cannot be identified as important for a symptom if it is not represented in the sample. With regards to the current sample, the lack of whole brain representation limits the spatial scope of the analyses, where i.e. right hemispheric strokes were more densely sampled than left hemispheric strokes, and prefrontal cortex was marginally affected. This lack of full or random sampling of the brain represents a common caveat in stroke research, because stroke lesions are not randomly or evenly dispersed throughout the brain, but are dependent on vascular organization and architecture and tend to occur in proximity to major arteries (Rorden et al., 2007; Zhao et al., 2020). In line with this, degree of voxel-wise lesion overlap between patients in the current sample was low, and although a sample size of 84 is comparable with common practice in MRI studies targeting stroke (Nickel & Thomalla, 2017; Nott et al., 2019; Sihvonen et al., 2017), further studies with even larger samples are needed.

Low power due to small sample sizes is common in neuroscience (Button et al., 2013), and might be especially pressing in stroke imaging research where inter-patient variability in lesions and symptoms is high, and large datasets are logistically and financially demanding to collect (Liew et al., 2020; Price et al., 2017). With reference to this fundamental constraint, the best hope for future stroke neuroimaging studies may lie in large-scale data-sharing initiatives such as the ENIGMA Stroke

Recovery database (Liew et al., 2020), where pooled and synthesized data from individual studies facilitates conduction of well powered studies on large and diverse samples.

However, in smaller samples with low lesion overlap, targeting disconnectivity through disconnectome maps may be particularly relevant, because such measures reveal common disruptions across spatially dispersed lesions (Griffis et al., 2019), resulting in a higher degree of disconnectome overlap compared to lesion overlap.

In conclusion, the current study represents a novel approach to assess the neural correlates of PSF in chronic stroke patients. By indirectly estimating structural network disconnections caused by the stroke lesions, we arrived at individual disconnectome maps capturing distal effects of focal damage. The results did not provide evidence that a structural disconnectome based approach demonstrates higher sensitivity to PSF than a VLSM approach. Nor did the results support the notion that lesions to particular regions or disconnections to specific networks contribute to PSF in the chronic phase. Importantly, our approach does not allow for claims about functional connectivity, and future studies should investigate whether the findings replicate with functional disconnectivity measures. Finally, methodological considerations regarding statistical power, lesion coverage- and overlap warrants caution when interpreting results.

CRediT authorship contribution statement

Kristine M. Ulrichsen: Conceptualization, Formal analysis, Writing - original draft. **Knut K. Kolskår:** Data curation, Writing - review & editing. **Geneviève Richard:** Data curation, Writing - review & editing. **Dag Alnæs:** Visualization, Writing - review & editing. **Erlend S. Dørum:** Data curation, Writing - review & editing. **Anne-Marthe Sanders:** Data curation, Writing - review & editing. **Sveinung Tornås:** Supervision, Writing - review & editing. **Jennifer Monereo Sánchez:** Data curation, Writing - review & editing. **Andreas Engvig:** Writing - review & editing. **Hege Ihle-Hansen:** Writing - review & editing. **Michel Thiebaut de Schotten:** Methodology, Software, Writing - review & editing. **Jan E. Nordvik:** Project administration, Funding acquisition, Writing - review & editing. **Lars T. Westlye:** Conceptualization, Funding acquisition, Project administration, Supervision, Formal analysis, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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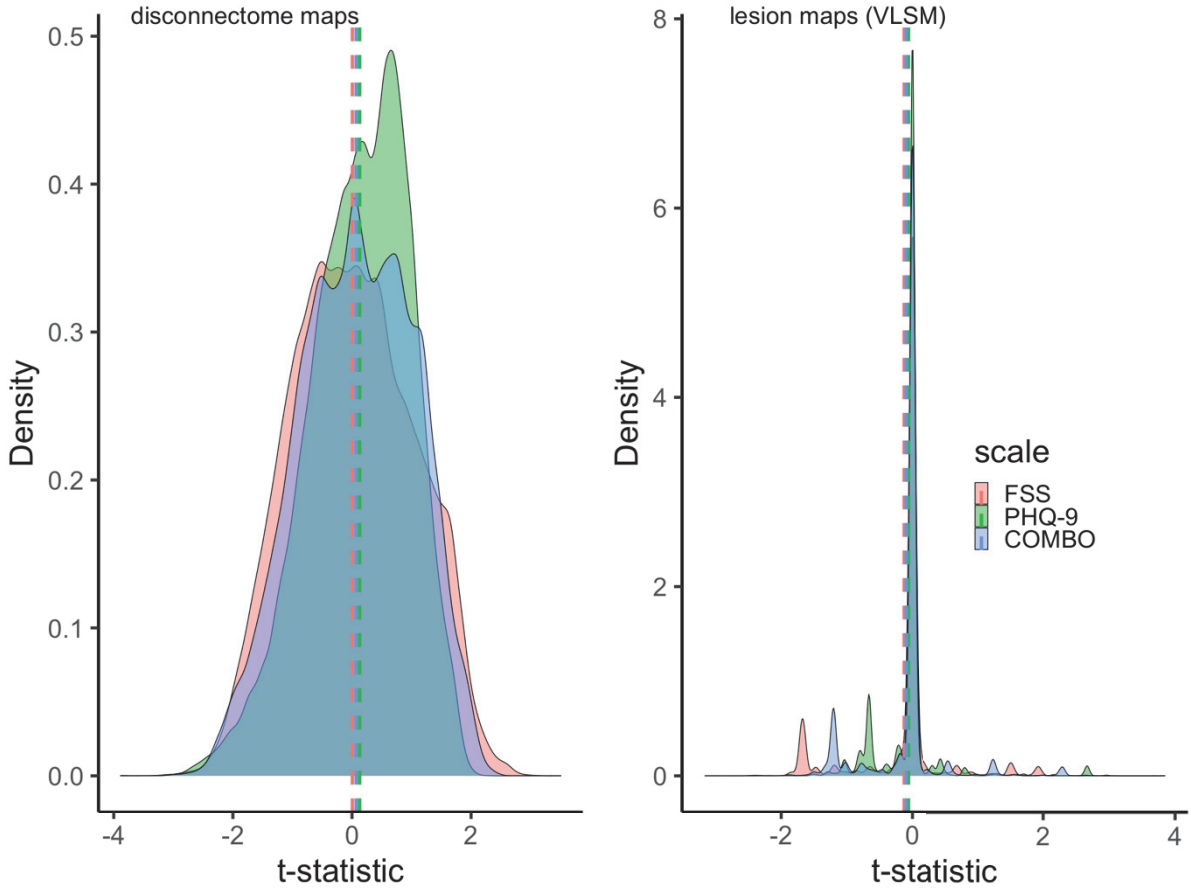
Supplementary material

Figure 1



Density plot of uncorrected t-statistics from permutation tests on disconnectome maps (left) and lesion maps (right), for FSS, PHQ-9, and the sum scores of FSS and PHQ combined.

Table 1

Number of uncorrected voxels with p < .05

Disconnectome maps	FSS	PHQ	FSS + PHQ
T1	844	1193	820
T2	1064	0	137
VLSM			
T1	56	2577	334
T2	232	0	24

Number of uncorrected voxels with p <.05 from permutation tests on disconnectome maps and lesion maps (VLSM) for FSS, PHQ, and the sum scores of FSS and PHQ combined.

Table 2

Varying priors on disconnectivity models	Prior	BF	δ & 95% CI
corrBF (FSS, mean_disconnectivity)	MediumNarrow	0.34	0.02 [-0.17 – 0.23]
corrBF (FSS, mean_disconnectivity)*	**DefaultMedium**	**0.26**	0.03 [-0.18 – 0.24]
corrBF (FSS, mean_disconnectivity)	Wide	0.20	0.03 [-0.18 – 0.24]
corrBF(FSS, n voxels > 50% disconnect)	MediumNarrow	0.38	0.05 [-0.15 – 0.26]
corrBF(FSS, n voxels > 50% disconnect)*	**DefaultMedium**	**0.29**	0.06 [-0.15 – 0.27]
corrBF(FSS, n voxels > 50% disconnect)	Wide	0.22	0.05 [-0.15 – 0.27]

*Models reported in manuscript

Table 3

Main models with outlier excluded	BF	δ & 95% CI
corrBF (FSS, mean_disconnectivity)	0.32	0.07 [-0.13 – 0.29]
corrBF (PHQ, mean_disconnectivity)	0.26	0.01 [-0.19 – 0.22]
corrBF (FSS, n voxels > 50% disconnect)	0.39	0.09 [-0.11 – 0.30]
corrBF(PHQ, n voxels > 50% disconnect)	0.29	0.05 [-0.16 – 0.26]
corrBF(FSS, number of voxels lesioned)	0.28	0.05 [-0.16 – 0.25]
corrBF(PHQ, number of voxels in lesion)	0.29	0.05 [-0.16 – 0.26]

Table 4

Model comparison by Bayes Factor	
One variable added in each model and compared against null model	Bayes Factor
"Null model FSS": lmBF(FSS ~ Age + PHQ) / intercept only	>150 ±0%
Null + sex / null	0.29 ±0.28%
Null + months since stroke / null	0.17 ±0%
Null + TOAST / null	0.16 ±0.42%
Null + lesion location / null	0.19 ±0.38%
Null + lesion size / null	0.16 ±0%
Null + mean disconnectivity / null	0.19 ±0%
Null + number of voxels disconnectivity probability >50% / null	0.19 ±0%

No models (except "null model") display Bayes factors >1, indicating that variables have low predictive value and that no extended models are preferred over the null model.