Graduate thesis

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Norwegian University of Science and Technology
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Department of Psychology

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Executive Function after Ischemic Stroke and the Effect of Cognitive and Brain Reserve: A Study of Sex Differences

Graduate thesis in Clinical Programme in Psychology
Supervisor: Ramune Grambaite
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Preface

The data used in this study is collected by a team of researchers at the Department of Neurology, Akershus University Hospital. It has been an honour to be allowed to use this data for my graduation thesis. It has been an amazing journey with a steep learning curve, and I could not have done it without my supervisors Ramune Grambaite and Elisabeth Kliem. You have my deepest gratitude and respect. Thank you for your patience, knowledge, ambitions, guidance, attention to detail and kindness. I'm lucky to have had you two in my corner. I even got to participate and present at the VasCog conference in September 2021! I want to thank Per Selnes for his time and guidance and discussions regarding the MRI variables. Many thanks to Odin Hjemdal and Jurate Saltyte-Benth for their input on the statistical analyses and essential feedback on what to improve. I also want to thank Mojtaba Habibi Asgarabad and Maede Etesamy for taking the time to read the thesis and give feedback. Many thanks to my parents for your love, kindness, acceptance and warmth. This last year would have been difficult without your company. The same goes for my wonderful friends. Finally, I want to thank my dear Ingrid Oliane Hårstad. Your support and love are a wonder, and your kindness, care and insight will continue to inspire me to be better.

Abstract

Introduction: Impairment in executive function (EF) is common after stroke, which can impact the patient's quality of life and rehabilitation participation. This explorative study had two aims: 1) Study sex differences in EF one week and three months after stroke, as well as change in EF during the first three months after stroke. 2) Explore possible sex differences in the relationship between cognitive and brain reserve proxies and EF after stroke. We looked at EF one week and three months after stroke, as well as change in EF during the first three months after stroke.

Method: 86 patients with ischemic stroke completed a battery of neuropsychological tests, including measures of EF, as well as other psychological, functional and medical screenings one week and three months after stroke, and an MRI three months after stroke. Male and female EF test scores were compared using independent sample t-test. Split way multiple linear regression (split by sex) was used to study the effect of cognitive and brain reserve on EF during the first three months after stroke. The reserve variables were premorbid IQ calculated from the National Adult Reading Test (NART IQ), education, career complexity and total intracranial volume (TICV).

Results: Females had higher mean raw scores and less clinical impairment (T-scores ≤ 35) on executive tests than males the first week after stroke. There were no significant sex differences in EF scores three months after stroke. The regression results showed that NART IQ was a significant predictor for male EF scores three months after stroke, while education was a significant predictor for female EF scores three months after stroke. Neither career complexity nor TICV were shown to be significant predictors for EF after stroke.

Conclusion: Our study's results indicate that there may be sex differences in EF impairment after stroke. The results also suggest that certain reserve variables may be associated with EF after stroke, and that these relationships could be sex-specific. Therefore, it might be useful to consider the use of specific reserve variables such as NART IQ and education when examining EF after stroke. However, there are few existing studies on this topic, so further research is warranted to clarify these relationships.

Abstrakt

Introduksjon: Svikt i eksekutiv funksjon (EF) er en vanlig utfordring etter hjerneslag. Dette kan påvirke pasientens livskvalitet og deltakelse i rehabilitering. Dette utforskende studiet har 2 mål: 1 Studere kjønnsforskjeller i EF en uke og tre måneder etter hjerneslag, samt endring av EF de første tre månedene. 2) Utforske mulige kjønnsforskjeller i hvordan kognitiv- og hjernereserve påvirker EF etter hjerneslag. Vi ser på EF en uke og tre måneder etter hjerneslag og endringer i EF de første tre månedene.

Metode: 86 pasienter med iskemisk hjerneslag gjennomførte en omfattende utredning av kognitiv funksjon (inkludert EF), psykiske symptomer, motorisk og selvstendig fungering og somatikk en uke og tre måneder etter hjerneslaget. En MR ble også gjennomført tre måneder etter hjerneslaget. EF skårer til menn og kvinner ble sammenlignet med uavhengig t-test. Multippel linjær regresjon ble brukt til å utforske relasjonen mellom reserve variabler og EF skårer etter hjerneslag for hvert kjønn. Reserve variablene som ble brukt var premorbid IQ basert på National Adult Reading Test skårer (NART IQ), utdanningsnivå, karriere kompleksitet og total intrakranielt volum (TICV).

Resultat: Kvinner hadde høyere gjennomsnittsskåre og mindre klinisk svikt (T-skårer ≤ 35) på EF testene enn menn den først uken etter hjerneslaget. Der var ingen signifikant kjønnsforskjell på EF testskårer tre måneder etter hjerneslaget. Regresjonsresultatet viser at NART IQ var en signifikant prediktor for EF tre måneder etter hjerneslag for menn, mens utdanning var en signifikant prediktor for EF tre måneder etter hjerneslag for kvinner. Våre resultat støtter ikke karriere kompleksitet eller TICV som gode prediktorer for EF etter hjerneslag.

Konklusjon: Resultatene fra dette studiet indikerer at det kan være kjønnsforskjeller i EF svikt etter hjerneslag. Resultatene viser at spesifikke reserve variabler kanskje er assosiert med EF etter hjerneslag, og at assosiasjonen muligens er kjønnsspesifikk. Det er derfor er det kanskje være en god ide å vurdere bruken av utdanning og NART IQ for å screene for EF svikt etter hjerneslag. Det eksisterer få studier knyttet til dette temaet, så videre forskning er nødvendig for å videre belyse disse relasjonene.

Introduction

Stroke

Stroke is defined as a neurological deficit caused by an acute focal central nervous system injury with a vascular cause such as cerebral infarction, intracerebral haemorrhage, or subarachnoid haemorrhage lasting more than 24 hours or leading to death with other aetiologies excluded (Sacco et al., 2013). The disturbed blood flow results in a lack of oxygen being delivered to cells in the brain, which causes the clinical symptoms associated with stroke. Depending on which areas of the brain are being deprived of oxygen, stroke presentation may vary, but the usual signs of stroke are sudden problems with balance, loss of vision in one or both eyes, numbness or weakness in face, arms or legs and slurred speech (Aroor et al., 2017). These symptoms can be characterized by the acronym BE FAST: Balance, Eyes, Face, Arms, Speech and Time (Aroor et al., 2017). Ischemic strokes are caused by a restriction of blood supply to tissue, usually caused by clots, emboli or artery constrictions (Fjærtoft et al., 2021). Roughly 86 % of reported strokes are ischemic strokes (Fjærtoft et al., 2021). The other 14 % are haemorrhagic strokes that are caused by ruptured blood vessels either within the brain (intracerebral/intracranial haemorrhage) or on the surface on the brain (subarachnoid haemorrhage) (National Collaborating Centre for Chronic Conditions, 2008).

Globally, over 13 million people suffer from stroke every year (Lindsay et al., 2019). Norway registered approximately 9000 stroke cases in 2020 (Fjærtoft et al., 2021). Stroke causes structural brain damage, and this can leave patients with short- or long-term cognitive impairment and motor dysfunction (Sun et al., 2014). It also increases the survivor's risk of developing psychiatric symptoms either directly though changes in the brain or indirectly as a reaction to the trauma and post-stroke impairments (Fure et al., 2006; Kliem et al., 2022; Rosenich et al., 2020). The consequences of stroke affect patients, their families and society, especially if the patients are younger and have decades of their lives left to live. Thanks to the achievements of modern medicine, stroke mortality rates are steadily decreasing (Towfighi & Saver, 2011). Increased use of chemical thrombolysis within 40 minutes of stroke onset is considered one of the major contributing factors for reducing the mortality rate of acute ischemic stroke (Akerkar et al., 2018). However, higher survival rates combined with a longer life expectancy and a growing global population will most likely lead to an increase of annual stroke cases and patients with impairment after stroke in the coming decades (Béjot et al., 2019; Engstad et al., 2012).

Therefore, knowledge on how specific individual factors affect stroke outcome and what can be done to reduce or compensate for impairment are especially relevant and necessary. Even with the recent decades' effort to increase knowledge regarding potential risk factors and biomarkers of impairment and recovery following stroke, predictive models still fail to explain pervasive interindividual differences (Rosenich et al., 2020; Stern et al., 2020). This heterogeneity in stroke impairment and recovery points to the need for further study (Makin et al., 2013).

Cognitive Impairment after Stroke

Short- and long-term cognitive impairment after stroke is associated with increased risk of reduced participation in rehabilitation, lack of adherence to treatment guidelines and lower quality of life (Brainin, Tuomilehto, Heiss, Bornstein, Bath, Teuschl, Richard, Guekht, & Quinn, 2015; Cumming et al., 2012; McVeigh & Passmore, 2006; Sun et al., 2014). It also greatly increases survivors' risk of developing dementia (Brainin, Tuomilehto, Heiss, Bornstein, Bath, Teuschl, Richard, Guekht, & Quinn, 2015; Hu & Chen, 2017). Cognitive impairment after stroke can range from mild cognitive impairment (MCI) to post-stroke dementia (Pendlebury & Rothwell, 2019). Damage to specific areas of the brain is more likely to affect certain cognitive domains (Makin et al., 2013). For example, damage to the cerebellar posterior lobe is associated with low scores on cognitive tests, while damage to the cerebellar anterior lobe is associated with motor impairment (Stoodley et al., 2016). The basal ganglia and other subcortical areas are commonly damaged by ischemic stroke (Prins et al., 2005; Venkataraman et al., 2022). Subcortical infarction is often associated with impairment of executive function (EF) and psychomotor speed, two of the most common cognitive changes after stroke (Cumming et al., 2012). This is likely because the infarctions disrupt pathways between the frontal and deep brain structures (Sachdev et al., 2004).

Due to variations in study designs and inclusion criteria, it is difficult to give general estimates of prevalence of either short- and long-term cognitive impairment after stroke (Pendlebury & Rothwell, 2019; Sun et al., 2014). However, it is estimated that between 30-70 % of stroke patients experience cognitive impairment three months to a year after stroke depending on factors such as age, country of origin, race, healthcare availability, stroke location, and stroke severity (Sun et al., 2014). Stroke patients usually experience more severe impairment in the acute phase, with up to 70-80 % of stroke patients experiencing impaired cognition shortly after stroke (Riepe et al., 2004). Impairment not necessarily related to stroke location is also to be expected in the acute phase and is likely caused by secondary stroke

responses such as inflammation and swelling impacting neural pathways (Becker, 2016; Jin et al., 2010). Most patients experience spontaneous improvement during the first three months, and then more gradual improvements during the first two years after stroke (del Ser et al., 2005). However, not all motor and cognitive functions are necessarily regained, and some stroke survivors have to live with long-term impairment (Brainin et al., 2015). Kapoor et al. (2017) studied cognitive impairment and societal participation restriction in stroke survivors with excellent functional recovery measured by the modified Rankin Scale (mRS = 0 or 1) and found that approximately 50 % of the participants had impaired cognitive function and participation restrictions two to three years after stroke. Cognitive impairment is therefore likely to negatively impact many stroke survivors, regardless of stroke severity or recovery of motor function. This underlines the importance of proper cognitive screening practices in stroke units and rehabilitation centres.

Sex and Gender Differences in Stroke

Sex usually refers to the biological attributes that are associated with physical and physiological features, such as chromosomes, hormone function and reproductive anatomy, while gender usually refers to the socially constructed roles, behaviours and identities attributed to females, males and gender-diverse people (Malik, 2020). It is in general not easy to distinguish between the two terms in publications and clinical trials because most studies neither specify nor define the use of the sex/gender variable in their publications. This study focuses on the biological construct of sex. However, we cannot dismiss the effect cultural gender roles have on several of the variables used in this study, such as years of education, career complexity, and even premorbid IQ. Thus, while we use the biological definition of sex in this study, we are likely studying a combination of gender and sex.

Sex differences have been found in stroke risk factors, stroke outcome and interactions with the health care system (Carcel et al., 2020). Males have a higher age-adjusted incidence of stroke compared to females, especially before the age of 74 (Bushnell et al., 2018; Carcel et al., 2020). Yet, a recent study found that there is no significant sex difference in lifetime risk of stroke, which may be explained by a longer life expectancy and the postmenopausal phenomenon in females (Feigin et al., 2018; Haast et al., 2012). Lifetime risk is a measure of the cumulative probability that a certain disease will develop in a person of a given age (>25 years) and sex when looking at the person's remaining lifespan. The postmenopausal phenomenon refers to the trend of postmenopausal females having an increased risk of stroke compared to menstruating females (Shekhar et al., 2017).

Studies on sex differences in stroke mortality shows varying results. A systematic review from 2009 found that the fatality (an occurrence of death by accident or from disease) one month after stroke was higher for females (24.7 %) compared to males (19.7 %) (Appelros et al., 2009). However, this was without controlling for confounding factors such as age, obesity and diabetes. The International Stroke outcomes study (INSTRUCT) found that while more females die of stroke, the long-term mortality rate for first-ever stroke was higher for males than females (female-male-ratio: .81 after one year) when controlling for confounding factors (Phan et al., 2017). They concluded that higher female mortality is mainly due to age, but also stroke severity, atrial fibrillation and pre-stroke functional limitations (measured by a combination of living independency before the stroke, pre-stroke Barthel Index (used to measure performance in activities of daily living (ADL)) and mRS). Females are also more likely to present with non-traditional stroke symptoms, such as urinary incontinence, problems with swallowing and coma (Di Carlo et al., 2003). This can cause a delay in recognition and treatment of stroke (Beal, 2014; Jerath et al., 2011; Lisabeth et al., 2009; Mandelzweig et al., 2006). This might also be one of the contributing factors as to why females usually experience more severe strokes compared to males, even when controlling for age, comorbidities and pre-stroke level of motor function and independence (Bonkhoff et al., 2021; Dehlendorff et al., 2015).

Studies have shown that females are often more disabled than males after stroke and experience more ADL limitations, lower quality of life, more pain, more problems with mobility and self-care, and are more likely to report depression and anxiety after stoke (Appelros et al., 2010; Bushnell et al., 2014; Carcel et al., 2019; Gall et al., 2018; Persky et al., 2010; Poynter et al., 2009). Phan et al. (2019) found that female stroke survivors exhibit consistently lower health-related quality of life compared to males, and that this was partly attributed to their advanced age, more severe strokes, pre-stroke dependence and post-stroke depression.

There are differing findings on sex differences in cognitive impairment after stroke. Only two of five studies included in Gall et al.'s (2018) review of sex differences in stroke outcome, found that males had a higher chance of experiencing cognitive impairment. Another two found that females had a higher chance of cognitive impairment after stroke, and one study found no sex difference. Research on sex differences in rehabilitation is also sparce and with conflicting results, but females seem to have a lower probability to achieve independence in ADL and motor abilities, as well as poorer vitality and mental health compared to men with similar stroke severity, age and onset-to-admission interval (Carcel et

al., 2020). A recent study on sex differences in recovery after a four week-long inpatient rehabilitation found that males and females showed similar recovery effectiveness, but females were still more likely to show worse clinical outcome and report higher levels of pain at discharge than males, corrected for age, most likely because females had lower motor function and reported more pain than males at admission (Kautzky-Willer et al., 2021).

Cognitive Reserve and Brain Reserve

The concept of reserve has been a topic of interest in research since the 1980's when Katzman et al. (1989) proposed it as a possible reason for why some patients with advanced brain pathology associated with Alzheimer's disease (AD) showed little to no clinical symptoms. Various models have been proposed since, trying to explain interindividual differences in resilience to aging, injury and pathology concerning cognition, function and clinical symptoms (Stern et al., 2020). Brain reserve and cognitive reserve are two such concepts of resilience. As defined by Stern et al. (2020), brain reserve is the concept of passive neuroprotective function caused by increased neural substrate, meaning larger brain volume and higher neural and synaptic count. It can be seen as a fixed resource that is shaped by lifetime experiences. Brain reserve is usually measured by variables such as brain volume, TICV, grey matter volume and white matter volume. Cognitive reserve is a measure of increased neurocomputational flexibility, and moderates how brain pathology and insult present and affect cognition, emotions and day-to-day function (Rosenich et al., 2020). Neural connectivity, increased neurogenesis and a more adaptable neural network are thought to be some of the underlying causes for cognitive reserve, making it a rather active concept compared to brain reserve (Stern et al., 2020). As it is not possible to directly measure cognitive reserve with today's medical knowledge and limitations, socio-behavioural proxies are used instead. Examples of such proxies are premorbid IQ, years of education, occupational attainment and social, leisure and physical activities, with years of education being the most widely used in current research (Rosenich et al., 2020). Most research uses just one proxy when looking at factors affecting outcome after injury, and the lack of validity studies on the use of different or multiple variables for cognitive and brain reserve makes it difficult to say which proxies are best suited for future research.

Cognitive Reserve, Brain Reserve and Stroke

Reserve theories have been applied to cognitive changes after stroke (Nunnari et al., 2014). Both longitudinal studies and cross-sectional studies have found that cognitive reserve (operationalized as years of education or premorbid IQ) has a protective effect on global

cognition and memory and reduces the risk of developing post-stroke dementia and aphasia both shortly after the stroke as well as long-term (Makin et al., 2018; Ojala-Oksala et al., 2012; Sachdev et al., 2014). High cognitive reserve increases survival rates after stroke (Ojala-Oksala et al., 2012). The protective effect of cognitive reserve on cognition is especially notable when vascular damage is mild or moderate (Ojala-Oksala et al., 2012). Umarova et al. (2017) found that longer education positively affects cognition in the acute phase after stroke, and that longer education is positively associated with both alertness, working memory, EF and global cognition after stroke. This indicates that both education dependent domains (working memory and EF) and education independent domains (alertness) are partly regulated by cognitive reserves. Their study also controls for measures of brain pathology (lesion load and age), which means their results show the regulating effect of education when having taken into consideration the degree of pathology.

Total intracranial volume (TICV) is currently one of the most common proxies for brain reserve. TICV is an estimation of the cranial cavity volume as outlined by the supratentorial dura matter or the cerebral contour (Eritaia et al., 2000). It is easily accessible by structural magnetic resonance imaging (MRI), but the measure has been criticized for being less sensitive compared to other brain variables such as measures of cortical surface (Luders et al., 2004; Toro et al., 2008). A systematic review of ten studies concluded that higher TICV usually has a protective role against brain pathology, causing delayed clinical manifestation of dementia and MCI. This indicates that TICV does at least partly function as a proxy for brain reserve (van Loenhoud et al., 2018). We struggled to find studies on TICV and post-stroke cognitive function but did find some studies using the variable brain volume instead of TICV. Mönch et al. (2020) studied the impact of brain volume on the clinical outcome of 107 ischemic stroke patients. They found that brain volume was a significant predictor for functional outcome and mortality, but not after correcting for age. Schirmer et al. (2020) found that larger brain volume was a significant predictor for lower mRS score after an acute ischemic stroke and that larger brain volume reduced the odds of worse long-term functional outcomes compared to smaller volumes.

Sex Differences in Reserve

While both sex differences and reserve have been topics of interest in stroke research for some time now, few have studied sex differences in the interaction of reserve and post-stroke cognition. Most existing studies about sex differences in cognitive and brain reserve are in the field of AD research.

Sex Differences in Brain Composition and Reserve

Malpetti et al. (2017) used Positron emission tomography (18F-FDG PET) technology and found that education and occupational complexity cause metabolic increases in different parts of the brain in healthy males and females. Males had increased activity in posterior associative cortices and females in the anterior limbic-affective and executive networks. In patients with AD, education and occupation level correlated with activity in the posterior temporo-parietal areas for males and the limbic systems for females. This indicated the involvement of different networks for each sex. Thus, the study indicates that cognitive reserve impact males and females differently, increasing efficiency in posterior default mode network and frontal executive network for males and females respectively.

Perneczky et al. (2007) tested the hypothesis that females are more affected by pathological brain damage than males. They did this by analysing the cerebral metabolic deficits (measured using 18F-FDG PET scans) caused by neurodegeneration in males and females with similar test scores on the CERAD neuropsychological test battery. After controlling for age and education, they found that males had lower glucose metabolism in regions typically affected by AD pathology compared to females. This implies that the same level of cognitive impairment is associated with greater brain pathology in males, indicating that males might be more resilient to neurodegeneration. This indicates a male specific reserve.

Sundermann et al. (2016) studied sex differences in verbal memory with different levels of neural dysfunction, measured by temporal lobe glucose metabolic rates (using 18F-FDG PET scans) in people with MCI and AD. They found that females had better verbal memory, despite similar levels of hypometabolism. This might indicate a form of sex-specific cognitive reserve that delays verbal memory decline in females with amnestic MCI.

Sex Differences in Alzheimer's Disease Clinical Severity and Reserve Proxies

When studying the association of adolescent cognitive ability with AD and other related disorders, Huang et al. (2018) found that lower adolescent memory for words is an female risk factor for AD and related disorders, while lower mechanical reasoning is a risk factor for males.

The literature available shows that there are sex differences in how occupational attainment affects the risk of developing AD. Qiu et al. (2003) aimed to identify specific

principal occupation categories related to developing dementia in older adults and found that the combination of a low level of education and manual work in production of goods was significantly associated with the development of AD and dementia for females, but not for males. Helmers et al. (2001) found in their study that being craftsmen or shopkeepers is a protective factor for developing AD for females and a risk factor for males. Santabarbara et al. (2019) found that both male and female farmers had a lower risk of developing AD. Male farmers had lower risk of developing AD than white collar workers, and female farmers had a lower risk compared to homemakers.

Subramaniapillai et al. (2021) reviewed seven studies that looked at how sex impacts the protective effect education has on AD development. Some of those studies found that education had no significant impact on risk of AD for either sex (Fratiglioni et al., 1991; Letenneur et al., 1999). But the majority of studies found that education reduced the risk of developing AD for females. Launer et al. (1999) found that less education significantly increased the risk of developing AD, and more so for females than males. Letenneur et al. (2000) found that years of education were negatively associated with decline in the Mini Mental State Examination (MMSE) scores for females but not for males. Pradier et al. (2014) found a positive relationship between MMSE-scores and education for both sexes, but males with AD had significantly higher MMSE-scores than women with AD after controlling for education and age. Koran, Wagener and Hohman (2017) studied sex differences in the association between AD biomarkers and cognitive decline. Their results suggest that females may be more susceptible to decline in EF, memory and hippocampal atrophy compared to males with similar levels of AD biomarkers. These sex differences were especially prominent among people with low education.

A recent study reported that sex impacts the risk factors for developing cognitive impairment in old age in rural parts of China (Wang et al., 2020). Females showed a higher prevalence of cognitive impairment after the age of 75 compared to males (62.7 % vs. 45.4 %). In general, old age, hearing impairment and dependence in activity of daily living were common risk factors for developing cognitive impairment for both sexes. However, poor social interactions in the neighbourhood and diabetes were also risk factors for males, and tea drinking was a protective factor. Female specific risk factors were vision impairment and illiteracy, and having completed six years of schooling was associated with less risk of cognitive impairment for females (Wan g et al., 2020).

Ross, Masters and Hummer (2012) studied how sex affected the relationship between education, health and survival in the US population using the National Health Interview

Survey-Linked Mortality Files. They found that higher education had a significantly larger effect on females' self-rated health compared to males and a negative impact on male mortality. If there are similar sex differences in how higher education impacts stroke patients, education might play an important role in levelling out observed sex differences in stroke literature such as higher male mortality and worse female outcome.

To summarize, current literature indicates that sex may have an impact on the association between reserve and stroke. There is evidence that reserves encourage growth in different brain areas for males and females, that males are more resilient to AD pathology, and that education seems to have a protective effect, especially for female cognition. It is still unclear whether the same sex differences observed in AD research will be present in stroke research.

Executive Function

EF is an umbrella term for a group of top-down cognitive functions that allows us to plan, monitor, initiate and inhibit complex and goal-oriented behaviour (Gilbert & Burgess, 2008). Selective attention, inhibition, working memory, cognitive flexibility, reasoning and problem solving are some of the cognitive functions that make up EF (Diamond, 2013). Impaired EF can make daily tasks more difficult to achieve and lower the overall quality of life (Povroznik et al., 2018). Research has linked EF to the development of conscience and specific social and moral skills in young children (Kochanska et al., 2000), children's reading, mathematics and general academic ability (Bull et al., 2011; Latzman et al., 2010; Thorell et al., 2013; Wasserman, 2012) as well as children's theory of mind and emotional regulation skills (Carlson et al., 2004; Carlson & Wang, 2007)

There is a general consensus that EFs are comprised by several core functions and processes (Diamond, 2013). There are currently several models trying to encompass the nuances of EF. Miyake et al.'s (2000) model of EF suggests that there are three core functions: inhibition, working memory and cognitive flexibility. These components rely on a simultaneous interplay of different processes to function properly, such as sensory processing and memory (Diamond, 2013). Miyake et al.'s model focuses on lower-order EF. It is thought that higher-order EF uses these three core functions allowing for more complex cognitive abilities such as reasoning, problem-solving and planning (Collins & Koechlin, 2012; Lunt et al., 2012). The tests used to measure EF in this study focus on lower-order EF, so using Miyake et al.'s model was considered suitable.

Inhibition

In the model of Miyake et al. (2000), inhibition is the ability to override initial drives and reactions and replace them with more appropriate or useful behaviour (Diamond, 2013). There are different types of inhibition: selective inhibition, motor inhibition and self-control. Selective attention is inhibitive control of attention. Motor inhibition is the ability to hinder bodily impulses or interrupt ongoing actions that are no longer appropriate. And self-control is a combination of being able to repress initial wants, being able to handle delayed gratification and being able to delay reactions (Diamond, 2013; Duque et al., 2017). Inhibition is an important ability to humans since it increases the chances of making good decisions, especially for long-term goals. People with impulsive tendencies have an increased risk of making risky decisions in harmful situations (Jurado & Rosselli, 2007). The medial orbitofrontal cortex (mOFC) is one of the main areas in the brain involving inhibition regarding decision and self-control (Bechara, Damasio, et al., 2000), and the frontobasal-ganglia have a main role in inhibiting motor impulses (Aron et al., 2007). Inhibition is usually measured using tests such as the continuous performance test (Epstein et al., 2003), interference tests (Delis, Kaplan & Kramer, 2001), Go/No-Go motor impulsivity task (Drewe, 1975) and the Iowa gambling task (Bechara et al., 1994).

Multiple studies have found that impulsivity and decision making are difficult for stroke survivors (Bechara, Tranel, et al., 2000; Binder, 1984; Poulin et al., 2013). Scheffer et al. (2016) found that patients with right frontal lobe stroke performed significantly worse on the Go/No-Go motor impulsivity task compared to controls. Cardoso et al. (2014) found that participants who had survived a stroke in either the frontal lobes or the cerebellar lobes had significant difficulties with impulsivity, compared to controls. They also found no significant differences in performance between the stroke types. This suggests that the prefrontal cortex is not alone in regulating EF.

Working Memory

Working memory is a type of short-term memory that allows for manipulation of stimuli no longer perceptually present (Diamond, 2013). These stimuli, either auditory or spatial, can be manipulated and used to solve problems due to functions such as attention shifting, stimuli updating and blocking out external and distracting stimuli (Squire et al., 2012). This is an important ability for reasoning and being able to mentally reorder items (Diamond, 2013). The dorsolateral prefrontal cortex and the cerebellum, especially the cortico-cerebellar circuitry, are important regions for an intact working memory (Cardoso et

al., 2014; Levy & Goldman-Rakic, 2000). Neuropsychological tests such as the Letter-Number Sequencing Test from the Wechsler Adult Intelligence Scale III and IV edition and the Spatial Span Test from the Wechsler Memory Span III edition are used to measure this component of EF (Wechsler, 1997, Wechsler & Naglieri, 2006).

Geldorp et al. (2013) found that stroke patients performed worse on a computerized delay-match-to-sample test compared to controls. In this test patients are asked to remember spatial, object or binding (spatial + object) cues. Stroke patients showed deficits when having to remember spatial or object cues, but performance on the binding component of the task were not significantly affected by the stroke. Roussel et al. (2012) found that verbal working memory was especially affected by frontal lobe lesions. However, the frontal lobe lesions affected the visual working memory in a more varied way and caused less discernible deficits when compared to patients with posterior lobe lesions and controls (Roussel et al., 2012).

Cognitive Flexibility

The third core function of the model of Miyake et al. (2000) is cognitive flexibility. Cognitive flexibility encompasses the ability to update mental processes and adjust to changes in the environment (Diamond, 2013). The ability to change one's mindset, differentiate between concepts and understand perspectives are benefits of cognitive flexibility (Diamond, 2013). The ability is mostly processed in the ventrolateral prefrontal cortex (Varjačić et al., 2018; Verdejo-Garcia et al., 2015).

Cognitive flexibility is thought to be a cornerstone for fluid intelligence, since it is a necessary ability to use higher-order EF such as problem solving, reasoning and abstract thinking (Dajani & Uddin, 2015; Ionescu, 2012). Examples of tests used to measure cognitive flexibility are fluency tasks and task switching tests such as the Colour Word Interference test (CWIT), the Trail Making Test A and the Trail Making Test B (TMT-A and TMT-B) from the neuropsychological test batteries Delis-Kaplan EF System battery (D-KEFS) (Delis et al., 2001) and the Halstead-Reitan battery (Delis et al., 2001; Reitan & Wolfson, 1985).

Tamez et al. (2011) found that TMT-A and TMT-B are sensitive to brain damage, but they did not find data supporting that the tests could differentiate between patients having suffered frontal vs non-frontal stroke. Muir et al. (2015) found that damage to the lateral cholinergic pathways and the superior longitudinal fasciculus caused by stroke were significantly correlated to difficulties with set shifting using TMT-B.

Study Aims

This explorative study has two aims:

(1) To explore possible sex differences in EF after ischemic stroke. We compared males' and females' measures of EF at one week and three months after stroke, as well as their change in EF (measured by subtracting test scores at one week after stroke from test scores at three months after stroke).

(2) To explore possible sex differences regarding the impact of brain and cognitive reserve on EF after stroke. More specifically, we aimed to explore whether there are sex differences in how well different proxies for cognitive reserve (years of education, premorbid IQ and career complexity) and brain reserve (TICV) predict EF one week and three months after stroke, as well as changes in EF during the first three months after stroke.

Method

Participants

This study uses data collected in the period April 2007 to April 2010 at the Stroke Unit of the Department of Neurology at Akershus University Hospital, Norway. Participants were consecutively recruited from the Stroke Unit.

The inclusion criteria of the original study were patients aged 40-79 years, with supratentorial stroke, a MMSE-score of 23 or higher and no apparent visual and/or auditory neglect that could impact their test results. Patients with previous hospitalizations for stroke, psychiatric or neurologic disorders (self-reported or documented in the patient's journal) as well as those who showed speech or language impairment during the MMSE and the clinical interviews were excluded from the study. Those who experienced a second stroke during the data collection period were also excluded. A neurologist determined type of stroke and other diagnoses based on clinical symptoms and available imaging data. All patients had either a computed tomography (CT) or a MRI scan done to diagnose the stroke. In addition, all patients participating in this study had an MRI scan done three months after stroke.

Initially, 97 patients were recruited for the original study and 86 patients participated in the follow-up three months after stroke. For a detailed description of this sample, see Selnes et al. (2015). For this project, seven of the 86 patients available for follow-up did not have a value for TICV calculated and had to be excluded from analyses including this variable. Two patients were not able to complete CWIT-3 and CWIT-4 one week after stroke, one patient were not able to complete CWIT-4 three months after stroke, one patient was not able to complete TMT-B one week after stroke and one patient had missing scores on the National Adult Reading Test (NART). The data analysis in this study is therefore based on the longitudinal data of 77-86 patients depending on the variable used in the analysis.

Design

This study and the authors' participation in the project is approved by the Norwegian Regional Ethics Committee (REK number 2009/1024) and all participants have given informed and written consent to allow for their data to be used for statistical analyses.

The patients completed a battery of neuropsychological tests one week and three months after stroke, as well as comprehensive psychological, functional and medical screenings. The testing was performed in Norwegian and by the same neuropsychologist. Results from screenings and tests included in the original study are not included if they are outside of the scope of this study or non-relevant to its aims.

Using the longitudinal data on tests measuring EF, this study analysed EF test scores at one week, three months and changes in test results from one week to three months after stroke. An overview of tests and screenings used are found in the chapter Measures and in Figure 1.

Measures

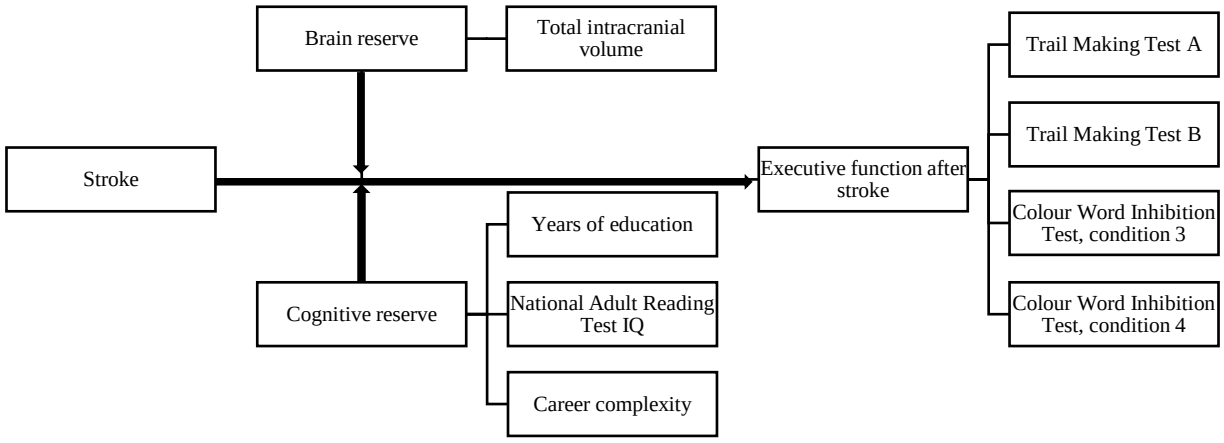
The data was collected while participants were monitored at the hospital and during follow-ups at the Department of Neurology.

Stroke Severity

The National Institutes of Health Stroke Scale (NIHSS) was used to measure neurologic impairment within the first day of hospitalization due to stroke and again during the follow-up three months after stroke. NIHSS is used to quantify stroke severity. The NIHSS consists of 11 items, measuring different abilities such as motor function, language and attention (Lezak et al., 2012). The scale goes from 0 (*normal function*) to 42 (*severe impairment*).

Figure 1.

Overview of Reserve Measures and EF Measures



Note. This figure gives an overview over reserve measures and tests used to measure EF after stroke.

Performance-based Cognitive Function

The participants completed a comprehensive battery of neuropsychological tests to measure different cognitive functions such as attention, processing speed, learning and recall. This study is limited to exploring EF after stroke. The tests used in this study are the following four measures: TMT-A and TMT-B and CWIT condition 3 and 4 from D-KEFS Since these tests use time to measure performance, the scores have been multiplied by -1 in all statistical analyses, so higher scores represent better performance.

This study uses raw scores when studying sex differences in EF and changes in EF over time after stroke, but T-scores are reported to give a better clinical understanding of EF impairment. Impaired EF has been defined as performing at least1.5 SD (i.e., T-score ≤ 35) under average performance on any of the EF tests. Change in EF scores are calculated by subtracting scores one week after stroke from scores three months after stroke. Positive values indicate improvement in EF and negative values indicate diminished abilities.

In this study, we sometimes use "EF tests" when referring to TMT-A, TMT-B and CWIT condition 3 and 4, even though they are subtests/conditions of the tests TMT and CWIT. We do this to increase readability.

TMT-A and TMT-B. TMT-A and TMT-B are from the Halstead-Reitan battery (Lezak et al., 2004; Reitan & Wolfson, 1985). American norms were used when calculating T-scores. T-scores norms are corrected for sex, ethnicity and age. The test has two parts. In TMT-A the participant is asked to draw a line connecting 25 numbered circles in ascending order. Visual scanning, attention and processing speed are main cognitive functions measured in this task, but motor functions also play a role. In TMT-B the participants are asked to connect numbers and letters in an alternating and ascending order (1-A-2-B-3-C- etc). This task measures divided attention as well as processing speed and visual scanning. The tests are scored with the number of seconds spent to complete the tasks, so lower scores indicate better performance.

CWIT. CWIT conditions 3 and 4 ("CWIT-3" and "CWIT-4") are from the D-KEFS (Delis et al., 2001). American norms are used when calculating T-scores, and the norms are corrected for sex and age. CWIT consists of four conditions, which measure different aspects of attention and inhibition. In the first condition, Colour Naming, the participant is asked to name a series of coloured squares. Condition two, Word Reading, consists of reading names of colours printed in black ink. Condition three is Inhibition, and the participants are asked to name the colours of the ink, while the words spell another colour. In the fourth condition, Inhibition/Switching, the participants are asked to read the word if the words are framed and

to name the colour of the ink if the words are not framed. The score is the time used to complete the tasks, so lower scores indicate better performance.

MMSE. The MMSE was designed as a screening test for evaluating cognitive impairment in older adults (Kurlowicz & Wallace, 1999). It gives an indication for cognitive functions and consists of 11 tasks focusing on temporal orientation, spatial orientation, short-term memory, attention and calculation, long-term memory, naming objects, repeating phrases, following three-step commands, writing sentences, reading and copying a drawing. The examination takes between five to ten minutes to complete.

Cognitive Reserve Variables

NART IQ. As a measure of premorbid IQ, this study used test scores on the NART. The NART is a 50-item word list that participants are asked to read out loud (Nelson & Willison, 1991). Correct pronunciation gives higher scores. We used the NART IQ formula presented by Anja Vaskinn et al. (2020) which allows for the same range in IQ scores as a previous recommended formula but without using education as a variable. This formula is suitable for our study, since we use both years of education and NART IQ as independent variables for cognitive reserve,

$$\text{NART IQ} = 129.5 + (\text{NART Errors}*(-.79)) + (\text{Age}*(-.12)).$$

Years of Education. Determining level of education can be simple, but differences in education systems internationally and individual cases of non-traditional education history makes it necessary to have education variables clearly defined. This study uses the definition of years of education used in the Halstead-Reitan Battery (Heaton, 2004). In general, only full years of successfully completed regular academic coursework is counted. Vocational training or coursework are usually not counted in "years of education". This system uses a standard number of years to "code for" degrees or diplomas, no matter how many years the person actually spent completing it: High school diplomas = 12 years, associate degrees = 14 years, bachelor's degrees = 16 years etc. The total amount of years of education was set to twenty years, the equivalent of a completing a doctoral degree.

Career Complexity. This study used the International Standard Classification of Occupation (ISCO) published 1988 (ISCO-88). The ISCO system was developed by the International Conference of Labour Statisticians to facilitate international comparisons of occupational statistics. The classification system consists of ten major occupational groups, each with their own submajor, minor and unit groups. This study sorted the ten major

occupation groups further into the following categories, using the same system as Foubert-Samier et al. (2012):

- 3: Intellectuals (legislators, senior officials, managers, professionals and clerks)
- 2: Mixed (technicians, associate professionals, service workers, shop and market sales workers, agricultural and fishery workers, craft and related trades worker, plant and machine operators and assemblers)
- 1: Elementary: elementary occupations
- 0: No career

The patient profiles were divided into the categories using information of occupational complexity from patient interviews. Every patient had at some point invested time in a career, so category 0 was left out from this study, leaving us with three occupational categories.

Brain Reserve Variables

Total Intracranial Volume. MRI scans were taken three months after stroke at Oslo University Hospital, using a Siemens Espree 1.5 T system. The scans consisted of one MPRAGE 3D sequence and 2D axial FLAIR (Fluid-attenuated inversion recovery) images. For more technical details see Selnes et al. (2015). Using the FreeSurfer image analysis suite version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/), cortical reconstruction and volumetric segmentation analyses were performed on the MRI scans. Of the resulting MR-measures only TICV was used in this study.

Statistics

The Statistical Package for Social Sciences (SPPS), version 28 (IBM Corp, 2021) was used to analyse the data, and R studio version 4.2.0 for visualization of results. Since this is an explorative study and our sample size is small, we used the standard significant levels of $p < .05$ for our analyses.

Testing Group Differences

T-tests are a type of inferential statistic used to determine whether there are significant differences between the mean value of two groups.

This study uses independent sample t-tests to compare patient demographic characteristics (continuous variables) of males and females, and to assess whether there are significant sex differences in EF test scores one week after stroke, three months after stroke and change in EF test scores within the first three months after stroke. For categorical

variables such as career complexity, the Chi-square-test is used to compare male and female demographic characteristics.

Since not all the demographic characteristics fulfil the assumption of normal distribution and due to differences in group sizes, non-parametric Mann Whitney U-test analysis was run for comparison. The independent t-tests and the Mann-Whitney U-tests gave similar results. Therefore, only t-test results are presented in this study.

To estimate effect sizes, Cohen's *d* was used for continuous variables. $d \geq .20$ indicates a small effect, $d \geq .50$ a medium effect and $d \geq .80$ a large effect (Cohen, 1988). Cramer's phi was used to estimate effect sizes for categorical variables. When the number of degrees of freedom is equal to 2, $\phi_c \geq .07$ indicate a small effect, $\phi_c \geq .21$ a medium effect and $\phi_c \geq .35$ a large effect (Cohen, 1988).

Regression Analysis

Since one of the aims of this study was to study possible sex differences in reserve impact on EF after stroke, multiple linear regression was deemed a suitable analysis option. Multiple linear regression is used to study the associations between one continuous dependent variable and two or more continuous and/or categorical independent variables. This allows us to better control for other impacting factors than just reserve variables, such as age and stroke severity in this study. Based on literature, we decided to use age and stroke severity (NIHSS within 24 hours after admission to hospital) as control variables.

After discussing with a statistician what regression methods would be best suited to explore study aim 2, we decided to use split way regression instead of regression with interaction terms. Split way analysis works by splitting the dataset into two groups and running separate regression analyses. This results in simple regression models for each sex:

$$\text{Females EF scores} = \beta_{0\,x} + \beta_1 reserveproxy + \beta_2 age + \beta_3 NIHSS$$

$$\text{Males EF scores} = \beta_{0\,x} + \beta_1 reserveproxy + \beta_2 age + \beta_3 NIHSS$$

To ensure a simple regression model, each reserve measure was individually used as an independent variable together with the control variables age and stroke severity. The EF test scores are the dependent variables. This study uses four EF tests scores at one week after stroke and three months after stroke and change in test scores during the first three months, meaning there are 12 dependent variables in total for each reserve measure. This results in 48 regression models for each sex.

Some of the regression models showed a few outliers. Males had six outliers

distributed across all regression models, and at most two outliers in the same model. Females had a total of two outlies. We compared models with or without outliers included, and most showed similar results with minor changes in β and R^2. The exception was the regression models for change in CWIT-3 scores for females. One female outlier drastically changed the models for the reserve variables years of education, career complexity and TICV. Removing the outliers made the reserve variables non-significant. We decided to include outliers in the data and are aware that this may to some degree weaken our model and affect its validity.

We also considered using multiple linear regression with interaction terms. These models would include a term representing the interaction between sex and reserve proxies (interaction term=sex*reserve proxy). If the interaction term is significant, there is a significant sex difference in how the reserve-proxy impacts EF. This method would therefore be well suited for the second aim of this study. However, preliminary analyses with split way regression indicated that the control variables, especially age, impact males and females differently. The control variables were only significant predictors for one of the sexes for some of the EF tests, and in general explained more data variance for females than for males. Given the unequal sample size for males and females, this is not ideal for regression models with only interacting terms for sex and reserve variables. While this can be corrected for by using interaction terms for the control variables, it would mean a more complex model, which is undesirable given our small sample size. Therefore, split way regression analysis was used in this study.

Correlation Analysis of Reserve Variables

To get a better understanding of the measures used for cognitive and brain reserve and their interaction with each other, we used Pearson and Spearman correlation analysis on the reserve variables. Spearman correlation was used in analyses with the categorical variable career complexity and Pearson correlation was used for the numeric variables NART IQ, education and TICV.

Results

Study Aim 1: Sex Differences in Executive Function after Stroke

Patient Characteristics

Patient and stroke characteristics are presented in Table 1. All participants were of Caucasian descent and spoke a Scandinavian language as their mother tongue. Stroke treatment was completed according to clinical guidelines. None of the patients received specialized cognitive rehabilitation during their first three months after stroke.

There were no significant sex differences in any of the patient characteristics, except for males having significantly bigger TICV than females ($t(77) = -6.02$, $p < .001$, $d = -1.44$).

T-scores for females and males are visualized in Figures 2.1 and 2.2, respectively. As the figures illustrate, female T-scores improve less than males and remain relatively stable from one week to three months. They are also more centred around the mean and show more uniformity compared to male scores, which are more spread out. Female scores on TMT-A and TMT-B are especially clustered compared to males as well as female CWIT-3 and CWIT-4 scores.

Table 1

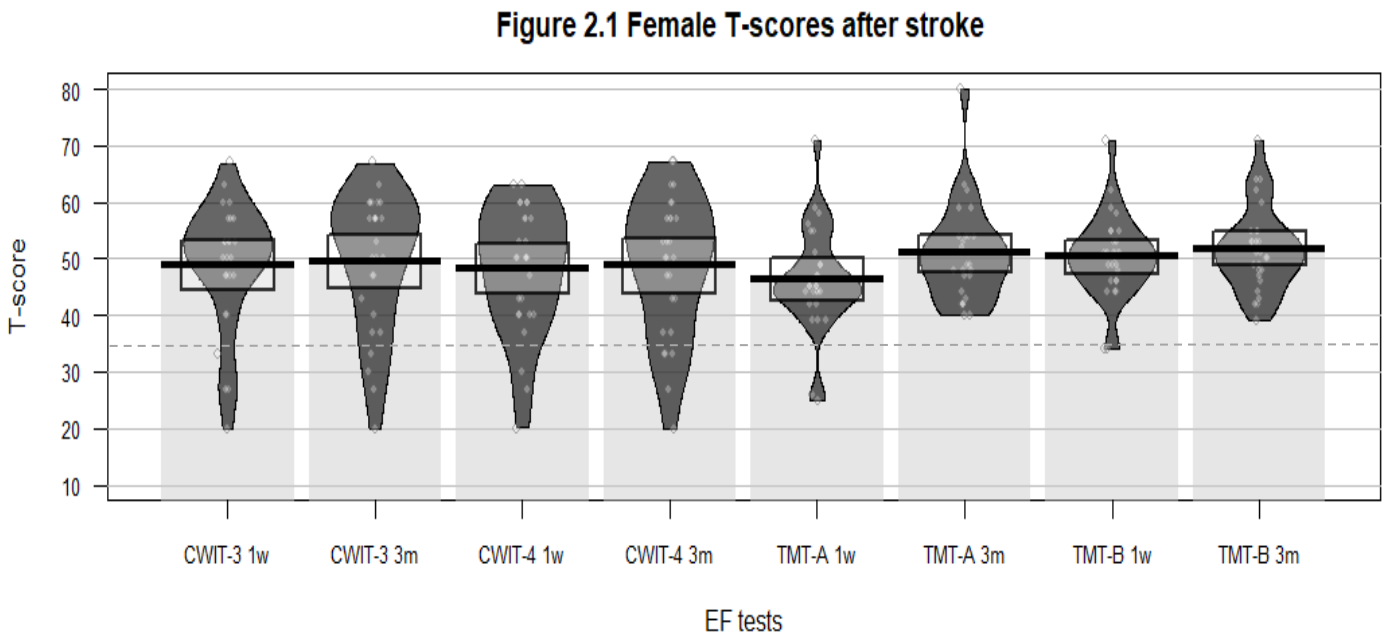
Patient Characteristics and Sex Differences

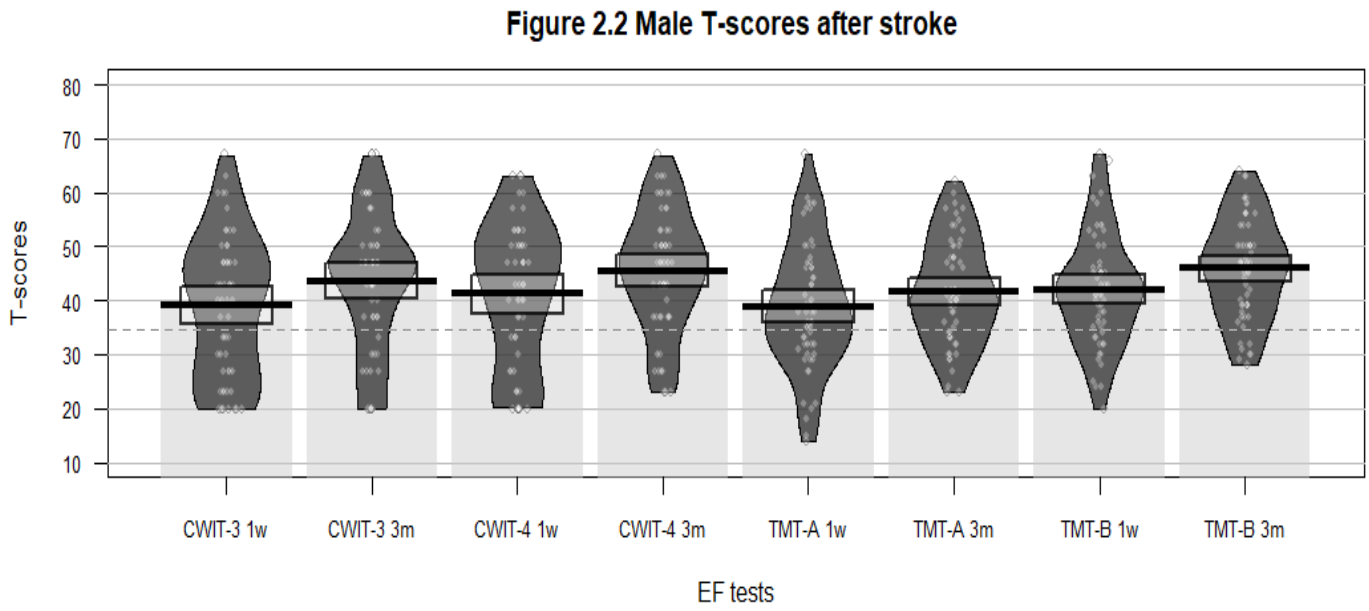
	Total n = 74	Males n = 48	Females n = 26	p	*d*/ ϕ_c
Age M (SD)	64.60 (9.30)	64.08 (9.86)	65.74 (7.99)	.447	.18
Years of education M (SD)	10.97 (2.91)	11.25 (2.86)	10.35 (2.96)	.187	-.31
NART IQ M (SD)	104.97 (8.83)	105.10 (9.15)	104.70 (8.24)	.847	-.05
Career N (%)					
Intellectuals	35 (40.70 %)	23 (65.70 %)	12 (34.30 %)	.727	.09
Mixed	34 (39.50 %)	23 (67.60 %)	11 (32.40 %)		
Elementary	17 (19.80 %)	13 (77.50 %)	4 (23.50 %)		
TICV cm^3 M (SD)	1589630.72 (160708.18)	1652902.78 (141139.50)	1460653.07 (115579.02)	**<.001**	-1.44
MMSE M (SD)	28.39 (1.76)	28.43 (1.87)	28.30 (1.49)	.783	-.07
NIHSS day 1 M (SD)	2.69 (2.58)	3.59 (3.34)	3.56 (3.46)	.962	-.01
NIHSS 3 months M (SD)	.71 (1.57)	.75 (1.72)	.31 (1.01)	.070	-.35
Stroke type N (%)	86	59 (68.60 %)	27 (31.40 %)	.766	.08
Lacunar	49 (57.00 %)	34 (69.40 %)	15 (30.60 %)		
Cortical	36 (41.90 %)	24 (66.70 %)	12 (33.30 %)		
Cerebral/unsure	1 (1.10 %)	1 (100.00 %)	0 (0.00 %)		

Note. Significant results are written in bold to increase readability. Percentages in the male and female columns represent the percentage of males/females for the category in total. For example: 24 males equal 66.70% of total participants with cortical ischemic stroke.

Figures 2.1 and 2.2

Male and Female T-scores on EF Tests One Week and Three Months after Stroke





Note. Pirateplots showing the distribution of T-scores on EF tests for females (2.1) and males (2.2). The pirateplots report individual T-scores as separate data entries. Noise (jitter) was added horizontally to reduce overlap among entries with similar values. The abbreviation 1w and 3m was used for tests taken one week and three months after stroke. T scores were used in order to indicate clinical symptom levels. Horizontal black lines indicate means. Standard deviation of the mean of each domain is indicated as transparent boxes. The dotted grey line represents the cut-off for impaired scores ($T \leq 35$).

Table 2

Patients with Clinical Impairment on EF Tests

		TMT-A	TMT-B	CWIT-3	CWIT-4
1 week					
Males	Impaired, n (%)	24 (40.70 %)	17 (28.80 %)	23 (39.00 %)	18 (30.50 %)
Females	Impaired, n (%)	2 (7.10 %)	2 (7.40 %)	4 (14.80 %)	3 (11.10 %)
3 months					
Males	Impaired, n (%)	17 (28.80 %)	8 (13.60 %)	14 (23.70 %)	9 (15.30 %)
Females	Impaired, n (%)	0 (0.00 %)	0 (0.00 %)	4 (14.80 %)	5 (18.50 %)

Note. The table shows how many female and male participants score T ≤ 35 on one or more of the EF tests.

Impaired Executive Function after Stroke

As shown in Table 2, males are more likely than females to experience EF impairment one week after stroke. Three months after stroke the sex differences in EF impairment have shrunk, but males are still more likely to experience clinical impairment in EF. Females did show an increase of impaired patients on CWIT-4 and an unchanged number of impaired patients on CWIT-3 three months after stroke.

Executive Function Scores One Week and Three Months after Stroke

Independent sample t-tests were performed to explore significant sex differences in test scores at one week and three months after stroke. While the means and standard distribution of ages in the male and female groups are not significantly different, the sexes have different norms for T-scores. For this reason, we compared independent t-test results using T-scores and raw scores.

As Figures 2.1, 2.2 and 3 illustrate, males have lower EF scores on all tests compared to females both one week and three months after stroke.

Males have significantly lower T-scores on all EF tests compared to females one week after stroke (TMT-A: $t(84) = 2.86$, $p = .005$, $d = .66$, TMT-B: $t(74.61) = -4.21$, $p < .001$, $d = .84$, CWIT-3: $t(82) = 3.34$, $p = .001$, $d = .78$, CWIT-4: ($t(82) = 2.34$, $p = .022$, $d = .55$). As Figure 3 shows, independent sample t-tests using raw scores show similar results except for CWIT-4 where the sex difference is not significant.

Three months after stroke, females scored significantly better on TMT-A ($t(84) = 4.24$, $p < .001$, $d = .98$) and TMT-B ($t(84) = 2.83$, $p = .006$, $d = .66$) compared to males. Female

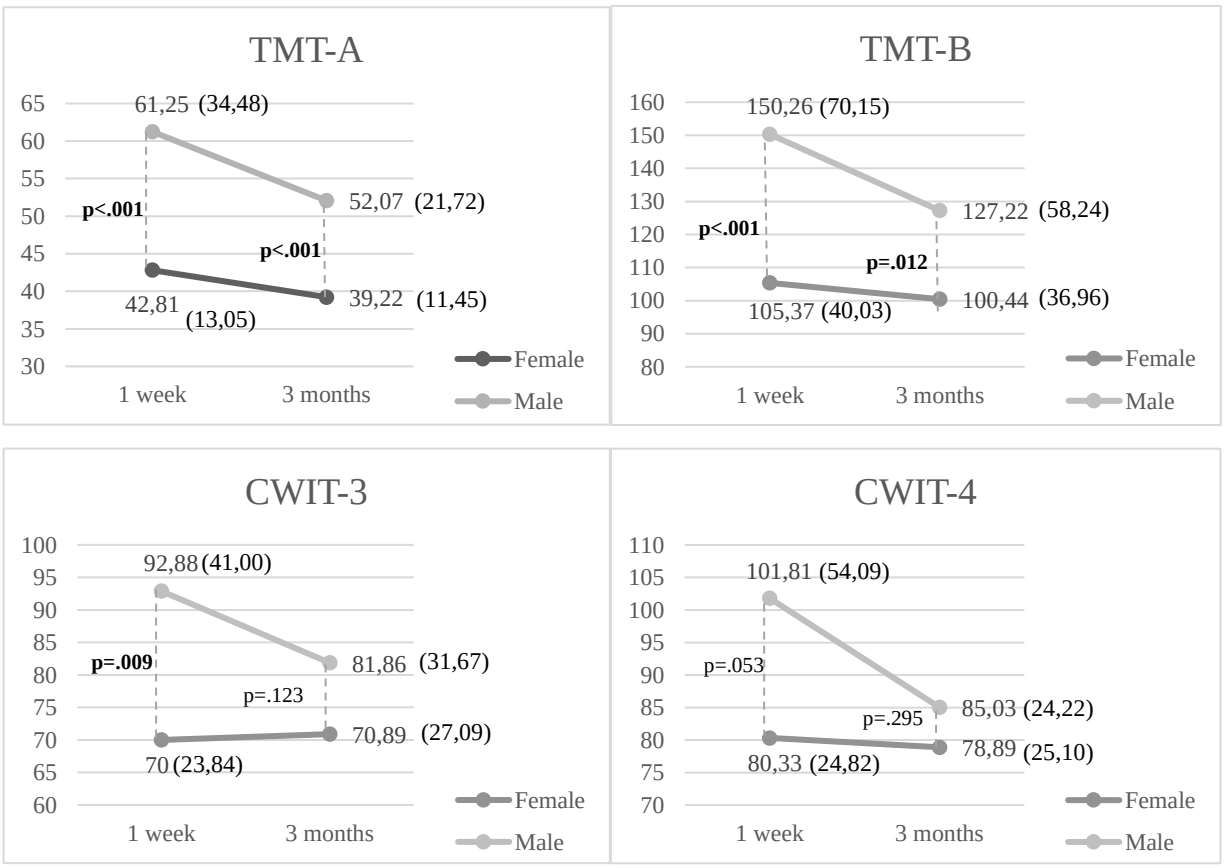
scores were also higher than males on CWIT-3 and CWIT-4 three months after stroke, but the differences are not significant for either raw scores or T-scores.

Change in Executive Function after Stroke

Independent sample t-tests were also used to check for significant sex differences in how much the EF scores changes or improves during the first three months. Males show significantly more improvement in measures of EF during the first three months compared to females, except for TMT-A where the differences between the sexes are non-significant. Cohen's *d* showed medium effect sizes for TMT-B and CWIT-3 and small effect size for CWIT-4.

Figure 3

Male and Female Scores on EF Tests after Stroke and Sex Differences



Note. The figure shows mean and standard deviation for male and female raw scores on EF tests one week and three months after stroke. The stapled lines and adherent p-value indicates significant sex differences in test scores. Significant results are written in bold to increase readability.

Table 3

Sex Differences in EF Change During the First Three Months after Stroke

EF tests	Males M (SD), N	Females M (SD), N	*t*	*df*	*p*	*d*
TMT-A	9.19 (24.84), 59	3.59 (12.25), 27	1.11	84	.271	.26
TMT-B	25.03 (33.99), 58	4.93 (22.94), 27	2.79	83	**.007**	.65
CWIT-3	14.02 (22.13), 57	-.89 (24.66), 27	2.78	82	**.007**	.65
CWIT-4	17.54 (43.00), 57	1.44 (14.52), 27	1.89	82	**.013**	.44

Note. Significant scores are written with bold to increase readability. Independent sample t-test of sex differences when measuring change in EF scores during the first three months after stroke. Change scores are calculated by subtracting raw test scores at one week after stroke from raw test scores three months after stroke (EF three months- EF one week). Raw scores (times spent on task) used.

Study Aim 2: Sex differences in the Impact of Reserve on Executive Function

Multiple linear regression was used to test if NART IQ, education, career complexity and TICV significantly predicted EF at one week, three months after stroke and change in EF from one week to three months.

Cognitive Reserve Variables

NART IQ as a Predictor for Executive Function. Table 4.1 shows the regression results of using NART IQ as a predictor for EF tests. NART IQ is a positive and significant predictor for male scores on all EF tests three months after stroke and for TMT-A and TMT-B one week after stroke. For females, NART IQ is a positive and significant predictor for TMT-B one week after stroke and for TMT-A and TMT-B three months after stroke. NART IQ is not a significant predictor for any of the change variables for either males or females. Regression models with NART IQ explain a higher percentage of data variance for females than males.

Age is a significant predictor for female TMT-A (β = -.57, p = .001), TMT-B (β = -.46, p = .006) and CWIT-3 (β = .40, p = .036) scores one week after stroke, and for TMT-B (β = -.46, p = .005) three months after stroke. NIHSS is not a significant predictor for females. Age was a significant predictor for male TMT-B (β = -.26, p = .036) scores one week after stroke, and for TMT-A (β = -.25, p = .043), TMT-B (β = -.34, p = .003) and CWIT-3 (β = -.27, p = .039) scores three months after stroke. NIHSS is not a significant predictor for males.

Table 4.1

NART IQ as a Predictor for EF Scores after Stroke

	Females						Males					
EF tests	**N**	**B(SE)**	**Beta**	**Sig.**	**95 %CI**	**R^2 (p)**	**N**	**B(SE)**	**Beta**	**Sig.**	**95 %CI**	**R^2 (p)**
1 week after stroke												
TMT-A	27	.30 (.25)	.19	.249	-.22,.82	**.48 (.002)**	58	**1.29 (.45)**	**.37**	**.006**	**.39, 2.19**	**.23 (.002)**
TMT-B	**27**	**2.16 (.73)**	**.45**	**.007**	**.63, 3.68**	**.53 (<.001)**	57	**2.96 (.90)**	**.40**	**.002**	**1.16, 4.75**	**.33 (<.001)**
CWIT-3	27	.83 (.53)	.29	.127	-.26, 1.92	**.32 (.030)**	56	.32 (.64)	.07	.625	-.98, 1.61	.10 (.140)
CWIT-4	27	.87 (.61)	.29	.167	-.39, 2.13	.16 (.268)	56	.90 (.87)	.15	.307	-.85, 2.64	.09 (179)
3 months after stroke												
TMT-A	27	**.54 (.25)**	**.39**	**.043**	**.02, 1.06**	**.32 (.029)**	58	**.89 (.27)**	**.41**	**.002**	**.43, 1.43**	**.29 (<.001)**
TMT-B	27	**2.03 (.67)**	**.45**	**.006**	**.65, 3.41**	**.54 (<.001)**	58	**2.90 (.69)**	**.47**	**<.001**	**1.51, 4.28**	**.44 (<.001)**
CWIT-3	27	1.58 (.62)	.48	.019	.29, 2.87	.26 (.074)	58	**1.06 (.45)**	**.31**	**.022**	**.16, 1.96**	**.22 (.003)**
CWIT-4	27	1.18 (.59)	.39	.056	-.03, 2.39	.23 (.102)	57	**1.05 (.35)**	**.40**	**.004**	**.36, 1.75**	**.23 (.003)**
Change in test scores (3 months - 1 week results)												
TMT-A	27	.24 (.31)	.16	.435	-.39, .88	.12 (.384)	58	-.40 (.39)	-.15	.305	-1.18, .38	.04 (.514)
TMT-B	27	-.13 (.61)	-.05	.834	-1.39, 1.13	.01(.982)	57	-.25 (.50)	-.07	.627	-1.25, .76	**.16 (.026)**
CWIT-3	27	.75 (.55)	.25	.186	-.38, 1.87	**.31 (.033)**	56	.39 (.36)	.16	.283	-.22, 1.11	.07 (.311)
CWIT-4	27	.31 (.37)	.18	.404	-.45, 1.07	.10 (.472)	56	.10 (.72)	.02	.895	-1.35, 1.54	.04 (.595)

Note. Separate models for each sex. Controlling for age and NIHSS. Significant models and significant reserve proxies are written in bold to make the results easier to read. B, beta, p, CI refer only to the specific predictor, R^2 indicates the amount of variance explained by the whole model, i.e., with all predictors included.

Education as a Predictor for Executive Function. Table 4.2 shows education as a predictor for EF tests after stroke. For females, education is a significant positive predictor for TMT-B at one week and a positive predictor for all executive tests three months after stroke. It is also a small positive predictor for change in CWIT-3 scores for females. Education is not a significant predictor for males.

Age is a significant predictor for female TMT-A ($\beta = -.50$, $p = .013$) scores one week after stroke. NIHSS is a significant predictor for female CWIT-3 ($\beta = .37$, $p = .034$) scores three months after stroke. Age was a significant predictor for male TMT-A ($\beta = -.34$, $p = .007$), TMT-B ($\beta = -.40$, $p = .001$), CWIT-3 ($\beta = -.31$, $p = .019$) and CWIT-4 ($\beta = -.26$, $p = .050$) scores one week after stroke, and for TMT-A ($\beta = -.41$, $p = .001$), TMT-B ($\beta = -.50$, $p < .001$), CWIT-3 ($\beta = -.39$, $p = .003$) and CWIT-4 ($\beta = -.29$, $p = .029$) scores three months after stroke. NIHSS is not a significant predictor for males.

Regression models with education explains a higher percentage of data variance for females than males.

Table 4.2

Education as a Proxy for EF Scores after Stroke

		Females						Males				
EF tests	**N**	**B(SE)**	**Beta**	**Sig.**	**95 %CI**	**R^2 (p)**	**N**	**B(SE)**	**Beta**	**Sig.**	**95 %CI**	**R^2 (p)**
1 week after stroke												
TMT-A	27	.98 (.84)	.22	.254	-.75, 2.71	**.48 (.002)**	59	2.28 (1.50)	.19	.135	-.74, 5.30	**.18 (.013)**
TMT-B	27	**7.73 (2.36)**	**.57**	**.003**	**2.85, 12.61**	**.56 (<.001)**	58	4.62 (2.94)	.19	.122	-1.27, 10.52	**.24 (.002)**
CWIT-3	27	3.33 (1.70)	.41	.063	-.20, 6.85	**.35 (.018)**	57	-3.05 (1.87)	-.21	.109	-6.80, .71	**.15 (.033)**
CWIT-4	27	2.82 (2.02)	.34	.177	-1.37, 7.01	.15 (.278)	56	-3.22 (2.53)	-.17	.209	-8.30, 1.86	.11 (.111)
3 months after stroke												
TMT-A	27	**2.93 (.68)**	**.76**	**<.001**	**1.52, 4.34**	**.55 (<.001)**	59	.92 (.94)	.12	.332	-.96, 2.79	**.20 (.007)**
TMT-B	27	**7.08 (2.18)**	**.57**	**.004**	**2.58, 11.58**	**.56 (<.001)**	59	2.92 (2.35)	.14	.219	-1.79, 7.64	**.30 (<.001)**
CWIT-3	27	**6.99 (1.83)**	**.77**	**<.001**	**3.21, 10.78**	**.42 (.005)**	59	.35 (1.40)	.03	.802	-2.45, 3.15	**.16 (.022)**
CWIT-4	27	**4.86 (1.85)**	**.57**	**.015**	**1.03, 8.69**	**.31 (.036)**	58	-.44 (1.11)	-.05	.697	-2.67, 1.80	.11 (.103)
Change in test scores (3 months - 1 week results)												
TMT-A	27	1.95 (.95)	.47	.050	-.00, 3.91	.24 (.093)	59	-1.36 (1.16)	-.16	.246	-3.70, .97	.05 (.394)
TMT-B	27	-.65 (2.02)	-.09	.749	-4.83, 3.53	.01 (.973)	58	-1.75 (1.50)	-.15	.248	-4.77, 1.26	**.16 (.026)**
CWIT-3	27	**3.67 (1.72)**	**.44**	**.044**	**.10, 7.23**	**.38 (.011)**	57	2.21 (1.03)	.28	.035	.16, 4.27	.13 (.067)
CWIT-4	27	2.04 (1.16)	.42	.093	-.37, 4.44	.18 (.192)	56	2.44 (2.06)	.16	.242	-1.70, 6.58	.06 (.342)

Note. Separate models for each sex. Controlling for age and NIHSS. Significant models and significant reserve proxies are written in bold to make the results easier to read. B, beta, p, CI refer only to the specific predictor, R^2 indicates the amount of variance explained by the whole model, i.e., with all predictors included

Career Complexity as a Predictor for Executive Function. For females, career complexity is a significant positive predictor for change in TMT-A and CWIT-3. It is also a positive significant predictor for TMT-A three months after stroke. For males, career complexity is not a significant predictor for any of the tests. Regression models with career complexity, age and NIHSS explains a higher percentage of data variance for females than males.

Age is a significant predictor for female TMT-A ($\beta = -.64$, $p < .001$), TMT-B ($\beta = -.59$, $p = .002$) and CWIT-3 ($\beta = -.49$, $p = .011$) scores one week after stroke, and for TMT-A ($\beta = -.39$, $p = .026$) and TMT-B ($\beta = -.59$, $p = .002$) scores three months after stroke. NIHSS is not a significant predictor for females. Age was a significant predictor for male TMT-A ($\beta = -.25$, $p = .043$), TMT-B ($\beta = -.34$, $p = .003$) and CWIT-3 ($\beta = -.27$, $p = .039$) scores one week after stroke, and for TMT-A ($\beta = -.45$, $p<.001$), TMT-B ($\beta = -.55$, $p < .001$), CWIT-3 ($\beta = -.39$, $p = .003$) and CWIT-4 ($\beta = -.28$, $p = .037$) scores three months after stroke. NIHSS is not a significant predictor for males.

Table 4.3

Career Complexity as a Proxy for EF Scores after Stroke

	Females						Males					
EF tests	**N**	**B(SE)**	**Beta**	**Sig.**	**95 %CI**	**R^2 (p)**	**N**	**B(SE)**	**Beta**	**Sig.**	**95 %CI**	**R^2 (p)**
1 week after stroke												
TMT-A	27	-2.92 (2.81)	-.16	.308	-8.73, 2.88	**.47 (.002)**	58	5.93 (5.65)	.13	.299	-5.40, 17.26	**.16 (.022)**
TMT-B	26	2.85 (9.52)	.05	.767	-16.84, 22.54	**.35 (.017)**	58	15.18 (11.02)	.16	.204	-7.92, 36.27	**.23 (.003)**
CWIT-3	27	-5.27 (6.03)	-.16	.391	-17.75, 7.21	.27 (.064)	57	-4.55 (6.96)	-.09	.516	-18.51, 9.41	.17 (.087)
CWIT-4	27	1.28 (7.03)	.04	.857	-13.26, 15.83	.08 (.575)	57	-6.40 (9.33)	-.09	.945	-25.11, 12.31	.09 (.181)
3 months after stroke												
TMT-A	**27**	**6.75 (2.72)**	**.43**	**.021**	**1.14, 12.37**	**.36 (.016)**	59	3.96 (3.47)	.14	.258	-2.99, 10.92	**.20 (.006)**
TMT-B	27	6.59 (8.66)	.13	.455	-11.34, 24.51	**.37 (.013)**	59	12.5 (8.71)	.17	.155	-4.89, 30.00	**.30 (<.001)**
CWIT-3	27	9.23 (7.57)	.25	.235	-6.42, 24.88	.11 (.450)	59	-1.08 (5.20)	-.03	.837	-11.49, 9.34	**.16 (.023)**
CWIT-4	27	8.93 (6.80)	.26	.202	-5.13, 22.98	.16 (.250)	58	-.91 (4.10)	-.03	.826	-9.14, 7.32	.11(.107)
Change in test scores (3 months - 1 week results)												
TMT-A	27	**9.68 (2.78)**	**.57**	**.002**	**3.92, 15.43**	**.41 (.006)**	59	-1.97 (4.37)	-.06	.654	-10.73, 6.79	.03 (.611)
TMT-B	27	3.74 (6.71)	.12	.583	-10.15, 17.63	.02 (.932)	58	-2.25 (5.65)	-.05	.692	-13.58, 9.08	**.14 (.045)**
CWIT-3	27	**14.51 (5.52)**	**.43**	**.015**	**3.09, 25.92**	**.43 (.005)**	57	4.77 (3.84)	.17	.220	-2.93, 12.48	.08 (.242)
CWIT-4	27	7.64 (3.81)	.38	.057	-.24, 15.53	.21 (.134)	57	6.22 (7.58)	.11	.415	-8.97, 21.42	.05 (.454)

Note. Separate models for each sex. Controlling for age and NIHSS. Significant models and significant reserve proxies are written in bold to make the results easier to read. B, beta, p, CI refer only to the specific predictor, R^2 indicates the amount of variance explained by the whole model, i.e., with all predictors included

Brain Reserve Variables

Total Intracranial Volume as a Predictor for Executive Function. For females, TICV is a significant and positive predictor for change in CWIT-3. It was not a significant predictor for males. Regression models with TICV, age and NIHSS explains a higher percentage of data variance for females than males.

Age is a significant predictor for female TMT-A ($\beta = -.64$, $p = .001$), TMT-B ($\beta = -.55$, $p = .009$) and CWIT-3 ($\beta = -.51$, $p = .016$) scores one week after stroke. NIHSS is not a significant predictor for females. Age was a significant predictor for male TMT-A ($\beta = -.39$, $p = .005$), TMT-B ($\beta = -.45$, $p < .001$) and CWIT-3 ($\beta = -.31$, $p = .029$) scores one week after stroke, and for TMT-A ($\beta = -.41$, $p = .001$), TMT-B ($\beta = -.50$, $p < .001$), CWIT-3 ($\beta = -.39$, $p = .003$) and CWIT-4 ($\beta = -.29$, $p = .029$) scores three months after stroke. NIHSS is not a significant predictor for males.

Table 4.4

TICV as a Proxy for EF Scores after Stroke

	Females					Males				
EF tests	**N**	**Beta**	**Sig.**	**95 %CI**	**R^2 (p)**	**N**	**Beta**	**Sig.**	**95 %CI**	**R^2 (p)**
1 week after stroke										
TMT-A	26	-.14	.430	.00, .00	**.44 (.005)**	53	-.11	.411	.00,.00	**.15 (.042)**
TMT-B	26	.03	.130	.00, .00	**.31 (.040)**	52	-.07	.621	.00, .00	**.22 (.007)**
CWIT-3	26	.06	.775	.00, .00	.28 (.059)	51	-.14	.303	.00, .00	.13 (.083)
CWIT-4	26	.34	.121	.00, .00	.16 (.259)	51	-.02	.870	.00, .00	.09 (.198)
3 months after stroke										
TMT-A	26	.27	.206	.00, .00	.21 (.157)	53	-.11	.440	.00, .00	**.16 (.040)**
TMT-B	26	.27	.156	.00, .00	**.38 (.013)**	53	-.05	.723	.00, .00	**.25 (.003)**
CWIT-3	26	.45	.037	.00, .00	.22 (.133)	53	-.07	.623	.00, .00	**.15 (.040)**
CWIT-4	26	.44	.044	.00, .00	.22 (.142)	52	-.18	.193	.00, .00	.12 (.102)
Change in test scores (3 months - 1 week results)										
TMT-A	26	.38	.069	.00, .00	.25 (.091)	53	.07	.643	.00, .00	.06 (.422)
TMT-B	26	.38	.094	.00, .00	.13 (.392)	52	.06	.675	.00, .00	**.16 (.032)**
CWIT-3	26	**.44**	**.017**	**.00, .00**	**.45 (.004)**	51	.11	.427	.00, .00	.08 (.280)
CWIT-4	26	.15	.495	.00, .00	.08 (.585)	51	-.06	.663	.00, .00	.07 (.364)

Note. Separate models for each sex. Controlling for age and NIHSS. Significant models and significant reserve proxies are written in bold to make the results easier to read. B, beta, p, CI refer only to the specific predictor, R^2 indicates the amount of variance explained by the whole model, i.e., with all predictors included

Correlations Between Brain Reserve and Cognitive Reserve Variables

Correlations results between brain reserve and cognitive reserve variables for both sexes are displayed in Table 5. The results show that cognitive reserve variables NART IQ, years of education and career complexity had a small to medium correlation to each other. The cognitive reserve variables NART IQ and years of education has a medium positive correlation ($p < .001$). Career complexity have a small, positive correlation to both NART IQ ($p = .003$) and years of education ($p < 001$). Similar results were found when running correlation analysis for the sexes separately, though the significant correlation between career complexity and NART IQ were not found for females.

The brain reserve variable TICV was not significantly correlated to any of the cognitive reserve variables.

Table 5

Correlation between Reserve Variables

	NART IQ	Education	TICV
Career (Total)	**.32**	**.49**	-.02
(M, F)	**(.36**, .18**)**	**(.53, .44)**	(.01, .23)
NART IQ (Total)		**.64**	.06
(M, F)		**(.61, .44)**	(.05, .12)
Education (Total)			.19
(M, F)			(.14, .17)

Note. Pearson correlation is used for analyses containing just NART IQ, education and TICV. Spearman's correlation is used for correlations including the variable career complexity. The (M, F) rows show correlation between the reserve variables for males and females respectively. Significant results are written in bold.

Discussion

Sex Differences in Executive Function after Stroke

This study sought to explore possible sex differences in EF after ischemic stroke. The results of our analyses imply that males experience significantly more EF impairment the first week after stroke compared to females. The sex differences in EF scores are not significant three months after stroke. Males show more improvement of EF during the first three months, and three months after stroke there are fewer male patients with clinically impaired EF scores. Female test scores remain comparably stable during the first three months after stroke, and the female patients with impaired T-scores on TMT-A and TMT-B at one week did no longer qualify as impaired three months after stroke. The number of impaired female patients measured by CWIT-3 did not change, but there was an increase of impaired patients measured by CWIT-4 (from three to five patients). CWIT-4 is a more challenging task compared to CWIT-3 and it measures different function (Switching/Inhibition vs Inhibition). If the patients' fall in EF is small, it is likely to be noticed first by CWIT-4, being the more complex task of the two.

The EF tests show differing numbers of impaired participants. This could be related to differences in test sensitivity, or it could be tied to survivors experiencing impairment of specific abilities measured more efficiently by either test. TMT-A and TMT-B also require functioning motor abilities and CWIT requires the ability to read and speak unhindered. Any difficulties with these functions would impact test scores.

Previous studies have looked at sex differences in TMT-A and TMT-B using healthy participants, and while females might be somewhat quicker than males, sex is currently not thought to significantly impact test scores (Foroozandeh, 2014; Tombaugh, 2004; Zec et al., 2015). CWIT have norms corrected for both sex and age, but as the t-test analysis using T-scores showed, the differences between males and females were still prevalent at one week after stroke. The sex differences in EF scores after stroke should therefore not be dismissed as a premorbid sex difference in EF.

Research on sex differences in cognitive impairment after stroke remains inconclusive. Our results support studies such as Yamamoto et al. (2011) who found that males had a higher risk of cognitive impairment after stroke (impairment defined as MMSE $\leq$ 24, no specification of time after stroke) and Cho et al. (2014) who found that males have a higher likelihood of memory impairment three months after stroke compared to females. This also aligns with some studies on traumatic brain injury (TBI). Niemeier et al. (2007) studied TBI

and their results indicated a female advantage in EF following TBI. However, the literature on sex differences in cognition after stroke is inconclusive. Our results contrast with Mellon et al. (2015) and Lobo et al. (2000). Mellon et al. (2015) found that females had a higher risk of experiencing cognitive impairment six months post-stroke. Lobo et al. (2000) concluded in their review of post-stroke dementia that females had a higher risk of developing post-stroke dementia than males. The reasoning for the differing results is still unclear, maybe because the interaction between sex and cognitive function after stroke is complex and affected by multiple factors such as age, time after stroke and cognitive and brain reserve.

Our results indicate that females may be better protected than males from EF impairment after mild ischemic strokes during the first three months after stroke, and that the effect of this protection might be especially prominent the first few weeks after the stroke. Since our participants had no significant sex differences in NART IQ, our findings are likely not solely explained by different premorbid cognitive function.

Future research with bigger samples is needed to study this possible female specific protective effect and how factors such as stroke severity and recovery time after stroke affect the interaction between sex and cognition. It will also be important to further study how this seemingly sex-specific protection affects female EF recovery if the survivor experiences significant impairment. Our data were less suited for this since few female survivors experienced clinical levels of impairment (T-scores ≤ 35).

Why females and males differ in EF scores and change in EF scores during the first three months after stroke is unknown. As shown in Table 1, males experience slightly more severe strokes (measured by NIHSS day one after stroke). The difference in stroke severity is not significant, but more severe stroke would explain at least partly why males suffer more EF impairment the first week and show more improvement compared to females. Other possible reasons for the difference in EF is statistical coincidence, differences in biology and hormones, emotional symptoms or even cultural differences impacting strategies and ways of thinking during testing. Sex-specific genetic, hormonal and neurotrophic factors are associated with cognitive function and have been suggested as possible reasons for sex differences in cognition after stroke (Cheng & Hurn, 2010; Galea et al., 2017; Hamson et al., 2016; Khattab et al., 2020; Oertelt-Prigione, 2012). The theory of differences in biology causing the EF differences after stroke has some support in research. It has also been found that females have increased volume in the frontal regions and higher inter hemispheric connectivity compared to males (Ingalhalikar et al., 2014; Matsui et al., 2000). It is also well established that the function of the prefrontal cortex is enhanced by estrogen (Keenan et al.,

2001; Maki & Dumas, 2009; Shanmugan & Epperson, 2014). There is also some evidence showing that sex affects secondary stroke responses such as inflammation and swelling which might impact sex differences in cognition, especially the first few weeks after stroke (Spychala et al., 2017).

Another possibility is that males are better able to compensate for EF impairment after stroke, seeing as they show more improvement during the first three months after stroke and have lower risk of developing post-stroke dementia (Lobo et al., 2000). Some studies in AD and MCI research have found results indicating that males' cognition is generally better protected from brain pathology than females' (Koran et al., 2017; Perneczky et al., 2007). It would be interesting to investigate whether males are more likely to regain cognition function compared to females after stroke because of a biological, innate male-specific reserve. Seeing the low rate of female EF impairment and general high scores compared to males in our study, our data do not support the indications of Perneczky et al. (2007) and Koran et al. (2017). However, we did see an increase of impaired female participants on CWIT-4 from one week to three months. This could indicate that females are less able to recover from EF impairment, especially regarding switching/inhibition tasks. More research is needed to clarify.

Varying results in sex differences in research on cognition after stroke can be an indication of multiple factors impacting the relationship of sex on cognition after stroke. Our findings could be the result of a smaller female sample not representing the full range of female impairment and recovery. They could also be related to the severity of stroke represented in our sample. However, since the majority of the Norwegian stroke population experience mild strokes and the NIHSS in our cohort is similar to the severity of the general Norwegian stroke population (Fjærtoft et al., 2021), the analysed sample and results are therefore generalizable. It is possible that females can compensate better than males when the stroke is mild, but experience more severe cognitive impairment if the stroke is moderate or severe. Time passed since stroke could also be a factor impacting sex differences, especially considering how our research showed sex differences one week after stroke, but not three months after stroke. More research is needed to clarify possible factors regarding sex differences in stroke and their underlying mechanisms. It is also important to keep in mind that the design of stroke studies vary and how this makes it difficult to accurately compare the results.

Sex Differences in the Impact of Reserve

This study also looked at possible sex differences in the interaction between different reserve variables and EF post-stroke. Our results indicated that NART IQ is a good predictor for EF three months after stroke for males and that education is a good predictor for EF three months after stroke for females. There was some support for career complexity as a reserve predictor for female EF scores, but not for males. There was little support for TICV as a predictor for EF after stroke for either sex.

NART IQ

NART IQ was significantly associated with all EF scores three months after stroke and with TMT-A and TMT-B scores one week after stroke for males. NART IQ was a significant predictor for female TMT-A and TMT-B scores three months after stroke and for TMT-B one week after stroke. NART IQ seemed to be a predictor for TMT-A and TMT-B regardless of sex. This study extends previous research, since none of the studies we found using NART IQ or other measures of premorbid IQ as a predictor for cognitive function after stroke included sex differences in their study (Alexander et al., 1997; Green et al., 2008; Makin et al., 2018; Vaskinn et al., 2020).

Education

Education was not a significant predictor for any EF tests for males. For females, it was a significant predictor for all EF tests at three months after stroke and for TMT-B one week after stroke. This trend is especially interesting for two reasons: 1) Males in this study have higher education than the females (non-significant difference), and 2) the education level in this study is low (somewhat artificially because of the classification method used, but also because older generations generally have shorter education compared to younger generations (Statistisk sentralbyrå, 2022)). Still, these results support current research where females have shown to be more affected by the neuroprotective effect of education compared to males (Koran et al., 2017; Launer et al., 1999; Letenneur et al., 2000; Pradier et al., 2014). It is difficult to say why males do not share the same protective benefit of education regarding EF. It could be related to the findings of Malpetti et al. (2017), who found that education and occupation complexity causes metabolic increase in different areas of the brain for males and females. Since females show increased activity in the anterior limbic-affective and executive networks and males show increase in the posterior associate cortices, it is possible that the observed differences are limited to EF and not general cognitive function. However, certain

studies in AD research indicate that male cognition is generally better protected from brain pathology than females', but that higher education reduces the differences between the sexes (Koran et al., 2017; Perneczky et al., 2007; Wang et al., 2020). Culture and gender expectations could also be an impacting factor. Males have historically had better opportunities to develop other reserve-benefitting skills such as practical skills, intellectual interests, hobbies and occupational advancements without it being tied to level of education. Interestingly, studies on mortality in Norway have shown that education increases lifetime expectancy and health for both males and females, but the protective effect is more noticeable in males with high level of education compared to females. Future studies looking into possible sex differences in how education is associated to cognitive function and physical health after stroke in older adults would be of interest.

Career Complexity

The career complexity variable showed no clear trends for any of the sexes. Career complexity was a significant predictor for TMT-A scores at three months after stroke and for change in TMT-A and CWIT-3 scores for females, but it was not a significant predictor for EF scores after stroke for males. However, as mentioned in the chapter Method, regression analysis without outliers found that career complexity was not a significant predictor for change in CWIT-3. Therefore, it is possible career complexity is positively associated with recovery of processing speed/attention for females, but more research is needed.

Career is closely tied to socioeconomic status. Arrich et al. (2005) found that low socioeconomic status was associated with increased morbidity and mortality after stroke. They also found that people who retired early had a significantly higher risk of dying from stroke than those who had not. Socioeconomic status can impact many factors important to one's health, such as stable housing, health care availability, quality of received health care, response time of emergency personnel as well as personal support systems and their resources (Hsia et al., 2018; Nelson, 2002; Pinquart & Sörensen, 2000; Weyers et al., 2008). A longitudinal study of a Canadian population studied sex differences in socioeconomical inequalities in health and found that while both sex and changes in socioeconomical positions (SEP) impacted health, there were no significant sex differences in the interaction of sex and SEP and their impact on health (Luchenski et al., 2008). In their study, females suffered poorer health compared to males. Norway is known for its high standards of living, but research show pervasive social inequalities in health and mortality connected to both socioeconomic status and level of education (Kravdal et al., 2015; Steingrímsdóttir et al.,

2012; Strand et al., 2010). The social differences are increasing in Norway, especially for females (Kravdal et al., 2015). It is possible that the increasing differences in SEP among Norwegian females is a contributing factor as to why reserve variables explain more data variance for females compared to males. More research on this topic is needed.

Total Intracranial Volume

TICV was a significant predictor for change in TMT-A for females but was otherwise not a significant predictor. The significance was likely caused by a female outlier, so the model has low validity. Our results do not support TICV as a possible association between TICV and EF. However, our recent abstract submitted to the WSC conference found a positive association between TICV and EF three months after stroke, but only in patients with impaired EF scores one week after stroke (Kliem, Roaldsnes & Grambaite, 2022). It is possible that the effect of reserve is best measured when there are clear or clinical signs of impairment after stroke. This may be especially important to keep in mind when studying cases of mild stroke, where cognitive and motor impairment might not be as prominent as in more severe stroke cases.

Because of the general lack of female EF impairment and change in EF scores from one week to three months we must be careful when interpreting the regression results for females. Lack of change in EF means that our regression models are more likely to analyse how reserve variables impact normal distribution of EF and not how specific reserve variables impact EF after stroke. Future studies would benefit from finding ways to differentiate between lack of impairment vs lack of cognitive improvement. Performing similar regression analysis using data where both sexes show impaired EF could also be beneficial.

Correlation Among Cognitive and Brain Reserve Variables

Our results show that the correlation between reserve variables is similar for males and females, though females had no significant correlation between career complexity and NART IQ. The reserve variables show a small to medium positive correlation to each other, but there was no significant correlation between the cognitive reserve and brain reserve variables. This supports Stern et al. (2020) suggestion to differentiate cognitive and brain reserve.

Strengths

Our study focuses on both sex differences in EF post-stroke, and the impact of reserve variables on EF. These are topics that have received little attention in stroke research, and the topic of sex differences in reserve impact is especially overlooked. We therefore hope this

study can help bridge the gap in knowledge and draw attention to the topic. Historically, sex has been overlooked as a biological variable in biomedical research. Not reporting sex or including only one sex in preclinical and clinical studies is considered a widespread problem (Sugimoto et al., 2019). A quantitative assessment of the biomedical literature published in 2009 found a bias of only using males (Beery & Zucker, 2011). It is only very recently, in 2016, that The National Institutes of Health (NIH) implemented a policy requiring the consideration of sex as a biological variable in the design, analysis and reports of all preclinical research founded by the NIH (Clayton & Tannenbaum, 2016; NIH, 2015). Stroke research is one of the many research topics prone to a male bias (Tsivgoulis et al., 2017). Studies of sex differences in cognition after stroke have found varying results and studies on sex differences in reserve and stroke research are especially sparse. We therefore consider our focus on sex differences a strength.

Another strength of this study is the use of longitudinal data. This allows for the observation of changes in EF. It is well established that patients experience changes in cognitive function for up to two years after stroke, but less so whether sex impacts the recovery of EF. The amount of time passed after stroke might be one of the reasons studies on sex differences in cognitive function after stroke are inconclusive.

Lastly, our study uses multiple measures of reserve variables, something which is seldomly done in reserve research. We also use several measures of EF, allowing us to compare differences between the tests and study how EF subfunctions are affected by stroke. This allows us to study the validity of these measures and provides useful insights regarding which measures to include in future studies.

Limitations

Statistics

Before discussing clinical implications, it is important to consider the limitations of this study. First and foremost, this is an explorative study. Therefore, the results have not been corrected for multiple testing. When testing multiple hypotheses, the chances of observing a rare event increase, thus increasing the probability of making a type 1 error (Fields, 2013). Normally this is counteracted using different statistical techniques such as the Bonferroni correction. Since this is an explorative study and our sample size is small, we decided to use the standard significant levels $p < .05$. We must therefore take into consideration that there is a higher risk of our results containing false positives and should therefore be interpreted with caution.

Another limitation is the group sizes and imbalanced distribution of sex. The data consists of noticeably more males than females, and the female sample size is smaller than preferred when performing multiple regression analyses (Voorhis & Morgan, 2007). This increases the chances of type II errors, i.e., false negatives, where the null hypothesis is incorrectly accepted and no significant difference between groups is reported (Fields, 2013). A smaller sample size also makes it more difficult to get significant results since there is less data to establish trends (Fields, 2013). This means that even though both groups show improvement in EF scores or show positive or negative associations in regression analyses, there is an increased probability that only males will register as significant.

Data and Method

This study uses longitudinal data collected one week and three months after stroke. Premorbid data for EF and motor functioning measures are not available. This makes it difficult to measure the actual loss of EF caused by the stroke. We had hoped that the EF change variables (from one week to three months) would compensate for this limitation, but it is not ideal since individual differences in recovery is expected. A small sample size and general lack of female EF impairment also limits the usefulness of change variables for regression analysis. Since we have few studies on female post-stroke EF and its changes, it is difficult to say whether the lack of change indicates lack of impairment or lack of recovery.

It is possible that the differences in EF scores and their association to reserve variables were present before the stroke. This would mean that the reserve measures are associated with pre-stroke cognition and the normative distribution of cognition, and less to how well the brain compensates for damage and protects against impairments after stroke.

Another potential drawback of this study is the possibility that the neuropsychological tests used to measure EF are not sensitive enough to register executive impairment experienced in daily life (Chan et al., 2008). As opposed to real life, which consist of several multi-step tasks with the additional need to prioritize sub-goals, prioritize activities, remembering daily tasks as well as having to inhibit any distracting stimuli while performing these tasks, conventional experimental tasks measuring EF demands relatively simple responses to single events (Chan et al., 2008). Since this study looks at mild ischemic strokes it is possible that the executive impairment experienced after stroke is noticeable in everyday life, but not picked up by neuropsychological tests. Studies have shown that many patients with frontal lobe lesion perform as well as controls on neuropsychological tests, but struggle more in everyday life and activities (Shallice & Burgess, 1991).

Research and Clinical Implications

The original stroke study that our data were collected for were not designed to be a study of sex, but the result of this study will hopefully be useful when designing future studies on sex differences after stroke.

Some research implications have already been discussed, such as sex differences in EF and impact of reserve variables. Since reserve is a concept that evolved from AD research the definition of reserve is more suited to explain gradual loss and neurodegeneration, not immediate loss from traumatic injury. This raises the question of when cognitive and brain reserve impact cognitive function after sudden damage. Is reserve tied to the slow recovery that is observed over the first few years after stroke, or is the protective effect of reserve more immediate, causing patients to suffer less cognitive impairment in the acute phase? Sterns' (2020) definition of cognitive reserve consists of elements like neurocomputational flexibility and the brain's ability to change and compensate for damage. These components could encompass both immediate compensation (i.e., fewer clinical symptoms and less cognitive impairment) as well as gradual improvement over time (recovery of cognitive function over time). Umarova et al. (2019) found that years of education predict both educational independent (alertness) and educational dependent (EF, global cognition, working memory) cognitive deficits in the acute stroke phase and that motor function in paretic arms also benefited from longer education in the acute phase. This indicates two things: 1) that reserve might be more than just normal distribution of cognition, and 2) that the effect of reserve is noticeable as early as the first week after stroke. Still, more research is needed to further illuminate the relationship of time, cognitive function and reserve, especially regarding possible sex differences.

Our study will hopefully be useful for future studies when deciding which reserve variables and EF tests to include in the design. From our results it seems that education and premorbid IQ/NART IQ shows the clearest association to post-stroke EF, though it is important to keep in mind the possible sex differences also associated to these measures. While our study found little support for TICV as a reserve measure, Kliems et al. (2022) findings regarding the significant association between TICV and EF-change in patients with impaired EF in the acute phase, signal the need of further study before any conclusions can be drawn. Reserve research would benefit from all reserve variables being studied with both only impaired participants and all participants to further our understanding of cognitive and brain reserve. As for EF measures, we believe this study showed that one must be careful when generalising EF test results. We still need to specify whether test differences are caused by

test sensitivity/validity or if it is related to specific EF impairments caused by stroke. We would therefore encourage future studies to include multiple measures of EF.

Having a better understanding of factors associated with executive impairment after stroke and how executive impairment changes with time is helpful for establishing good screening procedures for patient follow-up. The male bias in stroke research have caused a gap in our knowledge regarding the female experience of stroke. As this may impact patient care, future research on sex differences is desired. We must aim to close the gap, both in research and clinical work. It is also important to remember that sex as a factor in research should be viewed as an imperfect and temporary proxy for other unknown factors, such as hormones or differences in exposure to immunological triggers (home, work, role-related). We should strive to discover and understand the underlying source of the sex variation, since it is more useful for developing clinical treatments and preventative measures.

Research on interventions for cognitive impairment after stroke have yet to establish the efficacy of stroke rehabilitation programs. A review from 2019 looked at seven controlled studies examining the efficacy of psychological interventions versus either treatment as usual or active controls. It also reviewed 13 one-group pre-post studies (Merriman et al., 2019). They found some support for psychological intervention, though the effects were small. Gillespie et al. (2014) reviewed 44 trials using cognitive rehabilitation. There was some support for the efficacy of such programs, but the authors concluded that there was currently not enough quality research to support clear recommendation for clinical practice. Chung et al. (2013) reviewed 13 studies on the effect of cognitive rehabilitation programs for stroke and TBI. They found no evidence that the interventions were helpful for executive dysfunction. Since we still lack the evidence for effective rehabilitation interventions, the focus of clinical work should be on assisting stroke survivors with cognitive impairment in their daily life and educate them and their families about common stroke related issues such as executive and other cognitive impairments, as well as psychiatric symptoms. This can be done in rehabilitation wards, in collaborations with doctors, neuropsychologists and occupational therapists. Primary care physicians should also be included in this collaboration, considering their role in the patients' long-term physical and psychiatric health.

Managing expectations and making sure stroke survivors and their families get the assistance they need to live fulfilling lives is an important part of post-stoke care. Knowing that certain patient groups with low education and/or NART IQ are more likely to suffer from executive and cognitive impairment is helpful for clinicians during rehabilitation and follow-up. Education is especially easy to assess in clinical settings and therefore particularly useful

for identifying patients with increased risk of cognitive impairment after stroke. It is difficult to change certain risk factors impacting cognitive impairment after stroke, such as education, sex or premorbid IQ. However, psychoeducation on *how* these factors affect long-term stroke outcome and rehabilitation may help clinicians and other health care professionals improve patient care and may thus substantially impact the lives of stroke survivors.

Conclusion

This explorative study aimed to shed some light on 1) potential sex differences in EF after stroke, and 2) potential sex differences in the association between reserve variables and EF after stroke.

Sex is a topic in stroke research that needs to be further studied, especially regarding cognitive and brain reserve since there are few existing studies. We hope that this study can be of use when designing future studies of sex differences in stroke and reserve. While current research on sex differences in cognition after stroke is inconclusive, our results indicate that there are sex differences in EF in the acute phase of stroke (females performing better than males one week after stroke and males experiencing more EF improvement during the first three months after stroke) and that different reserve measures impacts EF differently for males and females (education being positively associated with female EF scores, and NART IQ being positively associated with male EF scores after stroke).

Cognitive impairment hinders patients' rehabilitation efforts and their reintegration and participation in society, and thus possibly decrease their overall quality of life (Cumming et al., 2012; Kapoor et al., 2017). Identifying the potential risk and protective factors that affect cognitive impairment might be useful for determining stroke patients in need of more detailed screening and extra resources.

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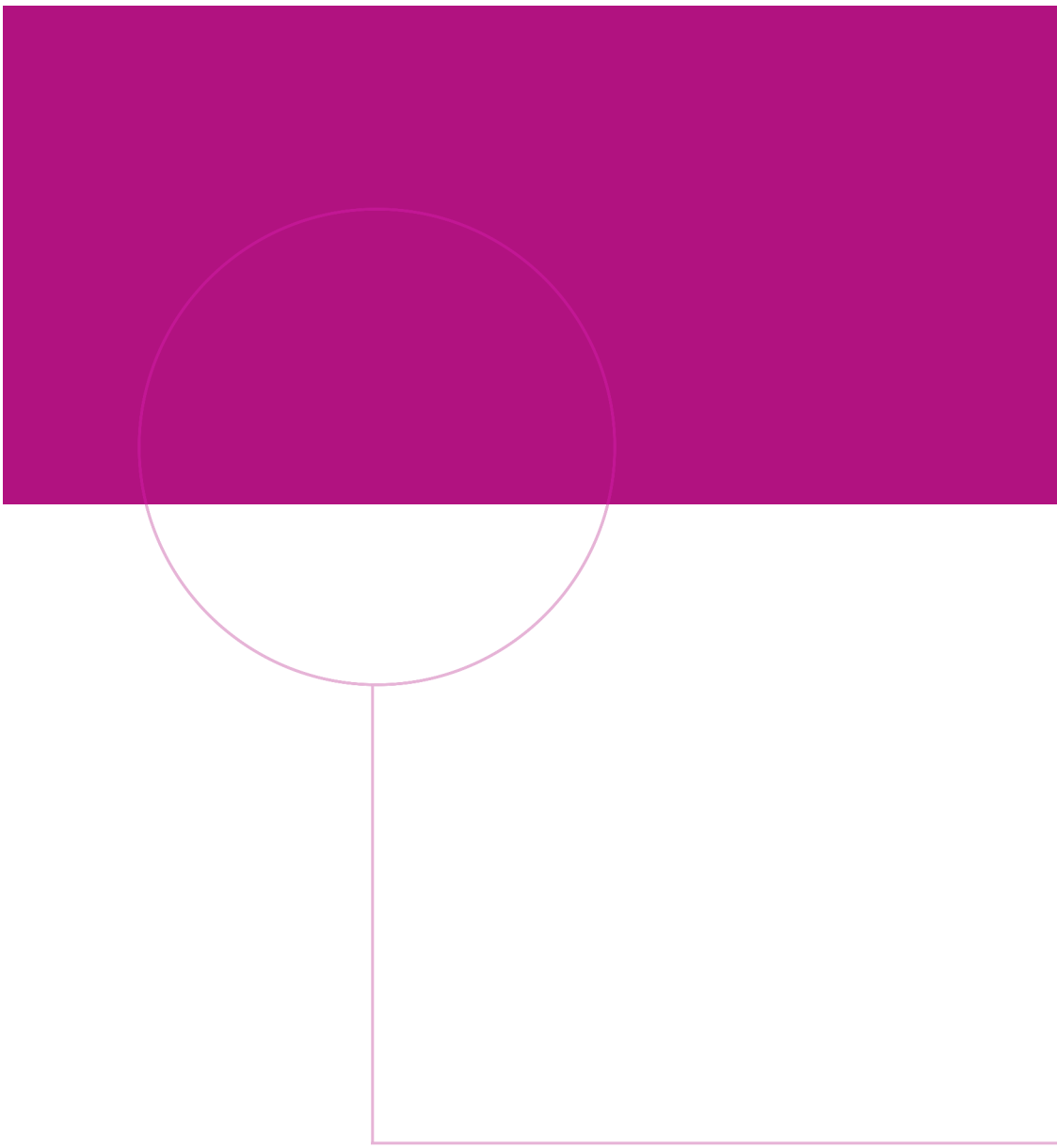

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