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Intraindividual Variability as a Measure of Neurological Integrity

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Abstract

The variability in response time a person shows within a certain task is called Intraindividual Variability (IIV). In neuropsychological research higher amounts of IIV has been shown to indicate cognitive decline and neurological disfunctions. Acquired brain injury such as stroke often result in cognitive decline. One of the tests frequently used in neuropsychological assessment post-stroke is the (digital) Trail Making Test (dTMT). The aim of this thesis is to investigate the influence of individual differences in age, months since the first stroke and level of education, of people with stroke on the IIV measured by means of dTMT. A group of 175 stroke survivors and 229 people without stroke participated in the present study. The outcome measures for IIV are the residualized Intraindividual Standard Deviation (rISD) and the Maximum Discrepancy score (MD). Results suggest that people with stroke can be distinguished from people without stroke based on higher amounts of IIV. Higher age of people that suffered stroke also predicted increased amounts of IIV. Months since the first stroke affected IIV measures from the TMT-A but not of TMT-B. Level of education did not affect IIV.

keywords: intraindividual variability, dTMT, stroke, MD, rISD,

Intraindividual Variability as a Measure of Neurological Integrity

Stroke is a group of conditions that interrupt the cerebral blood flow (Zhang et al., 2011). In the Europe Union (EU) the prevalence of stroke in the year 2000 was approximately 1.1 million new stroke events per year (Truelsen et al., 2006). This number is estimated to increase to 1.5 million new stroke events per year in 2025. Research on the costs of stroke in 1997 in the Netherlands showed that 3% of the annual Dutch healthcare budget was spent on patients that suffered from stroke (Evers et al., 1997). In the Netherlands stroke is number 2 on a list of most disabling diseases (Poos et al., n.d.). This has been calculated based on Disability Adjusted Life Years. Individuals with a history of stroke often experience cognitive decline (Lo et al., 2019). Cognitive decline is a broad term that describes decline in functioning of cognitive domains, for example memory or executive functioning. Cognitive decline is highly correlated with changes in the brain such as brain atrophy (Planche et al., 2019; Wang et al., 2021). In healthy ageing the brain volume changes which could result in cognitive problems (Aljondi et al., 2018). So, cognitive decline is a natural process while ageing. Stroke often causes brain damage which goes hand in hand with cognitive decline. The decline in cognitive performance in healthy ageing individuals may deteriorate when dealing with neurological diseases such as stroke, because of changes in the brain. After stroke, the onset of cognitive impairments may immediately appear, but often it is delayed (Brainin et al., 2014). Stroke appears to be a trigger for degenerative brain processes as the onset of dementia prevails 10 years earlier in people with stroke than in people without stroke (Ronchi et al., 2007). Furthermore, progression from cognitive impairments with no dementia (CIND) to dementia is accelerated by a previous stroke. The cognitive decline after stroke is accelerated compared to individuals without stroke. Heshmatollah and colleagues (2021) repeatedly assessed cognition in over 14,000 participants over 26 years in an population-based study. By matching people who experienced a stroke during that time with people of the same

sex and birth year without a stroke, they found that stroke patients even had steeper cognitive decline *before* the first-ever stroke than the matched person. The authors concluded that stroke is a risk factor for cognitive decline and stroke patients have a steeper decline already up to ten years *before* the first stroke (Heshmatollah et al., 2021). These findings illustrate that knowing if cognitive impairments are present may indicate future neurological disfunctions. Insight in the cognitive impairments and decline might benefit the patient as compensatory strategies of the brain might adapt structural alterations and provide more cognitive and neural reserve which may lead to better cognitive outcome (Barulli & Stern, 2013).

Lately, research has been focusing on a new measure to indicate cognitive decline; Intraindividual Variability (IIV; Stuss et al., 2003; Bielak et al., 2010). IIV is the fluctuation in performance from trial to trial of a reaction time (RT) task (Bielak et al., 2019). IIV is highly sensitive to subtle changes in cognitive ability and could therefore be an early marker of cognitive decline (Bielak et al., 2010). In a meta-analysis, including 13 studies, Mumme and colleagues (2021) studied the association of IIV with cognitive decline and dementia. They found that IIV was associated with cognitive decline or conversion to MCI/dementia, this finding was independent of the operationalization of IIV. IIV is an interesting measure for stroke survivors as stroke often leads to cognitive impairments. In addition, stroke is a risk factor for degenerative neurological diseases. It is for clinical practice and research relevant to further explore variables in stroke survivors that affect the IIV construct.

There are multiple types of variability described in the literature. First, *Inter*-individual variability, also referred to as *diversity* (Hultsch et al., 2002). This is the variability in response time within a single task of one person compared to the response time of another person on the same task at the same occasion. *Intra*-individual variability, is used when measuring variability of response time within one person. Comparing the variability in

response time across different tasks at one occasion, is referred to as *dispersion*. The variability in response time on one task, compared across multiple occasions is called *inconsistency*.

Bielak et al., (2019) distinguished IIV in between-person, the change of IIV compared to others, and within-person, the change in IIV of one person over time (referred to as inconsistency by Hultsch et al., 2002). Three age groups of healthy people were made, 20-24; 40-44 and 60-64 years. They were assessed on cognition with various tests like Symbol Digit Modalities Test at baseline and after 4 years and 8 years. The IIV was measured with a simple response time task and a choice response time task. The IIV within one person over the three assessments was not significantly associated with changes in cognitive performance. When comparing the IIV between persons, a negative relation between IIV and cognitive performance was found. So, in healthy individuals it appeared that a person with higher average IIV scores lower on cognitive performance than someone with a lower average amount of IIV. This effect is apparent in all age groups. Hultsch et al. (2002) found that older adults (ages 54-94) are more variable in all three types of variability, than younger adults (ages 17-36). The IIV is a potentially important predictor of cognitive performance. Hultsch and colleagues (2002) suggest that variability at one occasion, within-person (dispersion) or between-person (diversity), might influence long-term developmental change.

In another study, Hultsch and colleagues (2000) studied three groups of people, people with a neurological disfunction (mild dementia), somatically disturbances (arthritis) and healthy individuals. They measured response time on a simple- and choice- reaction time task, and two cognitive tasks to test episodic memory (word and story recognition). The variability of the response time on the reaction time tasks appeared to be related to the level of performance on the episodic memory tasks in all three groups. Also, this variability appeared to be a unique predictor of neurological status, independent of level of performance. So,

neurological status was predicted by one measure at one occasion. Based on these findings Hultsch et al. (2000) concluded that IIV could possibly be a behavioral indicator of disturbed neurological mechanisms. This conclusion has been confirmed in studies on people with traumatic brain injury (Stuss et al., 2003); Parkinson's disease (Burton et al., 2006; de Frias et al., 2012); symptoms of mild cognitive impairment (Christensen et al., 2005; LaPlume et al., 2021) and loss of consciousness in sport related concussions (Merritt et al., 2020). Hultsch and colleagues (2000) also stated that when IIV is influenced by neurological dysfunction, it might be a relative stable characteristic, because neurological dysfunction is a stable endogenous mechanism. The researchers confirmed this hypotheses as they found that more variability on one task indicated more variability on other tasks. This is consistent over multiple task domains and not due to random error. IIV appears to be a developmental phenomenon and a relatively stable individual characteristic (Hultsch et al., 2000; Rabbitt et al., 2001).

In healthy individuals inconsistency on response time tasks measured over multiple occasions, is highest in young children (ages 6-8), gets lower throughout adolescence (ages 18-29) and increases after adolescence throughout adulthood (ages 60-81) (Williams, 2005). Hultsch et al., (2002) did extensive research on all three types of variability (dispersion, diversity and inconsistency) over four age groups varying from young adults (age 17-36) to old adults (ages 75-94). In their research they found that with increasing age in adulthood al three types of variability increase. With regard to dispersion specifically, it appeared that older adults (ages 65-94) had more variability than younger adults (ages 17-64). Grewal et al., (2021) also found support for this association between cognitive variability and age-related cognitive decline. When adults get older, performance on cognitive tasks worsens and IIV increases (Nesselroade & Salthouse, 2004). In other words, with cognitive decline in ageing the variability of response time within one task also increases.

Not every individual with a history of stroke experiences the same amount of cognitive decline. One possible explanation is given by the cognitive reserve theory. Barulli and Stern (2013) defined cognitive reserve (CR) as "differences in cognitive processes as a function of lifetime intellectual activities and other environmental factors that explain differential susceptibility to functional impairment in the presence of pathology or other neurological insult" (Barulli & Stern, 2013, p. 502). To estimate CR often proxy variables like years of education, knowledge and socioeconomic status are used. Higher education has been associated with a slower transition from mild cognitive impairment (MCI) to dementia in Parkinson's patients (Poletti et al., 2011). People with higher education benefit more from literacy leisure activities which result in decreased odds of dementia (Lee & Chi, 2015), and more CR (indicated by higher education) has positive effects on the cognitive trajectory of Alzheimer patients (de Groot et al., 2018). Grand and colleagues (2015) found that years of education had no influence on the association between IIV and cognitive decline. On the contrary de Felice and Holland (2018) found that adults (aged 59-71) benefitted from cognitive reserve (measured in years of education). In addition, the amount of cognitive decline in executive functioning after stroke is less in people with high past leisure activity engagement compared to people with low past leisure activity engagement (Ihle et al., 2020). Ihle and colleagues state that leisure activity engagement might be a crucial cognitive reserve proxy. To understand individual difference in the amount of post stroke cognitive impairment the pre-morbid cognitive reserve should be considered (Umarova, 2016). Higher education is associated with more cognitive reserve and less post stroke cognitive decline is reported in patients with higher education. Christensen et al., (2005) found that higher IIV is related to lower education.

Neuropsychological assessment is used to assess cognitive functioning and can objectify impairments and decline. The National Institute of Neurological Disorders and

Stroke (NINDS) an Canadian Stroke Network (CSN) proposed a neuropsychological test battery to guide neuropsychological assessment for stroke patients. One of the tests in this neuropsychological test battery is the Trail Making Test (TMT), part A and B (Jaywant et al., 2018). In TMT part A the participant needs to connect numbers in circles (stimuli), counting upwards from 1 to 26. In TMT-B the connection of the 25 stimuli need to be of alternating sequence between numbers and letters such as 1-A-2-B. In neuropsychological assessment the TMT is often used because it is sensitive to a variety of neurological disorders (Fellows et al., 2017). The TMT measures processing speed, visual motor speed and flexibility in set shifting. Compared to the TMT-A, the TMT-B is a more complex cognitive task and requires executive control as it demands set switching. The TMT-B is therefore associated with measures of cognitively-based instrumental activities of daily living (IADL) such as meal planning (Jaywant et al., 2018). In digitalized assessment the digital Trail Making Test (dTMT) provides additional measurements and data such as inter stimulus intervals (Fellows et al., 2017). This data gives the opportunity to investigate IIV within the dTMT.

There is a growing body of literature that recognizes the importance of IIV as indicator of neurological integrity. Currently most research is focused on healthy individuals. Studying IIV with measures of the dTMT is of great clinical and research relevance. The aim of this thesis is to investigate the influence of individual differences of people with stroke on the IIV measured by means of dTMT. The first hypothesis is that people with stroke can be distinguished from people without stroke, based on higher measures of IIV measured by the dTMT. The second expectation is that with increasing months after stroke, IIV increases. The third hypothesis is that in people who suffered stroke, higher age indicates higher IIV. Lastly, the fourth hypothesis is that in stroke survivors a higher level of education indicates lower amounts of IIV.

Method

Participants

Archived data from research by the University of Groningen was used for the current study. The dataset originates from a study on validating a digitalized screening tool for mid-level and higher-order visual perceptual disorders. The original dataset contains two subsamples, 953 people with Acquired Brain Injury (ABI) and 282 Healthy Controls (HC). From the ABI group participants with a history of stroke were selected. Other inclusion criteria for the people who suffered stroke were sufficient visual acuity (>0.8) and all TMT ISI data being available. After selecting participants, the stroke group contained 175 people. In 19 people stroke was no further specified, 136 people suffered from ischemic stroke, 17 individuals suffered from hemorrhagic stroke and 3 people suffered a combination of ischemic and hemorhagic stroke. Inclusion criteria for HC were all TMT ISI data available, absence of self-reported neurological or visual impairments, a score of 24 or higher on the mini mental state examination (MMSE) and a minimum age of 18 years old. In order to match individuals of the ABI group to individuals of the HC group international individuals were excluded. A group of 229 healthy participants met the criteria, resulting in a total sample of 404 individuals. The demographic characteristics of the (sub)samples are shown in Table 1.

Table 1

Descriptive statistics of independent variables: gender, age, level of education and months since stroke

	Total			Stroke group			Healthy control group		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
Gender: frequency (%)									
	404	189 (46,8)	215 (53.2)	175	100 (57,1)	75 (42,9)	229	89 (38,9)	140 (61,1)
Age: Mean (SD)									
	58,23 (14,86)	58,71 (14,15)	57,80 (15,47)	61,91 (12,17)	62,61 (10.30)	60.99 (14,30)	55,41 (16,09)	54,34 (16,48)	56,09 (15,85)

Level of education:									
frequency									
Low	61	29	32	47	25	22	14	4	10
Middle	130	61	69	66	38	28	64	23	41
High	210	97	113	60	36	24	150	61	89
Months since stroke:									
Mean (SD) *Range*									
				14,23	14,85	13,41			
				(32,48)	(32,95)	(32,07)			
				0-281	*0-281*	*0-218*			

Design and Procedure

Data of the stroke group was obtained during post-injury clinical assessment at 18 locations of Royal Dutch Visio from 2015 till 2017. Data of the healthy control group was collected at the University of Groningen from 2015 till 2018. All data was obtained by educated and certified psychologists or graduate students with supervision of experienced psychologists. The same assessment protocol was used for ABI and HC by the administrators to ensure standardized assessment. The dataset contains variables such as age, level of education and many measures of cognitive performance. To investigate the hypotheses stated above the following variables are studied: gender; age; level of education; time in months since the first stroke and response time measures of the dTMT.

Materials

The DiaNAH is a digital test battery developed to assess people with acquired brain injury (ABI). The goal of the DiaNAH is to screen for mid-level and higher-order visual perceptual disorders. A tablet with 24.1 inch screen was used for the assessment. The test battery contains eleven digital neuropsychological tests (de Vries et al., 2018). The current study used response time data from the digital Trail Making Test (dTMT) part A and B to calculate IIV measures.

The (d)TMT consists of two parts, TMT-A is a simple visual motor speed task in which the participant has to draw a line from number to number, counting upwards. The TMT-B is a cognitive task in which the participant has to switch in cognitive sets by connecting in alternating sequence numbers and letters. The digital variant of the TMT has the benefit of accurately measured Inter Stimulus Intervals (ISI) (Fellows et al., 2016).

The ISI is the time in seconds that a participant needs to get from one stimulus to the other, for example, from one to two, from two to three and so on. Since both TMT part A and TMT part B contain 25 stimuli, there are 48 ISIs in total, 24 ISIs for each part of the TMT. The inter stimulus distance is the distance in cm of one stimuli to the other, for example the inter stimulus distance from one to two could be six cm and the distance from two to three, eight cm. The inter stimulus distance differs over all stimuli. To be able to compare one ISI to another the raw ISIs are divided by the corresponding inter stimulus distance. So, the time that a participant needed to get from 1 to 2 was divided by the distance in cm between one and two. After this the ISIs are comparable and can be used in calculating measures of IIV.

Measures

Different types of measures for IIV are described throughout the literature (Stawski et al., 2019). In the current study, two of these were calculated, the Maximum Discrepancy (MD) and the residualized Intraindividual Standard Deviation (rISD) (Schretlen et al., 2003). After correcting the ISI measures for distance from one stimulus to the other, as described above, the MD was calculated for TMT part A and TMT part B by subtracting the lowest ISI from the highest ISI. This resulted in two MD scores for each participant, MD A and MD B.

To calculate the rISD, first the raw ISD were calculated over all 24 ISIs of part A and 24 ISIs of part B. The raw ISD equals the standard deviation of an individual across trials, it is criticized as it fails to control for mean reaction time (Hultsch et al., 2008). Not correcting for mean reaction time likely causes higher standard deviations because of higher mean

performances (Bielak & Anstey, 2019). To calculate the rISD a regression analyses of the outcome measure and potential confounding variables was done. Potential confounding variables were age, level of educational (dummy variable with reference ‘low’) and gender. The outcome measure were the ISIs. The standard deviation of the residuals were calculated, this resulted in two rISD measures for each participant, rISD A and rISD B.

Analyses

Analyses were performed using IBM SPSS statistics version 27. The significance level was set at an p-value of .05. An parametric t-test is due to non-normality of the dependent variables not used. A non-parametric Mann-Whitney U test was performed to test whether people with a history of stroke could be distinguished from healthy controls based on measures of IIV. The assumptions of the non-parametric Mann-Whitney U test, non-normality, continuous dependent variable and similar distribution for both groups, were met. To test the remaining hypotheses, analyses were performed within the stroke group only. To test if the time since stroke, in months affected IIV, two single regression analyses with dependent variables rISD A and rISD B and predictor months after stroke were performed. In calculating rISD a correction for the effects of age and level of education was done. The rISD was therefore not used as a dependent variable in analyzing age and level of education. To test the influence of age and level of education on IIV two multiple linear regression analyses were performed. The dependent variables were MD A and MD B, with four predictors: age; months since stroke; and two dummy variables (low and high) for level of education with reference group ‘middle’. The predictors are added to the model in a fixed order thru enter. For both linear regression analyses no assumptions (homoscedasticity, independence of observations and normality) were violated. To calculate the effect size of the regression analyses Cohen’s f^2 is used.

Results

Table 2 contains the descriptive statistics of the dependent variables for both, the healthy control group and the group of people who suffered stroke.

Table 2

Descriptive statistics of the dependent variables MD A, MD B, rISD A and rISD B

Variable	Healthy control group (*N*=229) *M* (*SD*) *Range*	Stroke group (*N*=175) *M* (*SD*) *Range*
MD A	0.65 (0.57) *0.08 - 3.45*	1.41 (1.36) *0.16 – 10.01*
MD B	1.31 (1.22) *0.17 - 8.83*	3.43 (4.27) *0.27 – 40.85*
rISD A	3.88 (2.47) *1.04 - 19.41*	9.69 (7.59) *1.85 – 42.26*
rISD B	3.61 (2.87) *0.98 – 18.80*	9.30 (8.31) *1.27 – 42.31*

Differences in variability of response time between the stroke group and the healthy individuals were compared with the Mann-Whitney U test. The mean variability of people with a history of stroke is significantly higher than in people with no neurological damage. This result is found in all IIV outcome measures; MD A (U = 11058, p <.001) and B (U = 8887, p <.001), rISD A (U = 7093, p <.001) and B (U = 7661, p <.001).

Twelve people were excluded from the multiple regression analysis. Two because there was no data available on their level of education and ten people because the amount of months could not be calculated as there was no date of their first stroke available. In 12 other cases only the year of damage is reported. To minimalize the loss of respondents, June was filled in as month of stroke incident for these participants. The single regression analyses of the amount of months since the first stroke and rISD A and B shows only significant results for part A (R^2 = .03, F(1,162) = 4.89, p =.028**,** f^2= .029) and not for part B (p = .222). This indicates that the amount of months since the first stroke only increases the rISD of part A (B = .04, p =.028) . The results of the multiple linear regression analyses of age, months since

stroke and level of education on MD A and B, are shown in Table 3. The results show that the effect of the amount of months since the first stroke, is only present in MD A (f^2= .128). No significant results of months since stroke were found in MD B (p = .225). Higher amount of months after first stroke increases the IIV on the outcome measures based on ISIs of TMT part A (MD A and rISD A) but not of part B (MD B and rISD B).

The multiple linear regression analyses shows that age is a significant predictor for MD A (f^2= .046) and B (f^2= .028). The uniquely explained variance of age in MD A is 27.4 % and in MD B 20%. Both dummy variables of level of education (low and high) did not significantly contribute to the regression model. No evidence is found for increase of IIV due to higher levels of education in both MD A and MD B. Overall the predictors age, months since stroke and level of education explained 19 % of the variance in MD A and 4.2% in MD B.

Table 3

Multiple regression analysis of age, months since stroke, and education on MD A and MD B

Variable	MD A				MD B			
	B (SE)	Beta	t	Sig.	B (SE)	Beta	t	Sig.
(constant)	-.33(.52)		-.64	.522	-.35(1.73)		-.2	.841
Age	.03(.01)	.22	6.76	.003	.06(.03)	.17	2.15	.033
Months since stroke	.02(.003)	.36	2.07	<.001	.01(.01)	.07	.87	.387
Education (low)	.18(.25)	.06	.49	.469	.51(.85)	.05	.6	.551
Education (high)	-.08(.24)	-.03	.46	.748	-.49(.79)	-.05	-.62	.539
F (4,163)	9.36			<.001	1.73			.146
R^2	.44				.20			
Adjusted R^2	.17				.02			

Discussion

The purpose of the present study was to gain more knowledge and insights in IIV in response time of people with a history of stroke. Consistent with the expectations, people with a history of stroke had significantly higher amounts of IIV than healthy individuals as measured on the dTMT. This result supports the work of Naranjo and colleagues (2018) who studied attention in stroke patients with aphasia. They compared IIV in response speed of people with aphasia after stroke with healthy controls. One of their findings was that people that experienced stroke showed increased IIV compared to neurologically unimpaired individuals. The result of the current study supports this finding, and the work of other studies in this area linking IIV to neurological disfunctions such as mild dementia (Hultsch et al., 2000), traumatic brain injury (Stuss et al., 2003) and Parkinson's Disease (Burton et al., 2006).

The current study has also shown that in people who suffered stroke, higher age predicts higher IIV. This result matches those observed in earlier studies by Hultsch and colleagues (2002) as they found that all three types of variability: within one task over different occasions (inconsistency); within one person over different tasks (dispersion); and between individuals (diversity), were greater in older compared to younger participants. In addition, Bielak et al. (2019) also found a relationship between age and IIV. Both studies measured IIV in age groups of healthy individuals. The present study elaborates on these findings by establishing this relation in people who suffered stroke.

The expectation that with increasing months after stroke the IIV of a participant would increase, is partially confirmed. This effect was found in both IIV measures for TMT part A. More time between stroke and the dTMT assessment explained 19 % of the variance of the IIV of part A, but not of part B. Several explanations for this result are possible. First, higher amounts of months since stroke could be a mediator for higher age at the assessment. Ding

and colleagues (2019) researched predictors of post-stroke cognitive impairments (PSCI) and found that higher age contributed significantly on the probability of cognitive impairment within 6 to 12 months after stroke. Umarova (2016) studied neglect and degree of recovery in a people who suffered stroke. They found different factors that contribute to the presence and severity of neglect and degree of recovery. These factors are the severity of network impairment by stroke and pre-stroke brain- and cognitive reserve. Brain reserves are quantitative aspect of the brain such as brain size that could influence the functional outcome of pathology or neurological insults (Barulli & Stern, 2013). It might be that pre-stroke brain reserves, in combination with site of lesion explain differences in IIV better than merely the amount months since the first stroke. In addition, Heshmatollah and colleagues (2021) found that people who suffered a stroke showed more cognitive decline than healthy matched people 10 years *before* the stroke. *After* stroke an immediate decline in cognition (based on MMSE scores) and daily functioning was shown in people who suffered a stroke. It might be that the immediate decline in cognition that occurs after stroke explains most of the IIV. Dividing people with stroke in separate groups according to stage after stroke, such as acute, post-acute or chronic might be more fitting than amount of months after stroke.

Surprisingly, the current study has been unable to demonstrate that the level of education of people who suffered stroke impacts the amount of IIV. Heyanka and colleagues (2013) found that 59 % of people with high average intelligence and educational attainment show variability (more than 1 SD below the mean) in test results on a cognitive test battery. Although this intraindividual variability was measured within a cognitive test battery and not on response time, it raises thoughts about the variability in higher educated individuals. This might explain why level of education does not explain variance of IIV, because people with lower as well as higher education may show variability (although this might be due to different reasons). The expectation of the present study was that higher level of education

would increase cognitive reserve which could lead to lower levels of IIV. No effect of level of education is contrary to that of Christensen et al. (2005) who studied cross-sectional community data of healthy individuals and a number of cognitively impaired groups including dementia, mild cognitive impairment and aging-associated cognitive decline. They found that lower education was associated with increased variability. Christensen and colleagues measured the level of education based on the amount of years of education. Twelve or less years of education was labelled 'low', 13-14 'mid' and 15 years or more as 'high'. In the current study level of education is not based on the amount of years but on which level of education was followed by the participants, for example secondary school or university. This might explain the difference in outcome. In addition, Lee & Chi (2015) found in their study on cognitive reserve an interaction effect between years of education and literacy activities. The authors found that increased amount of literacy activities over the years might increase cognitive reserve. The operationalization of level of education in the present study might not be a good indicator for cognitive reserve. Cognitive reserve has been shown to influence IIV, but the amount of years of education or amount and type of leisure activities might be better proxies for cognitive reserve than level of education and therefore a better predictor of IIV.

This study has several limitations that should be considered when interpreting the findings. First, the rISD measures could not be used in all analyses as the level of education and age were already controlled for in calculating this outcome measure. Merely the MD measure was used in the analysis with these variables. This may have affected the results as the MD measure is a range score of the participants highest and lowest response time. The MD score may be more sensitive to random errors and external influences than the rISD score. One outlier in the ISIs of one participant due to attentional relapse or disturbances in the assessment could result in a high MD score. One might hypothesize that the MD score might therefore not reflect variability. The external influences are reduced as much as

possible by standardizing the protocol for the neuropsychological assessment. So, the limitations of the MD score were reduced as much as possible. Also the rISD and MD scores are both used in the analyses for between-person variability, both indicated significant differences between the two groups, suggesting that both measures can distinguish people who suffered stroke from neurologically unimpaired people. The MD score is calculated relatively easy, which increases the usability in clinical practice. It is therefore worth to further study the quality of the MD score as a measure of IIV.

Second, there could be a bias in the results as participants of whom not all ISIs were available were excluded. Severe cognitive deficits could result in not being able to finish the TMT part A or B. In addition, Specka and colleagues (2022) found that 10 % of healthy people who are low educated and 75 years and older fail to meet the 300 seconds requirement to finish the TMT. So, the results of the present study might not reflect the entire group of stroke survivors due to loss of participants because of failure to finish the TMT. The results may therefore merely reflect the people with mild or moderate cognitive deficits. Also not all data for calculating the amount of months after the first stroke were available. Filling in June might have unknown consequences for the outcome as it could differ up to six months from the real amount of months. By filling in June instead of January or December the maximum amount of months are limited to six instead of twelve. The effect of filling in June is most likely small as the amount of months after stroke ranges from 0 to 281. The amount of strokes a person experienced has not been taken into account. The months since the first stroke are calculated but participants might have experienced more strokes since, as a previous stroke increases the risk of another stroke (Zhang et al., 2012). No clear prevalence of multiple stroke has been found because most of the literature is focused on first stroke patients. A mixed group of participants who experienced one or more strokes might be a better reflection of clinical practice.

Future research could study the relation of IIV in pre-stroke cognitive decline as Heshmatollah and colleagues (2021) established that cognitive decline is present pre-stroke. The current study could be repeated using variables such as years of education and age at stroke onset. The age of onset might influence the IIV, as older individuals are more likely to show symptoms of pre-stages of dementia. The cognitive decline after stroke often results in dementia (Delgado et al., 2021). It would therefore be of great value to investigate IIV in stroke patients with and without signs of dementia. Lastly, for future practice it would be of great value to further explore the usability of the dTMT as it is often used in neuropsychological assessment and it captures lots of data on response time. Investigating the influence of the different parts (A and B) of the dTMT on IIV may be valuable. The relation between IIV and cognition is stronger for fluid cognitive domains such as processing speed, memory and reasoning than for crystallized cognitive domains such as verbal ability (Bielak et al., 2010). West and colleagues (2002) found that in tasks that require more executive control, the performance variability was greater for older (65-83 years) than for younger (19-29 years) adults as cognitive deficits generally increase with age. In simple tasks that required minimal executive control the variability was similar for both age groups (West et al., 2002). In line with this finding, Strauss et al., (2007) argue that increased variability is more evident in cognitively higher demanding situations, like switching cognitive sets or inhibit responses. Several authors found that with increasing complexity of the task the IIV gets more evident (West et al., 2002; Strauss et al., 2007, Bielak et al., 2010). The TMT-B requires executive control as it demands set switching. The TMT-A is a task that requires less executive control. Future research might investigate the influence of IIV based on the TMT-B compared to IIV based on the TMT-A in predicting cognitive functioning. Current research did not involve measures of cognitive functioning, this is recommended for future research. More research on

the dTMT is advised to see whether this neuropsychological test is sufficient for calculating IIV in different neurological patient groups.

This explorative research has provided a deeper insight in the effect of age, time since the first stroke onset and level of education of people who suffered a stroke on IIV in response time. This work supports the existing knowledge of IIV as an indicator of neurological integrity in people with a history of stroke. People with a history of stroke can be distinguished from healthy individuals by calculating the MD and rISD on the dTMT. The predictors age and months since the first stroke explained variance of the IIV based on TMT-A and less or none of the IIV based on TMT-B. The present findings suggest that the dTMT is a suitable test for calculating IIV measures. Future studies might focus on the difference of IIV based on TMT-A and TMT-B and cognitive functioning. This could have great practical implication, as the dTMT is an neuropsychological test that is available and used in many different patient groups, countries and settings.

References

Aljondi, R., Szoeke, C., Steward, C., Yates, P., & Desmond, P. (2019). A decade of changes in brain volume and cognition. *Brain Imaging and Behavior*, *13*(2), 554–563. https://doi-org.proxy-ub.rug.nl/10.1007/s11682-018-9887-z

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends in Cognitive Sciences 17*(10) 502-509. http://dx.doi.org/10.1016/j.tics.2013.08.012

Bielak, A. A. M., & Anstey, K. J. (2019). Covariation of intraindividual variability in cognitive speed and cognitive performance across young, middle, and older adulthood. *Developmental Psychology*, *55*(5), 994–1004. https://doi.org/10.1037/dev0000688

Bielak, A. A. M., Hultsch, D. F., Strauss, E., MacDonald, S. W. S., & Hunter, M. A. (2010). Intraindividual variability is related to cognitive change in older adults: Evidence for within-person coupling. *Psychology and Aging*, *25*(3), 575–586. https://doi-org.proxy-ub.rug.nl/10.1037/a0019503

Brainin, M., Tuamilehto, J., Heiss, W. D., Bornstein, N. M., Bath, P. M. W., Teuschl, Y., Richard, E., Guekht, A., & Quinn, T. (2014). Post-stroke cognitive decline: an update and perspectives for clinical research. *European Journal of Neurology 22*, 229-238. DOI: 10.1111/ene.12626

Burton, C. L., Strauss, E., Hultsch, D. F., Moll, A., & Hunter, M. A. (2006). Intraindividual Variability as a Marker of Neurological Dysfunction: A Comparison of Alzheimer's Disease and Parkinson's Disease. *Journal of Clinical and Experimental Neuropsychology*, *28*(1), 67–83. https://doi-org.proxy-ub.rug.nl/10.1080/13803390490918318

Christensen, H., Dear, K. B. G., Anstey, K. J., Parslow, R. A., Sachdev, P., & Jorm, A. F. (2005). Within-Occasion Intraindividual Variability and Preclinical Diagnostic Status: Is Intraindividual Variability an Indicator of Mild Cognitive Impairment? *Neuropsychology*, *19*(3), 309–317. https://doi-org.proxy-ub.rug.nl/10.1037/0894-4105.19.3.309

Delgado, J., Masoli, J., Hase, Y., Akinyemi, R., Ballar, C., Kalaria, R. N., & Allan, L. M., (2022). Trajectories of cognitive change following stroke: stepwise decline towards dementia in the elderly, *Brain Communications, 4*(3). https://doi.org/10.1093/braincomms/fcac129

De Felice, S., & Holland, C. A., (2018). Intra-Individual Variability Across Fluid Cognition Can Reveal Qualitatively Different Cognitive Styles of the Aging Brain. *Frontiers in Psychology, 9*: 1973. DOI: 10.3389/fpsyg.2018.01973

De Frias, C. M., Dixon, R. A., & Camicioli, R. (2012). Neurocognitive speed and inconsistency in Parkinson's disease with and without incipient dementia: An 18-month prospective cohort study. *Journal of the International Neuropsychological Society*, *18*(4), 764–772. https://doi-org.proxy-ub.rug.nl/10.1017/S1355617712000422

De groot, C., van Loenhoud, A. C., Barkhof, F., van Berckel, B. N. M., Koene, T., Teunissen, C. C., Scheltens, P., van der Flier, W. M., & Ossenskoppele, R. (2018). *Neurology 90*(2), 149-156. DOI: 10.1212/WNL.0000000000004802

De Ronchi, A., Palmer, K., Pioggiosi, P., Atti, A.R., Berardi, D., Ferrari, B., Dalmonte, E., & Fratiglioni, L. (2007). The Combined Effect of Age, Education, and Stroke on Dementia and Cognitive Impairment No Dementia in the Elderly. *Dementia and Geriatric Cognitive Disorders, 24*, 266-273. DOI: 10.1159/000107102

De Vries, S. M., Heutink, J., Melis-Dankers, B. J. M., Vrijling, A. C. L., Cornelissen, F. W., & Tucha, O., (2018). Screening of visual perceptual disorders following acquired brain

injury: A Delphi study. *Applied Neuropsychology: Adult, 25*(3), 197-209, DOI: 10.1080/23279095.2016.1275636

Ding, M., Xu, Y., Wang, Y., Li, P., Mao, Y., Yu, J., Cui, M., & Dong, Q., (2019). Predictors of Cognitive Impairment After Stroke: A Prospective Stroke Cohort Study. *Journal of Alzheimer's Disease, 71,* 1139-1151, DOI: 10.3233/JAD-190382

Evers, S. , Engel, G. & Ament, A. (1997). Cost of Stroke in the Netherlands From a Societal Perspective. *Stroke A Journal of Cerebral Circulation, 28* (7), 1375-1381.

Fellows, R.P., Dahmen, J., Cook, D., & Schmitter-Edgecombe, M. (2016). Multicomponent Analyses of a Digital Trail Making Test. *The Clinical Neuropsychologist, 31*(1), 154-167. https://doi.org/10.1080/13854046.2016.1238510

Grand, J. H. G., Stawski, R. S., & MacDonald, S. W. S. (2016). Comparing individual differences in inconsistency and plasticity as predictors of cognitive function in older adults. *Journal of Clinical and Experimental Neuropsychology, 38*(5), 534-550. http://dx.doi.org/10.1080/13803395.2015.1136598

Grewal, K. S., O'Connel, M. E., Kirk, A., MacDonals, S. W. S., & Morgan, D. (2021). Intraindividual variability measured with dispersion across diagnostic groups in a memory clinic sample. *Applied Neuropsychology: Adult* https://doi.org/10.1080/23279095.2021.1970552

Heshmatollah, A., Dommerhuijsen, L. J., Fani, L., Koudstaal, P. J., Arfan Ikram, M., Kamran Ikram, M., (2021). Long-term trajectories of decline in cognition and daily functioning before and after stroke. *Journal of Neurology, Neurosurgery & Psychiatry, 92*(11), 1158-1163. http://dx.doi.org.proxy-ub.rug.nl/10.1136/jnnp-2021-326043

Heyanka, D. J., Holster, J. L., & Golden, C. J. (2013). Intraindividual neuropsychological test variability in healthy individuals with high average intelligence and educational

attainment. *International Journal of Neuroscience*, *123*(8), 526–531. https://doi-org.proxy-ub.rug.nl/10.3109/00207454.2013.771261

Hultsch, D. F., MacDonald, S. W. S., Hunter, M. A., Levy-Bencheton, J., & Strauss, E. (2000). Intraindividual variability in cognitive performance in older adults: Comparison of adults with mild dementia, adults with arthritis, and healthy adults. *Neuropsychology, 14*(4), 588–598. https://doi-org.proxy-ub.rug.nl/10.1037/0894-4105.14.4.588

Hultsch, D. F., MacDonald, S. W. S., & Dixon, R. A. (2002). Variability in reaction time performance of younger and older adults. *The Journals of Gerontology: Series B, 57*(2), 101–115. http://dx.doi.org/10.1093/geronb/57.2.P101

Hultsch, D. F., Strauss, E., Hunter, M. A., & MacDonald, S. W. S. (2008). Intraindividual variability, cognition, and aging. The handbook of aging and cognition, 3rd ed., pp. 491–556

Ihle, A., Gouveia, É. R., Gouveia, B. R., Cheval, B., Sieber, S., Cullati, S., & Kliegel, M., (2020). Cognitive Reserve Attenuates 6-Year Decline in Executive Functioning after Stroke. *Dementia and Geriatric Cognitive Disorders, 48,* 349-353. DOI:10.1159/000506877.

Jaywant, A., Togli, J., Gunning, F. M., & O'Dell, M. W., (2018). The clinical utility of a 30-minute neuropsychological assessment battery in inpatient stroke rehabilitation. *Journal of the Neurological Sciences, 390,* 54- 62. https://doi.org/10.1016/j.jns.2018.04.012

LaPlume, A. A., Paterson, T. S. E., Gardner, S., Stokes, K. A., Freedman, M., Levine, B., Troyer, A. K., & Anderson, N. D. (2021). Interindividual and intraindividual variability in amnestic mild cognitive impairment (aMCI) measured with an online cognitive assessment. *Journal of Clinical and Experimental Neuropsychology,* 43(8), 796-812. https://doi.org/10.1080/13803395.2021.198286

Lee, Y., & Chi, I., (2015). Do cognitive leisure activities really matter in the relationship between education and cognition? Evidence from the aging, demographics, and memory study (ADAMS). *Aging & Mental Health, 20*(3), 252-261. http://dx.doi.org/10.1080/13607863.2015.1011081

Lo, J. W., Crawford, J. D., Desmond, D. W., Godefroy, O., Jokinen, H., Mahinrad, S., Bae, H., Lim, J., Köhler, S., Douven, E., Staals, J., Chen, C., Xu, X., Chong, E. J., Akinyemi, R. O., Kalaria, R. N., Ogunniyi, A., Barbay, M., Roussel, M., (…) Sachdev, P. S. (2019). Profile of and risk factors for poststroke cognitive impairment in diverse ethnoregional groups. *Neurology, 93*(24), e2257-e2271. doi: 10.1212/WNL.0000000000008612.

Merritt, V. C., Greenber, L. S., Meyer, J. E., & Arnett, P. A., (2020). Loss of Consciousness is Associated with Elevated Cognitive Intra-Individual Variability Following Sports-Related Concussion. *Journal of the International Neuropsychological Society, 27,* 197-203. DOI: 10.1017/s1355617720000727

Mumme, R., Pushpanathan, M., Donaldson, S., Weinborn, M., Rainey-Smith, S. R., Maruff, P., & Bucks, R. S., (2021). Longitudinal Association of Intraindividual Variability With Cognitive Decline and Dementia: A Meta-Analysis. *Neuropsychology, 35*(7), 669-678. https://doi.org/10.1037/neu0000746

Naranjo, N. P., Grande, D. D. R., & Alted, C. G., (2018). Individual variability in attention and language performance in aphasia: a study using Conner's continuous performance test. *Aphasiology 32*(4), 436-458. https://doi.org/10.1080/02687038.2017.1362686

Nesselroade, J.R., & Salthouse., T.A., (2004). Methodological and Theoretical Implications of Intraindividual Variability in Perceptual-motor Performance. *Journal of Gerontology: psychological sciences*, *59*(2), 49-55.

Planche, V., Coupé, P., Helmer, C., Le Goff, M., Amieva, H., Tison, F., Dartigues, J. F., & Catheline, G. (2019). Evolution of brain atrophy subtypes during aging predicts long-term cognitive decline and future Alzheimer's clinical syndrome. *Neurobiology of Aging*, *79*, 22–29. https://doi.org/10.1016/j.neurobiolaging.2019.03.006

Poletti, M., Emre, M., & Bonuccelli., U., (2011). Mild cognitive impairment and cognitive reserve in Parkinson's disease. *Parkinsonism & Related Disorders*, *17*(8), 579-586. https://doi-org.proxy-ub.rug.nl/10.1016/j.parkreldis.2011.03.013

Poos, M. J. J. C., Gommer A. M. (red), & Rodriguez, M.(red), (n.d.). Beroerte en sterfte. VZinfo, https://www.vzinfo.nl/beroerte/sterfte

Rabbitt, P., Osman, P., Moore, B. & Stollery, B., (2001). There are stable individual differences in performance variability, both from moment to moment and from day to day. *Quarterly Journal of Experimental Psychology, 54A*(4), 981-1003. DOI: 10.1080/02724980042000534

Schretlen, D., Munro, C., Anthony, J., & Pearlson, G. (2003). Examining the range of normal intraindividual variability in neuropsychological test performance. *Journal of the International Neuropsychological Society, 9*(6), 864-870. doi:10.1017/S1355617703960061

Specka, M., Weimar, C., Stang, A., Jöckel, K., Scherbaum, N., Sanchez Hoffmann, S., Kowall, B., & Jokisch, M. (2022). Trail Making Test Normative Data for the German Older Population. *Archives of Clinical Neuropsychology*, *37*(1), 186–198, https://doi.org/10.1093/arclin/acab027

Stawski, R. S., MacDonald, S. W. S., Brewster, P. W. H., Munoz, E., Cerino, E. S., & Halliday, D. W. R., (2019). A Comprehensive Comparison of Quantifications of Intraindividual Variability in Response Times: *A Measurement Burst Approach*, *The Journals of Gerontology 74*(3), 397–408. https://doi.org/10.1093/geronb/gbx115

Strauss, E., Bielak, A. A. M., Bunce, D., Hunter, M. A., & Hultsch, D. F., (2007). Within-Person Variability in Response Speed as an Indicator of Cognitive Impairment in Older Adults. *Aging, Neuropsychology, and Cognition, 14*(6), 608-630, https://doi.org/10.1080/13825580600932419

Stuss, D. T., Murphy, K. J., Binns, M. A., & Alexander, M. P. (2003). Staying on the job: The frontal lobes control individual performance variability. *Brain: A Journal of Neurology, 126*(11), 2363–2380. https://doi-org.proxy-ub.rug.nl/10.1093/brain/awg237

Truelsen, T., Piechowski-Jóźwiak, B., Bonita, R., Mathers, C., Bogousslavsky, J., & Boysen, G. (2006). Stroke incidence and prevalence in Europe: a review of available data. *European Journal of Neurology, 13*(6), 581–598. https://doi-org.proxy-ub.rug.nl/10.1111/j.1468-1331.2006.01138

Umarova, R. M., (2016). Adapting the concepts of brain and cognitive reserve to post-stroke cognitive deficits: Implications for understanding neglect. *Cortex, 97,* 327-338. http://dx.doi.org/10.1016/j.cortex.2016.12.006

Wang, J., Kochunov, P., Sampath, H., Hatch., K. S., Ryan, M. C., Xue, F., Neda, J., Paul, T., Hahn, B., Gold, J., Waltz, J., Hong, L. E., & Chen, S., (2021). White matter brain aging in relationship to schizophrenia and its cognitive deficit. *Schizophrenia Research, 230,* 9-16. https://doi.org/10.1016/j.schres.2021.02.003

West, R., Murphy, K. J., Armilio, M. L., Craik, F. I. M., & Stuss, D. T., (2002). Lapses of Intention and Performance Variability Reveal Age-Related Increases in Fluctuations of Executive Control. *Brain and Cognition, 49,* 402-419. DOI: 10.1006/brcg.2001.1507

Williams, B. R., Hultsch, D.F., Strauss, E.H., & Hunter, M.A. (2005). Inconsistency in Reaction Time across the Life Span. *Neuropsychology, 19*(1), 88-96. DOI: 10.1037/0894-4105.19.1.88

Zhang, Y., Chapman, A., Plested, M., Jackson, D., & Purroy, F., (2012). The Incidence, Prevalence, and Mortality of Stroke in France, Germany, Italy, Spain, the UK, and the US: A Literature Review. *Stroke Research and Treatment*, vol. 2012, Article ID 436125. https://doi.org/10.1155/2012/436125