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Component Processes and Neural Substrates of Set-shifting

Elisabeth Höst

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Handledare: Susanna Vestberg
Examinator: Sven Ingmar Andersson

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Abstract

Set-shifting has been described as the ability to alternate attention between simultaneous goals. The Trail Making Test (TMT) from the Delis-Kaplan Executive Function System (D-KEFS) measures set-shifting. This test is complex and demands different perceptual, cognitive, and motor skills, i.e. component processes, in addition to set-shifting. The first aim of this study is to explore the contribution of component processes in set-shifting in patients experiencing cognitive difficulties. The second aim is to evaluate the relationship between set-shifting and white matter hyperintensities (WMH) in the frontal and parietal lobes. The third aim is to evaluate the relationship between set-shifting and gray matter volume in the frontal and parietal cortices. WMH and gray matter volume were assessed using data from magnetic resonance imaging. Sixty-two patients were included, aged 60-80 years. All component processes showed a significant association with the set-shifting task, but only visual scanning and letter sequencing contributed significantly in predicting the unique variance in set-shifting. No relationships between set-shifting and WMH in the frontal and parietal lobes were found. Set-shifting was significantly associated with the volume of the right rostral middle frontal gyrus. However, after controlling for component processes no significant associations were found between set-shifting and gray matter volumes.

Key words: Trail Making Test, set-shifting, component processes, white matter hyperintensities, gray matter volume, executive functions, FreeSurfer, D-KEFS

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Introduction

The ability to alternate attention between two simultaneous goals is important for managing everyday performance, and is often referred to as *set-shifting* (Arbuthnott & Frank, 2000). Set-shifting is invoked whenever it is necessary to switch from one task to another (Cooper, Wutke, & Davelaar, 2012). In everyday life we are exposed to interruptions or new stimuli that demand our attention. Set-shifting is the ability to answer an interrupting phone call whilst chatting on the internet, or maintaining a conversation and at the same time responding to the needs of a small child.

Set-shifting tasks are widely used in clinical and experimental neuropsychology (Kramer et al. 2007). Since they are often complex, they demand different perceptual, cognitive, and motor skills in addition to set-shifting. Because these different skills, *component processes*, are not easily separated from set-shifting, the importance of controlling for them has been stressed (Kramer et al., 2007; Pa et al., 2010).

The TMT is one of the most widely used instruments in neuropsychological assessment of neurocognitive dysfunction (Fine, Delis, & Holdnack, 2011), and several versions of the TMT have been in use. The D-KEFS TMT is a neuropsychological instrument intended for assessing executive dysfunction (Delis, Kaplan, & Kramer, 2001a). It allows the clinician to investigate whether an individual's poor performance on a switching task, switching between numbers and letters, is due to a deficit in higher-level cognitive flexibility, i.e. set-shifting, or impairment in one or more of the component processes needed to perform the task (Fine et al., 2011). It can have significant diagnostic and treatment implications to accurately understand the reasons underlying a poor performance on a set-shifting task (Misdrabi & Gass, 2010). A slow motor function, deficits in visual perception, impaired abilities to sequence numbers or letters or impaired set-shifting ability can have different etiology, and thus demand different treatments.

Set-shifting is vulnerable to damages to the brain (Arbuthnott & Frank, 2000). Since set-shifting is considered an executive function (Cooper et al., 2012), the frontal lobes have been considered an important brain region. However, because performance on tests of set-shifting is dependent on both set-shifting abilities and component processes, the brain regions involved are not only those important for executive functions but also those regions important for various component processes (Pa et al., 2010). Consequently, it is important to control for component processes when exploring set-shifting's relationship to brain regions (Kramer et al., 2007).

Cardenas et al. (2008) point out that most imaging research has focused on the deficits of the episodic memory in the transition from normal aging to Alzheimer's disease, but also other cognitive domains, such as executive function and semantic memory may be markers of a developing Alzheimer's disease. Deficits in executive functions have been shown to predict the progression to dementia in individuals with mild cognitive impairment (MCI) (Clark et al., 2012), and the TMT has been shown to predict the conversion from MCI to Alzheimer's disease (Ewers et al., 2010).

Several terms are used in literature to describe what the TMT measures. Set-shifting (Friedman et al., 2008; Pa et al., 2010), task-switching (Sánchez-Cubillo et al., 2009), and cognitive flexibility (Kortte, Horner, & Windham, 2002) are all commonly used terms. One of the most frequently used is *set-shifting*, and in the present study this term will be used.

The present study is conducted in a clinical context within the research field of neuropsychology. It is a cross-sectional design based on previous research using quantitative data.

Executive Functions

The term *executive functions* covers many abilities and is thus difficult to define precisely. Executive functions have been described as "a collection of correlated but separable control processes that regulate lower level cognitive processes to shape complex performance" (Friedman et al., 2008, p. 201). A perhaps more direct attempt to define the concept is done by Lezak, Howieson, Loring, Hannay and Fischer (2004, p. 105), who describe executive functions as consisting of "those capacities that enable a person to engage successfully in independent, purposive, self-serving behavior". A person can have problems with self-care, performing useful work independently, and maintaining social relationships regardless of performance on tests of skills, knowledge, and abilities. However, as Lezak et al. (2004) point out, executive functions can affect cognitive functioning directly due to problems in planning, performing and monitoring cognitive tasks.

Executive function is not a unitary cognitive process, but instead is composed of several interrelated higher-level cognitive skills (Anderson, 2008). The term has been proposed to cover aspects of cognition such as inhibition, working memory, and set-shifting (Friedman et al., 2008). Other aspects are problem solving, modifying behavior, generating strategies or sequencing complex actions (Elliott, 2003).

The relationship between different aspects of executive functions has been investigated by Miyake et al. (2000). Three executive functions were selected: shifting

between mental sets, updating and monitoring of working memory contents, and inhibition of prepotent responses. The executive functions were investigated using a sample of 137 college students who were instructed to perform nine different tasks, three for each of the chosen executive function. A factor analysis revealed that the three executive functions correlate moderately with each other, and at the same time are clearly distinguishable and contribute differently to performance on tasks measuring executive functions. The authors refer to this as the unity and diversity of executive functions.

Several neuropsychological tests are used to measure executive function: The Stroop Color-Word Test assesses inhibition; The Wisconsin Card Sorting Test measures the ability to change cognitive sets (Hogan, 2007). The D-KEFS is a set of tests assessing executive functions including flexibility of thinking, inhibition, planning, problem solving, abstract thinking, and creativity (Delis et al., 2001a). It consists of nine tests that can be administered separately: Trail Making Test, Verbal Fluency Test, Design Fluency Test, Color-Word Interference Test, Sorting Test, Twenty Questions Test, Word Context Test, Tower Test, and Proverb Test.

Set-shifting and component processes. Set-shifting is a cognitive ability that requires individuals to shift attention or response patterns based on different rules. These higher-level cognitive skills are thought to be mediated by a predominantly frontal neural network (Pa et al., 2010).

Tests that require set-shifting are often used to measure executive functions (Hogan, 2007). As with many other neuropsychological tests the TMT is cognitively complex, and McDonald, Delis, Norman, Tecoma and Iragui-Madoz (2005) point out that instruments often used to assess set-shifting also measure component processes that are not easily separated from the set-shifting demands of the task. Friedman et al. (2008) highlight that understanding the structure of executive functions is difficult due to the task impurity problem, i.e. component processes.

The components can be difficult to distinguish because some are shared across tasks (Misdraji & Gass, 2010). Pa et al. (2010) discuss that set-shifting relies on several cognitive skills, and that if these are not independently measured and controlled for then performance on the set-shifting condition will be confounded by these skills and associated brain regions.

Crowe (1998) performed a study in which he tried to determine the differential contribution of factors considered assessed by TMT and to investigate the differences between performance on the set-shifting task, TMT-B, and a task measuring component

processes, TMT-A. Crowe writes that TMT-B is complex task that loads on several cognitive skills. After controlling for factors measured by TMT-A, poor performance on TMT-B may be contributed to lower verbal IQ, poor visual search, poor ability to maintain two simultaneous sequences, and decreased attention and working memory. Kortte et al. (2002) found that the TMT-B is more sensitive to deficits in set-shifting rather than deficits in the ability to maintain a complex response set, and suggests flexibility being one part of what makes TMT-B harder than TMT-A. Similar results are reported by Arbuthnott and Frank (2000).

In a literature review Sánchez-Cubillo et al. (2009) investigated which cognitive factors were identified as related to TMT performance. Among 24 studies visual search, perceptual/motor speed, speed of processing, working memory and general intelligence were the most frequently cited factors to contribute to TMT performance. In addition, TMT-B is more cognitively demanding considering alternating/flexibility, inhibition/inference control, working memory, mental tracking, and attentional set-shifting. The review (Sánchez-Cubillo et al., 2009) was followed by a study, assessing a sample of 41 healthy adults (mean age 59.4 years). The aim was to clarify the relative contribution from working memory, inhibition/interference control, task-switching ability and visuomotor speed to both direct TMT-A and TMT-B scores and derived scores, i.e. subtracting performance on TMT-A from performance on TMT-B. The results suggest that TMT-A requires mainly visuo-perceptual abilities whereas TMT-B reflects working memory and task-switching ability. They also found that subtracting performance on the TMT-A from performance on the TMT-B, minimizes the influence of visuo-perceptual and working memory demands, providing a relatively pure indicator of executive functions.

The studies presented above have all addressed the question of what abilities contribute to the performance of a set-shifting task. The results from the studies vary from suggesting higher cognitive abilities such as working memory to suggesting motor speed and visual search as important contributors. However, they all seem to agree on the importance of controlling for component processes. The D-KEFS TMT provides measures for some of the suggested component processes, as will be described below.

The Trail Making Test. Although the TMT is commonly used in assessing neuropsychological impairments, there still remain issues to address concerning what it actually measures.

Delis et al. (2001a) provide a review of the development of the TMT: A predecessor to the TMT has been in use since the 1930s, when it was called Distributed Attention Test and later the Partington Pathways Test. During the 1940s the Partington Pathways Test was gradually replaced by the TMT, with only minor alterations. Studies showing the test's ability to identify patients with brain damage attracted attention during the 1940s and the 1950s, and the TMT has since then been widely used in the clinical neuropsychology (Delis et al., 2001a).

In D-KEFS the two original subtests from the Halstad-Reitan test battery, TMT-A and TMT-B, have been modified, and are now called Number-Sequencing (TMT-number) and Number-Letter Switching (TMT-switch). Three additional conditions have been developed. The new conditions are: Visual Scanning (TMT-scan), Letter-Sequencing (TMT-letter), and Motor-Speed (TMT-speed). The primary measure is TMT-switch, which like TMT-B is a measure of cognitive flexibility (denoted set-shifting). By using the four other conditions it is possible to quantify and derive normative data for some of the component processes needed to perform the switching task. These fundamental component processes include visual scanning, number sequencing, letter sequencing, and motor speed. A poor performance on the switch condition can therefore be related to a difficulty in cognitive flexibility or a difficulty in one or more of the component processes.

Lezak et al. (2004) write that the many additional features in the D-KEFS take extra effort from the patient and extra time in administering and scoring from the examiner, and that the worth of this has not been established. Also the clinical usefulness of these modifications of familiar tests is, according to Lezak et al. (2004), unknown.

In a normative study of the D-KEFS TMT, Fine et al. (2012), showed that both years of education and vocabulary level yielded significant effect on all five conditions. The effect of both education and vocabulary level was largest for the TMT-switch followed by TMT-letter. Misdraji and Gass (2010) investigated the components involved in the TMT by adding a third subtest, Trail Speed, to the original TMT-A and -B. They found that age correlated with trail speed and set shifting but not with visual scanning. Years of education did not correlate with either speed, set shifting or visual scanning.

Mitchell and Miller (2008) tested the ecological validity of four of D-KEFS's tests: the TMT, the Tower test, the Verbal fluency test, and the Design Fluency test. They found that the D-KEFS TMT predict daily functioning in community-dwelling older adults, measured by DAFS-R (Direct Assessment of Functional Status's Revised Edition), a scale used to rate the individuals performance on several every-day tasks.

In the present study the term *TMT*, with the subtests *TMT-A* and *TMT-B*, will be used when an older version of the Trail Making Test (Reitan & Wolfson, 1985) is referred to. Sometimes *TMT* will be used when discussing the Trail Making Test in general, due to close similarities between the different versions. The *D-KEFS TMT* will be used for the particular test developed by Delis, Kaplan, and Kramer (2001c).

Neuroanatomical Substrates of Set-shifting

Knowledge of the underlying neuroanatomical correlates of set-shifting has come from studies of patients with known pathology of the brain but also from functional neuroimaging of healthy controls (Pa et al., 2010). Magnetic resonance imaging (MRI) uses magnetic fields to provide a picture of the distribution of specific substances, such as water and fat, in the brain. This creates a three-dimensional image of the brain (Banich, 2004). While MRI produces pictures of the anatomical structure of the brain, functional MRI (fMRI) is a method for making brain-behavior inferences (Banich, 2004). fMRI can detect which areas of the brain are activated during a specific task, e.g. a set-shifting task, by identifying brain areas that have an increase of active neurons. The activity of neurons also increases the presence of oxygen-rich blood, which has higher magnetic properties than deoxygenated blood, in brain areas activated during the task, and a picture of the brain activation can be derived.

The aging brain. Normal brain aging is characterized by a general decrease of volume of the gray and white matters, and an enlargement of the cerebrospinal fluid spaces (Lemaitre et al., 2012). The white matter volume in healthy brains increases until adulthood and remains relatively stable after that. However, the frontal lobes have shown more vulnerability to age related decrease of volume (Lemaitre et al., 2012).

WMH have been described as bright objects occasionally observed in MRI (Hopkins et al., 2006). Small discrete foci of WMH are seen in both healthy elderly individuals and individuals suffering from Alzheimer's disease and vascular dementia (Fazekas et al., 1987). A study of 77 adults, randomly selected from the general population, with no known focal lesion to the brain showed that 62 % of the individuals had WMH, and that there was a significant increase of WMH with age (Lindgren et al., 1994). The underlying substrate of WMH is not clear, as highlighted by Young, Halliday, and Kril (2008). They found that WMH involve a loss of vascular integrity. WMH have been shown to be related to attenuated

performance on tasks of processing speed and executive functions (Gunning-Dixon & Raz, 2000).

In healthy brains, the gray matter volume increases rapidly until puberty and then gradually declines during the lifespan (Riddle, DonLevy & Lee, 2010). With neurodegenerative diseases the rate of gray matter atrophy increases as seen in a study by Anderson et al. (in press). They found that the rate of gray matter atrophy was significantly greater in patients with Alzheimer's disease than in healthy control subjects, measured over a period of six months.

Focal lesions and set-shifting. Studies with patients with focal lesions in different parts of the brain have proven helpful in identifying those brain regions that play an important role in set-shifting.

Brain damage, particularly in the frontal lobes, are said to disrupt executive functions (Hogan, 2007). However, the abilities associated with executive functions can be disrupted after damage to a variety of brain regions (Banich, 2004). The terms *frontal lobe* and *executive* have previously been used interchangeably in research, but they are not identical, as pointed out by Miyake et al. (2000). The first is an anatomical term and the second is a functional term. Miyake et al. (2000) refer to previous research showing that individuals with damages in the frontal lobes not necessarily perform poorly on so called frontal lobe tasks, i.e. tasks measuring executive functions, whereas individuals with lesions outside the frontal lobes sometimes demonstrates impairments on such tasks.

In a study (Stuss et al., 2001) with 62 patients with either frontal or non-frontal single focal lesion, and a group of 19 controls, the patients with dorsolateral frontal damage were found to perform worse on the TMT-B. The patients with nonfrontal lesions were not impaired after being controlled for neglect and comprehension.

Patients with lesions in lateral prefrontal cortex performed significantly slower, and with more errors, on the D-KEFS TMT-switch condition than healthy controls even after controlling for performance on the four other conditions (Yochim, Baldo, Nelson, & Delis, 2007).

McDonald et al., (2005) found that patients with frontal lobe epilepsy performed significantly slower and with more errors on TMT-switch than patients with temporal lobe epilepsy and control group. In addition, the two patient groups did not differ from the control group on any of the other four conditions.

Degenerative diseases of the brain and set-shifting. Patients with degenerative diseases that affect different parts of the brain have been shown to perform poorly on tests that measure executive functions and set-shifting. Pa et al. (2010) found that patients diagnosed with Alzheimer's disease, corticobasal degeneration, and frontotemporal dementia performed significantly slower on D-KEFS TMT-number, TMT-letter and TMT-switch compared with healthy controls. Patients with MCI were slower than controls on the TMT-switch only. Kramer et al. (2007) studied the relationship between volume of, bilaterally, frontal, temporal, and parietal lobes and set-shifting. Included in the study were 101 subjects divided in four different groups: patients with Alzheimer's disease, frontotemporal dementia, semantic dementia, and healthy controls. Set-shifting was measured by two conditions, one set-shifting task and one task measuring component processes, of the Design Fluency from the D-KEFS. The purpose of the study was to determine the relationship between lobar volumes and set-shifting while controlling for component processes. They found that the performances on the two conditions of Design Fluency were significantly correlated with all six lobar volumes. When controlling for component processes, they found that only the left and right frontal lobes significantly correlated with set-shifting.

Cardenas et al. (2011) performed a longitudinal study with the aim to identify baseline tissue volume associated with baseline cognition and longitudinal cognitive decline. The population consisted of 71 participants, age 50-92, ranged along a continuum from healthy aging to impaired but not demented. They found that smaller frontal grey and white matter volumes and greatly increased ventricular cerebrospinal fluid volumes were associated with worse performance on executive functioning at baseline. They also found that smaller baseline bilateral dorsolateral prefrontal volume, particularly white matter, predicted future executive function decline. In this study, a composite executive function score from three D-KEFS tests: Verbal Fluency, Stroop, and TMT were used.

White matter hyperintensities and set-shifting. In a study of WMH in healthy elderly controls, patients with MCI, and patients with Alzheimer's disease, the volume of WMH has been shown to correlate significantly with age, particularly WMH in the frontal lobes (Chen, Wang, Chu, Huang, & Su, 2006). Patients with Alzheimer's disease had the greatest total volume of WMH, followed by patients with MCI, then controls. However, there was a large variation within each group and the difference did not reach a significance level.

Perry et al. (2009) studied the relationship between white matter tracts and performance on the TMT in a group of healthy adults. They found a relationship between age

and declined performance on the TMT-B and also between age and deterioration in white matter tracts connecting frontal regions and posterior association areas. WMH are said to disrupt these cortical connections, thus leading to cognitive impairment. In a study by Jacobs et al. (2012) a composite score for TMT-B and Stroop Color Word Task was used to test the association between executive functions and damage of three brain networks in patients with MCI. WMH in the frontal-parietal circuits were found to predict executive decline in patients with MCI and also was associated with executive decline at baseline.

Smith et al. (2011) found that lower performance on tests measuring executive function were associated with higher volumes of WMH. They also found that executive function correlated most strongly with specific locations of WMH, independent of the total volume of WMH. These areas were: bilaterally inferior frontal white matter, bilateral temporal-occipital and right parietal periventricular white matter, and bilaterally the anterior limb of the internal capsule.

Gray matter and set-shifting. Both structural and functional MRI have been used to explore the role of gray matter in set-shifting. The structural MRI studies were performed with patients suffering from degenerative diseases of the brain; the fMRI studies used healthy participants.

Structural findings. Pa et al. (2010) investigated the gray matter correlates of set-shifting in a sample of 160 participants with neurodegenerative disease, MCI and healthy controls. Set-shifting was assessed by three tests, each having a set-shifting condition, from the D-KEFS: Design Fluency, TMT, and Color Word Interference. They found that all three set-shifting tasks correlated with the gray matter volume in multiple widespread regions. After controlling for the component processes, the set-shifting performance across the three switching tasks was correlated with bilateral prefrontal cortex and posterior parietal cortex. However, no brain regions were significantly correlated with TMT after controlling for component processes. The authors discuss that this result can possibly be explained by a high multicollinearity between the set-shifting condition and the individual component processes on the TMT. TMT-number and TMT-letter, together with the nuisance variables, age, gender and result on Mini-Mental State Exam (MMSE), accounts for 66,9% of the variance on TMT-switch. Pa et al. (2010) did not control for all the component processes available from the D-KEFS TMT. The rationale for this is not accounted for, and there remain

questions as to what would have happened had they also used TMT-scan and TMT-speed in their study.

A 2-year longitudinal study (McDonald et al. 2012) investigated the relationship between regional atrophy and cognitive decline in a cohort of participants, MCI (n = 103) and healthy controls (n= 90). No significant correlations between lobar rates of atrophy and cognitive decline in healthy controls were found, thus all subsequent analyses were performed only on the group with MCI. They found association between bilateral dorsolateral frontal lobe atrophy rates and TMT-B decline. There was also an association between TMT-B decline and atrophy rates in left medial prefrontal and bilateral ventrolateral prefrontal atrophy. Newman, Trivedi, Bendlin, Ries and Johnson (2007) examined the relationship between gray matter volume and performance on TMT-B in 221 healthy adults. They found a relationship between TMT-B and bilateral inferior frontal gyri and left basal ganglia, while controlling for age, education, gender and total intra cranial volume.

Functional findings. fMRI studies have shown interesting results regarding which areas are activated during the performance of a set-shifting task. Even though the MRI scans make it impracticable to perform the TMT in the traditional way with pen and paper, inventive adaptations of the TMT have made it possible. In one fMRI study Zakazanis, Mraz, and Graham (2005) investigated the cerebral correlates of the TMT test using a custom-built fibre-optic writing device. The purpose was to investigate the difference in brain activity associated with performance on TMT-A and TMT-B in twelve healthy adults. In contrasting TMT-B versus TMT-A the most predominant regions of brain activity included the left-sided dorsolateral prefrontal cortex and medial frontal activity. Similar results were obtained in a study where seven healthy adults performed a verbal adaptation of the TMT-A and TMT-B (Moll, de Oliveira-Souza, Moll, Bramati, & Andreiuolo, 2002). Areas of increased activation during performance of TMT-B as compared to TMT-A were in the left hemisphere, mainly the lower part of the dorsolateral prefrontal cortex but also in premotor cortex, left medial frontal cortex and bilaterally in the intraparietal sulcus. Different results were acquired in an fMRI study of twenty healthy participants, using a computer programmed adaptation of the TMT. The analyses identified set-shifting with activity in the right inferior and middle frontal gyrus, the right precentral gyrus and left hemisphere temporo-parietal region (Jacobson, Blanchard, Connolly, Cannon, & Garavan, 2011).

The posterior parietal cortex role in attentional shifting has been investigated by Gurd et al. (2002) in an fMRI study. In trying to minimize the spatial and visual components the

participants were shifting between either semantic categories or overlearned sequences. They found that set-shifting can involve the parietal cortex without spatial or visual factors.

By using multichannel near-infrared spectroscopy Shibuya-Tayoshi et al. (2007) studied the activation in the prefrontal cortex in 41 healthy participants during performance of TMT-A and TMT-B. Multichannel near-infrared spectroscopy measures the oxygenation changes in blood while performing a task. They found an increased activation in a wide area of the prefrontal cortex during performance of TMT-B as compared to TMT-A. The findings also suggests that a majority of subjects use bilateral prefrontal cortex, while some subject use predominantly one side, either left or right.

Even though the frontal lobes are said to have an important role in higher-level cognitive skills, such as set-shifting, performance on tests of set-shifting also relies on brain regions that mediates the necessary component processes (Pa et al., 2010). Both studies of focal lesions and studies of degenerative diseases of the brain suggest that the frontal lobes, play an important role in set-shifting. More specifically, the dorsolateral prefrontal cortex seems to be of importance. There are however, evidence from both functional and structural MRI studies that also the parietal lobes, especially the posterior parietal cortex, may be of importance. The reason why different studies makes different findings can possibly be due to different methods. Some studies uses brain regions that have been well defined in advance; some studies use a more explorative approach. The size of the defined brain regions have also varied.

Aims and Hypothesis

As seen above, the cognitive complexity of a performance of the TMT-switch makes it important to separate set-shifting from the component processes that contribute to set-shifting. Further, several areas of the brain have been suggested to be important in set-shifting, both cortical and subcortical areas. Few studies consider both gray and white matter, as has been noted by Pa et al. (2010), this study might thus fill a gap in the study of set-shifting and its neural substrates in a population of patients experiencing cognitive difficulties. This study also uses all conditions measuring component processes in the D-KEFS TMT to explore their contribution to performance of TMT-switch. This is to my knowledge not done before in previous studies.

The first aim of this thesis is to explore the contribution of component processes in set-shifting, as measured by the D-KEFS TMT.

The second aim is to evaluate the relationship between set-shifting and WMH.

The third aim is to evaluate the relationship between set-shifting and gray matter brain volume.

The first hypothesis is that results on the D-KEFS TMT-switch correlate with WMH in the frontal and parietal lobes. The second hypothesis is that results on the D-KEFS TMT-switch correlates with gray matter volumes in specified regions in the cortices of the prefrontal and parietal lobes. However, after controlling for component processes, the TMT-switch will correlate more specifically with the prefrontal cortices.

Method

Participants

The present study was part of a larger research project, Tidig Demensdiagnostik I Skåne (TiDiS), with the aim to evaluate and develop methods for early and accurate diagnosis in patients experiencing cognitive difficulties. Included in the research project were consecutive patients who were referred, or self-referred, to three memory clinics in southern Sweden. The patients experienced cognitive impairment, or the impairment was confirmed or reported by next of kin. Inclusion criteria were: The patients should not be demented according to DSM-IV, they should have a result on the Mini Mental State Exam (MMSE) between 24-30, be aged 60-80 years, and they should understand Swedish well enough to understand information and instructions without the aid of an interpreter. Patients whose experience of cognitive impairment could be explained by other disorders, e. g. hydrocephalus, brain tumor or head trauma, were excluded, as were patients with alcohol abuse, severe depression, and recurrent episodes of psychosis.

Included in the present study were patients who by January 2012 had undergone both MRI and neuropsychological assessment. Inclusion criteria were: The patients should have performed all five conditions of D-KEFS TMT; the MRI and neuropsychological assessment should have been done within a period of three months from each other. Exclusion criteria were: other native language than Swedish, to avoid confounding results due to a lack of fluency in the Swedish alphabet; one or more of the D-KEFS TMT conditions completed out of time limit.

Seventy-six patients fulfilled the criteria for inclusion in the study. Four patients were excluded due to other native language than Swedish, 10 were excluded due to completing one or more of the conditions out of time limit, leaving a total of 62 patients. Table 1 displays demographic characteristics. Included were 37 women and 25 men, age min 60 and max 80

years with a mean of 70.77. The results of the MMSE give an indication of the cognitive level of the group. The mean value of the MMSE for the sample was 28.35. This is well above the cut off score of 24, which is considered indicative of significant impairment in cognitive functioning. Although scoring at a higher level does not mean that the patient is free of impairment (Hogan, 2007).

The mean time between the neuropsychological assessment and the MRI was 37,79 days, min 4 and max 81.

The present study was part of the project Tidig Demensdiagnostik I Skåne which was approved by the Regional Ethical Review Board in Lund. Written consent was acquired from all participants.

Table 1

Demographic Characteristics of Patients (N=62)

Characteristics	<i>M</i>	<i>SD</i>	range	<i>n</i>	%
Age, years	70,77	5.60	60 - 80		
Sex					
Female				37	59.7
Male				25	40.3
MMSE ^a	28,35	1,73	25-30		
Education ^b					
preG				14	22.6
G				27	43.5
postG				15	24.2

Note. ^a Mini-Mental State Exam. ^bEducation, data is missing from 6 patients. preG = Swedish öfolkskolaö or ögrundskolaö; G = örealskolaö or ögymnasieskolaö; postG = öhögskolaö

Material

The D-KEFS TMT. Executive function was measured using the D-KEFS TMT (Delis et al., 2001a). All five conditions were examined. A short description of the five conditions follows below.

TMT-scan is a measure of visual scanning and visual attention. It gives a measure of the visual scanning skills required by the switching task in TMT-switch.

TMT-number measures the ability of sequencing numbers, but it also requires visual scanning, visual attention, and motor functions. This condition is similar to the traditional TMT-A.

TMT-letter measures the ability to sequence letters but, as in TMT-number, it also requires visual scanning, visual attention and motor functions.

TMT-switch is a task in which the individual switches back and forth between connecting numbers and letters in sequence. It is similar to the traditional TMT-B, and is considered to measure a classic executive function: cognitive flexibility, denoted set-shifting in this study.

TMT-speed provides a base-line measure of the motor-component tapped by TMT-number, -letter, and -switch.

The five conditions of the D-KEFS TMT have time limits (Delis et al., 2001). The time limits for TMT-scan, -number, -letter, and -speed are 150 seconds, for TMT-switch it is 240. The performance is measured by the time (seconds) it took to complete the task. Both raw scores and age-corrected scores were used. Raw scores were used in parametric statistics, to get a larger variance. Standardized age-corrected scores were used in rank order correlations, to control for the influence of age in the analysis. The D-KEFS TMT has a clear age effect, especially TMT-switch. No Swedish norms have been developed, since most of the tests in the D-KEFS, including the TMT, is considered independent of cultural belonging (Delis, Kaplan, & Kramer, 2001b). American norms were used. The norms are based on a sample of 1750 individuals, aged between 8 and 89 years, and are for the adult population arranged in intervals of ten years (Delis, Kaplan, & Kramer, 2001c).

Brain MRI acquisition. All patients were imaged at a 3 T Siemens Trio MR system.

White matter hyperintensities. The WMH were visually evaluated through fluid-attenuated inversion recovery (FLAIR) sequences of the MRI. Fazekas rating scale (Fazekas et al., 1987) was used to describe the hyperintense signal abnormalities.

Fazekas rating scale consists of two parts: one describing the WMH surrounding the ventricles and the other describing hyperintensities in the deep white matter, separated from the ventricles. Of interest in this study were the deep white matter hyperintensities (DWMH) in the frontal and parietal lobes, in the left and right hemispheres. DWMH were rated from 0-

3, where 0 = absence of hyperintensities, 1 = punctuate foci of hyperintensities, 2 = beginning confluence of loci, and 3 = large confluent areas.

The rater (AG) was trained by an experienced neuroradiologist and was blinded to diagnosis and clinical data.

Gray matter volume. A high resolution (1 x 1 x 1 mm³ voxel size) T1-weighted scan (TR/TE: 1950 ms /3 ms, flip angle 9) acquired in the coronal plane was used for image analysis with Freesurfer software, version 5.1.0 (<http://surfer.nmr.mgh.harvard.edu>).

Cortical reconstruction and volumetric segmentation was performed using FreeSurfer. FreeSurfer is a freely available automated set of tools for analysis and visualization of structural and functional brain imaging data. Briefly, FreeSurfer modifies the representation of the cortical surface, inflates it to be able to visualize the activity buried inside the sulci (Fischl, Sereno & Dale, 1999). A spherical atlas, based on cortical folding patterns, makes it possible to accurately localize structural and functional features of the brain (Fischl, Sereno, Tootell, & Dale, 1999). Parcellation of the cerebral cortex into units are based on gyral and sulcal structure (Desikan et al., 2006; Fischl et al., 2004).

The regions of interests (ROI) of FreeSurfer is based on anatomical boundaries, whereas much research in neuropsychology is done using functional ROIs, sometimes manually outlined. The dorsolateral prefrontal cortex has non-consistently defined boundaries in the literature, whereas Freesurfer has set boundarys according to gyri and sulci. Converting the dorsolateral prefrontal cortex and the posterior parietal cortex, which are of interest in this study, into one of the fixed ROIs of Freesurfer has been done using the Desikan-Killiany brain atlas (Desikan et al., 2006).

In the frontal lobes the rostral middle frontal ROI was selected as it approximately corresponded to the dorsolateral prefrontal cortex, the area defined by Brodmann's areas 9 and 46 (Murray & Ranganath, 2007). In the parietal lobes, three gyralbased ROIs , the Superior parietal, Inferior parietal and the Supra marginal were selected to be the equivalent of the posterior parietal cortex. The posterior parietal cortex is situated posterior to the postcentral sulcus and anterior to the parieto-occipital sulcus bordered by the Sylvian fissure (Sack, 2009). A composite score was created, called the *posterior parietal*. Figure 1 displays the selected ROIs based on the gyral based atlas of Desikan-Killiany.

Head size differs markedly among individuals (Buckner et al., 2004). Intra cranial volume represents an estimate of premorbid brain size before potential global and local atrophy. Thus, inclusion of a head size measure as a covariate, is important in volumetric

analysis. Volumetric data were corrected for differences in head size by using the intra cranial volume data as a predictor in the regression analysis.

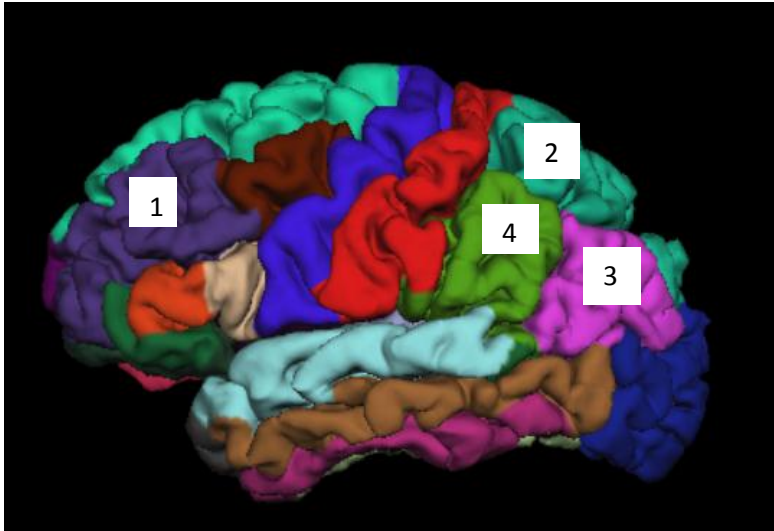


Figure 1. Gray Matter ROIs. Gray matter ROIs based on Desikan-Killianyø's gyral based atlas (Desikan et al., 2006). 1= Rostral middle frontal; 2= Superior parietal; 3= Inferior parietal; 4= Supra marginal.

Procedure

The patients underwent physical and neurological examinations, as well as neuropsychological assessment and MRI.

The neuropsychological assessment was conducted at three specialized memory clinics. It consisted of a test battery designed to assess different cognitive domains, such as memory, verbal skills, visuo-spatial skills, and executive function. The D-KEFS TMT was part of this test battery and was selected as a measure of set-shifting performance.

Demographic data and MMSE data was used to describe the sample.

The MRI data was analyzed with different procedures for the WMH and the gray matter volume. A rater reviewed the brain MRIs and determined the grade of hyperintensities according to the Fazekasø rating scale (Fazekas et al., 1987), as described above.

The gray matter volume was measured using a freely available automated computer program, FreeSurfer (<http://surfer.nmr.mgh.harvard.edu>). Prior to the FreeSurfer analysis, the images were examined and, if needed, corrected to facilitate analysis. No checking of the output was done. Due to a time-consuming processing of images, data was only available for 39 cases.

The results from the neuropsychological assessment, the WMH ratings, and the results from the FreeSurfer analysis were gathered in a database and analyzed using parametric and non-parametric statistics.

Statistical analysis

The Statistical Package for the Social Sciences (IBM SPSS Statistics version 20, Inc., Chicago, IL, USA) was used to analyze all statistical data. Both parametric and non-parametric statistical methods were used. Non-parametric methods have been used to analyze the rank-order data from the WMH ratings.

Pearson product-moment correlation coefficient was used to examine the relationship between age and the five conditions of the D-KEFS TMT. The amount of variance in TMT-switch, explained by results on TMT-scan, -number, -letter, and -speed, was determined using standard multiple regression. A sequential multiple regression analysis was conducted to explore the ability of component processes to predict results on TMT-switch after controlling for age.

The relationship between TMT-switch and WMH in the left and right, frontal and parietal, lobes were investigated using Spearman rank correlation test, a non-parametric statistical method. The age-corrected scaled scores from the D-KEFS manual (Delis et al., 2001a) were used to control for age.

Pearson product-moment correlation coefficient was used to investigate the relationship between the five conditions of the D-KEFS TMT and grey matter volumes in the frontal and parietal cortices. Sequential regression analysis was applied to investigate the relationship between performance on TMT-switch and grey matter volumes, by hierarchically introducing age, intra cranial volume, and component processes.

According to previous studies, age and, to a lesser extent education, are related to performance on the original TMT (Tombaugh, 2004; Zalonis et al., 2008) and the D-KEFS TMT (Fine et al., 2011), with decreasing performance on the TMT with increasing age and lower level of education. Age was included as an independent variable in the sequential regression analyses. Five cases were missing data in the variable of education. Since it could not be considered a randomly missing data (Tabachnick & Fidell, 2007), and mean substitution were not possible due to it being a categorical value, a decision was made to exclude the variable from the analyses.

Gender has shown little, if any, relationship with the traditional TMT (Tombaugh, 2004; Zalonis et al., 2008), and was not included as a variable.

Results

A presentation of the results from the statistical analyses follows below. First the descriptive statistics from the performance on the D-KEFS TMT are presented, after that the relationship between the conditions from the D-KEFS TMT. Then the results from the analysis of the D-KEFS TMT's correlation with WMH are presented. Lastly, the gray matter volumes from the FreeSurfer analysis are displayed together with their associations with the results from the D-KEFS TMT.

Relationship between the D-KEFS TMT Conditions

The means and standard deviations for each of the D-KEFS TMT conditions are presented in Table 2. Both raw scores and age-corrected standardized scores are displayed in the table. The average score of the standardized scores is 10, with a standard deviation of three (Delis et al, 2001c). The standardized scores vary little, ranging from 10.53 to 11.23, a result slightly above average. The raw scores, on the other hand, show a greater variety with a mean of 26.84 seconds on the performance on TMT-scan and a mean of 126.61 seconds on the performance on TMT-switch.

Table 2

Mean Scores on the D-KEFS TMT (N= 62)

Variable	M	SD	Min	Max
TMT-scan Raw score	26.84	7.23	15	47
Standardized score	10.81	2.73	3	15
TMT-number Raw score	48.85	21.17	24	126
Standardized score	10.73	3.49	1	16
TMT-letter Raw score	51.21	19.19	18 ^a	105
Standardized score	10.53	2.58	4	15
TMT-switch Raw score	126.61	49.66	54	239
Standardized score	9.53	3.35	1	15
TMT-speed Raw score	36.97	18.86	17	124 ^b
Standardized score	11.23	2.54	1	14

Note. ^a univariate outlier due to extremely fast performance on TMT-letter. ^b univariate outlier due to an extremely slow performance on TMT-speed. Standardized scores are age-corrected (Delis et al., 2001).

A standard multiple regression analysis was performed between TMT-switch as the dependent variable and TMT-scan, -number, -letter, and -speed as independent variables. Prior to analyses the variables were evaluated for accuracy of data entry, e.g. missing data and accuracy of input, linearity, and fit between their distributions and the assumptions of multivariate analysis. Results of the evaluation led to transformation of the variables to reduce positive skewness, reduce the number of outliers, and improve normality. Results on TMT-scan and TMT-switch were transformed using square root, results on TMT-number, -letter, and -speed were logarithmically transformed. Figure 2 shows histograms for the variables, before and after transformation. After transformation two cases were found to be univariate outliers: one case because of an extremely fast result on TMT-letter and one case because of an extremely slow result on TMT-speed. These cases were deleted from the analysis, leaving a total of 60 patients.

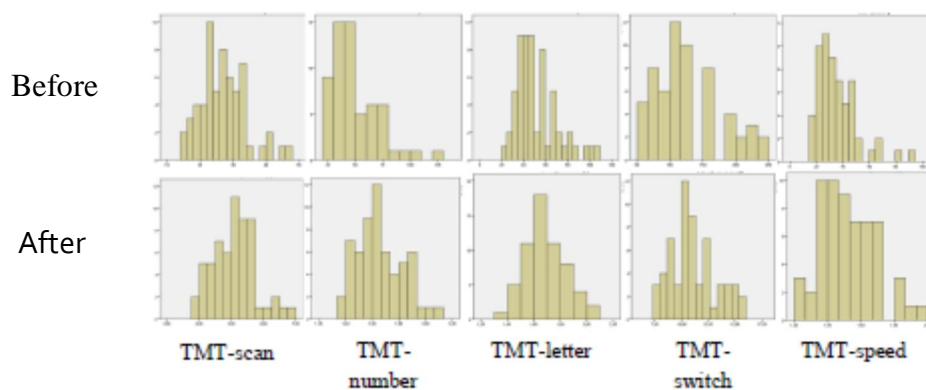


Figure 2. The variables before and after transformation. Variables TMT-scan transformed using square root, TMT-number was logarithmically transformed, TMT-letter was logarithmically transformed, TMT-switch transformed using square root, and TMT-speed was logarithmically transformed.

Table 3 displays the means, standard deviations, and relationships between the five conditions of the D-KEFS TMT after the transformation. Included in the table is also the variable Age.

All conditions of the D-KEFS TMT showed a moderate to strong significant correlation with each other. Age correlated moderately with TMT-scan, -letter, and -switch, but there were no significant correlations between age and TMT-number and -speed.

No variables correlated more than $r = .59$, and no tolerance values of > 0.1 ; results that indicate that there are no multicollinearity. No multivariate outliers were found using Mahalanobis distance at $p < .001$ (Tabachnick & Fidell, 2007).

Table 3

Means, Standard Deviations, and Correlations for the transformed variables of D-KEFS TMT and Age (n=60)

Variables	<i>M</i>	<i>SD</i>	1	2	3	4	5	6
1. TMT-scan	5.11	0.66		.55**	.45**	.59**	.40**	.42**
2. TMT-number	1.66	0.17			.57**	.51**	.43**	.16
3. TMT-letter	1.69	0.15				.52**	.42**	.38**
4. TMT-switch	11.09	2.15					.33**	.36**
5. TMT-speed	1.52	0.17						.11
6. Age	70.50	5.38						

Note. TMT-scan and TMT-switch transformed with square root, TMT-number, -letter, and -speed logarithmically transformed. ** $p < .01$.

Table 4 displays the unstandardized regression coefficients (*B*), the standardized regression coefficients (β), the Part correlation coefficients, and values for R , R^2 , and adjusted R^2 . R for regression showed significant results, $F(4, 55) = 10.82$, $p < 0.01$. The adjusted R^2 value of .40 indicates that 40 % of the variability in TMT-switch is predicted by the scores on the other four conditions, measuring component processes, in the D-KEFS TMT. Results on TMT-scan and TMT-letter contributed significantly to predict the variation in TMT-switch. TMT-scan is the more important contributor to the result on TMT-switch, as indicated by both β and part correlation. Although TMT-number and TMT-speed correlated significantly with TMT-switch, they did not contribute significantly to regression.

Table 4

Standard Multiple Regression Predicting Results on TMT-switch from TMT-scan, -number, -letter, and speed (N=60)

Variables	<i>B</i>		<i>Part</i>
TMT-scan	1.27**	0.39	.32
TMT-number	1.74	0.14	.10
TMT-letter	3.78*	0.27	.21
TMT-speed	0.08	0.01	.01
			$R^2=.44$
			Adj. $R^2= .40$
			$R= .66^{**}$

Note. TMT-scan and TMT-switch transformed with square root, TMT-number, -letter, and -speed logarithmically transformed. * $p > .05$. ** $p < .01$.

Based on the result of the standard multiple regression analysis a sequential regression analysis was conducted to investigate if an addition of information regarding results on TMT-scan and TMT-letter improved prediction of results on TMT-switch, beyond that of age. TMT-scan and TMT-letter were chosen due to their significant contribution to predict variation in TMT-switch. Age was included at a first step, then TMT-scan and, in the last step, TMT-letter.

Table 5 displays the unstandardized regression coefficients (*B*), Standard Error (SEB), the standardized regression coefficients (β), the value for R Square Change (Sr^2_i) and values for R , R^2 , and adjusted R^2 . R was significantly different from zero at the end of each step. After step 3, with all the independent variables included, $R^2 = 0.44$, $F(3, 56) = 14.24$, $p < .01$. The adjusted R^2 indicated that 40 % of the variability in TMT-switch is predicted by age, results on TMT-scan, and results on TMT-letter. Age was entered at step 1, explaining 13% of the variance of TMT-switch. After entry of TMT-scan, the explained variance was 36%. In the final step, only TMT-scan and TMT-letter were statistically significant, with TMT-scan recording a higher beta value, $\beta = 0.42$, $p < 0.01$, than TMT-letter, $\beta = .31$, $p < 0.01$. Age did not contribute significantly to the prediction of results on TMT-switch in the complete model.

Table 5

Sequential Regression Analysis Predicting result on TMT-switch from age, TMT-scan, and TMT-letter (N = 60)

Variables	<i>B</i>	<i>SE B</i>		Sr^2_i	R^2	<i>Adj. R²</i>	<i>R</i>
Step 1				0.13	0.13	0.11	0.36**
Age	0.14	0.49	0.36				
Step 2				0.23	0.36	0.34	0.60**
TMT-scan	1.73	0.38	0.53				
Step 3				0.07	0.43	0.40	0.66*
TMT-letter	4.37	1.65	0.31				

Note. TMT-scan and TMT-switch was transformed with square root, TMT-letter was logarithmically transformed. * $p < .05$. ** $p < .01$

The D-KEFS TMT and White Matter Hyperintensities

White matter hyperintensities. Table 6 displays the ratings of DWMH in the frontal and parietal lobes. In each of the frontal lobes 14.5% and 8.1%, respectively, of the patients were rated as having an absence of DWMH, and in each of the parietal lobes 24.2 % were rated as having an absence of DWMH. Most ratings of DWMH in the four areas of interest were of punctuate foci, 58.1 % - 67.7 %. In all the four regions, 4.8% of the patients were rated as having confluent areas of DWMH.

Table 6

Description of the DWMH ratings (N=62)

DWMH	Rating	Number	Percent
Frontal right hemisphere	0	9	14.5
	1	39	62.9
	2	11	17.7
	3	3	4.8
Frontal left hemisphere	0	5	8.1
	1	42	67.7
	2	12	19.4
	3	3	4.8
Parietal right hemisphere	0	15	24.2
	1	36	58.1
	2	8	12.9
	3	3	4.8
Parietal left hemisphere	0	15	24.2
	1	37	59.7
	2	7	11.3
	3	3	4.8

Note. Fazekas rating scale was used to evaluate WMH (Fazekas et al., 1987). 0 = absence, 1 = punctuate foci, 2 = beginning confluence of loci, and 3 = large confluent areas.

Relationship between set-shifting and white matter hyperintensities. The relationship between the results on the D-KEFS TMT, age and DWMH in the frontal and parietal lobes was investigated using Spearman rank order correlation as displayed in Table 7. To compensate for the impact of age on the results, age-corrected standardized scores were used.

DWMH in the frontal and parietal lobes, left and right, correlate significantly with each other. The correlations are positive and strong, ranging from $r_s = .60$ to $r_s = .86$. No significant correlations were found between DWMH in the frontal lobes and any of the D-KEFS TMT conditions. The DWMH in the parietal lobes showed weak, but significant, negative correlations with TMT-scan, suggesting that a higher rating of DWMH is associated with a poorer performance on TMT-scan.

Table 7

Correlation Matrix for the D-KEFS TMT and DWMH (N= 62)

Variables	1	2	3	4	5	6	7	8	9
1. DWMH Fr RH		.86**	.71**	.71**	-.10	-.13	-.12	-.06	-.02
2. DWMH Fr LH			.60**	.62**	-.12	-.11	-.14	-.10	-.00
3. DWMH Par RH				.74**	-.25*	-.20	-.16	-.09	-.08
4. DWMH Par LH					-.29*	-.14	-.12	-.11	-.04
5. TMT-scan						.51**	.41**	.61**	.36**
6. TMT-number							.58**	.53**	.57**
7. TMT-letter								.55**	.44**
8. TMT-switch									.29*
9. TMT-speed									

Note. Spearman rank order correlation. Fr= Frontal. Par= Parietal. RH= Right Hemisphere. LH= Left Hemisphere. * $p < .05$. ** $p < .01$.

The D-KEFS TMT and Gray Matter Volume

Gray matter volume. Table 8 displays data, in mm^3 , of the gray matter volumes produced by FreeSurfer, together with a measure of the ICV.

Table 8

Descriptives of the volumes of gray matter ROIs (n= 39)

Variable	M	SD	Min	Max
RH RMF	12822.54	1583.85	9353.00	16089.00
LH RMF	12254.97	1612.92	8883.00	15387.00
RH PP	32470.33	3236.06	26444.00	42943.00
LH PP	30574.21	3134.35	23122.00	38258.00
ICV	1228862.38	185683.60	940081.00	1629063.00

Note. Measures in mm^3 . RH= Right Hemisphere. LH= Left Hemisphere. RMF= Rostral Middle Frontal. PP= Posterior Parietal. ICV= Intra Cranial Volume.

Relationship between the D-KEFS TMT and gray matter volume. Prior to analyses the variables were evaluated for accuracy of data entry, linearity, and fit between their distributions. Shapiro-Wilk's test of normality and graphs shows no deviation from normality for the variables. Two cases were univariate outliers because of their extremely small volume in the left posterior parietal gray matter, and extremely large volume in right posterior parietal gray matter, respectively. The first outlier was retained in the study as the value was not too different from the remaining distribution, and the mean value and the value for the 5% Trimmed mean were very similar. The case was also found to have small, although not extreme, gray matter volumes in the other ROIs. The second outlier deviated substantially from the rest of the distribution, and was deleted from the study, leaving 38 cases in the sample.

Table 9 displays the correlations between volume in the gray matter ROIs produced by Freesurfer, the D-KEFS TMT and age. The volume in the gray matter ROIs were found to correlate significantly with each other. The correlations were strong and positive, ranging from $r = .61$ to $r = .79$. The intra cranial volume correlated significantly with volume in the posterior parietal ROIs, and also with the right rostral middle frontal ROI. These correlations were positive and moderate to strong. A moderate significant correlation was seen between the ICV and the D-KEFS TMT-scan, -letter, and -switch. The only gray matter ROI that showed a significant correlation with any of the conditions from the D-KEFS TMT was the right rostral middle frontal ROI that correlated moderately with TMT-switch.

A sequential multiple regression analysis was employed to investigate the ability of the Right rostral middle frontal ROI to predict the result on TMT-switch, after controlling for the influence of age and ICV, and TMT-scan and TMT-letter. Results of evaluation of assumptions was satisfactory regarding normality, linearity, multicollinearity, and homoscedasticity of residuals. With the use of a $p < .001$ criterion for Mahalanobis distance no outliers were found.

Table 10 displays the unstandardized regression coefficients (B), Standard Error (SEB), the standardized regression coefficients (β), the R Square Change (Δsr^2_i), and values for R , R^2 , and adjusted R^2 .

R was significantly different from zero at the end of the two first steps but not at the end of the third. The adjusted R^2 value of 0.53 indicates that more than half of the variability in TMT-switch is predicted by the independent variables in the analysis. Age and intra cranial volume was entered at step 1, explaining 29 % of the variance in TMT-switch. After entry of TMT-scan and TMT-letter, the explained variance was 55 %. In the last step the right rostral

middle frontal gray matter volume was added, and the total variance explained by the model was 60 %, $F(5,32) = 6.12, p < .001$. The last step, the gray matter volume, only added another 4% to the model and was not statistically significant. In the final model only TMT-scan was statistically significant, with a beta value of $\beta = .46$.

Table 9

Correlation matrix for Gray Matter Volume, the D-KEFS TMT and Age (n=38)

Variable	1	2	3	4	5	6	7	8	9	10	11
1. RH RMF		.65**	.61**	.68**	.59**	.10	.01	.20	.34*	-.13	.14
2. LH RMF			.70**	.59**	.25	-.21	-.10	-.03	.10	-.19	.13
3. RH PP				.79**	.35*	-.26	-.23	-.06	-.01	-.30	-.16
4. LH PP					.44**	-.14	-.16	-.09	.01	-.18	-.03
5. ICV						.40*	.14	.39*	.43**	.08	.54**
6. TMT-scan							.51**	.53**	.67**	.36*	.51**
7. TMT-number								.58**	.54**	.38*	.18
8. TMT-letter									.62**	.49**	.54**
9. TMT-switch										.35*	.50**
10. TMT-speed											.27
11. Age											

Note. RH= Right Hemisphere. LH= Left Hemisphere. RMF= Rostral Middle Frontal. PP= Posterior Parietal. ICV= Intra Cranial Volume. TMT-scan and TMT-switch was transformed with square root, TMT-number, TMT-letter, and TMT-speed was logarithmically transformed. * $p < .05$. ** $p < .01$.

Table 10

Sequential Regression Analysis Predicting result on TMT-switch from Age, TMT-scan, TMT-letter, and Gray Matter Volume in the Right Rostral Middle Frontal (n=38)

Variables	<i>B</i>	<i>SE B</i>	<i>Sri</i> ²	<i>R</i> ²	<i>Adj. R</i> ²	<i>R</i>
Step 1			0.29	0.29	0.25	0.54**
Age	0.14*	0.06	0.38			
ICV	0.00	0.00	0.22			
Step 2			0.27	0.55	0.50	0.74**
TMT-scan	1.29**	0.44	0.43			
TMT-letter	4.45*	2.10	0.32			
Step 3			0.04	0.60	0.53	0.77
RH RMF	0.00	0.00	0.27			

Note. TMT-scan and TMT-switch transformed with square root, TMT-letter was logarithmically transformed. RH RMF= Right hemisphere rostral middle frontal. **p*< .05. ***p*< .01

Discussion

The aims of this study were to explore the contribution of component processes in a set-shifting task in patients experiencing cognitive difficulties, and to investigate the relationship between set-shifting and its association with WMH and gray matter volumes in the frontal and parietal lobes.

Set-shifting and Component Processes

The first aim was to explore the relationship between set-shifting and component processes.

Consistent with the study made by Sánchez-Cubillo et al. (2009) there is a strong correlation between TMT-switch and TMT-number, and in the present study there are also strong correlations between TMT-switch and TMT-scan and TMT-letter, and a moderate correlation with TMT-speed. The direction of the correlations suggests that poorer performance on TMT-switch is made by patients who also perform poorly on the other conditions.

TMT-switch correlated moderately to strong with the other conditions, but only TMT-scan and TMT-letter contributed significantly in predicting the unique variance of the TMT-switch. The importance of visual scanning in set-shifting is a finding consistent with previous research made by Crow (1998). Even though there was a significant correlation between

TMT-switch and both TMT-number and TMT-speed, the two latter tasks did not contribute significantly to prediction of performance on the TMT-switch. One interpretation is that the performance on the set-shifting task is so cognitively demanding that a person's motor-speed abilities are not crucial for the performance on TMT-switch. It is also possible that too few of the patients had an attenuated motor speed. This may be an effect of the inclusion criteria, where patients who did not complete the tests within time limits were excluded. This is also implied by the results on TMT-speed, where the mean score corrected for age was 11.23. Likewise, number sequencing is a highly automated skill that may not demand the same cognitive effort as the set-shifting task.

Age was not found to add to the prediction of TMT-switch after the last step of the sequential regression analysis. This may be due to the restricted range of age in the patients. They were between 60 and 80 years old. It is possible that age might be a predictor of TMT-switch if there had been a larger variance in age.

Set-shifting and its Neural Substrates

Another aim of the study was to evaluate the relationship between set-shifting and WMH and gray matter volume, respectively.

The first hypothesis predicted that TMT-switch would correlate with WMH in the frontal and parietal lobes. The correlation analysis undertaken to investigate the relationship between the results on TMT-switch and WMH in the frontal and parietal lobes showed no significant results. This result did not confirm the findings in previous research, suggesting that WMH is related to a slower performance on tasks of processing speed and executive functions (Gunning-Dixon & Raz, 2000; Smith et al., 2011). The posterior parietal lobes showed weak significant correlations with TMT-switch. This possibly reflects the parietal lobe's importance in visuospatial tasks. In each lobe, between 75.8 % and 91.9 % of the cases were rated as having a presence of WMH. This suggests that WMH can be present in individuals without influencing the performance on set-shifting tasks.

The second hypothesis was that results on TMT-switch correlates with gray matter volumes in the frontal and parietal cortices, more specifically the rostral middle frontal gyri and the posterior parietal region.

The results on TMT-switch correlated significantly only with the gray matter volume in the right rostral middle frontal ROI, suggesting that less gray matter volume in this area means poorer performance on the TMT-switch. This indicates further that the found association is not just an effect of the results on TMT-switch correlating with a general loss of

gray matter volume throughout the brain, caused by age or degenerative diseases of the brain. The finding is consistent with literature proposing prefrontal functioning in set-shifting tasks (McDonald et al., 2005; McDonald et al., 2012; Pa et al., 2010; Shibuya-Tayoshi et al., 2007; Yochim et al., 2007). Some studies have found bilateral involvement in the set-shifting task (McDonald et al., 2012; Pa et al., 2010). This is not supported by the results in this study. It does support the results Jacobson et al. (2011) found during an fMRI study, of a right sided frontal activation. Still, some studies have suggested a left sided involvement in set-shifting (Moll et al., 2002; Zakazanis et al., 2005), both fMRI studies.

The importance of controlling for component processes when investigating set-shifting has been stressed in literature (Kramer et al., 2007; Pa et al., 2010). Forty percent of the variance in TMT-switch could be predicted from knowing the scores on the other four conditions. However, a sequential regression analysis showed that while controlling for age, intra cranial volume, TMT-scan, and TMT-letter the volume of the right rostral middle frontal ROI did not contribute significantly to the prediction of the performance on TMT-switch. Based on literature, it is likely that cortical atrophy, leading to a reduction in gray matter volume, would explain some of the variance in set-shifting, but the findings do not support this. This result may be due to lack of power in this sample ($n=38$).

The literature is discrepant, as seen above, in what the neural substrates of set-shifting are. Kramer et al. (2007) suggest that the different results may be due to methodological issues, since set-shifting cannot be measured outside the context of component processes. The different brain imaging techniques can also be said to influence the results of the studies (Shibuya-Tayoshi et al., 2007). In some studies smaller, well defined, areas are considered relevant for set-shifting. Other studies have more diffuse, less defined areas.

Limitations

One problem with the results of the D-KEFS TMT is the time limits of the five conditions. This means that the maximum raw score can be only 150, in the cases of TMT-scan, -number, -letter, and -speed, and 240, in the case of TMT-switch. This means that ten patients were excluded from the study due to slow performance on one or several of the conditions. The underlying reason for the patients not finishing within the time limit is unknown, and may be attributed to either set-shifting or any of the component processes. However, it is a possibility that these were the individuals with the poorest performance on the set-shifting task and the most WMH and loss of gray matter volume. This is unfortunate, as they probably would have made a contribution to the study by increasing the variance of

the variables. However, these are the instructions of test administration, and also in a clinical context with people experiencing cognitive difficulties it is probably not ethical to make a person continue beyond these limitations (Delis et al., 2001a).

Several issues regarding the chosen methods for the gray matter analyses can be addressed. Freesurfer is a freely available program, making it possible to analyze large samples with an automated procedure. The gray matter volumes were not controlled after the Freesurfer analysis. It is thus possible that the program has made wrong measurements, and may have resulted in volumes that were not correct. However, only a few outliers were observed, and the distribution of normality did not show signs of deviation.

The selection of brain regions in the study was based on literature. It is possible though, that areas relevant for the study were missed out. For example, the periventricular hyperintensities may show a significant relationship with TMT-switch, as found in the study by Smith et al. (2011).

There were also some difficulties in translating previously defined relevant areas in the frontal and parietal cortices to the automated anatomical ROIs from the inbuilt atlases of FreeSurfer. The outlines of the functional ROIs were not consistent in literature, with variation in both location and size. The posterior parietal ROI used in this study were composed of three different ROIs from the Desikan-Killiany atlas. It is likely that the posterior parietal ROI covered too large an area, and it is also likely that the rostral middle frontal ROI may have covered a smaller area than the functional dorsolateral prefrontal cortex. The ROIs may have excluded relevant brain areas and included less relevant areas.

A variable that was excluded from the study was education. It is possible that education would have contributed in predicting performance on TMT-switch. It could be of relevance to explore the role of education in this sample of restricted age range.

Several statistical analysis were performed in this study, but no Bonferroni correction was performed to control for the probability of a type1 error, due to few significant results.

Future research

One way of including individuals who performed the D-KEFS TMT so slowly that they did not complete the test within the time limits, would be to use the measures of set-loss error and time-loss error provided in the D-KEFS manual (Delis et al., 2001a).

Set-shifting was only measured by one neuropsychological test, TMT-switch. There exists other tests that are said to measure set-shifting, for example Verbal Fluency, Color-Word Interference and Design Fluency of the D-KEFS (Delis et a., 2001) that may, or may

not, show different results in which component process are used and what the neural correlates are.

If WMH and gray matter volume do not predict the performance on the D-KEFS TMT-switch, in a group of patients experiencing cognitive difficulties, then what does? This group of patients might be heterogenous and nothing is known of their diagnosis or other cognitive functioning. It might be worth looking for other factors too, such as psychological factors, contributing to the performance on TMT-switch.

Conclusions

All conditions of the D-KEFS TMT showed an association with TMT-switch, but only TMT-scan and TMT-letter contributed significantly in predicting the variance of TMT-switch.

According to this study there are no significant relationships between the results of the TMT-switch and the WMH in the frontal and parietal lobes, in a group of elderly individuals experiencing cognitive impairments.

Even though there was a significant association between TMT-switch and the right rostral middle frontal ROI, the association was no longer significant after controlling for age, intra cranial volume and component processes.

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