Abstract

Background: Transient Ischemic Attack (TIA) can lead to lasting changes in brain structure and function resulting in cognitive impairment. Cognitive screening tools may lack sensitivity for detecting cognitive impairments, particularly executive function, which tends to be the earliest affected domain in vascular cognitive impairment.

Aim: In this preliminary study, we examine a working memory (WMem) task as a sensitive measure of cognitive impairment in TIA.

Method: Patients referred to a TIA clinic for transient neurological symptoms completed a general cognitive screening tool (Montreal Cognitive Assessment; MoCA), and a WMem task (2-N-back) in a cross-sectional design.

Results: TIA patients (n=12) showed significantly reduced WMem performance on the N-back compared to patients diagnosed with mimic clinical conditions with overlapping symptoms (n=16). No group differences were observed on the MoCA.

Conclusions: Assessing WMem may provide a sensitive measure of cognitive impairment after TIA, with implications for cognitive screening in TIA services to triage patients for further neuropsychological support, or for interventions to prevent vascular dementia.

Introduction

Transient Ischemic Attack (TIA) is defined as a transient episode of cerebral ischemia not associated with permanent cerebral infarction lasting <24hours (Easton et al., 2009). The rapid resolution of overt symptoms combined with a focus on stroke prevention, means that little/no time is given for thorough neuropsychological evaluation (Kjörk, Blomstrand, Carlsson, Lundgren‐Nilsson, & Gustafsson, 2016). However, recent findings suggest that TIA may lead to lasting changes in brain structure and function, with a third of patients experiencing persistent mild cognitive impairments (van Rooij, Kessels, Richard, De Leeuw, & van Dijk, 2016). In primary care settings, TIA patients were also more likely to consult for fatigue, psychological and cognitive impairment compared with controls, for which they were not routinely offered rehabilitative support (Turner, Calvert, Feltham, Ryan, & Marshall, 2016).

Lack of recognition of these neurological and cognitive symptoms means that TIAs are often poorly characterised. If left untreated, cognitive impairment can adversely impact on quality of life, daily activities, and employment (Kjörk et al., 2016). Understanding these cognitive consequences could help characterise TIA and design tailored multidisciplinary interventions (e.g. lifestyle changes, medication, cognitive rehabilitation) that improve functional recovery and avoid further cognitive decline (Charoenkitkarn, Kasemkitwattana, Therrien, Thosingha, & Vorapongsathorn, 2009).

Currently, the extent and duration of cognitive impairment post-TIA remains unclear (Ganzer, Barnes, Uphold, & Jacobs, 2016; van Rooij et al., 2016), with prevalence estimates ranging from 29 to 68% for mild cognitive impairments (van Rooij et al., 2016). This heterogeneity might relate to the cognitive assessments used. Existing research has focused on traditional cognitive screens, including the Montreal Cognitive Assessment (MoCA (Nasreddine et al., 2005)) and modified Telephone Interview for Cognitive Status (TICS-m (Brandt, Spencer, & Folstein, 1988)). These global screens are often preferred because they are quick to administer during busy

clinics or in waiting rooms but lack the specificity to probe relevant cognitive abilities, including executive function which tends to be the earliest affected domain in vascular cognitive impairment (expected post-stroke) (Sachdev, Brodaty, Valenzuela, Lorentz, & Koschera, 2004). Moreover, since these screening tools were developed to delineate cognitive impairment due to dementia, they may be insensitive to milder impairments in younger populations (van Rooij et al., 2016). The limited number of studies using more comprehensive neuropsychological batteries show lower rates of cognitive impairment post-TIA relative to general screening tools, but highlight specific deficits in executive function (Sörös, Harnadek, Blake, Hachinski, & Chan, 2015).

Core executive functions include inhibition, working memory (WMem), and cognitive flexibility. Disruption to frontal-subcortical circuits and pre-frontal ischaemia, resulting from interruption of the anterior cerebral circulation, as well as hippocampal dysfunction caused by posterior cerebral circulation ischaemia, are thought to underlie these executive function deficits post-TIA (Charoenkitkarn et al., 2009; Zamboni et al., 2017). Infarcts in the middle cerebral artery (MCA) have also been associated with greater likelihood of cognitive impairment on measures designed to capture global cognitive performance (Weaver et al. 2021; Jaillard et al. 2010). Anecdotally, TIA patients often report difficulties with remembering information and using this information to respond to what is going on around them (Stroke Association, 2014), which relates closely to WMem. WMem supports several important cognitive processes (e.g. learning, active listening, long-term memory) that are crucial for vocational and social activities (Moser et al., 2018). Variation in WMem might therefore be a sensitive indicator of mild disturbances, including TIA or pre-symptomatic vascular cognitive impairment. However, WMem is not measured in standardised cognitive screens such as the MoCA (Nasreddine et al., 2005) and Addenbrooke's Cognitive Examination-iii (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006), meaning the presence and impact of WMem deficits may be under-recognised in TIA.

The neuropsychological and neuroanatomical profile of TIA and vascular patients indicates WMem could be a sensitive indicator of cognitive status. We therefore compared the WMem performance of patients diagnosed with TIA against those with a mimic clinical condition with overlapping neurological symptoms but without the pathophysiological changes that characterise TIA (e.g. migraine, seizures, syncope; (Nadarajan, Perry, Johnson, & Werring, 2014)) via a brief, computerised, N-back task that was feasible to apply during busy clinics. N-back tasks require participants to maintain and update a dynamic rehearsal set while responding to each item, placing complex demands on WMem (Kane, Conway, Miura, & Colflesh, 2007). Global cognitive function was also measured using the MoCA (Nasreddine et al., 2005), a frequently used test for patients with cerebrovascular disease in clinical settings.

This study used a cross‐sectional, between-groups design to compare the cognitive performance of TIA and mimic patients. We hypothesised that WMem performance would be reduced amongst patients with TIA versus a mimic condition.

Materials and Methods

Ethical approval for our procedures was obtained from the NHS Research Ethics Committee (16/WS/0153). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants provided informed consent prior to data collection.

Participants and Recruitment

Patients were recruited concurrently via convenience sampling from a TIA clinic at a regional neurosciences centre (North Bristol Trust, UK). All patients were referred with transient neurological symptoms where the referrer suspected a TIA.

Exclusion criteria for all groups included other neurological disease, significant psychiatric disorder, severe cognitive impairment, or active/previous substance abuse. Patients taking medication known to affect cognitive performance such as medication acting on the GABA-ergic system e.g. benzodiazepines, gabapentin, were also excluded.

Data Collection

All patients were seen within 48hours of symptom onset and received brain imaging (CT or MRI), electrocardiogram, blood pressure measurement and completed the MoCA and N-back task in-clinic; prior to a face-to-face consultation with a consultant neurologist/physician where a diagnosis was made. Where brain imaging showed evidence of acute ischaemia in a vascular territory consistent with a patient's symptoms, this confirmed the ischaemic nature of the symptoms and a TIA diagnosis was made. Where brain imaging did not show evidence of acute ischaemia, but also did not show an alternative cause for a patient's symptoms, the diagnosis was made according to the opinion of the consultant, considering clinical presentation and other factors (e.g. vascular risk factors) in accordance with usual care. Patients with mimic conditions presented with similar symptoms to a TIA (e.g. visual disturbances, headache, numbness, weakness) but did not have acute ischaemic changes or other diagnoses based on brain imaging. To minimise potential bias, both patients and researchers were blind to the diagnostic grouping (TIA versus mimic) at the point of data collection.

Participants completed a clinical interview and the MoCA (v7.1). WMem performance was assessed using a brief 2-N-back task in which participants viewed a series of numbers from "0" to "4", presented in a random sequence using PsychoPy©. On each presentation participants were asked to indicate, using a computer keyboard, whether the currently presented stimulus was the same as the stimulus presented *2*-trials back or different. Participants completed 10 practice trials and 120 experimental trials (*M* task duration= 322.14s), with a 25% chance of each trial being a target. A fixation cross was presented between trials in the centre of the screen for 300ms, and

stimuli remained on the screen until participants responded.

Analysis

Differences in the demographic profiles of the TIA and mimic groups were first tested using a *t*-test (age) and Chi-square tests (gender and education). A one-way analysis of variance (ANOVA) with Bonferroni correction for multiple testing was then performed to examine effects of diagnostic group (TIA, mimic) on the MoCA (total score) and N-back (sensitivity and reaction time (RT)).

Results

Study participants

Twelve TIA patients (mean age 67 (±10), 6 females) and 16 patients with mimic conditions (mean age 53 (±17), 9 females) took part. Characteristics for both groups are presented in Table 1. Between group differences in age were identified, whereby the TIA group were significantly older than the mimic group. No group differences in gender or education level were present.

<< Insert Table 1 here >>

General cognitive performance

Seven TIA and nine mimic patients showed clinically significant cognitive deficits on the MoCA according to the cut-off score (MoCA total score of 26) proposed by Nasreddine et al. (2005). Age was negatively correlated with MoCA total score, $r(28)=-0.40$, $p=0.037$, and was therefore included as a covariate in subsequent analyses. An ANCOVA showed there were no significant between-group differences in the total score (see Table 2). Descriptive statistics for MoCA subscale scores are presented in the Supplementary Materials.

<< Insert Table 2 here >>

Working memory performance

WMem performance during the N-back task was quantified using d', a sensitivity index based on signal detection theory. This measures a participant's ability to differentiate a target from a non-target and is based on z-scores of Hit (correctly classifying a stimulus as the same as the stimulus presented 2-trials back) and False Alarm (incorrect classification of a different stimulus as the same as the stimulus presented 2-trials back) rates, using the formula: d' = zHit−zFalse Alarm (Macmillan & Creelman, 1990). It is relatively robust to differences in response bias and the preferred measure for assessing N-back performance (Haatveit et al., 2010). Descriptive statistics for Hit and False Alarm rates are presented in the Supplementary Materials.

Across the study cohort, general cognitive performance on the MoCA (total score) was positively correlated with d', $r(28)=0.36$, $p=0.06$.

Age was negatively correlated with d', $r(28)=-0.44$, $p=0.02$, and was therefore included as a covariate in subsequent analyses. The ANCOVA showed performance was significantly reduced in the TIA group (see Table 2 and Figure 1).

Age was not significantly correlated with RT to targets, $r(28)=0.08$, $p=0.692$. Independent samples t-tests showed no statistically significant differences between diagnostic groups in RTs for Hits, $t(26)=-0.31$, $p=0.761$, or False Alarms $t(26)=-0.19$, $p=0.854$.

<< Insert Figure 1 here >>

Discussion

The current study investigated the cognitive consequences of TIA using a traditional cognitive screening tool (MoCA), and a targeted WMem assessment (N-back) designed to provide a sensitive indicator of the executive function deficits commonly found in TIA and vascular impairment. We provide evidence to support our hypothesis that WMem performance is significantly reduced in TIA patients compared to those with mimic conditions, and that associated measures of global cognitive ability such as the MoCA, are insensitive to these deficits.

Our results are the first to show that WMem, a core executive function, is altered following TIA and complement recent studies showing deficits in executive functions (Sachdev et al., 2004; Sörös et al., 2015; van Rooij et al., 2016). These results further emphasize the need to consider cognitive impairment, especially relating to executive function, during the routine work-up of TIA patients.

Further research is required to explore the functional impact of post-TIA WMem impairments. WMem (ability to hold information in mind temporarily) is relevant to activities of daily living, including vocational and social activities, therefore the reductions in WMem performance revealed in this study may have important consequences for TIA patients' independence and quality of life (Fitri, Fithrie, & Rambe, 2020). Identification of post-TIA WMem impairments might therefore prompt further vocational or occupational assessments and inform multidisciplinary rehabilitation plans (e.g. reduce environmental distractions, reminders to take medications, increase efficiency of encoding rehabilitation strategies).

The marginal correlation observed between the MoCA and N-back indicates WMem performance may also provide a sensitive marker of more generalized cognitive impairments including attention, concentration, and recall. Nevertheless, we maintain that the sensitivity of the N-back to group differences between the mimic and TIA cohorts suggests that WMem is more than a simple proxy measure of general cognitive impairment. In this case, a brief WMem task might be used to triage patients for more comprehensive neuropsychological assessment, which is unlikely to be feasible for all TIA patients within routine clinical practice. The N-back is simple to administer and lends itself to use in busy, time-pressured, TIA clinics such as the UK National Health Service TIA clinic at North Bristol Trust where this study was carried out. Our participants were able to independently perform the task following a short briefing during which they were given the opportunity to ask questions. With further development, N-back tasks could be readily

streamlined and administered on portable devices with automated algorithm score generation to facilitate completion in-clinic or remotely via tele-neuropsychology, to aid care provision.

Further studies also need to determine the mechanisms and clinical sensitivity of post-TIA WMem impairments (van Rooij et al., 2016). Changes in frontal lobe circuitry, particularly the degradation of white matter tracts connecting to posterior and subcortical regions, could underlie the effects observed here and in previous studies measuring executive function (Sörös et al., 2015). Measures of frontal white matter integrity could establish whether post-TIA WMem impairment reflects underlying white matter microvascular disease, and might be an early objective marker of vascular cognitive impairment. Longitudinal investigations of patients with and without post-TIA WMem impairments will help determine the predictive value of WMem for future vascular cognitive impairment and dementia. Importantly, if WMem provides an early marker of vascular cognitive impairment, it may have utility for selecting patients who may be candidates for targeted preventative interventions such as tight blood pressure control. This also warrants further investigation.

The current study should be considered in the context of several limitations. Our sample sizes are small and reflect the exploratory nature of the study; the generalisability of the findings is therefore limited. Nevertheless, they add to previous evidence of executive dysfunction in TIA and provide impetus for future studies to examine WMem post-TIA. Future studies should examine the persistence and functional consequences of the acute WMem performance reductions demonstrated here. Assessing cognition at multiple time points will help elucidate the long-term effects of TIA, as well as the impact of transient factors (e.g. stress or delirium). N-back performance is dependent not only on WMem but also attention and processing speed. Future studies should therefore examine a range of validated WMem tasks to isolate distinctive WMem components (e.g. capacity, interference), as well as measures of attention and processing speed to characterise any overlapping deficits (Moser et al., 2018) and evaluate the sensitivity and

specificity of these WMem tasks. Strengths of this study include the unique focus on WMem functioning in TIA using a targeted assessment capable of identifying mild cognitive impairments, within realistic clinic settings, and the blinding of both patients and researchers to the diagnostic grouping during data collection.

In conclusion, altered WMem appears to be relevant in TIA. Changes in frontal lobe circuitry potentially indicative of early vascular impairment are thought to underlie these effects, as well as the contribution of WMem to multiple cognitive processes pertinent to daily activities. Our results have important implications for neuropsychological assessment, rehabilitation, and preventative interventions in TIA.

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Ethics Standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Data Availability Statement: Anonymous data that support the findings of this study will be made openly available on the Open Science Framework [OSF public data archive].

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