Significant Group-Level Brain Activity during Trail-Making Test Performance

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Acknowledgments

This replication study is supported by the Cognitive Science and Psychology branch of ULAB (Undergraduate Lab at Berkeley) at the University of California, Berkeley. We would like to express our sincere gratitude to our graduate student mentor, Logan Thomas, for his guidance throughout the study and for his valuable feedback. We would also like to thank all of the members of ULAB Board, who gave us encouragement, input, and the resources to complete this replication.

Abstract

The trail-making test (TMT) is a neuropsychological test that is often used to identify cognitive impairment and dementia. This paper replicates a study that utilized the TMT and an fMRI to determine differences in brain activity across 36 healthy participants between the ages of 52 and 85 years old. Two TMTs were given, three trials of TMT-A and three trials of TMT-B, and data was collected on the speed and accuracy of which the participants completed each of the six trials. The replication is focused specifically on determining if there are neuroanatomical regions of the brain that show significantly different activity during the TMT-A and TMT-B, as well as if there was positive or negative activation in those areas. Significant group-level activation in brain regions during the TMT-A versus TMT-B was found using Python, and activation in those significant clusters during both tests was compared using a t-test. The replication yielded different t-statistics compared to the original study as slightly different significant clusters were analyzed. The hypothesis was that overall, both trail-making tests would show positive activation in regions of the brain involved with spatial learning, coordination, and memory retrieval when compared to group-level activation of the control condition. Moreover, since TMT-A and TMT-B require different cognitive skills, it was hypothesized that the TMT-B would show increased activation compared to TMT-A in regions of the brain dealing with task-switching and memory retrieval.

Key Terms: Alzheimer's Disease, Trail-making test, neuropsychological, fMRI, clusters, voxels, group-level activation

Introduction

Alzheimer's Disease

Alzheimer's Disease (AD) is among the most prevalent forms of cognitive failure in older adults. In 2020, 5.8 million Americans aged 65 or older were diagnosed with AD (Alzheimer's Association, 2020). AD is a progressive, neurodegenerative disease characterized by cognitive decline and caused by neuronal loss, plaques containing the peptide β amyloid, and neurofibrillary tangles (Nussbaum & Ellis, 2003). Common symptoms include impairment in memory, judgment, decision-making, orientation, and speech (National Institute on Aging, 2017).

The Trail-Making Test

The trail-making test (TMT), first introduced in 1938, is a neuropsychological test used to assess mental flexibility, visual search speed, task switching, and psychomotor speed. Often, the TMT is used as a screening tool for neurological disorders such as AD because individuals with AD display cognitive deficits in areas such as memory, visual attention, and executive function (Shindo et. al, 2013).

The test consists of two parts: TMT-A, in which the subject is asked to draw lines to connect numbers in an ascending numerical sequence and TMT-B, in which the subject is asked to draw lines to connect numbers and letters in ascending numeric and alphabetic order. On both tests, there are two conditions imposed: to perform the task as quickly as possible while maintaining accuracy and to always keep the tip of the pen on the page. Both tests are scored by relating the time of completion to the number of errors made (Salthouse, 2011).

Current literature on the Trail-Making Test and AD

There has been limited research examining cognition in Alzheimer's patients using the TMT.

One study explored the regional perfusion patterns of the brain by measuring oxygenated blood flow in 18 AD patients with poor performance on the TMT-A and 36 AD patients with good performance (Shindo et al., 2013). It was found that the group who scored poorly on the TMT-A had reduced activity in the bilateral superior parietal lobule, which deals with spatial orientation, compared to the group who scored well on the TMT-A (Shindo et al., 2013).

Another study compared differences in TMT performance among three groups: normal controls, mild cognitive impairment (MCI), and AD. The downside of this study is that the AD sample size was much smaller than the MCI and control groups due to cognitive limitations that prevented AD participants from completing the TMT. However, the study found that TMT error rate was less susceptible to age differences than time to completion; hence, errors may be a consistent measure of impairment across one's lifespan. It was also found that error rate and time to completion were not dependent on one another, indicating that both variables could be independently meaningful. Therefore, it is possible that these two variables could have clinical significance in assessing individuals for AD (Ashendorf et al., 2008).

Functional Magnetic Resonance Imaging of the TMT

Functional Magnetic Resonance Imaging (fMRI) is a type of imaging that can be used to measure and map brain activity by detecting oxygenated blood flow in the brain. The fMRI creates an activation map that shows which parts of the brain are active during the scan in order to determine areas of the brain used for critical functions, and to guide treatment (Radiological Society of North America, 2018). An fMRI machine can be used in conjunction with the TMT to determine which parts of the brain are active during the completion of the test. Voxels, which are small cubes of brain tissue, can also be analyzed to show correlation between regions of the brain and different TMT tests.

One study used the TMT along with an fMRI and virtual stylus to gather data on 12 right-handed healthy adults (Konstantine et al., 2005). The results showed increased brain activity in the frontal regions of the brain (Konstantine et al., 2005). In addition, certain neuroanatomical regions in the left frontal lobe have been found to be more strongly associated with TMT performance than the right frontal lobe. Evaluating response speed, patients with left frontal damage were slower than patients with right frontal or non-frontal damage (Stuss et al., 2001). Likely due to its greater complexity, the TMT-B elicited activity from more areas of the brain. A particularly large cluster of activity in the left hemisphere was observed to be more sensitive to TMT-B than to TMT-A, including the middle frontal gyrus, precentral gyrus, cingulate gyrus, superior frontal gyrus, medial frontal gyrus, and insula (Zakzanis et al., 2005). Voxel-based lesion-behavior analyses also identified a significant association between damage in the dorsolateral prefrontal cortex (DLPFC) and TMT-B total errors (Kopp et al., 2015). Left hemispheric DLPFC activity, in particular, was found to directly impact TMT performance, since the left cerebral hemisphere is typically involved in tasks requiring rapid action and cognitive shifts, such as switching between numbers and letters in the TMT-B (Zakzanis et al., 2005). Other lesion studies have also found similar results in which patients with DSPFC damage were more impaired in TMT-B than other patients with other frontal lobe lesions (Stuss et al., 2001).

Outside the frontal lobe, the left temporal regions were observed to have considerable brain activity in TMT-B. Zakzanis et al. (2005) identified a pattern between the middle and superior temporal gyri of the left temporal lobe and impaired performance on TMT-B. Similarly, Nickel et al. (2003) found that participants with hypometabolism in the regions identified by Zakzanis et al. (2005) had significantly impaired TMT performance. Both findings are consistent with the left temporal lobe's role in working memory.

Present Study

The present study replicates both TMT-(A+B)-fixation and TMT-(B-A) conditions to look for regions of the brain that indicate significantly different activation during trail-making test tasks. The replication focuses on analyzing activation to determine if there are differences in activity between TMT-A and TMT-B, and if there are any overall changes in activation while completing the trail making tests. In TMT-(B-A), positive activation indicates that there is more activation in the brain during TMT-B than TMT-A and negative activation indicates that there is more activation in TMT-A than TMT-B. TMT-(A+B) compares the effects of both TMTs to the fixation condition, which controls for attention as participants are asked to stare at a black cross on a white screen. In TMT-(A+B), positive activation refers to increased activation in brain regions as compared to the control condition and negative activation shows decreased activation compared to the control.

Methods

Participants

Participants (N=37) in the original study were recruited from one local community and were between the ages of 52 to 85. The participants were screened for any neurological or psychiatric conditions. All participants included in the analysis had a score of 2.5 standard deviations above the mean on the Montreal Cognitive Assessment test, which was used to assess cognitive impairment. Other inclusion criteria included being right-handed, not having a history of substance abuse, and being fluent in English.

MRI-Compatible Tablet Set-up

In order to replicate a traditional pen-and-paper TMT that was compatible with an MRI, a

stylus and touch-screen tablet were paired with an augmented reality system. The tablet was positioned at the waist of each participant and the task was projected above using an MRI-compatible projector. Therefore, the participants were able to complete the TMT tasks while in the supine position.

Procedure

Each participant was familiarized with the TMT before the three trials of the TMTs were run, in order to minimize differences in the trials due to the participants becoming more acclimatized to the set-up and task. The instructions for both the TMT-A and TMT-B tasks were also explained to the participants and each run of the TMT-A consisted of 25 numbers to link and each run of the TMT-B consisted of 13 numbers and 12 letters (A-L) to link. There were three trials of the fMRI time series data collected for each participant, with two runs within each trial, so there were six trials conducted in total. One run consisted of two 40-second TMT-A tasks alternated between two 60-second TMT-B tasks. For 10 seconds in between each TMT-A or TMT-B task, there was a 10-second visual fixation condition where the participant had to focus on a black cross in a white background to control for attention.

Behavioral Outcome Measures

In order to assess performance on the TMT and conduct data analysis, the completion time needed to be measured for each run of each participant. However, the researchers predicted that not all participants would be able to complete either the TMT-A or TMT-B within the allotted time during each run. Therefore, a normalized metric, seconds-per-link (SPL) was developed and divided the total completion time for each TMT section by the number of links correctly drawn on the tablet. Another measure, the number of errors (N_E) was also calculated to make sure the results of the tablet-based TMT were similar to the results of the paper-based

TMT. Lastly, TMT-(A+B) was calculated by averaging the measures collected during all 6 trials to assess the overall effect of both tasks and TMT-(B-A) was calculated by subtracting the measures for TMT-A from the measures of TMT-B. The purpose of calculating TMT-(B-A) was to separate the TMT-B results from the TMT-A results.

Replication Data Analysis

Many tests were performed on the data collected for TMT-(A+B) and TMT-(B-A) to assess the effects of age on seconds-per-link, the correlation between the paper-based TMT and the novel-based TMT, as well as brain activity during both TMT tasks. The replication of the present study focuses on the two outcome measures, TMT-(A+B)-fixation and TMT-(B-A). The replication for the first outcome measure tests for overall differences in activation between TMT-A and TMT-B compared to a control condition. Replicating the latter outcome measure assesses regions of the brain with significantly different activity during the TMT-A vs TMT-B task.

Python and Jupyter Notebook were used to complete all replication analysis. First, the fMRI data collected for all participants was masked to locate the significant activation clusters and a subset of voxels in various regions of the brain was assessed. Then, an independent sample t-test was used for voxels that were significantly non-zero for all participants. P-values was calculated to determine whether there was a significant difference in the mean of the results between TMT-(A+B) and fixation, as well as between TMT-A and TMT-B. Ten different clusters were analyzed to find the four regions in each brain activation map that were most significant and had the greatest amount of positive or negative activation (shown by the most positive or negative t-statistics). The clusters were considered significant if the t-statistics gave a p-value less than 0.05 and the four regions identified had the lowest p-values. Positive activation for

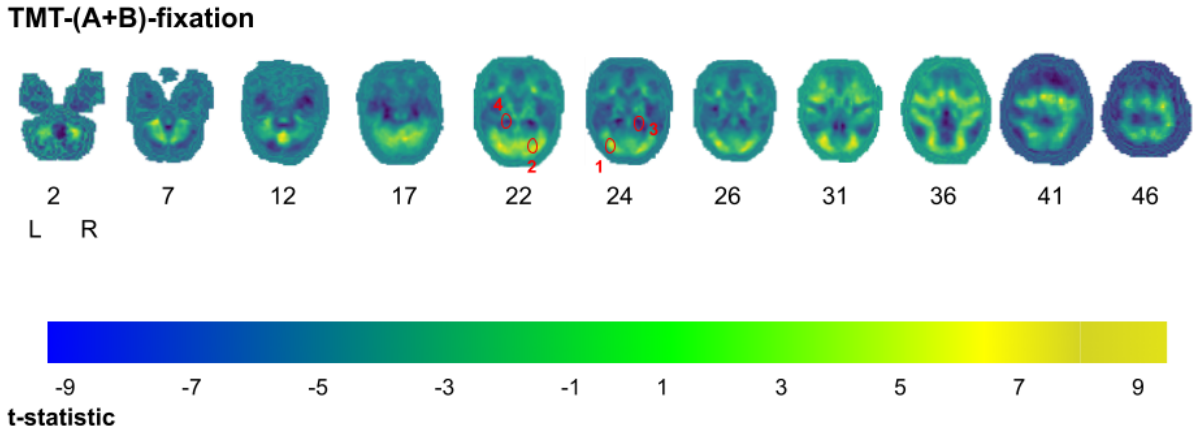
TMT-(A+B)-fixation is defined as increased activity in both trail making tests compared to the fixation control and negative activation is defined as decreased activity. However, positive activation for TMT-(B-A) refers to increased activity in TMT-B compared to in TMT-A and negative activity means decreased activity in TMT-B compared to in TMT-A. The purpose of this replication was to identify certain regions of the brain that were activated during both TMT tests and whether there was an effect on activation based on the type of TMT given (TMT-A or TMT-B).

Results

Four significant clusters appeared in the replication of the fMRI scans for TMT-(A+B)-fixation, including the left angular gyrus, right angular gyrus, thalamus, and the left posterior cingulate gyrus. The left and right angular gyri both experienced positive activation (t = 8.914, t=5.023); furthermore, the left angular gyrus experienced the most significant activation of all brain regions during TMT-A and TMT-B compared to fixation (Table 1, Figure 1). This differs from the original study which did not indicate significant activation in this region, in fact, it was noted as experiencing negative activation. The most positively activated region noted in the original study was the left superior frontal gyrus, a region in which this replication did not find a significant t-statistic value. However, the study did mention positive activations in the regions surrounding the visual cortex as well as the parietal lobes and upper cerebellum, which is a similar pattern to the replication's generated brain scans and t-statistic values (Figure 1). The thalamus along with the left posterior cingulate gyrus showed negative activation (t=-4.819, t=-8.380) (Table 1, Figure 1). This is comparable to the original study in which the left posterior and anterior cingulate gyri were found to have less activation in TMT-A and TMT-B than during fixation. Additionally, the areas of negative activation follow similar patterns to the original

study which found areas of the bilateral temporal lobes and hippocampus to have less activation during the TMT tests than in fixation.

Figure 1.



Group-level activation map for the overall performance on TMT-(A+B) compared with the fixation control. Negative t-statistics show negative activation and positive t-statistics show positive activation.

Table 1. Significant Clusters of Group-Level Activation during the TMT-(A+B) performance contrasted with the fixation control

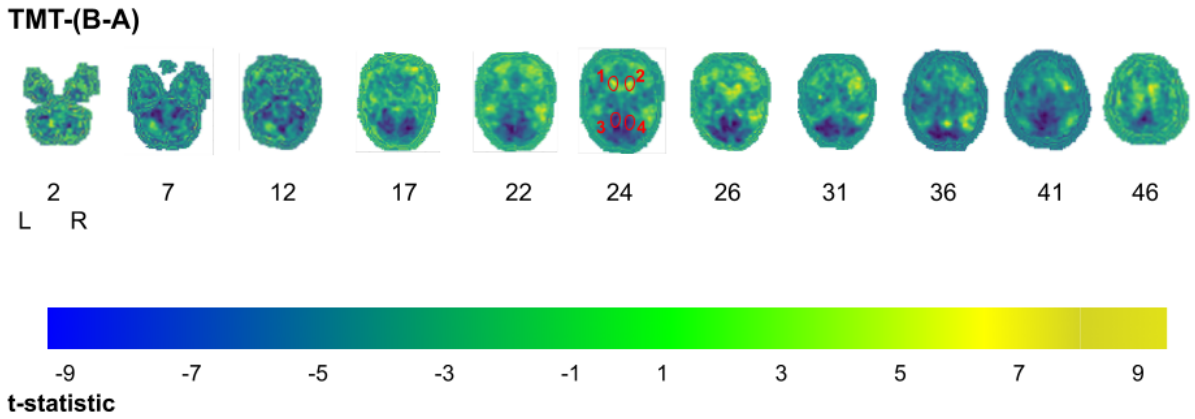
TMT-(A+B)-fixation

Cluster Number	Center of Mass (x,y,z)	Peak Value (t-statistic)	Anatomical Regions
1	(15, 24, 19)	8.914	Left angular gyrus
2	(12, 22, 36)	5.023	Right angular gyrus
3	(27, 24, 34)	-4.819	Thalamus
4	(29, 22, 24)	-8.380	Left posterior cingulate cortex

The replication of the fMRI scans for TMT-(B-A) yielded different significant clusters, activation patterns, and t-statistics compared to the fMRI scans from TMT-(A+B)-fixation (Table 1, Table 2). In the TMT-(B-A) replication, most of the negative activity, corresponding to

increased activity in TMT-A compared to TMT-B, was located in the left posterior cingulate gyrus (t=-6.567) and thalamus (t=-5.778), similar to the results of negative activation in TMT-(A+B)-fixation (Table 1, Table 2). Significant positive activations with p-values below 0.05, referring to increased activity in TMT-B compared to in TMT-A were scattered across the frontal and temporal lobes, and mostly in the caudate nucleus (Figure 2, Table 2). While the original study did not show significant positive activation all across the frontal lobe, the results did yield one significant cluster within the left inferior frontal gyrus, similar to the present replication (Figure 2). Negative activation in the original study yielded similar activation patterns compared to the present replication's results. Moreover, the t-statistics calculated in the present replication differed from the t-statistics from the original study because slightly different significant clusters, or coordinates of voxels, were analyzed in the replication.

Figure 2.



Group-level activation map for the performance on TMT-(B-A). Negative t-statistics show negative activation and positive t-statistics show positive activation.

Table 2. Significant Clusters of Group-Level Activation during the TMT(B-A) performance

TMT-(B-A)

Cluster Number	Center of Mass (x,y,z)	Peak Value (t-statistic)	Anatomical Regions
1	(48,24,25)	5.054	Left caudate nucleus
2	(48,24,35)	4.541	Right caudate nucleus
3	(17,24,26)	-6.567	Left posterior cingulate cortex
4	(22,24,33)	-5.778	Thalamus

Discussion

In this replication of the original study, four significant clusters were identified for both the TMT-(A+B) and TMT-(B-A). The clusters that were analyzed and the t-statistics from the replication differed from those that were analyzed in the original study. In addition, the replication of TMT-(B-A) showed positively and negatively activated regions with significant t-statistics, indicating that the TMT-B utilizes dissimilar brain regions and cognitive skills compared to TMT-A, supporting the major part of the hypothesis.

The analysis for TMT-(A+B)-fixation revealed significant regions of positive activation for the left angular gyrus and right angular gyrus. The original study also observed activity in prefrontal regions for TMT-(A+B)-fixation, particularly in the inferior and middle frontal gyri. There is an abundance of literature that identifies both the left and right angular gyri as crucial in numerous tasks and processes related to number processing, attention and spatial cognition, and memory retrieval (Seghier, 2013). Specifically, the angular gyri has been shown to mediate spatial representations of numbers, as required by both portions of the TMT (Seghier, 2013). The left angular gyrus also yielded the greatest t-statistic in the replication analysis, making it the most significant cluster. Additionally, the left angular gyrus has been observed in numerous

studies to dominate number-processing tasks and recent research also found the right angular gyrus to be a highly consistent region involved in visual-spatial attention (Seghier, 2013).

In the TMT-(A+B)-fixation, a significant region of negative activation (decreased activity during TMT-(A+B) compared to fixation) was observed in the thalamus and left posterior cingulate cortex. The thalamus has been shown to be a critical node with several connections to other regions of the brain, and is crucial for supporting cognitive functions that decline with aging (Fama & Sullivan, 2015). The left posterior cingulate cortex's specific cognitive function is largely unknown. However, it is considered to be a central node of the default mode network (DMN) (Leech et al., 2012). Prior studies of whole-brain network organization revealed that the thalamus is also structurally and functionally correlated to DMN regions (Anticevic et al., 2012). Deactivation of regions associated with the DMN has been shown to increase retrieval of learned information. More deactivation is associated with more efficient stimulus processing, whereas more DMN activation is associated with less efficient stimulus processing (Anticevic et al., 2012). The decreased activity of the left posterior cingulate cortex and the thalamus during TMT-(A+B) compared to fixation are thereby consistent with the literature.

The replication of the fMRI scans for TMT-(B-A) revealed four significant clusters in the caudate nucleus, left posterior cingulate cortex and thalamus. In Figure 2, the positive activation occurred in the left caudate nucleus and the right caudate nucleus. The caudate nucleus is mainly associated with motor functions, but it also plays a role in associative learning and attention (Grahn et al., 2008). Thus, the replication results are consistent with the existing scientific literature that identified TMT-B to be involved in visual ability, motor functioning and cognitive processes (Corrigan & Hinkeldey, 1987).

Negative activations (decreased activity in TMT-B compared to TMT-A) were focused in the thalamus and left posterior cingulate cortex. Like mentioned previously, the thalamus is involved in relaying sensory and motor signals and the regulation of consciousness and alertness (Fama & Sullivan, 2015). The posterior cingulate cortex on the other hand, has been linked to memory recollection and configurational learning (Leech et al., 2012). The activation in these brain regions help explain the decrease in TMT-B activity since the posterior cingulate cortex and thalamus are more involved in rote memory compared to executive functioning (Corrigan & Hinkeldey, 1987). Therefore, the replication results are consistent with the scientific literature regarding the trail making test. Furthermore, activation in these regions point to larger implications for neurodegenerative diseases such as Alzheimer's, which can be studied using the TMT.

To identify the brain activation regions for this study, the replicated fMRI results were compared with a database of MRI scans in axial slices (Micheau & Hoa, 2020). However, it is important to note a discrepancy in prior studies regarding the labelling of neuroanatomical regions, imposing a limitation for the present study. The nomenclature employed differs according to the particular domain of study. For example, activation in the angular gyrus may be referred to as a part of the temporoparietal junction in the domain of social cognition but referred to as the posterior middle temporal gyrus and temporo-parieto-occipital cortex in language domain (Seghier, 2013). Therefore, it is highly probable that other neuroanatomical regions overlapped with the regions that were identified in the present study.

The methods used by the present study can potentially be used to identify regions that are more likely to impact cognitive flexibility, and can be further examined in individuals with neurodegenerative disorders such as AD. DMN, in particular, has been identified by other studies

to be especially vulnerable and affected by AD (Mevel et al., 2011; Lehmann et al., 2015) . It consists of multiple subsystems that converge on nodes, including two crucial areas affected by AD: the posterior cingulate cortex and hippocampal formation (Mevel et al., 2011). The function of the DMN varies, as different regions of the network are active during different cognitive functions (Mevel et al., 2011). Changes in the DMN's connectivity have been detected in past fMRI studies during preclinical stages of AD (Lehmann et al., 2015). Moreover, the resting fMRI revealed significant disruptions in DMN connectivity in individuals with AD, specifically within the superior and middle frontal, posterior cingulate cortex, middle temporal, superior parietal and hippocampal formation (Koch et al., 2012; Mevel et al., 2011). Past studies hypothesize that such disruptions can be attributed to a reduced ability to pause DMN activity to switch from a "default mode" to a "task-mode" in cognition (Mevel et al., 2011). Given the DMN's significance in our study and the related literature, the DMN's connectivity can be evaluated with fMRI and the TMT to potentially be used as noninvasive tests to diagnose AD.

Conclusion

The original study explored the regions of the brain, via fMRI, that were activated during various tasks in TMT-A and TMT-B. Results showed areas of the brain that were most activated during both TMTs and allowed for further analysis into linking those regions with their role in cognitive function. The present study replicated the fMRI data for both TMT-A and TMT-B and used the Python programming language within the Jupyter Notebook environment to find areas within the brain that showed significant activation in TMT-(A+B)-fixation and TMT-(B-A). The replication results showed some overlap with the original study regarding positive or negative activation in anatomical regions, although the t-statistics calculated differed. The replication

supported the hypothesis that activation was present in key areas involved in processing, and also indicated regions of the brain not explicitly discussed in the original paper but that were linked via previous research. The methods used in both the original and present study can be used in the future to identify key areas of the brain that impact cognitive function, which can then be contrasted in healthy individuals and cognitively impaired individuals, such as those with AD, to clinically screen for neurodegenerative disorders.

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