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Cognitive and connectome properties detectable through individual differences in graphomotor organization

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ABSTRACT

We investigated whether graphomotor organization during a digitized Clock Drawing Test (dCDT) would be associated with cognitive and/or brain structural differences detected with a tractography-derived structural connectome of the brain. 72 non-demented/non-depressed adults were categorized based on whether or not they used 'anchor' digits (i.e., 12, 3, 6, 9) before any other digits while completing dCDT instructions to "draw the face of a clock with all the numbers and set the hands to 10 after 11". 'Anchorers' were compared to 'non-anchorers' across dCDT, additional cognitive measures and connectome-based metrics. In the context of grossly intact clock drawings, anchorers required fewer strokes to complete the dCDT and outperformed non-anchorers on executive functioning and learning/memory/recognition tasks. Anchorers had higher local efficiency for the left medial orbitofrontal and transverse temporal cortices as well as the right rostral anterior cingulate and superior frontal gyrus versus non-anchorers suggesting better regional integration within local networks involving these regions; select aspects of which correlated with cognition. Results also revealed that anchorers' exhibited a higher degree of modular integration among heteromodal regions of the ventral visual processing stream versus non-anchorers. Thus, an easily observable graphomotor distinction was associated with 1) better performance in specific cognitive domains, 2) higher local efficiency suggesting better regional integration, and 3) more sophisticated modular integration involving the ventral ('what') visuospatial processing stream. Taken together, these results enhance our knowledge of the brain-behavior relationships underlying unprompted graphomotor organization during dCDT.

1. Introduction

The clock drawing test, one of the most commonly used tests by neuropsychologists (Rabin et al., 2005), provides an economical and comprehensive assessment of multiple cognitive domains including, but not limited to, graphomotor/visuoconstructional abilities, executive functioning, and access to semantic knowledge (Cosentino et al., 2004; Libon et al., 1996; Royall et al., 1998). Performance on the clock drawing test has also been shown to indicate the integrity of subcortical structures (Samton et al., 2005) as well as focal brain dysfunction (Tranel et al., 2008). Determinations of 'impaired' from 'unimpaired' performance, particularly during bedside screening when limited time and tools may be available, have traditionally focused on gross or visually observable errors in output by clinical populations, especially individuals with dementias. Less work has been done studying clock drawing test performance-based outcomes reflecting successful performance, i.e., lacking gross or observable errors. It may be that

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subtle individual differences may signal larger distinctions in cognition and/or brain structure worth considering. Advances in digital technology allow for a closer inspection of successful clock drawing performance including the efficient use of time and graphomotor output to facilitate performance (Davis et al., 2010; Penney et al., 2010a). Likewise, advances in brain network analysis or brain connectomics have emerged as an exciting way to examine neural organization (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). We used a digital CDT (dCDT) to determine what subtleties in successful clock drawing performance revealed about higher-level cognition and underlying brain connectomics.

The Clock Drawing Task (CDT) (digital or not), requires participants to “draw the face of a clock with all the numbers and set the hands to 10 after 11”; it has long provided an assessment of multiple cognitive domains (Cosentino et al., 2004; Libon et al., 1996; Royall et al., 1998). For example, evidence suggests the CDT requires executive functioning during the Command condition (Cohen et al., 2014; Cosentino et al., 2004) when participants must initiate, unassisted, CDT task demands. Likewise, a larger brain network including prefrontal as well as right parietal and bilateral temporal regions is thought to be involved in Command condition performance compared to Copy and/or ‘pre-drawn’ CDT trials (Matsuoka et al., 2011). Thus, spontaneous graphomotor organization during the CDT Command condition, e.g., deliberately placing the 12, 6, 3, and/or 9 to ensure adequate spacing of all numbers, may promote executive functioning in the form of greater efficiency during the task. It may also signal better cognitive functions and underlying neural organization more generally when compared to individuals who lack such organization. It follows that such a distinction may differentiate groups of individuals with otherwise grossly intact performance.

Borrowing techniques from graph theory in mathematics, connectomics examines the brain as a ‘graph’ or network, thus allowing us to gain insight into integrative patterns of brain connectivity. Indeed, instead of focusing on few connections linking select regions-of-interest, connectomics allows for a graph-theoretical assessment of system properties in order to quantitatively understand how brain regions or ‘nodes’ communicate and interact. Additionally, advanced graph-theoretical ‘modularity analysis’ investigates how a group of nodes preferentially interact among themselves to form a community or module, which can then be compared between groups of brain networks to assess for ‘modular’ differences (GadElkarim et al., 2012; Ye et al., 2015). Understanding not only the cognitive differences associated with graphomotor organization during the CDT but also their connectome neurocircuit underpinnings may enhance our knowledge of the brain-behavior relationships that underlie unprompted (graphomotor) organization during bedside evaluations of overall cognitive performance.

The overarching goal of this study is to determine the cognitive and neural phenotypes of adults who, without prompting, use graphomotor organization during CDT compared to adults who do not use such organization. We hypothesize that individuals who ‘anchor’ digits 12, 6, 3, and/or 9 (i.e., deliberately place these numbers to ensure adequate spacing of all digits) will be more efficient in completing a digitized version of the CDT (Davis et al., 2010; Penney et al., 2010a). We will measure efficiency by quantifying total graphomotor output in strokes and time to completion in milliseconds (Cohen et al., 2014; Penney et al., 2010b). We further hypothesize that these same individuals will display better executive functioning using independent test measures when compared to ‘non-anchorers’. Given that prefrontal, temporal and parietal regions have been implicated in CDT performance including the organization of spatial information such as the layout of numbers (Ino et al., 2003; Lee et al., 2008; Matsuoka et al., 2011; Parks et al., 2010; Samton et al., 2005; Tranel et al., 2008), we hypothesize that individuals who organize their CDT output (versus those who do not) will also show more efficient neural networks associated with these brain regions.

2. Materials and methods

2.1. Participants

Participants, 55 years or older, were recruited through community outreach (e.g., advertisements, fliers) for a larger program of research at the University of Illinois at Chicago (UIC) Department of Psychiatry that included a study of Type 2 diabetes and depression. Informed consent was obtained according to the Institutional Review Board guidelines at UIC and in accordance with the Declaration of Helsinki.

An initial telephone screen determined study eligibility. At this screen, exclusion criteria for consideration as a healthy control included a diagnosis of any Axis I disorder (including depression), a history of head trauma or loss of consciousness, a history or presence of any neurological disorders (e.g., dementia, stroke, seizure), and/or substance abuse or dependence. A history of stable or remitted medical disorders was not an exclusionary factor.

Following the telephone screen, participants were scheduled for cognitive (e.g., Mini Mental State Examination; MMSE) (Folstein et al., 1975) and affective (e.g., Structured Clinical Interview for the DSM-IV; SCID) (Spitzer et al., 1992) screens, administered by a trained research assistant, for determination of final inclusion or exclusion. Additionally, either a board certified (AK) or board eligible (OA) psychiatrist completed the 17-item Hamilton Rating Scale of Depression (HAM-D) (Hamilton, 1960) for final determination of the absence of depression. Non-depressed adults were defined by a HAM-D ≤ 8 and an absence of depressive symptoms based on the SCID. All raters were blind to telephone screen information.

Of the 90 participants eligible for inclusion based on the above criteria, 13 were excluded for: antidepressant use for nerve pain/insomnia-2; missing behavioral data-4; English as a second language-6; or having a diagnostic history of depression-1. This left 77 eligible participants.

2.2. Neuropsychological protocol

2.2.1. The Digital Clock Drawing Test (dCDT) (Davis et al., 2010; Penney et al., 2010b)

The dCDT was developed by the Lahey Clinic and Massachusetts Institute of Technology in collaboration with the Clock Sketch Consortium and uses digital pen technology developed by Anoto, Inc. The pen works as an ordinary ballpoint pen while capturing pen position 80 times/s ± 0.002. Thus, the data reported by the pen is time-stamped; allowing the pen to capture the final product (i.e., the clock drawing) as well as the behavior that produced it for more accurate classifications than would be possible without this technology.

As with the CDT, the dCDT utilizes one trial of two conditions: Command and Copy. In the Command condition, participants are asked to “draw the face of a clock with all of the numbers and set the hands to 10 after 11.” The Copy condition asks participants to copy a model of a clock with the hands set for ‘10 after 11’. The Copy condition is always presented immediately after the Command condition is complete so as not to spoil spontaneous output during the Command condition. Below are the parameters for the current research. It should be noted that the observance of anchoring behavior does not require digital technology although the dCDT software does allow for the confirmation of digit order and the classification of anchoring. We utilized dCDT scoring software to automatically capture other behavior that would be difficult to obtain otherwise including total number of strokes and total time to completion outlined below.

- *Anchors* – Anchors, i.e., digits used to set guidelines for where the remaining digits will be placed on the clock face during the Command condition, served as our measure of prospective planning. Anchor digits (numbers 12, 3, 6 and/or 9; Table 1) had to be drawn before all other digits. Two or four anchors could be used, as these digits set the framework for all other digits within the clock.
- *Total Number of Strokes* – calculated as the total number of distinct graphomotor marks (i.e., strokes) completed with the pen during clock drawing to Command and to Copy.
- *Total Time to Completion* – calculated as the total time taken to complete the dCDT during the Command condition and again during the Copy condition. Time was documented from when the participant starts drawing, i.e., initial ink on the page, to the end of the clock's final element.

2.2.2. Additional cognitive tasks

A larger neuropsychological protocol tested cognitive domains of executive functioning (EF), attention and information processing (AIP), learning/memory/recognition (LMR), and semantic language (SEM). These domains, based on theoretical groupings of similar test variables of interest (VOIs) as published in the