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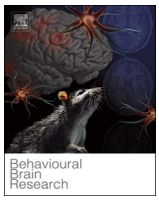

Research report

White matter integrity mediates decline in age-related inhibitory control

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ABSTRACT

Previous DTI studies have reported associations between white matter integrity and performance on the Stroop interference task. The current study aimed to add to these studies of inhibitory control by investigating how the differences in age and in white matter integrity relate to Stroop performance, and to examine whether the effect of age on Stroop performance is mediated by white matter integrity. 179 healthy adults from 20 to 80 years old were recruited in the study. DTI data were processed through TRACULA and the mean fractional anisotropy (FA) of 18 major white matter tracts were extracted and used for statistical analysis. Correlation analysis showed a strong negative relationship between age and the Stroop interference score (I_G). Higher I_G indicated better inhibitory control. Simple linear regression analyses indicated that most of the tracts showed negative relationships with age, and positive relationships with I_G. Moderation effect of age on the relationship between FA and I_G was tested on tracts that significantly predicted I_G after multiple comparison corrections, but none of these moderations were significant. Then we tested if these tracts mediated the effect of age on I_G and found significant indirect effects of age on I_G through the FA of the left corticospinal tract and through the right inferior longitudinal fasciculus. Our results highlight the role of a number of major white matter tracts in the processes supporting the Stroop inhibitory performance and further pinpointed the lower white matter integrity of specific tracts as contributors to the decrease in inhibitory control ability associated with the Stroop test in older age.

1. Introduction

Inhibitory control entails important subcomponents, including attentional control and response inhibition. Attentional control, also known as selective attention, is the capacity to choose what to pay attention to and what to ignore [1]. Response inhibition is the ability to inhibit an inappropriate response (prepotent or automatic) in a given context and respond appropriately in a goal-directed behavior [2]. Examples of tasks that engage both attentional control and response inhibition include the Stroop task [3], the go/no-go task [4], and the Simon task [5], all of which have been examined in functional activation tasks to evaluate the associated brain regions activated.The Stroop task is associated with increased activation in the dorsolateral prefrontal cortex (PFC), the anterior cingulate cortex (ACC), the inferior frontal gyrus (IFG), the inferior parietal gyrus (IPG), and the inferior temporal cortex, whereas the Simon task involves the dorsal premotor and the posterior and superior parietal cortices [6]. The go/no-go task has been shown to activate the pre-supplementary motor area (pre-SMA) and the fusiform gyrus [7]. The prefrontal gyrus is recruited in all of these tasks while the parietal and temporal lobes are also recruited in some of these tasks.

With such a widespread network of regions coordinating the processing of inhibitory control tasks, long-distance axonal tracts are crucial for inter-cortical communication. Integrity of the axonal tracts can be indirectly measured with diffusion tensor imaging (DTI), which detects the diffusion of water molecules by modeling the anisotropy of the diffusion gradient. Water diffusion is more anisotropic in intact axons than in damaged ones [8–10], and thus, intact white matter microstructure is associated with higher fractional anisotropy (FA) and lower diffusivity values than damaged white matter.

Previous aging studies have found associations between white matter integrity and age-related decline in performance on inhibitory control tasks such as the Stroop test. [11] collected Stroop test performance from 49 healthy subjects consisting of 13 younger adults, 20 younger elders and 16 advanced elders. Their data showed a strong positive correlation between Stroop interference and white matter integrity of genu of the corpus callosum, bilateral anterior corona radiata, and bilateral anterior limb of internal capsule, all of which connect frontal regions with other parts of the brain. In particular, anterior corona radiata and the anterior limb of internal capsule connect the frontal regions with parts of the thalamus. Better Stroop performance was also associated with higher FA in thalamic-frontal connections in a

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number of other studies [12–14]. Reginold et al. [14] tested 33 healthy subjects age 54–76 years old using a set of neuropsychological tests that included the Stroop test. They found that higher FA in the corpus callosum, corticospinal/bulbar tract, and thalamic projection tracts were associated with better Stroop performance. Hughes et al. [13] showed that mean FA values in the thalamo-frontal tracts decreased significantly with increasing age and the volume of the thalamo-frontal projections was associated with Stroop test performance.

Aging studies conducted on tasks that recruit similar cognitive processes as the Stroop further showed fronto-parietal involvement. Grieve et al. [12] reported associations between executive control and FA of bilateral regions from the prefrontal cortex to the parietal lobe and extended to anterior portions of the thalamus by using executive maze and attention switching tasks. Radial diffusivity, another measure of white matter integrity, of frontoparietal white matter tracts were also correlated with task switching processes in older adults [15]. Overall, integrity of axonal tracts connecting frontal brain regions with thalamic projections and with the parietal lobes were most frequently found to be correlated with age-related decline in inhibitory control tasks requiring attentional control and response inhibition.

While a number of studies have examined the association between white matter integrity and inhibitory control tasks [16–25], few studies have directly examined if the integrity of white matter tracts quantified with DTI measures explain the age-related decline in inhibitory control tasks [11] using mediation model, which is a more stringent test of directional relationships than simple regression. Mediation analysis conducts a series of regression models to evaluate whether the data is consistent with a directional hypothesis. Thus, while it does rely on regression and the data still has the limitation of being cross-sectional, the models do test for directionality of effects [26].

Our study administered the Stroop task to a large group of healthy adults ranging from 20 to 80 years old, and used mediation analysis to determine whether the variability observed with aging in Stroop performance is mediated (or explained) by the variability in the FA of 18 major white matter tracts, which were automatically generated by the software Tracts Constrained by Underlying Anatomy (TRACULA; [27]) that is part of FreeSurfer (https://surfer.nmr.mgh.harvard.edu). These tracts consisted of major pathways connecting prefrontal regions to other lobes such as the bilateral superior longitudinal fasciculus (SLF) as well as pathways connecting bilateral temporal lobes with posterior regions such as the inferior longitudinal fasciculus (ILF). Other tracts found to be associated with inhibitory control in previous studies were also extracted, including the anterior thalamic radiation (ATR) and the corpus callosum. Given that anterior regions suffer greater age-related atrophy than posterior regions [28], age-related variability in performance for inhibitory control tasks should be explained by variability in white matter integrity of tracts connecting prefrontal regions with other brain regions, such as the SLF, whereas there should be little association between age-related Stroop performance and white matter tracts connecting posterior regions, such as the ILF. Given the large age range in our sample, we tested for both linear and quadratic age trends in the white matter integrity of tracts as well as the interaction between age and white matter integrity on Stroop performance to examine if the white matter to Stroop performance differs by age. For tracts did not show significant interaction (moderation) effect of age, indicating that the relationship between white matter integrity and Stroop performance does not differ by age, we investigated if the white matter integrity of the tracts mediated the effect of age on Stroop performance.

2. Experimental procedures

2.1. Participants

Participants were taken from a larger study, Reference Ability Neural Networks (RANN study), but the data presented here have not been published before. Actual sample size and subject exclusion is described in Section 2.5. Participants were recruited using established market mailing procedures to equate the recruitment procedures of all participants. Participants who responded to the mailing were screened for inclusion (right handed and English speaking) and exclusion criteria (myocardial Infarction, congestive heart failure or any other heart disease, brain disorder such as stroke, tumor, infection, epilepsy, multiple sclerosis, degenerative diseases, head injury (loss of consciousness > 5 mins), mental retardation, seizure, Parkinson's disease, Huntington's disease, normal pressure hydrocephalus, essential/familial tremor, Down Syndrome, HIV Infection or AIDS diagnosis, learning disability/dyslexia, ADHD or ADD, uncontrolled hypertension, uncontrolled diabetes mellitus, uncontrolled thyroid or other endocrine disease, uncorrectable vision, color blindness, uncorrectable hearing and implant, pregnancy, lactating, any medication targeting central nervous system, cancer within last five years, renal insufficiency, untreated neurosyphillis, any alcohol and drug abuse within last 12 months, recent non-skin neoplastic disease or melanoma, active hepatic disease, insulin dependent diabetes, history of psychosis or ECT, major depressive, bipolar, or anxiety disorder within the past 5 years). Individuals that passed the telephone screen were further screened in person and a Mattis Dementia Rating Scale (DRS) score of at least 130 was required for inclusion in the study. DRS had a mean = 140, with SD = 2.9, and ranged from 130 to 144. Informed consent, as approved by the Internal Review Board of the College of Physicians and Surgeons of Columbia University, was obtained prior to study participation, and after the nature and risks of the study were explained. Participants were paid for their participation in the study.

2.2. Behavioral measure: Stroop task

Inhibitory control was assessed by the Golden Stroop task [29]. There were three types of cards in the Stroop test: (1) word cards contain black color words and the word is to be read; (2) color cards contain solid squares or XXXXXs in different colors and the color is to be named; and (3) color-word cards contain incongruent color words (for example, the word 'red' printed in the color blue) and the color of the printed text is to be named while suppressing automatic reading of the word. For the Golden Stroop task, participants have to name as many items as they can in 45 s for each card. The outcome variables are the number of items completed for the word card (W raw word score), the color card (C raw color score), and the color–word card (CW raw color–word score), respectively. The predicted color-word score (Pcw) is calculated based on the raw word (W) and raw color (C) scores. The predicted numbers of items named in 45 s in the color-word condition (Pcw) is calculated as $Pcw = 45/\{[(45 * W) + (45 * C)]/(W * C)\} = (W*C)/(W + C)$.

Golden's interference score (I_G) is calculated by subtracting this score from the actual color–word score (I_G = CW-Pcw) [29]. Pcw is an estimate of the number of words read if there were no interference from reading of the word and is based on the number of words read in the word and the color conditions. CW is the actual number of items named on incongruent colored words which requires inhibition of word reading. If inhibition is impaired, then the number of items named in the color word condition should be less than the average number of items named in the word and the color conditions, resulting in a negative I_G score. Therefore, the lower the I_G score, the greater the impairment in inhibitory control.

2.3. MRI acquisition

MRI images were acquired in a 3.0T Philips Achieva Magnet using a standard quadrature head coil. A T1-weighted scout image was acquired to determine subject position. One hundred sixty-five contiguous 1 mm T1-weighted images of the whole brain were acquired for each subject with an MPRAGE sequence using the following parameters: TR 6.5 ms, TE 3 ms; flip angle 8°, acquisition matrix 256 × 256, and