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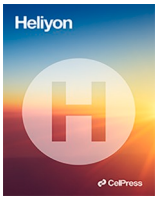

Research article

Cortical neurite microstructural correlates of time perception in healthy older adults

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ABSTRACT

The human experience is significantly impacted by timing as it structures how information is processed. Nevertheless, the neurological foundation of time perception remains largely unresolved. Understanding cortical microstructure related to timing is crucial for gaining insight into healthy aging and recognizing structural alterations that are typical of neurodegenerative diseases associated with age. Given the importance, this study aimed to determine the brain regions that are accountable for predicting time perception in older adults using microstructural measures of the brain. In this study, elderly healthy adults performed the Time-Wall Estimation task to measure time perception through average error time. We used support vector regression (SVR) analyses to predict the average error time using cortical neurite microstructures derived from orientation dispersion and density imaging based on multi-shell diffusion magnetic resonance imaging (dMRI). We found significant correlations between observed and predicted average error times for neurite arborization (ODI) and free water (FISO). Neurite arborization and free water properties in specific regions in the medial and lateral prefrontal, superior parietal, and medial and lateral temporal lobes were among the most significant predictors of timing ability in older adults. Further, our results revealed that greater branching along with lower free water in cortical structures result in shorter average error times. Future studies should assess whether these same networks are contributing to time perception in older adults with mild cognitive impairment (MCI) and whether degeneration of these networks contribute to early diagnosis or detection of dementia.

1. Introduction

Timing is a crucial characteristic of human behavior as it structures how sequential information is perceived, experienced, and remembered [1], consequently guiding many aspects of social behavior. That is why human interaction with the environment, which is vital for survival, normally occurs in a dynamic context [2].

Timing depends on various factors including perception, learning, memory and voluntary motor action and control [3]. Studies have demonstrated that human perception and action are understood in terms of synergetic concepts of a dynamical system [4,5]. Action improves our timing perception via dynamic interaction between sensory and motor systems [6]. Particularly, timing-based

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action depends on the interaction of a dynamic network of brain structure, which associates temporal sensory information and memory traces of time, to generate behavior based on perceptual decisions [7]. Integration of time with sensory input is necessary to recognize and interpret temporal aspects of the sensory information that guide action. Thus, the ability to adjust behavior dynamically in different contexts is a critical component of the execution of voluntary movements with strict temporal control. Multiple frameworks exist for the neural mechanisms of timing, and the existence of these general frameworks highlights the key question that concerns whether the representation of temporal information is dependent on a specialized system, distributed across a network of neural regions, or is computed in a local task-dependent manner [8]. Moreover, context dependent perception and action of timing planning underpin the same internal mechanism [8].

It has been theorized that shorter range timing is automatic, reflecting engagement of processes associated with the production of skilled movements while longer range timing is cognitive, being dependent on systems associated with attention and working memory [8]. More particularly, the timing scale of multi-seconds is identified to characterize human timing mechanisms which participate in the conscious perception of time. In our study, we observed dynamic timing behavior including both reactive and anticipatory coordinative patterns between self and environment which is essential for survival in the real world [4]. This behavior could be understood as two complementary modes of a dynamic system, not differential brain processes. Frontal and prefrontal areas were associated with anticipatory behavior whereas reactive processes were mediated by classical sensory and motor areas [4]. In this attentional demanding and ruled-based behavior, the brain must constantly monitor external stimuli and attempt to link relevant sensory information with action-based behavior [9]. This is a mechanism by which multiple behavioral demands are combined and applied to perceptual as well as action processes [9].

While timing is an inherent characteristic of human behavior and is gradually developed as a sense of duration over normal development, no explicit biological systems exist, such as for sight, hearing, and taste. As such, there has been an explosion of research into the neural underpinnings of timing [10–12]. Recent meta-analyses have emphasized the complex network of brain regions involved in timing, including but not limited to the supplementary motor area, cerebellum, and basal ganglia, highlighting the multi-modal nature of temporal processing [13–15]. Some studies also reported the involvement of the prefrontal/parietal lobes and thalamus in the perception of time [16,17].

Timing is an integral feature of human behavior that matures into a nuanced sense of duration, with numerous reviews and meta-analyses shedding light on the ways in which aging and neurodegenerative conditions affect time perception [18–22]. A task frequently employed to study this is the 'time-to-contact' task, which assesses an individual's ability to predict the moment an approaching object will arrive at a target location, thus engaging cognitive and perceptual timing mechanisms. Findings from this task reveal that aging can influence these timing faculties, with older adults often displaying variations in performance, indicating significant insights into the cognitive and perceptual dynamics of timing as it relates to age [22,23]. These insights are particularly revealing, as they underscore the differential effects of aging on time perception not just broadly but also in the specific context of tasks like ''time-to-contact'' [23,24].

A few studies have investigated the neuroanatomical correlates of time perception in aging adults. Recent findings have shown that time estimation and time judgment are different between younger and older adults, having older adults demonstrate shorter time estimation intervals [25] and lower sensitivity to time regardless of the duration range tested [26]. However, there are contradicting studies that have also claimed that time perception is not altered as a result of age [27], further emphasizing that more research on the neural underpinnings of how humans perceive time is needed to confirm such findings.

Neuroimaging discloses imperative information and implications for understanding healthy aging and identifying structural changes that characterize age-related neurodegenerative diseases [28]. One of the major risk factors for neurodegenerative diseases is aging, which can impact the neurite layouts throughout the brain as gray matter microstructure have the capacity to rapidly remodel [29]. As such, studying brain microstructure is crucial in understanding the physiological changes associated with aging, along with potential diseases that may accompany age. However, previous neuroimaging studies mainly analyzed crude measures of brain structure such as regional brain volume and cortical thickness associated with performance in timing tasks [13]. Recent studies on brain microstructural correlates of time perception have been primarily limited to investigating white matter microstructure utilizing diffusion tension imaging (DTI) [30,31]. While DTI measures can be relatively sensitive, these measures have inherent limitations when it comes to measuring microstructural properties in cortical regions, as conventional DTI measures are affected by partial volume and biased in cortical brain regions [32–35].

Recently, neurite orientation dispersion and density imaging (NODDI) has shown great promise for measuring cortical microstructural changes in health and disease [36,37]. The NODDI model provides biologically interpretable indices that derive three parameters: 1) the neurite density index (NDI), describing the density of packed neurites by compiling volume fraction in a given voxel; 2) the orientation dispersion index (ODI), which measures orientational configuration of neurites in a given voxel; and 3) the free-water isotropic volume fraction (FISO), which represents the free water content within neural tissue [38]. Various studies have successfully utilized NODDI to characterize alterations in gray matter microstructure in clinical population such as Alzheimer's disease and Schizophrenia [29,38].

In relation to the aging brain, NODDI studies have demonstrated mixed results, either showing a widespread decrease in ODI with age with no significant changes in NDI throughout the cortex or a decrease in NDI with no significant changes in ODI [39,40]. Other studies have also shown an increase in ODI with age in the hippocampus and thalamus, regions with highly myelinated subcortical structures [38]. However, it has been generally accepted that ODI and NDI decrease with age [38]. In terms of FISO, aging is associated with gray and white matter tissue loss, and the resulting enlargement of interstitial space could lead to increase in free water content [41]. Therefore, higher FISO indicates greater pathology and/or atrophy.

Neuroimaging studies that analyzed crude measures of brain microstructure during timing tasks identified the contribution of the

intraparietal and cingulate areas in the distributed neural network-based model for time perception [13]. Additionally, a prior study that conducted ROI analyses to investigate microstructural properties within cortical regions in the healthy aging brain revealed dorsolateral prefrontal, inferior frontal, inferior parietal, lateral and superior temporal, and sensory regions demonstrating change with age [38]. ROIs identified in this study reflect what was found in the previous literature, confirming the identified neural networks that are impacted by age [1,42]. Previous studies also demonstrated mixed results for age-related changes to free water content and orientation dispersion indices in the brain [38–41]. This study further supports prior findings that demonstrated an increase in cortical free water content and a decrease in cortical neurite orientation dispersion with age [39,41], signifying their potential role as predictors of time perception accuracy.

The critical brain structures engaged in time perception include the prefrontal and parietal lobes, thalamus, basal ganglia and cerebellum [17,25]. More particularly, the parietal area plays a critical role as a bridge between perception, action and cognition in the dynamic timing system [9]. Time perception and motor timing rely on very similar structures, including the premotor cortex (PMC), primary motor cortex (MI), primary somatosensory cortex (SI) [43,44], and medial wall motor areas in the cingulate cortex, as well as parts of the basal ganglia and the thalamus [45]. This overlap can be explained mostly by the nature of the context-dependent timing behavior, but it can be generalized that one's sense of time is generated by the simultaneous engagement of networks involved with motor sequence learning and timing that requires the precise representation of temporal information [13].

Here, we have addressed limitations of previous studies and examined for the first time the extent to which cortical microstructural properties predicted time perception in older adults. In this study, we utilized a multivariate analysis, rather than a univariate analysis, to analyze the distributed pattern of neural networks predicting multi-second range of timing durations. Measures of time perception were taken through average error times during performance in a nonverbal time estimation task [46,47]. We hypothesize microstructure properties of the frontal, parietal and temporal regions, along with the basal ganglia and thalamus regions to be the highest predictors of time perception. We expect those with higher FISO and lower ODI and NDI to show poorer performance in time estimation.

2. Materials and methods

2.1. Participants

Forty-two healthy controls (HC) (age 65–85 years old, mean (SD): 71.97(5.02)) were recruited from the local community at Stanford for this study. The details of the demographics and cognition have been provided in Table 1. All participants were required to meet certain criteria to be eligible for this study. These criteria included being right-handed and not exhibiting any signs of suicidality or significant psychiatric disease. Additionally, participants could not be currently using psychotropic medications, opiates, or thyroid medications (with some exceptions for permitted medications including cholinesterase inhibitors and hypertension medications if stable for at least two months). They could not have claustrophobia, be using non-MRI-compatible materials, or have a history of post-traumatic or psychotic disorders, bipolar disorder or any other significant neurologic disease. This included conditions like potential and likely dementia, vascular dementia, Parkinson's or Huntington's disease, brain tumor, progressive supranuclear palsy, epilepsy, subdural hematoma, and multiple sclerosis. Participants were required not to have untreated high blood pressure, a history of major head injury, or present or past alcohol or substance misuse (addiction within the last two years). Furthermore, they must not have any substantial systemic or unsteady medical conditions.

The study involved a comprehensive series of neuropsychological evaluations for qualified participants. The Mini International Neuropsychiatric Interview (M.I.N.I.), a structured clinical assessment, was used as the initial step to identify primary psychiatric disorders. Further, eligible participants were required to achieve a score of 7 or less on the geriatric depression scale (G.D.S.), indicating a low level of depression, a score of 24 or higher on the Mini-Mental State Examination (MMSE), a measure of overall cognition, and a satisfactory score on the Instrumental Activities of Daily Living (I.A.D.L.) scale, which assesses functional capability in eight separate activities of daily living, ensuring their ability to perform daily tasks independently. The Clinical Dementia Rating (C.D.R.) was used as an additional tool to rule out memory problems (CDR = 0), thereby ensuring the participants' cognition was accurately assessed. Informed consent was obtained from each participant, and the study was approved by Institutional Review Board at Stanford University.

2.2. Time-Wall Estimation task

The Time-Wall Estimation task is a nonverbal time estimation test modeled after a task originally included in the Unified Tri-

Table 1
Participant characteristics.

	N = 42	Range
Age (SD)	72.0 (5.0)	65–84
Sex, Female (%)	69.0 %	
Years of Education (SD)	22.1 (1.6)	18–27
MMSE (SD)	28.4 (1.7)	24–30
CDR (SD)	0	0

Services Cognitive Performance Assessment Battery (https://psychologydictionary.org/unified-tri-service-cognitive-performance-assessment-battery-utcpab/) [46]. The overall objective of the task is to assess one's ability to estimate the time at which a target, moving vertically at a fixed rate, will have traveled a specified distance. After the target is two-thirds of the way down, it will pass behind a wall and become invisible. The task is to press the space bar at the exact moment the target would pass through the notch marked at the bottom of the display (Fig. 1). Thus, it draws on processes relating to both motion perception [48] and prediction. By default, the task runs for 20 trials, each lasting between 2 and 10 s. Average error time across trials was used to measure individual's accuracy in time perception. The average error time was calculated for each individual by dividing the difference between the response time and target time by the target time ($\frac{T_{Response} - T_{Target}}{T_{Target}}$)

2.3. MRI acquisition and preprocessing

The multi-shell dMRI data were acquired using a 3T GE system (General Electric Healthcare, Milwaukee, WI, USA) with a 32-channel head coil (Nova Medical, Wilmington, MA, USA). The image acquisition was performed using the advanced multiband echo-planar imaging (EPI) method (multiband factor of 3), which included a 2.0 mm^3 isotropic spatial resolution in 80 diffusion directions with a diffusion gradient strength b = 2855 s/mm^2 and 30 diffusion directions with a diffusion gradient strength b = 710 s/mm^2 at CNI (Center for Cognitive and Neurobiological Imaging, https://cni.stanford.edu). Each dMRI image also contained nine images without diffusion weighting (b = 0 $\frac{s}{mm^2}$). Another dMRI scan was conducted using the inverse phase encoding direction. This scan included 6 diffusion directions (b = 2855 s/mm^2) and two non-diffusion-weighted images to correct the EPI distortion. The other dMRI parameters are TR/TE = 2800/78 ms, matrix size = 112 × 112, and 63 axial slices. In addition, structural MRI data were collected using MPRAGE pulse sequence using 0.45 inversion time, 12° flip angle and 1 mm slice thickness.

The dMRI data preprocessed using FSL (fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and MRTrix3 (mrtrix.org) toolboxes. This included denoising, addressing geometric EPI distortion using FSL's TOPUP function, correcting eddy current distortion, performing slice-by-slice motion correction and outlier detection, as well as bias field correction using ANTs N4BiasField Correction, and two participants were removed from the study due to the excessive motion. The T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences were collected to identify white matter hyperintensities (WMHs). The study included only healthy older adults, and thus, we didn't have to exclude any subjects due to high WMHs. The NODDI toolbox (available at https://www.nitrc.org/projects/noddi_toolbox), which employs a multicompartment model offering unique biophysical insights into tissue beyond what other diffusion measures provide, was utilized to compute NODDI metrics. These metrics include neurite density (intracellular volume fraction, ICVF), neurite arborization (orientation dispersion index, ODI), and extracellular volume fraction (FISO). NODDI plays a crucial role in the field by enabling the estimation of microstructural properties of gray matter, which leads to the quantification of neurite morphological changes associated with different neurological and psychiatric disorders in vivo [49]. Therefore, NODDI may provide a novel insight into aging of gray matter microstructure.

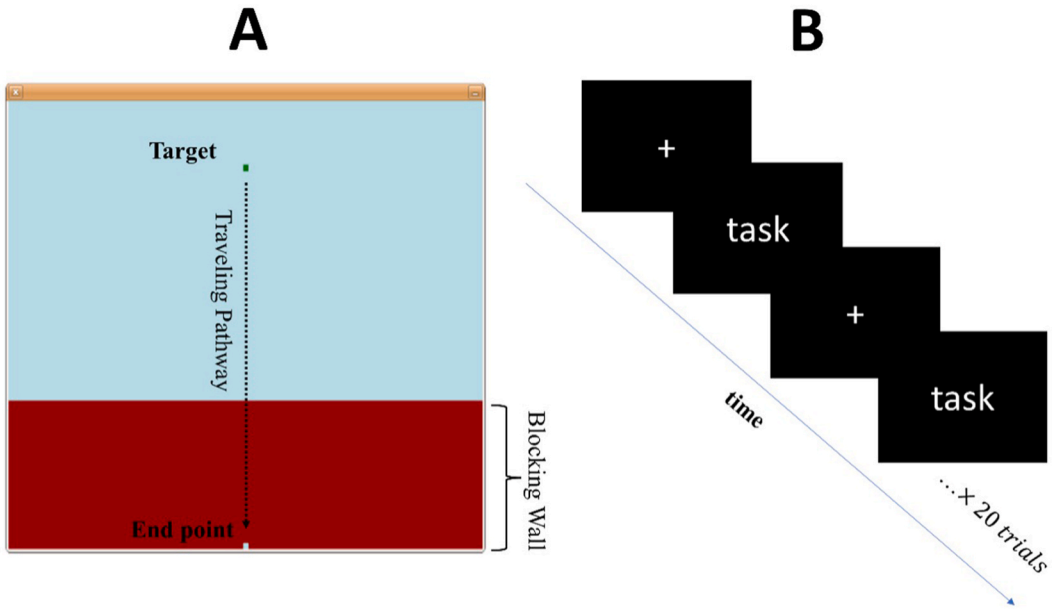

Fig. 1. Time-Wall Estimation task (A) and paradigm (B).

2.4. Surface mapping analysis

The FreeSurfer (Version 6.0.0 available at http://surfer.nmr.mgh.harvard.edu) pipeline was performed for cortical reconstruction of the T1-weighted image, including skull stripping, gray and white matter segmentation, as well as reconstruction and inflation of the cortical surface. If necessary, the pipeline also involved brain segmentation slice-by-slice quality control produced by the automated steps. The cortical thickness, surface area, gray and white matter volumes were estimated through automatic procedure based on the Freesurfer atlas. Further, the Human Connectome Project's multi-modal parcellation (HCPMMP) [50] was utilized, which includes 180 cortical brain regions per hemisphere and is based on the cortical architecture, function, connectivity, and topography of healthy individuals. The HCP provided the original annotation files, and they were converted to the standard cortical surface in FreeSurfer using fsaverage. This average parcellation was then transformed into each participant's cortical surface and converted to volumetric masks. Finally, the 360 masks representing single cortical brain regions yielded by the HCPMMP were linearly transformed into each subject's diffusion native space. The transformation was manually checked in ITK-SNAP, and manual orientation was applied if necessary. The transformed regions served as anatomical landmarks from which ICVF, ODI, and FISO were extracted across the cortex. Also, each subject's cortical metrics were resampled based on the cortical regions defined in the HCPMMP atlas.

2.5. Support vector regression (SVR) analyses

The SVR analyses were performed using the Multi-Voxel Pattern Analysis (MVPA) toolbox on MATLAB [51] to identify cortical neurite microstructural measures that are predictive of individual's average error time in the Time-Wall Estimation task. Regional gray matter neurite microstructural measures were used as input to the SVR model after adjusting for age and intracranial volume. Separate linear SVR models were fit for each of set of neurite measures (i.e., ODI, FISO, NDI). A leave-one-subject-out cross-validation was used to obtain an unbiased estimation of the average error times. In each iteration, data from one subject were left out as a test case and the remaining subjects' data were used to train the SVR model. This procedure was repeated such that data from each and every subject were left out once as test case and the accuracy of the model was then quantified as the correlation between the predicted and actual average error times across test cases. This process confirms the independence of training and test cases, providing an estimate of generalizability of the model to independent datasets. Finally, the statistical significance of the SVR models were tested against null models using nonparametric permutation testing with 2000 iterations.

For each SVR model, the weights of brain regions' contribution to SVR model were examined and regions with SVR weights more than 2SD from the mean were identified as regions that contributed the most to predicting average error time. Particularly, in each iteration of cross-validation, the SVR model used the training data to search for a weight vector that maximized the prediction accuracy of the error time. This weight vector represents the importance of a particular brain region's NODDI properties in predicting error time. These weight vectors were averaged across different iterations and the average weight vector was used to represent the contribution of each brain region in predicting error time.

For the purpose of comparison, we also fit separate SVR models using conventional measures of gray matter structure including regional gray matter thickness, volume and surface area.

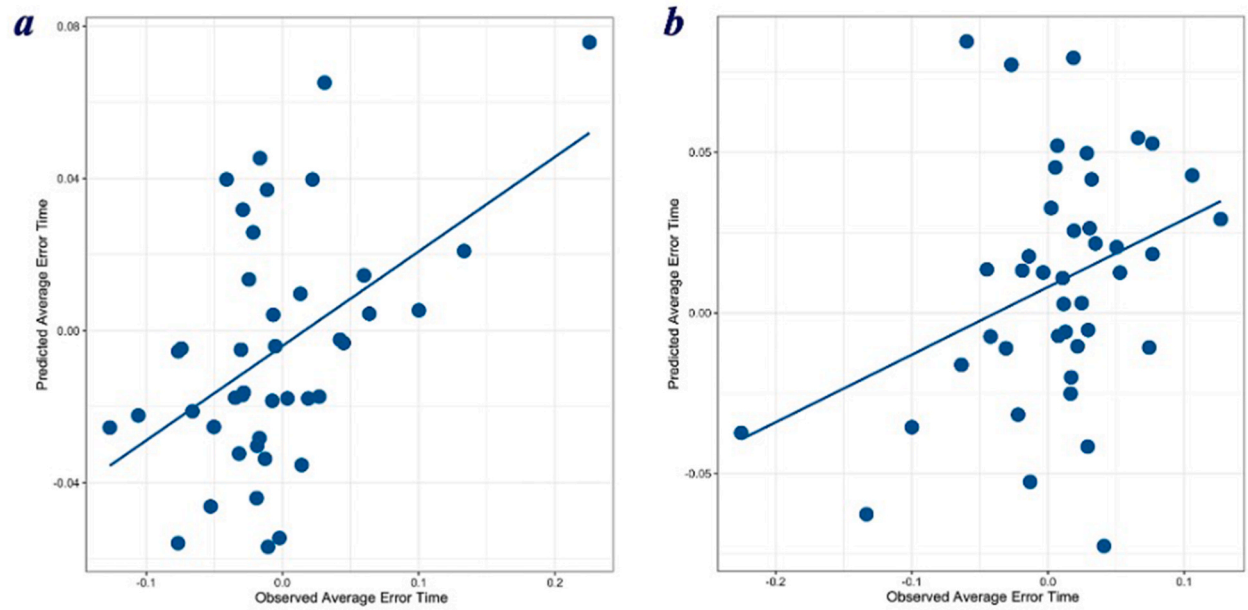

Fig. 2. Correlations between predicted and observed average error time for ODI (a) and FISO (b) cortical microstructures. FISO: free-water isotropic volume fraction; ODI: orientation dispersion index (ODI).

3. Results

SVR analyses showed that the cortical ODI and FISO measures were significant predictors of average error-time in healthy older adults. Particularly, leave-one-subject-out results revealed that the SVR model based on cortical ODI and FISO measures predicted average error time with a correlation accuracy of $r = 0.44$ ($p = 0.016$) and $r = 0.35$ ($p = 0.033$), respectively (Fig. 2). The model based on cortical NDI measures was not significant ($p > 0.05$). The conventional cortical metrics including cortical thickness, surface area and gray matter volume were not significant predictors of average error time (p's > 0.34, $r < 0.014$). We further examined which brain regions contributed the most to predicting average error time. ODI measures in the dorsolateral prefrontal cortex, ventral stream visual pathway, auditory association regions, medial and lateral temporal lobe, the MT + Complex, superior parietal lobe, putamen, posterior cingulate and posterior opercular regions were the most significant predictors of average error time (Table 2, Fig. 3a). For FISO, the lateral temporal, ventral stream visual pathway, medial temporal lobe, nucleus accumbens, anterior cingulate cortex, medial and prefrontal cortex, inferior frontal gyrus, and orbital and polar frontal lobes were the top contributing ROIs (Table 2, Fig. 3b). Finally, we found a significant negative correlation between the majority of cortical ODI values and the average error time. Simultaneously, we noted a positive correlation between cortical FISO and the average error time. Table 3 presents the top ten regions of interest (ROIs) showcasing these correlations-.

4. Discussion

This study aimed to identify the cortical microstructural measures associated with time perception in healthy older adults. Our work highlighted for the first time the cortical microstructural properties in specific brain regions that predict time perception in older adults utilizing SVR and microstructural NODDI. We found that neural networks associated with attention and cognitive control, episodic and spatial memory, autonomic motor function, and the processing of visual input for cognitive operations were the most significant predictors of time perception abilities in healthy older adults. Specific networks included prefrontal, medial frontal, temporal, parietal, and anterior cingulate networks. We specifically demonstrated that lower FISO and higher ODI in these regions are

Table 2
Top contributing ROIs for predicting the average error time using the cortical ODI and FISO.

ODI WM Cortical and Subcortical Microstructure			FISO WM Cortical and Subcortical Microstructure		
Region of Interest (ROI)	***Network***	***Square of Weight (WSF)***	***Region of Interest (ROI)***	***Network***	***Square of Weight (WSF)***
L_a9-46v	Dorsolateral Prefrontal	8.75×10^{-6}	L_TE1p	Lateral Temporal	1.72×10^{-5}
L_VVC	Ventral Stream Visual	8.00×10^{-6}	L_VVC	Ventral Stream Visual	1.37×10^{-5}
R_STGa	Auditory Association	7.48×10^{-6}	R_PeEc	Medial Temporal	1.29×10^{-5}
R_PreS	Medial Temporal	6.69×10^{-6}	L_PHA3	Medial Temporal	1.18×10^{-5}
R_TE2a	Lateral Temporal	6.39×10^{-6}	L_VMV1	Ventral Stream Visual	1.11×10^{-5}
R_PH	MT + Complex and Neighboring Visual Areas	6.06×10^{-6}	R_Accumbens	Subcortical	1.00×10^{-5}
R_VIP	Superior Parietal	5.94×10^{-6}	L_a32pr	Anterior Cingulate and Medial Prefrontal	9.52×10^{-6}
L_putamen	Subcortical	5.61×10^{-6}	L_p47r	Inferior Frontal	9.00×10^{-6}
R_7 m	Posterior Cingulate	5.41×10^{-6}	R_p10p	Orbital and Polar Frontal	7.79×10^{-6}
R_OP4	Posterior Opercular	5.39×10^{-6}	L_10v	Anterior Cingulate and Medial Prefrontal	7.74×10^{-6}
L_7 PC	Superior Parietal	5.36×10^{-6}	R_s32	Anterior Cingulate and Medial Prefrontal	7.60×10^{-6}
L_p32pr	Anterior Cingulate and Medial Prefrontal	5.31×10^{-6}	L_SCEF	Paracentral Lobular and Mid Cingulate	6.98×10^{-6}
R_DVT	Posterior Cingulate	4.70×10^{-6}	R_IP2	Inferior Parietal	6.97×10^{-6}
L_VMV2	Ventral Stream Visual	4.61×10^{-6}	R_FOP1	Posterior Opercular	6.91×10^{-6}
L_VentralDC	Subcortical	4.51×10^{-6}	L_7Am	Superior Parietal	6.68×10^{-6}
L_Thalamus	Subcortical	4.51×10^{-6}	R_23d	Posterior Cingulate	5.99×10^{-6}
R_VMV3	Ventral Stream Visual	4.50×10^{-6}			
R_a10p	Orbital and Polar Frontal	4.45×10^{-6}			
L_V4t	MT + Complex and Neighboring Visual Areas	4.38×10^{-6}			
L_IFSp	Inferior Frontal	4.31×10^{-6}			
R_V6	Dorsal Stream Visual	4.27×10^{-6}			
R_TE1a	Lateral Temporal	3.96×10^{-6}			

a9-46v: Area anterior 9-46v; VVC: Ventral Visual Complex; STGa: Superior Temporal Gyrus region a; PreS: PreSubiculum; TE2a: Area TE2 anterior; PH: Area PH; VIP: Ventral IntraParietal Complex; 7 m: Area 7 m; OP4: Area OP4/PV; 7 PC: Area 7 PC; p32pr: Area p32 prime; DVT: Dorsal Translational Visual Area; VMV2: VentroMedial Visual Area 2; VMV3: VentroMedial Visual Area 3; a10p: Area anterior 10p; V4t: Area V4t; IFSp: Inferior Frontal Sulcus posterior; V6: Sixth Visual Area; TE1a: Area TE1 anterior; PeEc: Perirhinal Ectorhinal Cortex; PHA3: Parahippocampal Area 3; a32pr: Area p32 prime; p47r: Area anterior 47r; SCEF: Supplementary and Cingulate Eye Field; IP2: Area IntraParietal 2; FOP1: Frontal Opercular Area 1.

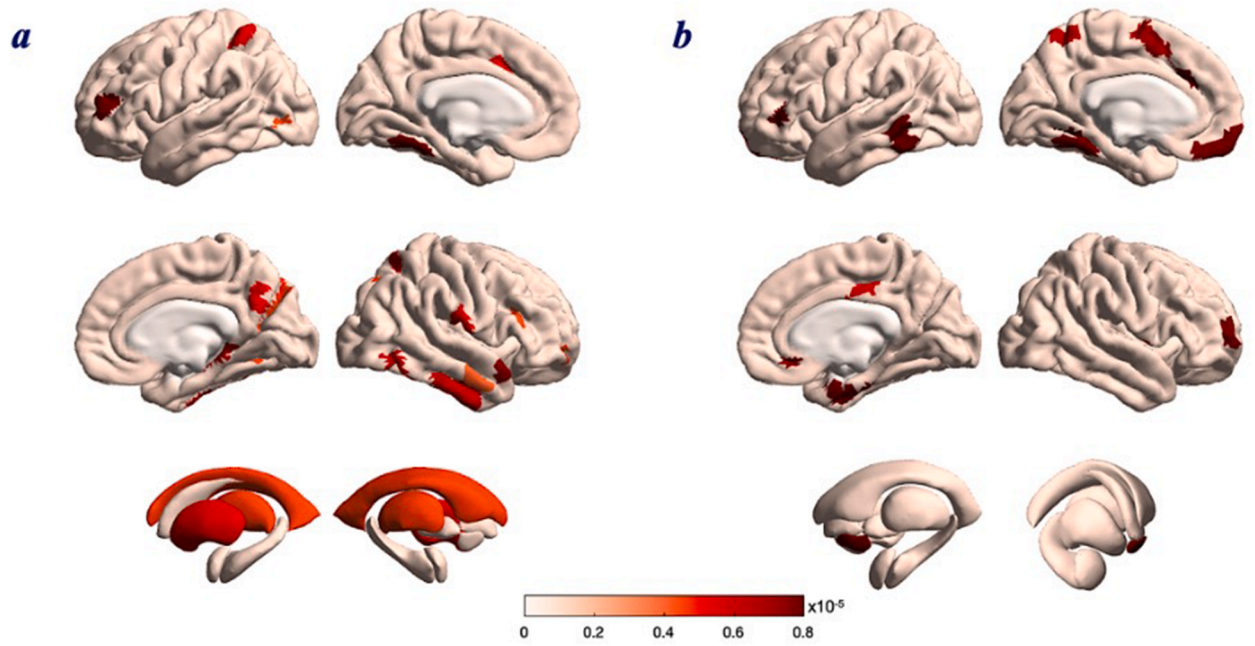

Fig. 3. Top contributing ROIs are overlayed on the brain's cortical and subcortical surfaces for predicting the average error time using the cortical ODI (a) and FISO (b). FISO: free-water isotropic volume fraction, ODI: orientation dispersion index (ODI). The darker color represents higher prediction weights. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Top ROI regions showed significant correlations between the average error time and cortical ODI and FISO.

Region of Interest (ROI)	Network	r value	p value
odi_L_PCV	Ventral_Stream_Visual	−0.5380929	0.000237429
odi_L_VMV2	Ventral_Stream_Visual	−0.52231637	0.000388048
odi_L_VVC	Ventral_Stream_Visual	−0.50359711	0.000674397
odi_L_7 PC	Superior_Parietal	−0.48338094	0.001183614
odi_R_VIP	Superior_Parietal	−0.48127921	0.001252452
odi_L_TE2a	Lateral_Temporal	−0.478153	0.001361425
odi_R_OP4	Posterior_Opercular	−0.47725872	0.001394106
odi_R_7PI	Superior_Parietal	−0.46424828	0.001954752
fiso_L_3b	Somatosensory_and_Motor	0.643836776	4.23E-06
fiso_L_MIP	Superior_Parietal	0.605286668	2.17E-05
fiso_L_7Am	Superior_Parietal	0.593914575	3.38E-05
fiso_L_23d	Posterior_Cingulate	0.584292866	4.85E-05
fiso_L_p32	Anterior_Cingulate_and_Medial_Prefrontal	0.571317037	7.76E-05
fiso_L_SFL	Dorsolateral_Prefrontal	0.571153167	7.81E-05
fiso_L_PEF	Premotor	0.566140776	9.31E-05
fiso_L_24dv	Paracentral_Lobular_and_Mid_Cingulate	0.563021347	0.000103782
fiso_L_L01	MT+_Complex_and_Neighboring_Visual_Areas	0.554972657	0.000136548
fiso_L_31pv	Posterior_Cingulate	0.552704707	0.000147338

associated with better performance in the time estimation task.

In this study, we specifically targeted the microstructural properties of the frontal, parietal, and temporal lobes, as well as the basal ganglia and thalamus, due to their established roles in the neurocognitive networks involved in time perception. The frontal lobes, particularly the prefrontal cortex, are central to planning complex cognitive behavior and making decisions about when actions should be initiated, thus playing a pivotal role in timing tasks that require cognitive processing and temporal integration [52]. The parietal cortex, on the other hand, contributes significantly to processing sensory information and integrating it with temporal cues, crucial for tasks that demand spatial-temporal reasoning [53]. The temporal lobes facilitate the encoding and retrieval of temporal information and are involved in perceptual tasks that integrate sequences of events over time, which is essential for understanding patterns in timing tasks [54].

Furthermore, the basal ganglia and thalamus have been implicated in the modulation of timing processes through their extensive connections with the cortical areas. The basal ganglia are particularly integral to the regulation of motor timing and the development of habitual timing patterns, critical for tasks requiring consistent temporal intervals [55]. The thalamus supports these processes by

coordinating timing information across different sensory modalities and maintaining cortical alertness, necessary for precise time estimations [56]. By focusing on these areas, our study leverages their known functional responsibilities to explore how their microstructural changes might influence time perception in older adults. Although regions such as the cerebellum and occipital lobe also play roles in timing and perceptual tasks, our study prioritized those regions most directly linked to the cognitive and perceptual dimensions of the timing tasks employed, aiming to delineate the neural underpinnings of time perception within this specific context. Future studies could expand this focus to include a broader array of brain regions, thereby providing a more comprehensive understanding of the neural architecture underlying time perception across different tasks and conditions.

Specific subcortical regions, such as the nucleus accumbens that was not found to contribute to time perception in the literature, were identified in this study. This region is associated with the limbic system and regulates limbic functions of motivation, affect, and reward [57]. The contribution of the nucleus accumbens can be explained by the nature of the Time-Wall Estimation task. While the task is a measure of motion prediction and time perception, the objective of the task is to press the space bar at the exact moment the target would pass through the notch marked at the bottom of the display. The nucleus accumbens is the neural interface between motivation and action, having the nature of the Time-Wall Estimation task explain its role in time perception for this study.

Notably, both the ODI and FISO measures exhibited significant results, highlighting their effectiveness in estimating average error time. However, it is worth mentioning that the NDI measure did not yield any significant prediction. It is intriguing to observe the close relationship between NDI and ODI, as they are both linked to the synaptic connections in the cortex [58]. While NDI indicates neurite density, ODI is more prominently expressed within the brain cortex, which suggests that ODI holds a greater influence in conveying information between brain regions. The observed increase in neurite arborization coupled with the decrease in extracellular structure expansion (as evidenced by the decreased FISO measure) implies enhanced network efficiency. It provides valuable insights into how ODI emerged as the strongest predictor of time perception, considering its involvement in highly distributed neural processes. In addition, the models constructed based on conventional measures of brain structure such as regional brain volume and cortical thickness were not significant predictors of average error time in the task. These further emphasize the sensitivity of ODI and FISO measures in predicting time perception ability in older adults.

In this study, we utilized the heightened sensitivity of NODDI measures to derive biologically meaningful indices that allowed us to determine which ROIs contribute to time perception. This approach overcomes the limitations of conventional diffusion measures (such as Fractional Anisotropy (FA)), which are less sensitive to detecting cortical microstructural changes related to aging. However, there are still some limitations that could be improved in future research. First, this study investigated the neural networks involved in perceiving a range of durations, requiring enhancement of the study design to compare neuroanatomical measures for short and long-time durations under different timing conditions. Second, to obtain a comprehensive understanding of the neurobiological measures, there is a need for multimodal neuroimaging methods to measure brain activity to obtain a better sense of neurobiological measures.

5. Conclusion

This study utilized a multivariate analysis to investigate the combination of neural networks predicting a range of multi-second timing durations. We indicated that microstructure properties of the frontal, parietal and temporal regions, along with the basal ganglia would be the highest predictors of time perception. We also found that those with higher FISO and lower ODI showed poorer performance in time estimation. Unlike other studies, this study examines the prediction of both short and long timing durations with multivariate analysis, rather than univariate analysis. NODDI measures, which have increased sensitivity to certain brain changes at the cellular level, were used for the first time to identify the neural networks that are playing a key role in predicting time. Future studies should assess whether these same networks are contributing to time perception in older adults with mild cognitive impairment (MCI) and whether degeneration of these networks contribute to early diagnosis or detection of dementia.

Disclosures

Trudy Kim, Elveda Gozdas, Ali Rahimpour, and Dr. Hosseini do not have financial interests or potential conflicts of interest to report.

Ethics declarations

This study was reviewed and approved by the Institutional Review Board at Stanford University, with the approval number: 40335.

Data availability

Data associated with our study has not been deposited into a publicly available repository and will be made available upon request.

CRediT authorship contribution statement

Trudy Kim: Writing – original draft, Project administration, Investigation, Formal analysis, Data curation. **Ali Rahimpour Jounghani:** Writing – original draft, Validation, Methodology, Data curation. **Elveda Gozdas:** Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **S.M. Hadi Hosseini:** Writing – review & editing, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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