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Research Article

Exploring age and hemispheric differences in cortical plasticity after iTBS using fNIRS

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ABSTRACT

Non-invasive brain stimulation applied to the prefrontal cortex (PFC) has been shown to improve cognitive outcomes in older adults with cognitive impairments (Miller et al., 2023). However, the differential impact of left versus right dorsolateral prefrontal cortex (DLPFC) stimulation on prefrontal oxygenation levels, as well as its modulation across age groups, remains insufficiently understood.

45 adults completed a within-subjects design completing 4 cognitive tasks before and after intermittent TBS (iTBS) stimulation applied to the left and right DLPFC (F3 and F4). FNIRS was recorded concurrently, with 12 optode channels spanning across the left, medial and right prefrontal cortex measuring oxygenation levels in response to cognitive task performance.

Age-related effects were observed with younger adults showing significant increased HbO in response to left iTBS during inhibition tasks. Learning tasks revealed bilateral increases in middle-aged participants and decreases in older adults after right DLPFC stimulation. Working memory showed bilateral increased HbO after right iTBS stimulation in both younger and middle-aged adults. Older adults revealed a decrease in HbO post iTBS, that was centred in the midline after right iTBS, but bilateral after left iTBS.

Our novel findings show the dispersion of oxygenation level changes in the ipsilateral and contralateral hemispheres during excitatory TBS on the DLPFC was age dependent. In younger adults' subsequent task related brain activity was 'up-regulated', whereas older adults revealed 'down-regulation' reflecting increased efficiency. These findings cast new light on the dynamic properties of brain stimulation that is highly influenced by age-related factors and cognitive task.

Introduction

The Dorsolateral Prefrontal Cortex (DLPFC) is a brain area associated with domain general executive control functions such as task switching, executive attention, inhibition, planning, decision making and working memory (Friedman & Robbins, 2022). The DLPFC is a key area of age-related structural deterioration, including significant loss of grey and white-matter volume and cortical thickness in older age (Lemaitre et al., 2012; Salat et al., 1999). Functionally, the brain can adapt to structural decline via the implementation of neural compensatory strategies to retain cognitive functioning in old age, also known as neuroplasticity (Reuter-Lorenz & Park, 2014). For example, healthy older adults exhibit bilateral prefrontal activity on tasks which young adults show lateralized activity (Cabeza et al., 2002), demonstrating the ability of the brain to redistribute activity to support cognitive function. Failure to implement effective neural strategies is associated with accelerated cognitive decline in old age (Cabeza et al., 2002).

Given the importance of neuroplasticity in maintaining cognition in ageing, several approaches have been investigated in the literature. One method of inducing neuroplasticity artificially is via repetitive transcranial magnetic stimulation (rTMS) that has shown positive outcomes in individual with cognitive decline (Miller et al., 2023). A more efficient type of rTMS was devised by Huang and colleagues (2005) that showed delivering triplets of pulses 5 times a second (5 Hz, theta frequency), known as Theta-Burst Stimulation (TBS), induces equivalent effects to traditional methods but with shorter induction times (Blumberger et al., 2018). Intermittent TBS (iTBS) was traditionally considered the excitatory form of TBS, and involves bursts of high-frequency magnetic pulses, delivered at 50 Hz, in a pattern of three pulses at 5 Hz, with an inter-burst interval of 200 ms, repeated every 10

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s, for a total of 600 pulses per session (Huang et al., 2005). However, this notion has become increasingly challenged in the literature with studies showing large inter- and intra- individual variability (Schilberg at el., 2017). In addition, recent concurrent functional neuroimaging data has identified different effects of iTBS stimulation dependent on the hemisphere of stimulation, with stimulation on the left DLPFC resulting in decreases in HbO, and on the right revealing increases (Miller and Burke, 2025). Gorban et al. (2023) found that priming the motor cortex (M1) with iTBS did not produce significant hemodynamic changes in response to a single TMS pulse compared to sham, further questioning the persistence of LTP-like effects after iTBS induction. Despite this iTBS is thought to influence cognition via two mechanisms; 1) by inducing theta wave oscillations associated with working memory, attention and concentration (Aftanas & Golocheikine, 2001; Klimesch, 1999) and 2) by inducing effects akin to Long Term Potentiation (LTP) i.e., the strengthening of synaptic connections, although this latter effect was found in rat models (Lee et al., 2021). Meta-analytic evidence shows promising effects of DLPFC-targeted iTBS interventions on cognitive functioning in older adults with age-related neurodegenerative diseases, demonstrating large significant effects on global cognition compared to sham stimulation (for review see Miller et al., 2023).

Literature on iTBS effects across age groups is sparse with middle-aged adults often excluded from experimental designs. Despite this paucity, previous studies generally suggest younger participants are considered to be more responsive to iTBS due to a larger capacity for neuroplasticity and priming (Opie et al., 2017). In contrast, older adults generally show reduced plasticity responses to TBS protocols (Lu et al., 2024), possibly due to age-related decline in synaptic plasticity mechanisms caused by reduced NMDA receptor function or GABAergic changes (Diao et al., 2022).

Despite the increasing use of iTBS in the literature, most studies have focused on the behavioural effects of iTBS such as changes in reaction time, and there remains limited evidence regarding influences on neural function and cortical haemodynamics. Limited studies in this area have shown increases in theta wave activity and cortical excitability following iTBS when measuring with electroencephalography (EEG) (Diao et al., 2022; Ding et al., 2021). More recently, evidence from magnetic resonance imaging (fMRI) has shown iTBS over the left DLPFC results in increased BOLD activity in the stimulated cortex (Chang et al., 2024). However, most neuroimaging techniques are not compatible for concurrent use with TMS. Firstly, both TMS and fMRI produce strong magnetic fields which creates significant safety risks. Secondly, when combined safely, the magnetic fields generated by TMS can interfere with signals in fMRI and EEG, creating artifacts, distorted images and low signal-to-noise-ratio (Mizutani-Tiebel et al., 2022; Varone et al., 2021).

Continuous neuroimaging of TMS-induced effects can be achieved safely and effectively with the use of functional near-infrared spectroscopy (fNIRS). FNIRS is a non-invasive neuroimaging technique that measures the absorption of near-infrared light to detect changes in blood oxygenation levels, reflecting neural activity, i.e., the hemodynamic response. Similarly to fMRI, fNIRS relies on the principle of neurovascular coupling, that when neurons become active, there is an associated increase in local oxygenated blood flow that is accompanied by a corresponding decrease in deoxygenated blood (Phillips et al., 2016). This multi-modal approach offers potentially important insights into the causal effects of brain stimulation on neural functioning.

Functional near-infrared spectroscopy (fNIRS) is particularly well-suited for concurrent use with TMS, as its non-metallic and non-magnetic components ensure compatibility. Moreover, fNIRS has proven sensitive in detecting hemodynamic changes during and after theta-burst stimulation (TBS), with studies reporting cortical oxygenation alterations consistent with stimulation-induced modulation of prefrontal and motor networks (Vesia et al., 2013; Nettekoven et al., 2014; Orosz et al., 2021). To our knowledge, this is the first study to investigate the haemodynamic effects of iTBS on cognitive processing using fNIRS across the lifespan. One previous study examined the haemodynamic effects of cTBS, the inhibitory form of TBS, to the left DLPFC on the emotional Stroop task using fNIRS and found a bilateral decrease in prefrontal oxygenation after stimulation (Tupak et al., 2013). Therefore, we anticipated excitatory iTBS to induce an increase in oxygenation under the site of stimulation associated with task performance. In another paper (Miller et al., 2025, under review), we found improvements in working memory performance in middle-age and older adults and faster attentional processing in young adults following iTBS. The focus of the current study was to investigate iTBS-induced changes in blood oxygenation in the DLPFC in response to these cognitive tasks post-stimulation.

The dorsolateral prefrontal cortex (DLPFC) is critical for working memory, attention, and inhibitory control, making it a key target for non-invasive brain stimulation. Intermittent theta-burst stimulation (iTBS) can induce excitatory neuroplastic changes, but the haemodynamic correlates of these effects are not fully understood. Functional near-infrared spectroscopy (fNIRS) provides a TMS-compatible, non-invasive measure of cortical oxygenation, enabling direct investigation of stimulation-induced neural modulation. Building on our previous findings (Miller et al., 2025, under review) showing improved working memory in middle-aged and older adults and faster attentional processing in young adults after iTBS, we hypothesised that in working memory and attention tasks, iTBS will increase DLPFC HbO responses during these tasks, reflecting neuroplastic facilitation. However, sequence learning and inhibition no behavioural effects were observed previously suggesting no significant haemodynamic changes. Finally, we also predict iTBS-induced HbO responses may vary across young, middle-aged, and older adults, reflecting age-related differences in cortical plasticity. This study leverages iTBS-fNIRS to provide novel insights into prefrontal neurovascular and cognitive modulation across the adult lifespan.

Methods

Please note a subset of the participants included in the present study also contributed to a separate study examining cognitive outcomes following iTBS (Miller et al., 2025, under review). The current manuscript focuses specifically on fNIRS-measured hemodynamic responses, whereas the other study reports behavioral and cognitive effects.

Participants

Participants took part in this study and were equally split into 3 age groups (young, middle, and older) with 15 participants in each group. The younger group were aged between 19–25 years old, the middle group were 44 – 59 years old, and the older group were aged between 60–73 years (see Table 1 below). Participants had no known neurological, developmental or psychological deficits and had normal or corrected to normal vision. Participants were right-handed and monolingual. Years of education is known to affect cognitive functioning, so we measured this among our sample and found similar levels across age groups with all groups mainly reaching higher education at university level. Mood may also affect cognitive performance and so the geriatric depression scale (GDS) was utilized at the beginning and end of testing. All participants revealed an absence of low mood as indicated by averages of < 2 on this scale, both before and after testing. Finally, a Montreal cognitive assessment (Nasreddine et al., 2005) provided an assessment of cognitive status with results > 26 indicating normal cognitive function in all participants

Prior to taking part, participants were provided with an information sheet, completed a medical history questionnaire, and provided their written informed consent. The study was approved by the University of Leeds Ethics Committee on 29/10/2021 (PSYC-347) and fully abided by the British Psychological Society Code of Human Research Ethics (Oates et al., 2021), as well as the Declaration of Helsinki (World Medical

Table 1
Demographic table showing average scores for each age group. Variables include years of education (YoEd), the cognitive screening tool the Montreal cognitive assessment (MoCA), and the geriatric depression scale (GDS) at the first (1st) and last (2nd) session.

Pt Group	Gender	Age range	YoEd	MoCA	GDS 1st	GDS 2nd
Young Group	Female = 7 Male = 8	M = 20.93 SD = 1.05	15.8	27.93	0.93	0.73
Middle Group	Female = 10 Male = 5	M = 54.27 SD = 5,23	16.2	28.13	1.4	1.13
Older Group	Female = 7 Male = 8	M = 66.33 SD = 4.58	16.53	27.87	0.67	0.73

Association, 2013).

Study design

Participants attended two iTBS sessions spaced 1-week apart that focused on either left or right DLPFC stimulation. During these sessions, fNIRS was recorded while participants performed a series of 4 cognitive tasks, both before and after iTBS, but not concurrently with iTBS stimulation. For details of the protocol and task layout please refer to Fig. 1.

Cognitive tasks

The cognitive tasks (Whybird et al., 2021) and behavioural results are described in detail elsewhere (Miller et al., 2025 under review). Eye movements were monitored throughout the tasks using an Eyelink 1000 Hz eyetracker (SR Research Ltd) with the stimulus displayed on a 21″ LCD monitor. Participants sat in a dark room absence of visual and auditory distractions with heads rested on a chinrest and responded to the tasks with either their eye's or via a touch-screen LCD monitor. Frequent light, chat and rest breaks between tasks, alongside randomization of tasks reduced fatigue effects. Cognitive tasks comprised:

Attention task – A Posner cueing paradigm (Shimozaki, 2010) with 30 cued and 30 un-cued trials, designed to assess **top-down versus bottom-up attentional control**. Trials were grouped into blocks with 15-second rest periods, lasting approximately 3 min.
Anti-saccade task – Based on Hallett (1978), this assessed **inhibitory control** by requiring participants to suppress reflexive saccades toward a prepotent stimulus. Each block contained 30 anti-saccade (no-go) and 30 pro-saccade (go) trials, presented in randomized order with rest breaks, lasting ~ 3 min in total.
Corsi-back task – A computerized version of the Corsi span task (as described by Kessels et al., 2000), assessing **working memory**. Participants recalled sequences of 3–5 items in reverse order after a delay. The task consisted of 24 trials, divided into three blocks of eight with rest intervals, lasting ~ 5–6 min.
Sequence learning task – Adapted from Burke et al. (2013), this task measured **short-term sequence learning ability**. Participants completed 10 sequence sets, with each sequence repeated four times and separated by 10-second rest periods, lasting ~ 4–5 min in total.

Reaction time and accuracy (both eye and hand responses) and fNIRS were recorded during all tasks pre- and post- stimulation for comparisons. Further details of the attention, inhibition, and sequence learning tasks can be found in Whybird et al. (2021), and of the Corsi task in Brunetti et al. (2014).

Functional near-infrared spectroscopy (fNIRS)

A 12 channel Oxymon Mk II fNIRS system (Artinis Medical Systems) was used to measure changes in the concentration of oxygenated blood (HbO), deoxygenated blood (HbR) and total change in oxygenation (tHb = HbO-HbR) in μmol/L. Data was collected at a frequency rate of 120 Hz, and the differential path factor (DPF) was adjusted for age related differences (Duncan et al., 1996) in the brain using the formula: DPF = 4.99 + 0.067*(ageˆ0.814), or for those older than 50, the max DPF was used as described by Ranchod et al (2023). The optodes were attached to a black neoprene head cap that absorbed external light and were

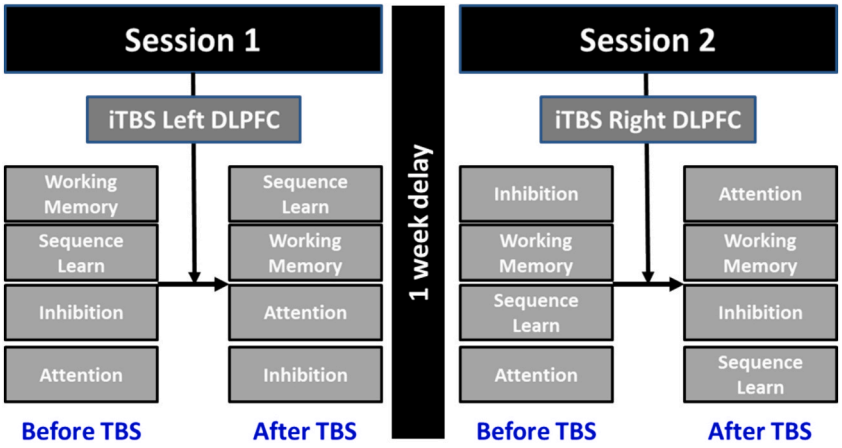


Fig. 1. Example session structure and task order for individual participants across two laboratory visits, spaced approximately one week apart. In Session 1, participants completed a randomized set of cognitive tasks before receiving iTBS to either the left or right dorsolateral prefrontal cortex (DLPFC) and then completed the same tasks again in a new randomized order after stimulation. In Session 2, participants first received placebo stimulation at the vertex, followed by a randomized set of cognitive tasks. They then underwent active iTBS to the DLPFC in the hemisphere opposite to Session 1, after which they completed another randomized set of cognitive tasks. FNIRS was recorded during cognitive tasks.

organised symmetrically over the DLPFC of both hemispheres, with approximately 30 mm distance between the source and detector optodes resulting in a penetration depth of around 8 mm. The optode template design comprised 3 detector and 8 receiver optodes (see Fig. 1) resulting in 8 split and 4 unsplit channels spanning the left, midline and right prefrontal cortex. To reduce movement artefacts, participants were asked to remain as still as possible, the cap was secured using an elastic chin strap to maintain optimal optode-scalp contact, and all fNIRS cables were attached to a drip stand for stability. Real time concentration changes in HbO, HbR and total Haemoglobin change (tHb) were displayed using Oxysoft (Version 3.0.103.3) (Artinis Medical Systems, n.d.). Recording using fNIRS was taken before and after iTBS stimulation, during the cognitive tasks.

FNIRS is non-invasive, safe, portable, and tolerant to movement artefacts (Irani et al., 2007; Pinti et al., 2020). Recording both oxygenation and deoxygenation levels can also provide confidence on the signal being derived from neurovascular coupling mechanisms.

TMS protocol

TMS was administered using a Magstim Rapid^2 (Magstim Company Ltd). Intermittent TBS (iTBS) was administered with a figure of 8 coil at an optimal 45° angle to the cortex (Thomson et al., 2013). The non-invasive brain stimulation consisted of administering triplets of 50 Hz electromagnetic pulses every 200 ms at 50 % of the TMS machine power output, repeated every 10 s for 190 s, with total stimulation consisting of 600 pulses (Huang et al., 2005; Pabst et al., 2022).

The TMS coil was held by hand perpendicular to the scalp, with the centre of the coil above the region of interest; this was area F3 of the left hemisphere (LH), corresponding to the left DLPFC, or area F4 of the right hemisphere (RH), corresponding to the right DLPFC (Herwig et al., 2003). The International 10–20 EEG was used to identify the DLPFC using F3 and F4 when the cap was placed over CZ using naison and inion measurements (Herwig et al., 2003). The hemisphere of stimulation was randomised across participants to control for order effects at the group level, and counterbalanced within participants to ensure each hemisphere was stimulated once. The TMS system sent automatic triggers to the fNIRS system; these were used solely to align the fNIRS data with the onset and offset of the cognitive tasks, and no neural responses were recorded during stimulation.

One limitation of the design is the increased distance of the TMS coil from the scalp of ~12 mm due to the optode profile. We chose to keep the optode cap in place during stimulation despite not recording fNIRS during this period to ensure within subject pre and post consistency in fNIRS recording. We aimed to minimise noise and variability that are common with repositioning and movement of the cap and ensure a post-stimulation duration of 5 min to the start of the cognitive tasks. Previous studies have identified 40 % of the maximum stimulator output (MSO) over the DLPFC produces effective and consistent behavioural/cognitive effects (Miller et al., 2025; Whybird et al., 2021; Burke et al., 2013). In addition, Kaminski et al (2011) recommends that using a fixed MSO is better than using RMT for stimulation in the prefrontal cortex as applied here. We therefore used MSO and adjusted the stimulator output for the increased coil-to-scalp distance by using the equation 40*(0.03*12 mm) = 54, and then rounded this to 50 % of stimulator output as suggested by Stokes et al., (2005). TMS is generally well-tolerated and painless for most participants (Najib and Horvath, 2014). There are well established safety protocols for TMS which were followed during this study, and TMS is safe when used in accordance with these protocols (Rossi et al., 2021). No participant had any counterindication to TMS during this study.

Data analysis

All data files were converted into a *.NIRS format using the oxysoft2matlab function (MatLab R2022a, Mathworks Inc) and stored in folders according to the Brain Imaging Data Structure (BIDS) framework. FNIRS data is subject to biological and technical artefacts and so prior to pre-processing the QTNirs toolbox was used to identify suboptimal channels for each participant. Channels that did not reach a cut-off of 70 % signal quality during testing were excluded from further analysis (see Fig. 2, left- and right-sided images). Data quality was excellent, with all 15 participants per age group retained for analysis. Each cognitive task and age group included between 12 and 15 high-quality datasets per optode channel, ensuring robust statistical power and uniform coverage across the prefrontal cortex. A sensitivity analysis was conducted to evaluate the sensitivity of the source and detector optodes using the raw data. This was performed post data acquisition and prior to preprocessing. The points of the optode placement were digitised and then registered with a standard brain model (Colin 27), using Montreal Neurological Institute (MNI) coordinates in AtlasViewer (Aasted et al, 2015). The profile shown in Fig. 2 indicated a uniform distribution of sensitivity across the optode array.

Data was then subjected to a standard pre-processing pipeline (see supplementary material figure 1) within the NIRS toolbox administered in the MatLab environment (BrainAnalyzer, Santosa et al., 2018). A bandpass filter (0.001 – 0.25 Hz) removed physiological noise before data was converted from haemodynamic intensity raw data into optical density (OD) using the modified Beer-Lambert Law. A GLM was used with a FIR basis function to model the fNIRS task data. The FIR was chosen over canonical models due to expected prolonged responses in older adults. Data were down sampled to 1 Hz prior to GLM. We modelled the hemodynamic response using an FIR basis function spanning 40 s post-stimulus with 2 s bins, resulting in 20 regressors per condition. Using the event triggers generated from the Eyelink software to the fNIRS laptop we could accurately align the fNIRS data with the onset and offset for each of the cognitive tasks individually for accurate offline analysis. We utilized a block design and modelled each task independently i.e., modelled separately the cued, uncued, pro-saccade and anti-saccade blocks individually. A 30 s epoch from the start of each block was averaged within participants to each task with HbO and HbR calculated as a change from baseline (10 s rest prior to task), before generating group level HbO and HbR responses. Changes in HbO and HbR from baseline were calculated independently for each of the 12 channels to each of the conditions (attention, inhibition, working memory and sequence learning) and for each hemisphere (left iTBS and right iTBS). These group level results were followed by t-tests to identify significant effects.

The resultant data shown below was subjected to Bonferroni correction (family-wise error correction) for multiple comparisons as shown by the reported q values. In addition, to ensure our data was neuronally driven and not noise related, an additional level of control was performed on the results data whereby significant changes in oxyhaemoglobin (HbO) was only selected if there was a corresponding negative correlation with deoxyhaemoglobin (HbR) providing confidence that the data was showing clear neurovascular coupling in the response (Kinder et al., 2022).

Results

Summary of behavioural effects

The behavioural results showing the effects of iTBS on cognitive performance are reported elsewhere (Miller et al., 2025, under review). To summarise: young adults showed significantly faster reaction times post iTBS in the attention task, with faster responses observed post left hemisphere iTBS DLPFC stimulation. Age was a significant covariate in the ANCOVA model, while interactions involving hemisphere and trial were marginal and non-significant. In addition, iTBS significantly improved both reaction time and accuracy to the working memory task in middle-aged and older adults, with age emerging as a significant predictor of performance and no significant effects observed for

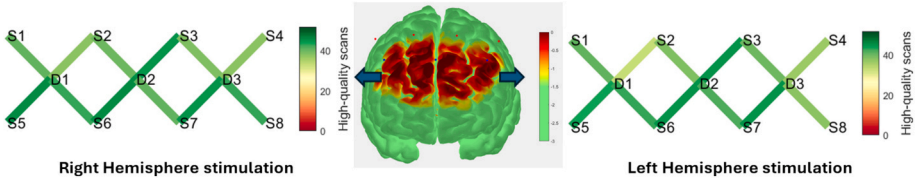


Fig. 2. The mean sensitivity profile of the optode array from all participants is shown in the centre brain image. Red/orange regions indicate optimal signal and sensitivity during recordings. Heatmaps for all 12 optode channels for the RH stimulation (shown on left of image) and LH (shown on right side of figure) indicating > 35/45 channels reached above 70 % signal quality across all channels in our testing group. Three detector (D1, D2, D3) and 8 transmitter optodes (S1, S2, S3, S4, S5, S6, S7 and S8) resulted in an 8- split and 4- unsplit channel array across the whole PFC region spanning both hemispheres. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

hemisphere or trial. The behavioural results showed no significant effects of iTBS on performance on the sequence learning and inhibition tasks for any age or hemisphere of stimulation.

Change in oxygenation levels (HbO) in response to iTBS stimulation on the DLPFC

The results presented in Fig. 3 are a summary of beta coefficients (β) that show the difference in HbO before iTBS to after iTBS (after-before). The difference data is summarized across all optodes and split by hemisphere, cognitive task and age group.

We applied a repeated measures ANOVA on beta coefficients on the difference between before and after iTBS for each task and hemisphere across all channels. We found a significant main effect of $p < 0.001$ for hemisphere of stimulation ($F_{(1, 11)} = 79.6$, $\eta^2 = 0.137$), cognitive tasks ($F_{(3,33)} = 12.65$, $\eta^2 = 0.054$), and age group ($F_{(2,22)} = 17.83$, $\eta^2 = 0.039$), with a hemisphere*task*age interaction ($F_{(6,66)} = 6.01$, $p < 0.001$, $\eta^2 = 0.083$). Bonferroni corrected post-hoc tests revealed higher activity in the left hemisphere in the young adults for attention ($p < 0.001$) and sequence learning task ($p = 0.018$). Higher HbO after left iTBS in the middle age group for attention and inhibition ($p < 0.001$), with working memory revealing significant higher HbO after right iTBS ($p = 0.039$). Finally, older adults revealed higher activity after left iTBS in the inhibitory task ($p = 0.017$). Age differences across hemispheres and tasks revealed generally higher activity in younger compared to older adults ($p < 0.001$), with a similar but reduced difference between middle-age and the older group ($p = 0.026$). Only marginal increases were found between younger and middle-aged groups ($p = 0.056$). Fig. 3 shows differences in beta values for each task and age-group. [nb: for more detailed break-down of optode effects in the left, midline and right hemisphere see supplementary material figure 2].

Significant within/between group effects: age, hemisphere and task effects

The following data reports the significant difference in HbO after iTBS once baseline (before iTBS) has been removed. This results in a contrast with before iTBS (weighted as −1) and after iTBS (weighted as + 1). The data is presented separately for young, middle and older adults to show differences of effects dependent on age. In addition, each of the cognitive tasks are reported independently. Please note that all data in the tables report Bonferroni corrected p values (i.e., $q < 0.05$) and also the corresponding HbR to ensure neurovascular coupling took place.

Working memory

Significant increases in HbO was observed in the Corsi task for young and middle-aged participants after right iTBS on the DLPFC bilaterally. Conversely, older adults revealed significant decreases in HbO after iTBS mainly in the midline (see Fig. 4). Left hemisphere iTBS resulted in some significant decreases in older adults, however corresponding increases in HbR did not support this finding

Sequence Learning

No significant changes were found from before to after iTBS in young adults. However, middle-aged adults revealed left hemisphere increases after left iTBS alongside midline decreases in activity (see Fig. 5). Less pronounced increases in HbO were observed after right iTBS with activity focused on the right DLPFC. Older adults showed distal decreases in HbO in the midline after right hemisphere iTBS, with a positive increase in HbO under the site of stimulation

Inhibition

In the inhibition task, only young adults revealed significant increases in HbO post left iTBS on the DLPFC. The effects here show bilateral increases, but only contralateral activity reached our stringent activation threshold (see Fig. 6).

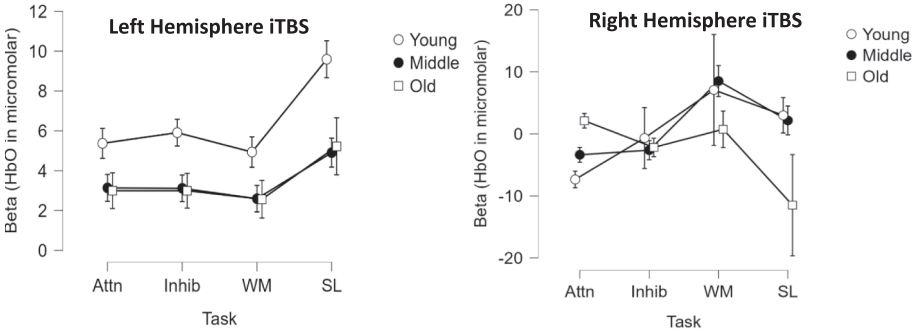
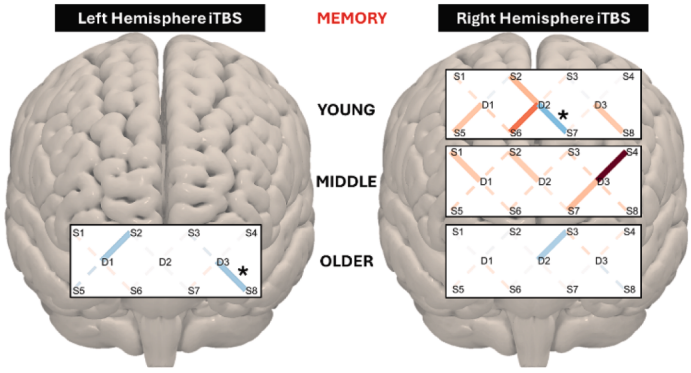
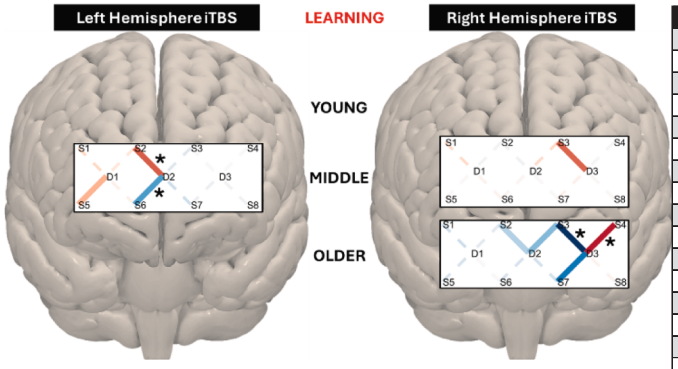


Fig. 3. Graph on the left shows the difference in HbO beta coefficients after-before iTBS stimulation on the left hemisphere for each of the cognitive tasks: attention (Attn), inhibition (Inhib), working memory (WM) and sequence learning (SL). Each line represents mean HbO data across all optodes for young (white circles), middle-aged (black circles) and older adults (white squares). Error bars indicate standard deviations from the mean.



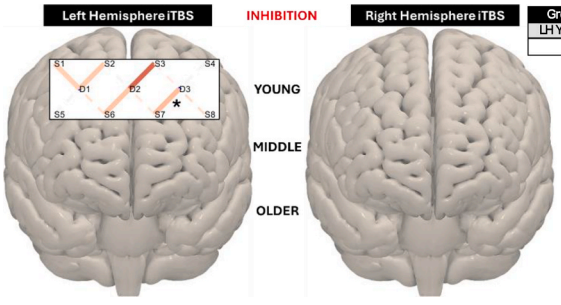
Group	Source	Detector	Type	Beta	SE	t-stat	p	q
LH Older	2	1	HbO	-12.063	3.704	-3.256	0.002	0.048
	2	1	HbR	1.579	1.155	1.367	0.175	0.606
	8	3	HbO	-2.876	0.842	-3.415	0.001	0.034
	8	3	HbR	6.012	1.400	4.294	0.000	0.003
RH Young	6	2	HbO	30.939	5.668	5.459	0.000	0.000
	6	2	HbR	-2.818	2.030	-1.388	0.169	0.493
	7	2	HbO	-25.531	6.339	-4.028	0.000	0.002
	7	2	HbR	6.557	1.877	3.492	0.001	0.010
	8	3	HbO	12.173	4.131	2.947	0.004	0.032
	8	3	HbR	-0.881	2.297	-0.383	0.702	0.917
RH Middle	1	1	HbO	9.031	3.153	2.864	0.005	0.040
	1	1	HbR	-0.225	1.270	-0.177	0.860	0.975
	4	3	HbO	19.712	1.554	12.684	0.000	0.000
	4	3	HbR	-2.564	1.019	-2.517	0.014	0.088
	7	3	HbO	10.001	2.949	3.391	0.001	0.012
	7	3	HbR	-1.168	0.969	-1.205	0.232	0.604
RH Older	3	2	HbO	-10.684	3.398	-3.144	0.002	0.021
	3	2	HbR	0.725	0.780	0.930	0.355	0.782

Fig. 4. A pictorial representation of the significant ($p < 0.05$) optodes for young, middle and older adults are overlayed onto an image of the brain after left iTBS (left image) or right hemisphere iTBS (right brain image). Increases in activity from baseline are shown as warm colours (red) and decreases as cool colours (blue) for the working memory Corsi task. Details of the significant channels (source and detector) contrasts of after – before in the Corsi task are presented in the table to the right of the image. SE refers to standard error, and q is Bonferroni corrected probability (p). Both HbO (oxygenated) and HbR (deoxygenated) are provided as evidence of channels showing neurovascular coupling, with asterisks denoting channels where both reach $q < 0.05$. NB: For all images of the brain, the location of optode/probeset arrays are not anatomically accurate. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



Group	Source	Detector	Type	Beta	SE	t-stat	p	q
LH Middle	**2**	**2**	**HbO**	**34.961**	**5.609**	**6.233**	**0.000**	**0.000**
	2	**2**	**HbR**	**-18.893**	**1.784**	**-10.591**	**0.000**	**0.000**
	6	**2**	**HbO**	**-24.813**	**4.761**	**-5.212**	**0.000**	**0.000**
	6	**2**	**HbR**	**6.302**	**1.653**	**3.812**	**0.000**	**0.005**
RH Middle	3	3	HbO	5.344	0.890	6.006	0.000	0.000
	3	3	HbR	-0.886	1.156	-0.766	0.446	0.923
RH Older	**4**	**3**	**HbO**	**4.328**	**0.564**	**7.676**	**0.000**	**0.000**
	4	**3**	**HbR**	**-6.306**	**1.161**	**-5.432**	**0.000**	**0.000**
	1	1	HbO	-11.016	5.790	-1.903	0.061	0.354
	1	1	HbR	1.053	1.761	0.598	0.552	0.945
	2	2	HbO	-12.420	4.359	-2.849	0.006	0.044
	2	2	HbR	-0.125	1.152	-0.108	0.914	0.970
	3	2	HbO	-17.673	4.158	-4.251	0.000	0.001
	3	2	HbR	-1.560	1.016	-1.534	0.129	0.478
	3	**3**	**HbO**	**-44.607**	**3.539**	**-12.605**	**0.000**	**0.000**
	3	**3**	**HbR**	**-4.884**	**1.511**	**-3.233**	**0.002**	**0.017**
	7	3	HbO	-25.573	3.812	-6.708	0.000	0.000
	7	3	HbR	-1.966	1.609	-1.222	0.225	0.701

Fig. 5. Layout and details are as above, however this image shows significant contrasts of before – after in the sequence learning task. Only middle and older age groups revealed significant effects here. As before SE refers to standard error, and q is Bonferroni corrected probability (p). Both HbO (oxygenated) and HbR (deoxygenated) are provided as evidence of channels showing neurovascular coupling and asterisk denote channels where both HbO and HbR reach $q < 0.05$.



Group	Source	Detector	Type	Beta	SE	t-stat	p	q
LH Young	7	3	HbO	21.088	6.437	3.276	0.001	0.018
	7	3	HbR	-7.716	2.086	-3.699	0.000	0.006

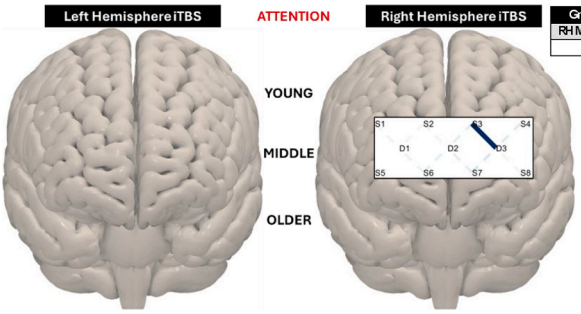
Fig. 6. Layout and details are as reported for Fig. 4 above, however this image shows significant contrasts of before – after in the inhibition (anti-saccade) task. Only the younger age group revealed significant effects here. As before SE refers to standard error, and q is Bonferroni corrected probability (p). Both HbO (oxygenated) and HbR (deoxygenated) are provided as evidence of channels showing neurovascular coupling and the asterisk show where both reach $q < 0.05$.

Attention

Finally, the attention task showed reduced HbO in both middle and older adults post right hemisphere iTBS on the DLPFC. This effect only reached our threshold for the middle-aged group on the ipsilateral hemisphere (see Fig. 7).

Discussion

The purpose of this study was to investigate the neural effects of iTBS of the DLPFC in healthy adults, across age groups. The findings showed that iTBS had the greatest effects on neural activity during the working memory and sequence learning tasks, with specific age-related effects. In



Group	Source	Detector	Type	Beta	SE	t-stat	p	q
RH Middle	3	3	HbO	-9.296	0.734	-12.666	0.000	0.000
	3	3	HbR	0.124	0.647	0.192	0.848	0.982

Fig. 7. Layout and details are as reported for Fig. 4 above, however this image shows significant contrasts of before – after in the attention task. Only the middle age group revealed significant effects here. As before SE refers to standard error, and q is Bonferroni corrected probability (p). Both HbO (oxygenated) and HbR (deoxygenated) are provided as evidence of channels showing neurovascular coupling.

the older adult group, we observed reduced HbO concentration in both the ipsilateral and contralateral hemisphere (DLPFC) following left-iTBS during the working memory task. In this group we also found decreased HbO in the midline optodes (medial DLPFC) following right iTBS. Conversely, middle and young adults revealed increased HbO bilaterally after right iTBS to the working memory task. These significant effects in middle-aged and older adults align with enhanced task performance in both accuracy and reaction time, independent of stimulation hemisphere (Miller et al., 2025, under review). A significant increase in HbO was also found in the sequence learning task for middle-aged adults bilaterally in response to both left and right iTBS, with predominant decreases for older adults after right iTBS. These changes in oxygenation levels were not translated in alterations in behavioural effects post stimulation for any age group. Young adults were the only age group to show increased HbO effects after left iTBS to the inhibition task and only middle-aged adults revealed significant decreases after right iTBS to the attention task. Interestingly these effects were not reflected in the behavioural data, as only young adults revealed improved reaction times after left DLPFC stimulation during the attention task. Taken together, these findings demonstrate the differential effects of iTBS on neural activity across age groups, highlighting age-related variations in hemispheric responses and task-specific neural adaptations that are often not directly reflected in behavioural outcomes. Additionally, the observed changes in HbO concentration highlight the crucial role of the DLPFC in memory and learning.

Working memory

In the current study, iTBS influenced neural activity in the working memory task in young and middle-aged adults, with right-ITBS inducing increases in HbO concentration bilaterally in these groups. This is in agreement with previous literature on iTBS, demonstrating LTP-like properties after a single session of iTBS (Meng et al., 2020). However, despite neural effects in young adults, no improvement in working memory performance (reaction time) was found following iTBS (Miller et al, 2025 under review). This suggests that these neural changes were not sufficient to induce a behavioural effect, and/or that performance was already at ceiling in this age groups. For middle-aged adults this increased HbO after right iTBS did infact improve reaction time and accuracy, but the behavioural effect was not hemisphere specific, maybe indicating more of a potential for improvement in this cohort and potentially encouraging bilaterality. Contrary to our predictions, and a novelty of the present study, was that both left and right iTBS resulted in a reduction in HbO concentration in older adults during the working memory task. In addition, this reduction in HbO resulted in significantly faster reaction time and greater accuracy during the working memory task following iTBS (Miller et al., 2025, under review). The results from the current study suggest that the improved neural efficiency following left and right iTBS improved processing speed in the working memory task. According to the Neural Noise Hypothesis, the decline in cognitive ability in older age is partly due to random and spontaneous electrical activity that is unrelated to external stimuli or task processing (Cremer & Zeef, 1987). This increased background electrophysiological noise in the brain can interfere with accurate processing and transmitting of information, leading to less efficient neural processing. In line with this hypothesis, Voytek and colleagues (2015) found greater electrophysiological noise in older adults than younger adults which significantly mediated age-related working memory decline. Furthermore, evidence from right-hemisphere brain damaged patients and neuroimaging studies have shown visuospatial working memory performance on tasks like the one used in the present study is associated with processing in the right-hemisphere (De Renzi et al., 1977; Jonides et al., 1993). Therefore, the reduction in HbO concentration following iTBS in older adults may reflect a suppression of task-irrelevant neural activity in the left-hemisphere to support more focused neural activity in the right hemisphere. This may also support greater efficiency in network recruitment as previous evidence has shown iTBS of the left DLPFC can alter functional connectivity in the default mode network (DMN) by reducing functional connectivity with the anterior cingulate cortex known to alleviate depressive symptoms (Singh et al., 2020). Indeed, the midline reduction in activity was observed after right iTBS supporting this suggestion.

Sequence learning

The sequence learning task resulted in higher neural activity along the midline and ipsilaterally in middle-aged adults after left iTBS, with only ipsilateral increases after right iTBS in this age group. Conversely decreased activity ipsilaterally was found in older adults after right DLPFC in sequence learning. Interestingly, the sequence learning task invokes the most significant shifts in HbO after iTBS stimulation in response to iTBS especially in older adults and it is therefore surprising that this doesn't translate into a behaviourally meaning effect. A previous study by Gann and colleagues (2021) found iTBS of the DLPFC improved functional connectivity between frontal, hippocampal and striatal networks during a motor sequence learning task. Therefore, the increase in DLPFC activity in the current study may reflect an enhancement of network efficiency of the fronto-striato-hippocampal network during sequence learning in middle-age groups. Similarly to the findings of Gann & colleagues (2021), this change in neural activity during the sequence learning task did not translate into behavioural effects (Miller et al., 2025, under review). This may be because sequence learning involves the recruitment of wider neural networks and cortical regions beyond the DLPFC. Evidence shows patients with parietal and temporal lesions display impairments in spatial memory when compared to healthy controls, demonstrating the key involvement of the parietal and temporal lobes in sequence learning (Bohbot et al., 1998; Esfahani-Bayerl et al., 2016; Glikmann-Johnston et al., 2008; Shimozaki et al., 2003). Thus, stimulation of the DLPFC alone may not be sufficient to establish a behavioural change on the sequence learning task.

Interestingly, as was found for the working memory task, older adults revealed an opposite response with a decrease in HbO, possibly also reflecting improved efficiency utilizing a more optimal LTD-like process (see age related section below). It should be noted that the sequence learning task was relatively simple with no manipulation of information needed unlike the more complex working memory task. Additionally, this task was externally paced, meaning there is minimal motivation for improvement in reaction time which may also be reflected in the null behavioural effects. Future studies may consider using alternative learning tasks that more explicitly target the prefrontal cortex.

Inhibition & attention

The current study found significant increases in HbO across the PFC during the inhibition task in young adults after left iTBS. Interestingly, this did not result in improved behavioral effects and reaction times, although this may be because younger adults are already operating at ceiling levels in this task. In younger adults, fMRI studies have shown inhibitory processing, such as in this nogo task, is strongly lateralized to the right frontal gyri among other areas (Garavan et al., 1999). Given the left iTBS used here resulted in a single highly significant channel increase in right DLPFC then this could provide a potential avenue for increasing inhibitory control in those who show inhibition deficits. It is likely that inhibitory control is more bilateral in older populations (Cabeza, 2002) and hence single hemisphere stimulation may not be sufficient to influence this network, and positive effects may require bilateral or multisite approaches in this age-group. Additionally, effects may require multiple sessions for network adjustments to be made and may explain why improvements in behavioural measures are also not observed. In general, younger people are more responsive to neuroplasticity (Burke and Barnes, 2006) and iTBS, and it is possible that older adults may already be firing at maximum and are not able to increase this firing rate in response to the inhibition task. It may also be worth noting that previous evidence has shown that during the go/nogo task, a similar task measuring inhibition, the go component is associated with theta-wave oscillations in the parietal cortex, whereas the nogo component is associated with beta-wave oscillations in the lateral orbitofrontal cortex (Bokura et al., 2001; Karamacoska et al., 2018). Thus, potentially a different stimulation band in Beta range could have resulted in a more effective response.

In Miller et al. (2025, under review) young adults demonstrated faster RT on the attention task following iTBS, and although we observed consistently decreased HbO in young adults after right iTBS, this did not result in statistically significant effects. Only after right iTBS did middle and older adults reveal significant decreases in HbO, although this did not translate into increase reaction times. It is possible we may have improved neural efficiency in these older age groups, but not to a level that affects behavioural responses. This discrepancy may be due to the DLPFC not being the optimal region for stimulation in this context, as the DLPFC is responsible for executive control, while the attention task in this study involved reflexive eye movements. Instead, involuntary eye movements towards unexpected stimuli are associated with the Ventral Attention Network (VAN) involving the Ventrolateral Prefrontal Cortex (VLPFC) and Temporoparietal Junction (TPJ) (Solís-Vivanco et al., 2021).

Age related effects

One generalized novel finding in this study is that younger and middle-aged adults tend to increase neuronal responses post iTBS on the DLPFC to memory/learning tasks, whereas older adults show decreases in HbO interpreted here as LTD-like effects. Despite improvements in performance in the working memory task, no differences were observed in the sequence learning task in any age groups post stimulation. One potential explanation for this difference is possibly due to the effective states of neurons during stimulation and/or during subsequent cognitive tasks. In support of this, a consensus in the brain stimulation literature suggests that neuronal state at the point of stimulation is critical for determining stimulation effects aka state-dependency (Silvanto et al., 2008). This theory has been used to support the "individual differences" observed in TMS studies (Ridding and Ziemann, 2010). It is known from previous literature that ageing resulting in a generalized increase in neural activity across brain networks (i.e., hyper-excitability) in prefrontal cortex (Luebke and Amatrudo, 2012) and hippocampus (Wu et al., 2002) that have a negative consequence on cognition. Given this hyperexcitable state then it may be the case that iTBS has the reverse effect on these neurons in older adults, and in fact decreases neural firing resulting in a more optimal down-regulation. This may suggest different ages need different stimulation intensities. Indeed, a recent study by Zhang and colleagues (2022) identified improvements in young adults on a verbal fluency task at an optimal stimulation threshold of 70 % resting motor threshold (RMT) on the DLPFC. This threshold also resulted in a maintained concentration change in HbO post stimulation with no significant effects observed at 50 % or 100 % RMT. This highlights the importance of iTBS intensity of effects within the brain and may also provide some future focus on understanding how this intensity may be adjusted with age and neuroplasticity. In line with this, younger and middle-aged adults probably have potential for increased firing and up-regulation of the network that this makes them more susceptible to LTP-like effects. Given this insight, we support the notion that brain stimulation should not be viewed as a passive system receiving stimulation, but potentially that the brain utilizes the energy entering the brain and actively "adapts" it to support the individual brain in the appropriate way. In other words, neuroplasticity is not a passive response to a stimulation, but an active adaptation to energy entering the system that can be manipulated dependent on the current need.

Strengths and limitations

This study had several strengths and limitations. A key strength of the current study was the stringent reporting of significant effects, by including corrected q values, and only presenting results that show a significant yet opposite response in HbO and HbR. This approach ensured that the findings reflected a true neurovascular coupling (Kinder et al., 2022). Another strength was to mitigate any issues with data quality by conducting the QTNIRS quality check to identify and remove suboptimal datasets, resulting in only high quality fNIRS measurements included in the final analysis. This study may be limited due to the fNIRS system in which the optodes created a 12 mm coil-to-scalp gap. Magnetic field strength decreases rapidly with distance (Bohning, 2000), therefore any gap between the TMS coil and scalp could reduce the magnetic field reaching the cortex. Despite this, results from the current study and Miller et al., (2025, under review) showed clear cognitive and neural effects following iTBS. Future TMS-fNIRS studies should consider using low profile optodes to reduce the coil-to-scalp distance. Finally, we used a FIR basis function to model the data due to the increased flexibility needed given differences between age groups in reaction time responses. This trade-off, while flexible, may have reduced statistical power and sensitivity when compared to canonical approaches.

Future directions

This study utilized fNIRS to measure pre- and post-iTBS neural activity during cognitive tasks, and the link between these neural effects and age. A promising future approach would be to conduct a correlation or mediation analysis to investigate the association between neural activity changes and corresponding behavioural outcomes. Such analyses could reveal whether the observed neural changes directly contribute to the improvements in task performance, or if they are mediated by other factors. Additionally, to gain a deeper understanding of neural responses to iTBS, it would be valuable to explore neural noise by analyzing the

standard deviation (SD) or standard error (SE) of neural activity measurements. This approach could help to identify variability in neural responses, which may be indicative of underlying neural noise. Understanding individual variability is particularly important given the known individual differences in response to TMS (Hamada et al., 2013; Hinder et al., 2014). We have found that effects of iTBS are more widespread than originally considered with clear alterations in neuronal firing not only at the site of stimulation, but across the whole of the prefrontal cortex after only a single session. Future directions could be to establish even wider network effects of stimulation in parietal and temporal brain areas. Given the clear age-related difference between up-regulation in younger participants and down-regulation in older participants in response to the same stimulation type and location, this warrants further investigation for understanding how brain stimulation can be individually catered to potential therapeutic interventions.

This study investigated the neural mechanisms of iTBS, utilizing fNIRS to reveal the haemodynamic effects of stimulation during cognitive tasks across young, middle and older age groups. The findings indicated that iTBS induced changes in neural activity during the working memory and sequence learning tasks, with opposite LTP and LTD-like effects for younger and older adults respectively. These changes may reflect greater efficiency in neural processing or network recruitment in the DLPFC. We propose that brain stimulation is not a passive effect, but related to network need, and thus individuals may be able to actively utilize the brain stimulation in different ways to up- or down- regulate to provide optimal effects for cognitive benefit. Overall, this research contributes to our understanding of the neuromodulatory effects of iTBS and shows the potential for iTBS to be used in clinical interventions to optimise neural and cognitive functioning. Future research should explore the potential clinical applications of iTBS in enhancing neuroplasticity as a way of decelerating cognitive decline.

CRediT authorship contribution statement

Amy Miller: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Richard Allen:** Writing – review & editing, Supervision. **Rumana Chowdhury:** Writing – review & editing, Supervision. **Melanie Burke:** Supervision.

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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Data from the same participant cohort have also been reported in a separate manuscript (Miller et al., 2025 – under review), which investigates cognitive outcomes. The analyses presented here are distinct and focus exclusively on neuroimaging outcomes.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroscience.2025.10.006.

References

Aasted, C., Yücel, M., Cooper, R., Dubb, J., Tsuzuki, D., Becerra, L., Petkov, M., Borsook, D., Dan, I., Boas, D., 2015. Anatomical guidance for functional near-infrared spectroscopy: AtlasViewer tutorial. Neurophotonics 2 (2), 020801.

Aftanas, L.I., Golocheikine, S.A., 2001. Human anterior and frontal midline theta and lower alpha reflect emotionally positive state and internalized attention: high-resolution EEG investigation of meditation. Neurosci. Lett. 310 (1), 57–60.

Blumberger, D.M., Vila-Rodriguez, F., Thorpe, K.E., Feffer, K., Noda, Y., Giacobbe, P., Knyahnytska, Y., Kennedy, S.H., Lam, R.W., Daskalakis, Z.J., Downar, J., 2018. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet (London, England) 391 (10131), 1683–1692.

Bohbot, V.D., Kalina, M., Stepankova, K., Spackova, N., Petrides, M., Nadel, L., 1998. Spatial memory deficits in patients with lesions to the right hippocampus and to the right parahippocampal cortex. Neuropsychologia 36 (11), 1217–1238. https://doi.org/10.1016/s0028-3932(97)00161-9.

Bohning, D.E., 2000. Introduction and overview of TMS physics. Transcranial Magnet. Stimulat. Neuropsychiatry 13–44.

Bokura, H., Yamaguchi, S., Kobayashi, S., 2001. Electrophysiological correlates for response inhibition in a Go/NoGo task. Clin. Neurophysiol. 112 (12), 2224–2232.

Brunetti, R., Del Gatto, C., Delogu, F., 2014. eCorsi: implementation and testing of the Corsi block-tapping task for digital tablets. Front. Psychol. 5, 939.

Burke, S., Barnes, C., 2006. (2006) Neural plasticity in the ageing brain. Nat. Rev. Neurosci. 7, 30–40.

Burke, M.R., Bramley, P., Gonzalez, C.C., McKeefry, D.J., 2013. The contribution of the right supra-marginal gyrus to sequence learning in eye movements. Neuropsychologia 51 (14), 3048–3056.

Cabeza, R., 2002. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol. Aging 17 (1), 85–100.

Cabeza, R., Anderson, N.D., Locantore, J.K., McIntosh, A.R., 2002. Aging gracefully: compensatory brain activity in high-performing older adults. NeuroImage 17 (3), 1394–1402.

Chang, K.Y., Tik, M., Mizutani-Tiebel, Y., Schuler, A.L., Taylor, P., Campana, M., Vogelmann, U., Huber, B., Dechantsreiter, E., Thielscher, A., Bulubas, L., Padberg, F., Keeser, D., 2024. Neural response during prefrontal theta burst stimulation: Interleaved TMS-fMRI of full iTBS protocols. NeuroImage 291, 120596. https://doi.org/10.1016/j.neuroimage.2024.120596.

Cremer, R., Zeef, E.J., 1987. What kind of noise increases with age? J. Gerontol. 42 (5), 515–518.

De Renzi, E., Faglioni, P., Previdi, P., 1977. Spatial memory and hemispheric locus of lesion. Cortex; a journal devoted to the study of the nervous system and behavior 13 (4), 424–433. https://doi.org/10.1016/s0010-9452(77)80022-1.

Diao, X., Lu, Q., Qiao, L., Gong, Y., Lu, X., Feng, M., Su, P., Shen, Y., Yuan, T.F., He, C., 2022. Cortical inhibition state-dependent iTBS induced neural plasticity. Front. Neurosci. 16, 788538. https://doi.org/10.3389/fnins.2022.788538.

Ding, Q., Zhang, S., Chen, S., Chen, J., Li, X., Chen, J., Peng, Y., Chen, Y., Chen, K., Cai, G., Xu, G., Lan, Y., 2021. The effects of intermittent theta burst stimulation on functional brain network following stroke: an electroencephalography study. Front. Neurosci. 15, 755709.

Duncan, A., Meek, J.H., Clemence, M., Elwell, C.E., Fallon, P., Tyszczuk, L., Cope, M., Delpy, D.T., 1996. Measurement of cranial optical path length as a function of age using phase resolved near infrared spectroscopy. Pediatr. Res. 39 (5), 889–894. https://doi.org/10.1203/00006450-199605000-00025.

Esfahani-Bayerl, N., Finke, C., Braun, M., Düzel, E., Heekeren, H.R., Holtkamp, M., Hasper, D., Storm, C., Ploner, C.J., 2016. Visuo-spatial memory deficits following medial temporal lobe damage: A comparison of three patient groups. Neuropsychologia 81, 168–179. https://doi.org/10.1016/j.neuropsychologia.2015.12.024.

Friedman, N.P., Robbins, T.W., 2022. The role of prefrontal cortex in cognitive control and executive function. Neuropsychopharmacology 47 (1), 72–89.

Garavan, H., Ross, T.J., Stein, E.A., 1999. Right hemispheric dominance of inhibitory control: An event-related functional MRI study. Proc. Natl. Acad. Sci. U.S.A. 96 (14), 8301–8306. https://doi.org/10.1073/pnas.96.14.8301.

Glikmann-Johnston, Y., Saling, M.M., Chen, J., Cooper, K.A., Beare, R.J., Reutens, D.C., 2008. Structural and functional correlates of unilateral mesial temporal lobe spatial memory impairment. Brain : A Journal of Neurology 131 (Pt 11), 3006–3018. https://doi.org/10.1093/brain/awn213.

Gorban, C., Zhang, Z., Mensen, A., Khatami, R., 2023. The comparison of early hemodynamic response to single-pulse transcranial magnetic stimulation following inhibitory or excitatory theta burst stimulation on Motor Cortex. Brain Sci. 13 (11), 1609.

Hamada, M., Murase, N., Hasan, A., Balaratnam, M., Rothwell, J. C., 2013. The role of interneuron networks in driving human motor cortical plasticity. Cerebral cortex (New York, N.Y.: 1991), 23(7), 1593–1605.

Hallett, P.E., 1978. Primary and secondary saccades to goals defined by instructions. Vis. Res. 18 (10), 1279–1296. https://doi.org/10.1016/0042-6989(78)90218-3.

Herwig, U., Satrapi, P., Schönfeldt-Lecuona, C., 2003. Using the International 10-20 EEG System for Positioning of Transcranial Magnetic Stimulation. Brain Topogr. 16, 95–99. https://doi.org/10.1023/B:BRAT.0000006333.93597.9d.

Hinder, M.R., Goss, E.L., Fujiyama, H., Canty, A.J., Garry, M.I., Rodger, J., Summers, J.J., 2014. Inter- and Intra-individual variability following intermittent theta burst stimulation: implications for rehabilitation and recovery. Brain Stimul. 7 (3), 365–371.

Huang, Y.Z., Edwards, M.J., Rounis, E., Bhatia, K.P., Rothwell, J.C., 2005. Theta burst stimulation of the human motor cortex. Neuron 45 (2), 201–206.

Irani, F., Platek, S.M., Bunce, S., Ruocco, A.C., Chute, D., 2007. Functional near infrared spectroscopy (fNIRS): an emerging neuroimaging technology with important applications for the study of brain disorders. Clin. Neuropsychologist 21 (1), 9–37. https://doi.org/10.1080/13854040600910018.

Jonides, J., Smith, E.E., Koeppe, R.A., Awh, E., Minoshima, S., Mintun, M.A., 1993. Spatial working memory in humans as revealed by PET. Nature 363 (6430), 623–625. https://doi.org/10.1038/363623a0.

Kaminski, J.A., Korb, F.M., Villringer, A., Ott, D.V., 2011. Transcranial magnetic stimulation intensities in cognitive paradigms. PLoS One 6 (9), e24836.

Karamacoska, D., Barry, R.J., Steiner, G.Z., Coleman, E.P., Wilson, E.J., 2018. Intrinsic EEG and task-related changes in EEG affect Go/NoGo task performance. Int. J. Psychophysiol. 125, 17–28.

Kessels, R.P., van Zandvoort, Postma, A., Kappelle, L.J., de Haan, E.H., 2000. The Corsi Block-Tapping Task: standardization and normative data. Appl. Neuropsychol. 7 (4), 252–258. https://doi.org/10.1207/S15324826AN0704_8.

Kinder, K.T., Heim, H.L., Parker, J., Lowery, K., McCraw, A., Eddings, R.N., Defenderfer, J., Sullivan, J., Buss, A.T., 2022. Systematic review of fNIRS studies reveals inconsistent chromophore data reporting practices. Neurophotonics 9 (4), 040601.

Klimesch, W., 1999. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res. Rev. 29 (2–3), 169–195.

Lee, C.W., Wu, H.F., Chu, M.C., Chung, Y.J., Mao, W.C., Li, C.T., Lin, H.C., 2021. Mechanism of intermittent theta-burst stimulation in synaptic pathology in the prefrontal cortex in an antidepressant-resistant depression rat model. Cereb. Cortex 31 (1), 575–590.

Lemaitre, H., Goldman, A.L., Sambataro, F., Verchinski, B.A., Meyer-Lindenberg, A., Weinberger, D.R., Mattay, V.S., 2012. Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and gray matter volume? Neurobiol. Aging 33 (3), 617–e1.

Lu, Q., Huang, S., Zhang, T., Song, J., Dong, M., Qian, Y., Teng, J., Wang, T., He, C., Shen, Y., 2024. Age-related differences in long-term potentiation-like plasticity and short-latency afferent inhibition and their association with cognitive function. General Psychiatry 37 (1), e101181.

Luebke, J.I., Amatrudo, J.M., 2012. Age-related increase of sI(AHP) in prefrontal pyramidal cells of monkeys: relationship to cognition. Neurobiol. Aging 33 (6), 1085–1095. https://doi.org/10.1016/j.neurobiolaging.2010.07.002.

Meng, H.J., Cao, N., Zhang, J., Pi, Y.L., 2020. Intermittent theta burst stimulation facilitates functional connectivity from the dorsal premotor cortex to primary motor cortex. PeerJ 8, e9253.

Miller, A., Burke, M., 2025. Diverse and distributed haemodynamic effects of theta burst stimulation in the prefrontal cortex. Neuroimage Reports 5 (3), 100282.

Miller, A., Allen, R.J., Juma, A.A., Chowdhury, R., Burke, M.R., 2023. Does repetitive transcranial magnetic stimulation improve cognitive function in age-related neurodegenerative diseases? a systematic review and meta-analysis. Int. J. Geriatr. Psychiatry 38 (8), e5974.

Miller, A., Allen, R. J., Chowdhury, R., & Burke, M. R. (2025). Enhancing Human Cognition with Intermittent Theta-Burst Stimulation: A Cross-Sectional Pilot Study Across Age Groups. *Ageing, Neuropsychology and Cognition* – under review.

Mizutani-Tiebel, Y., Tik, M., Chang, K.Y., Padberg, F., Soldini, A., Wilkinson, Z., Voon, C. C., Bulubas, L., Windischberger, C., Keeser, D., 2022. Concurrent TMS-fMRI: technical challenges, developments, and overview of previous studies. Front. Psych. 13, 825205.

Najib, U., Horvath, J.C., 2014. Transcranial magnetic stimulation (TMS) safety considerations and recommendations. Transcranial Magn. Stimul. 15–30.

Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H., 2005. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J. Am. Geriatr. Soc. 53 (4), 695–699.

Nettekoven, C., Volz, L.J., Leimbach, M., Pool, E.M., Rehme, A.K., Eickhoff, S.B., Fink, G. R., Grefkes, C., 2014. Inter-individual variability in cortical excitability and motor network connectivity following multiple blocks of rTMS. Neuroimage 98, 81–90.

Oates, J., Carpenter, D., Fisher, M., Goodson, S., Hannah, B., Kwiatowski, R., Prutton, K., Reeves, D., Wainwright, T., 2021. BPS Code of Human Research Ethics. British Psychological Society.

Opie, G.M., Vosnakis, E., Ridding, M.C., Ziemann, U., Semmler, J.G., 2017. (2017) Priming theta burst stimulation enhances motor cortex plasticity in young but not old adults. Brain Stimul. 10 (2), 298–304. https://doi.org/10.1016/j.brs.2017.01.003.

Orosz, A., Jann, K., Federspiel, A., Horn, H., Dierks, T., Hubl, D., 2021. Theta burst stimulation over the dorsolateral prefrontal cortex: combined TMS-fNIRS evidence for modulation of cortical activity. Neuroimage 225, 117504.

Pabst, A., Proksch, S., Mede, B., Comstock, D.C., Ross, J.M., Balasubramaniam, R., 2022. A systematic review and meta-analysis of the efficacy of intermittent theta burst stimulation (iTBS) on cognitive enhancement. Neurosci. Biobehav. Rev. 135, 104587.

Phillips, A.A., Chan, F.H., Zheng, M.M.Z., Krassioukov, A.V., Ainslie, P.N., 2016. Neurovascular coupling in humans: physiology, methodological advances and clinical implications. J. Cereb. Blood Flow Metab. 36 (4), 647–664.

Pinti, P., Tachtsidis, I., Hamilton, A., Hirsch, J., Aichelburg, C., Gilbert, S., Burgess, P.W., 2020. The present and future use of functional near-infrared spectroscopy (fNIRS) for cognitive neuroscience. Annals of the New York Academy of Sciences 1464 (1), 5–29. https://doi.org/10.1111/nyas.13948.

Ranchod, S., Rakobowchuk, M., Gonzalez, C., 2023. Distinct age-related brain activity patterns in the prefrontal cortex when increasing cognitive load: a functional near-infrared spectroscopy study. PLoS One 18 (12), e0293394.

Reuter-Lorenz, P.A., Park, D.C., 2014. How does it STAC up? Revisiting the scaffolding theory of aging and cognition. Neuropsychol. Rev. 24 (3), 355–370.

Ridding, M.C., Ziemann, U., 2010. Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J. Physiol. 588 (13), 2291–2304.

Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmöller, J., Hallett, M., 2021. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. Clin. Neurophysiol. 132 (1), 269–306.

Salat, D.H., Kaye, J.A., Janowsky, J.S., 1999. Prefrontal gray and white matter volumes in healthy aging and Alzheimer disease. Arch. Neurol. 56 (3), 338–344.

Santosa, H., Zhai, X., Fishburn, F., & Huppert, T. (2018). The NIRS brain AnalyzIR toolbox. Algorithms, 11(5), 73.

Shimozaki, S.S., 2010. Uncued and cued dynamics measured by response classification. J. Vis. 10 (8), 10.

Singh, A., Erwin-Grabner, T., Sutcliffe, G., Paulus, W., Dechent, P., Antal, A., Goya-Maldonado, R., 2020. Default mode network alterations after intermittent theta burst stimulation in healthy subjects. Transl. Psychiatry 10 (1), 75.

Shimozaki, S.S., Hayhoe, M.M., Zelinsky, G.J., Weinstein, A., Merigan, W.H., Ballard, D. H., 2003. Effect of parietal lobe lesions on saccade targeting and spatial memory in a naturalistic visual search task. Neuropsychologia 41 (10), 1365–1386. https://doi.org/10.1016/s0028-3932(03)00042-3.

Silvanto, J., Muggleton, N.G., Walsh, V., 2008. State-dependency in brain stimulation studies of perception and cognition. Trends Cogn. Sci. 12 (12), 447–454.

Solís-Vivanco, R., Jensen, O., Bonnefond, M., 2021. New insights on the ventral attention network: active suppression and involuntary recruitment during a bimodal task. Hum. Brain Mapp. 42 (6), 1699–1713.

Thomson, R.H., Cleve, T.J., Bailey, N.W., Rogasch, N.C., Maller, J.J., Daskalakis, Z.J., Fitzgerald, P.B., 2013. Blood oxygenation changes modulated by coil orientation during prefrontal transcranial magnetic stimulation. Brain Stimulation 6 (4), 576–581.

Tupak, S.V., Dresler, T., Badewien, M., Hahn, T., Ernst, L.H., Herrmann, M.J., Deckert, J., Ehlis, A.C., Fallgatter, A.J., 2013. Inhibitory transcranial magnetic theta burst stimulation attenuates prefrontal cortex oxygenation. Hum. Brain Mapp. 34 (1), 150–157.

Varone, G., Hussain, Z., Sheikh, Z., Howard, A., Boulila, W., Mahmud, M., Howard, N., Morabito, F.C., Hussain, A., 2021. Real-time artifacts reduction during TMS-EEG co-registration: a comprehensive review on technologies and procedures. Sensors (Basel, Switzerland) 21 (2), 637.

Voytek, B., Kramer, M.A., Case, J., Lepage, K.Q., Tempesta, Z.R., Knight, R.T., Gazzaley, A., 2015. Age-related changes in 1/f neural electrophysiological noise. J. Neurosci. 35 (38), 13257–13265.

Whybird, M., Coats, R., Vuister, T., Harrison, S., Booth, S., Burke, M., 2021. The role of the posterior parietal cortex on cognition: an exploratory study. Brain Res. 1764, 147452.

World Medical Association, 2013. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310 (20), 2191–2194. https://doi.org/10.1001/jama.2013.281053.

Wu, W.W., Oh, M.M., Disterhoft, J.F., 2002. Age-related biophysical alterations of hippocampal pyramidal neurons: implications for learning and memory. Ageing Res. Rev. 1 (2), 181–207.

Zhang, B.B.B., Kan, R.L.D., Giron, C.G., Lin, T.T.Z., Yau, S.Y., Kranz, G.S., 2022. Dose-response relationship between iTBS and prefrontal activation during executive functioning: a fNIRS study. Front. Psych. 13, 1049130.