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Unilateral repetitive transcranial magnetic stimulation differentially affects younger and older adults completing a verbal working memory task

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ABSTRACT

Functional neuroimaging studies have found that lateralization of activity in the dorsolateral prefrontal cortex (dlPFC) is reduced with aging. In the present study, repetitive transcranial magnetic stimulation (rTMS) was used to disrupt dlPFC activity in order to test the relationship of dlPFC laterality and age in verbal working memory (WM). Young (n = 36) and older (n = 35) subjects received 1 Hz-rTMS (sham or active) to left or right dlPFC and WM performance was assessed pre- and post-stimulation via the n-back task. Significant increases in WM accuracy were observed following rTMS in the right dlPFC and sham conditions, but not with the left dlPFC stimulation. This was accompanied by a decrease in left P1 latency was also observed following left dlPFC stimulation. In contrast, older adults did not show a disruption in WM performance following rTMS in any of the stimulation conditions and exhibited increased left P3 amplitude following left stimulation. Our results show that changes in prefrontal laterality are evident with increasing age (left stimulation affects younger adults while older adults are not affected by stimulation) and this change is associated with specific neurophysiologic measures.

1. Introduction

Numerous functional imaging studies have found a change in the laterality of activity of the prefrontal cortex during cognitive tasks. In these studies, younger adults show lateralized activity whereas older adults show bilateral prefrontal activity and many of these studies have correlated increased bilateral activity to increased performance [54,65,10]. These studies led to the HAROLD (Hemispheric Asymmetry Reduction in Older Adults) theory [8]. This model views this bilateral prefrontal activity seen in healthy older adults as compensatory, such that the activity in the contralateral hemisphere is advantageous for task performance [66,65], (Daselaar et al., 2003). Using rTMS, Cotelli et al. [12] also have found evidence for this theory, where left stimulation facilitates a naming task in younger adults and both left and right stimulation cause facilitation in older adults.

When attention is directed toward a stimulus, there is posterior cortical activity that is proposed to be responsible for stimulus driven top-down modulation [2,31,50]. Previous studies have shown that rTMS to the inferior frontal gyrus during a working memory task reduces the amplitude of a positive visual evoked potential (VEP) deflection around 100 ms (P1) after stimulus onset [64]. Reduced P1 amplitude has been correlated with top-down modulation from the prefrontal cortex [55] and older adults show deficits in top-down suppression of P1 amplitude [24]. Patients with unilateral dlPFC lesions also demonstrate a contralesional deficit in early visual processing [2]. Therefore, a potential mechanism for the shift in prefrontal activity with increasing age is a change in top-down control mechanisms executed on the P1 component [25]. Age-related differences in later physiologic markers have also been well described and it has been suggested that P3 amplitude may correlate with compensation Daffner et al. [14,15].

This current study was designed to examine age-related changes in the lateralization of working memory networks. Unilateral rTMS was used to disrupt left and right dlPFC function during the performance of a working memory task in a group of healthy young and older adults. The overarching hypothesis was that unilateral stimulation would differentially affect the groups both behaviorally and physiologically (measured via evoked potentials) due to differences in laterality with increasing age. If the bilateral dlPFC activity is in fact compensatory, unilateral disruption should not alter working memory performance in older adults. We propose that a potential mechanism for this compensatory adaptation is related to a change in the hemispheric

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Table 1
Participant demographics ± standard deviations, and between-group comparisons. Each participant scored within 2 standard deviations of their age matched normative values.

	Left dlPFC		Right dlPFC		Sham dlPFC	p =
	Young	Older	Young	Older	Young	Older	
Sex (no. female)	12 (6)	12 (6)	12 (6)	11 (6)	12 (6)	12 (6)	
Age (yr)	26.1 (2.0)	68.8 (6.7)	25.5 (2.2)	66.8 (4.5)	26.3 (1.7)	68.36 (7.4)	
Education (yr)	16.7 (1.3)	17.5 (1.7)	16.7 (1.8)	17.5 (1.5)	16.8 (1.0)	17.5 (1.3)	$p > 0.2$
IQ	124.6 (5.6)	127.6 (4.6)	123.2 (8.7)	125.3 (4.4)	124.5 (8.8)	127.4 (5.4)	$p > 0.17$
Stroop (Tscore)	54.5 (7.1)	50.4 (3.9)	53.7 (4.8)	49.8 (4.5)	55 (6.5)	49.3 (3.6)	$p > 0.2$
Trail making (sec)	35.9 (7.5)	42.9 (6.4)	34.1 (6.9)	44.2 (5.8)	38.9 (8.5)	41.2 (6.5)	$p > 0.2$

specialization of top-down control from the prefrontal cortex to cognitive networks, such that processing becomes more bilateral with increasing age.

2. Methods

2.1. Subjects

Seventy-one right-handed volunteers participated in this study and included two groups: 36 young adults (average age 26 ± 5.9) and 35 older adults (average age 68 ± 6.2). Handedness was obtained using the Oldfield Handedness Inventory [48]. Neuropsychological tests were administered to ensure that the groups did not differ on measures of intelligence [Weschler Abbreviated Scale of Intelligence/WASI [63]], inhibition [Stroop Color and Word Test [26]], and attention/set-shifting [Trail Making Test [53]]. All subjects had at least a high school education. Exclusionary criteria included left-handedness, history of neurological disease [seizures, migraine], history of neurosurgery, birth complications, head trauma, psychiatric illness, substance abuse, and diabetes. Subject demographics are summarized in Table 1.

2.2. Study design

Subjects were randomized into one of three rTMS stimulation groups (left dlPFC, right dlPFC, or sham dlPFC). Each participant then completed pre-stimulation working memory tasks. rTMS was then administered over the pre-assigned dlPFC location (left, right, or sham) between the pre-stimulation and post-stimulation blocks. EEG activity was recorded during both pre- and post-stimulation working memory testing. The total time for subjects to complete the cognitive tasks was 30 min.

Subjects were seated in front of a 17-inch monitor at a distance of approximately 60 cm. They were told to keep a comfortable posture, and to avoid eye and facial movements. They kept their forearms resting on the chair and their right index finger resting on the target button. Subjects were instructed to press the button as quickly and accurately as possible. Subjects were familiarized with the tasks by completing a short practice trial of each task. Each practice block contained 15 novel stimuli and practice trials were completed to a criterion level of performance (75% accuracy or greater).

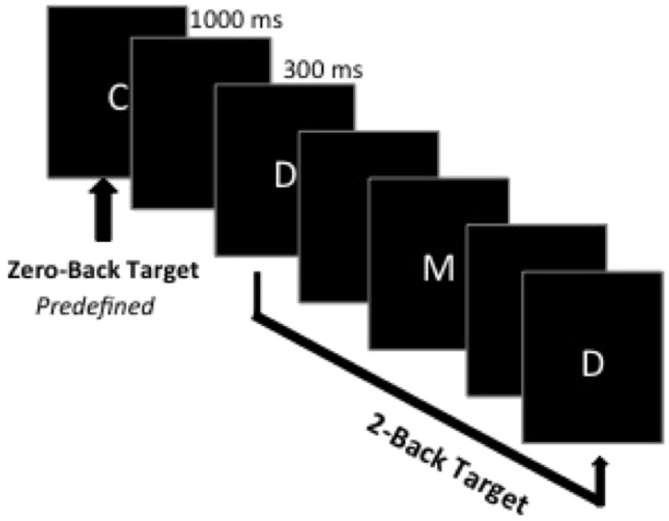

Fig. 1. Detailed methodology of the verbal n-back task conditions. Arrows indicate correct responses.

2.3. N-back task

Participants completed both a zero back and two back task (Fig. 1). One-back task was not included due to the fact that we did not want the effects of magnetic stimulation to wear off due to timing for additional testing. Stimulus presentation and data acquisition were managed by STIM2/Neuroscan (Charlotte, NC, USA). The stimuli were 9 white capital letters [B, C, D, F, G, H, J, K, M]. Vowels and the consonants L, W, and Y were excluded from the letter set to minimize the

Table 2
Means and standard deviations of performance measures (accuracy, RT-reaction time in ms) for the zero and 2-back conditions in both the young and older groups. RTs represent reaction times from correct trials only.

Accuracy					RT				
	Young		Older			Young		Older	
	Pre	Post	Pre	Post		Pre	Post	Pre	Post
Zero-back condition									
Left	98.1 (2.2)	94.5 (1.4)	97.8 (1.9)	98.1 (1.4)	Left	356.9 (87.9)	327 (71.7)	447.0 (73.3)	431.9 (74.8)
Right	99.2 (1.3)	98.5 (3.2)	96.9 (2.8)	94.3 (0.9)	Right	347.9 (73.5)	321.5 (70.9)	427.4 (55.3)	453.9 (114.3)
Sham	96.1 (8.7)	99.1 (1.2)	96.5 (2.5)	96.7 (1.3)	Sham	384.4 (89.5)	326.1 (69.9)	461.3 (69.5)	463.7 (80.8)
2-back condition									
Left	87.4 (1.5)	89.3 (1.2)	81.5 (8.1)	84.4 (7.8)	Left	470.6 (20.9)	428.6 (20)	550.9 (82.7)	515.7 (70.6)
Right	89.1 (1.1)	93.7 (1)	80.2 (5.8)	85.4 (4.6)	Right	449.3 (33.5)	427.9 (22.9)	533.9 (51.9)	469.5 (69.3)
Sham	88.8 (9.5)	92.0 (1.1)	79.3 (5.1)	83.7 (5.6)	Sham	506.6 (14.4)	461.7 (17.5)	533.4 (83.8)	499.6 (75.7)

pronounceability of strings of consecutive letters to decrease subject's ability to use verbal strategies [46]. Only the verbal version of this task was utilized in the interest of maximizing post-test time due to possible decreasing effectiveness of stimulation effects.

In the zero-back task, subjects indicated whether or not each stimulus matched two predefined stimuli shown at the beginning of the block. The stimulus was shown on the screen for 300 ms followed by a blank screen for 1000 ms. The identity of each stimulus was presented pseudo-randomly to ensure an even distribution of match trials. For the 2-back task, subjects had to match the current stimulus with the stimulus before the previous one. Each zero-back block consisted of 160 trials (50 targets) and each 2-back block consisted of 180 trials (60 targets) subjects completed one block of each. No lures were utilized. There were 4 unique versions of each task and these were assigned to be different pre and post stimulation for each subject, no subject completed the same version of the task pre and post stimulation. Each stimulus was presented pseudo-randomly, to ensure an even distribution of match trials. Subjects pressed the target button for a match; no button was pressed for a non-target response. Accuracy scores were calculated by dividing the sum of the correctly identified target responses plus the correctly identified non-target responses by the number of total trials. This allowed for correction of subjects pressing a button in response on non-target responses in order to obtain a high accuracy score.

2.4. EEG recording

Experiments were conducted in a sound-attenuated, electrically shielded room (Industrial Acoustics Company, Bronx, NY, USA). An electrode cap containing 64 Ag/AgCl electrodes was placed on the scalp with the reference electrode between midline central (Cz) and midline central parietal (CPz) (impedances of ≤ 10 kΩ). Four electrodes were used to monitor eye movements: one above and one below the left eye and two more lateral to the left and right eyes. The electroencephalogram and electro-oculogram were continuously digitized at 500 Hz (DC, 100-Hz band pass) with a 64-channel electroencephalography (EEG) system (all EEG recording and initial analysis software from Compumedics-Neuroscan, Charlotte, NC, USA) and stored for off-line analysis.

2.5. ERP analyses

Impedances were kept below 10 kΩ throughout the experiment. In off-line analyses, electrodes were referenced in a linked mastoid configuration, and corrected for direct current drift and eye blink artifacts [67]. All EEG sweeps were visually inspected for additional artifacts before being included in the ERP averages, trials that exceeded ± 100 uV for horizontal eye movements were rejected and trials contaminated by excessive artifact were rejected. No > 10% of the trials were rejected due to artifacts. ICA was not used to identify noise components. Individual EEG sweeps for each working memory task were sorted and averaged. Incorrect trials were not analyzed.

ERPs were averaged − 200 to 1000 ms from stimulus onset. ERPs were band pass filtered at 0.1–30 Hz and baseline was calculated from − 100 ms to stimulus onset. Peak measures were used for quantifying the VEP P1 and N1, which resulted in a latency and amplitude measure. The P1 was defined as the largest positive peak between 50 and 150 ms. The N1 was defined as the largest negative peak between 120 and 220 ms. The P3 was defined using a window measure as the mean amplitude between 300 and 500 ms. This time window was chosen because the grand-averaged effects were observed in this window. The left and right parietal electrodes used for analysis were P3/5 and P4/6, these electrodes were chosen to represent a lateralized response.

2.6. Repetitive TMS

Repetitive TMS was administered using a Rapid Stimulation stimulator (Magstim, UK, 2.2 Tesla) with a 70-mm-diameter figure-8 coil to the right or left dlPFC at 1 Hz, 90% resting motor threshold for 900 pulses. Before the experiment, individual resting motor threshold (RMT) was determined as the minimum stimulus intensity able to elicit a visible muscle twitch in the right hand in 5 of 10 consecutive single-pulse stimulations. RMT calculation was completed in both actual stimulation and sham conditions. Individual RMTs were used to prevent variation in stimulation efficacy due to factors such as skull thickness [56]. For subjects assigned to the sham group, the switch to the sham coil was performed after the subject had completed the first round of behavioral testing and it was presumed that the time difference between the RMT acquisition and rTMS administration was enough for subjects to not detect sham TMS administration; all subjects were TMS naïve. Other studies have used vertex stimulation as a control for rTMS and in the current study subject blinding to sham stimulation was not assessed and this is a limitation of the present study. The authors do not feel that there would be a significant benefit from using a control site stimulation, however this could be an avenue for future research.

The left and right sites were stimulated with the center of the figure of 8 coil half way between the electrodes AF3 and F3 (left dlPFC) or AF4 and F4 (Right dlPFC) of the EEG 10–20 system as according to a previously detailed anatomical localization procedure Fitzgerald et al. [19,21]. A mechanical arm maintained the coil in a fixed position. The handle of the coil was angled backward 45° away from the midline in that position and its correct positioning was repeatedly checked by the experimenter during the stimulation. The pattern of stimulation consisted of a continuous 1 Hz train which was given at 90% RMT, which has been shown to temporarily reduce cortical excitability when compared to 100% RMT Valero-Cabre et al. [60]. For sham rTMS, a sham coil was used which mimics the sound given by rTMS. The same intensity and timing of rTMS was used for sham stimulation, with subjects counterbalanced between left (n = 6) and right (n = 6) dlPFC sham stimulation. All subjects tolerated rTMS and did not report any adverse effects.

2.7. Statistical analyses

Analyses were performed with SPSS (IBM Corp., Version 19). The significance level was $p < 0.05$. Pre-stimulation effects of load on latency and amplitude were assessed by a two-way repeated-measures analysis of variance (RM-ANOVA) including load (zero-back, 2-back) and hemisphere (left, right).

To determine the post-stimulation changes, a three-way RM-ANOVA was performed including stimulation (pre, post), hemisphere (left, right), and load (zero-back, 2-back). Each stimulation group was then analyzed separately in order to determine the stimulation effects of each group (within groups analysis).

Behavioral data were measured in terms of accuracy ([n correct target responses + n correct non-target responses]/[total trials]) and RT (interval from the onset of the stimulus to the subject's response). Both accuracy and RT data were analyzed using within subjects RM-ANOVA with time (pre, post-stimulation) as within subjects factors and side of stimulation (left, right, sham dlPFC) as a between subjects factor.

3. Results

3.1. Left prefrontal stimulation disrupted practice effects observed in younger and older adults in other stimulation conditions

Prior to stimulation, older adults showed a reduced accuracy (old: 80.6% ± 6.3, young: 88.5% ± 4.3, $F_{1,69} = 37.9$, $p < 0.001$) and increased RT (542.7 ± 70.7 ms vs. 475.5 ± 85.1 ms; $F_{1,69} = 22.5$,

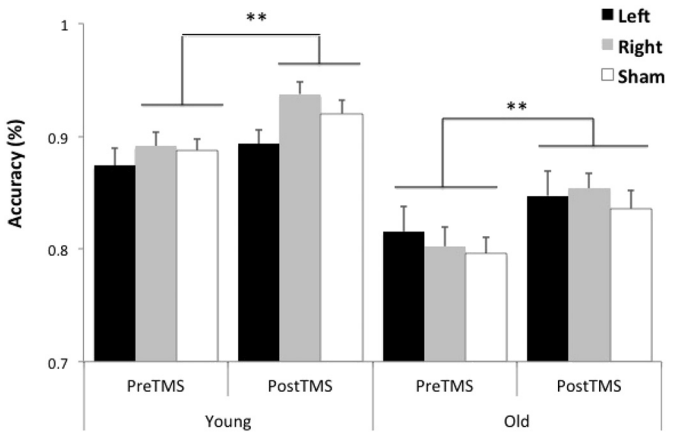

Fig. 2. Left stimulation reduced the working memory practice effect observed in the other groups in the younger adults. Stimulation did not affect practice effects observed in older adults. A positive accuracy difference represents an increase in accuracy from pre- to post-stimulation for the 2-back condition. In the younger group, there were practice related increases in accuracy in the right and sham stimulation groups ($p = 0.001$ and $p = 0.007$, respectively). However, in the older group, all three stimulation groups showed increased accuracy from pre- to post-stimulation (left, $p = 0.009$, right, $p = 0.001$, sham, $p = 0.001$). There was no change following stimulation for the zero-back condition (Table 2).

$p < 0.001$) compared to younger adults in the 2-back condition.

Following stimulation, the zero-back condition showed no change in accuracy (pre: 96.4% ± 0.5, post: 94.3 ± 1.7), while there was an overall increase in accuracy in the 2-back condition (pre: 84.6% ± 0.6, post: 88.2 ± 0.6) (stimulation × load: $F_{1,70} = 15.3$, $p < 0.001$). This effect trended toward significance between the groups (stimulation × load × age: $F_{1,70} = 3.1$, $p = 0.08$). There were no group differences in RT as both groups showed a decreased RT following stimulation (stimulation: $F_{1,70} = 20.6$, $p < 0.001$). These results suggest an effect of practice (increased accuracy, decreased RT) from completing the task twice.

In the within groups analysis, left dlPFC stimulation showed a difference between the groups. The older group showed an increase in accuracy following left ($F_{1,11} = 9.6$, $p = 0.009$), right ($F_{1,11} = 22.5$, $p = 0.001$) and sham ($F_{1,11} = 22.3$, $p = 0.001$) stimulation (Fig. 2). The younger group showed an increase in accuracy following right ($F_{1,11} = 19.1$, $p = 0.001$) and sham ($F_{1,11} = 10.7$, $p = 0.007$), but not left stimulation. There were no differences between the left and right sham stimulation groups in accuracy ($p > 0.1$) or RT ($p > 0.2$). 10 of the 12 young subjects showed a decrease in accuracy following left stimulation. In contrast, 11 of 12, and 9 of 12 younger adults showed improvement in accuracy following right and sham stimulation, respectively.

3.2. Unilateral prefrontal stimulation affected ipsilateral P1 (latency, amplitude) in younger adults

The stimulation-related hemispheric changes of the P1 (50–150 ms) peak were altered with unilateral stimulation.

3.2.1. P1 latency

There was a three-way stimulation × hemisphere × age interaction ($F_{2,70} = 4.8$, $p = 0.011$). In the younger subjects, the left hemisphere had a shorter latency following left stimulation (Fig. 3C, stimulation × hemisphere, $F_{1,11} = 13.9$, $p = 0.005$), this effect was not observed in older adults ($F < 2$).

3.2.2. P1 amplitude

The older adults showed a decreased right amplitude, while the younger adults did not show any lateralized changes following right stimulation (Fig. 3D, stimulation × hemisphere × age, $F_{1,70} = 24.4$, $p < 0.001$). Following right stimulation, the younger subjects showed a decreased amplitude in the right hemisphere (stimulation × hemisphere: $F_{1,11} = 5.6$, $p = 0.042$). The older adults showed a reduced right amplitude in all three stimulation conditions (left: $F_{1,11} = 12.4$, $p = 0.005$; right: $F_{1,11} = 6$, $p = 0.034$; sham: $F_{1,11} = 16.4$, $p = 0.002$).

3.2.3. P3 amplitude

P3 amplitude decreased following left stimulation in younger adult and was not affected in the older adult group. The older adults showed an increased amplitude in the 2-back condition following stimulation (Fig. 4, stimulation × load × age, $F_{1,70} = 9.1$, $p = 0.004$). There was no change in the amplitude in the zero-back condition. Specifically, following left stimulation the younger adults showed a decreased P3 amplitude following stimulation (stimulation × load × age, $F_{1,70} = 4.6$, $p = 0.045$).

4. Discussion

This study was designed to determine if prefrontal activation changes observed in aging [66] could be reproduced using rTMS. The first main finding was that practice effects of working memory were disrupted in younger adults following left dlPFC stimulation, while rTMS did not disrupt practice effects in older adults. The second main finding was that age-specific lateralized changes in evoked potentials following stimulation showing physiologic evidence for changes in frontal resources with increasing age.

Our behavioral results showed a significant increase in accuracy and a quickening of response times following stimulation in all but the young group following left dlPFC stimulation, which represented a disruption in performance. Other studies have observed similar disruption in practice effects following left dlPFC stimulation while completing verbal working memory tasks [22]. Other studies have found disruption in verbal working memory following right stimulation [29,42]. However, many more commonly rTMS studies implicate the predominate role of the left frontal cortex in the completion of verbal working memory tasks ([42–45], Feredoes et al. [18,20]).

The fact that this same disruption was not observed in older adults following left stimulation suggests that there may be functional differences in the laterality of the prefrontal networks. The baseline differences between young and older adults are important to consider; however, as there was no significant difference between the groups pre-stimulation, we can infer that the lack of significant improvement following left stimulation is due to the stimulation effects and not ceiling effects. Additionally, baseline differences between younger and older adults in working memory and the networks that support working memory are expected [49] and only able to be controlled for by conducting both within and between subjects analyses.

There are limited studies utilizing rTMS to study laterality changes in frontal resources with increasing age. Rossi et al. [56] compared the effects of rTMS applied to the left or right dlPFC during episodic retrieval in healthy younger and older adults. In the young adults right frontal stimulation interfered more with recognition memory. This asymmetry was not present in the older adults, as recognition memory performance was impacted by both right and left frontal stimulation. As we hypothesized that older adults using a bilateral prefrontal network was a compensatory mechanism, we would expect to find less lateralized effects with left or right stimulation, varying from Rossi et al.'s results because the older adults could use the remainder of the bilateral network to complete the task.

In the current experiment, both left and right stimulation caused lateralized effects on P1 in younger adults, suggesting that magnetic stimulation has effects on the contralateral hemisphere as well. Several studies have shown that the frontal cortex has important top-down control over visual evoked potentials, as early as 100 ms [55]. Patients with unilateral dlPFC lesions completing a hemifield discrimination

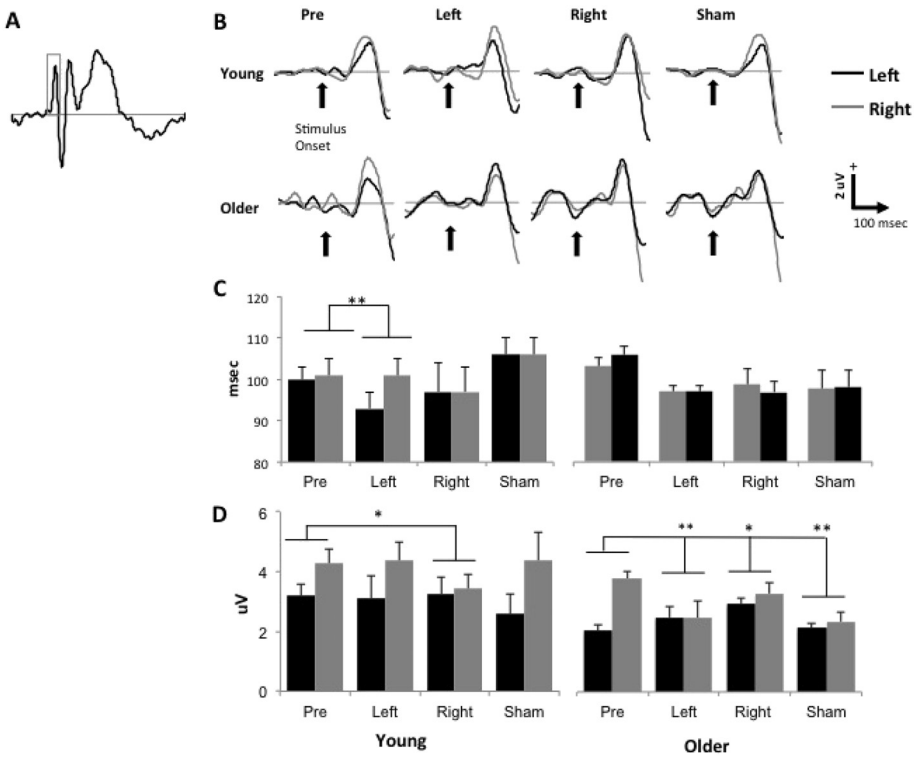

Fig. 3. Unilateral prefrontal stimulation affected ipsilateral posterior P1 modulation in younger adults. (A) Representative P1 peak is highlighted (B) Pre- and post-stimulation P1 peaks for the left and right electrodes (C) In the younger subjects, there was an left lateralized reduction in P1 latency following left stimulation ($p = 0.005$). (D) Following right stimulation there was a right lateralized reduction in P1 amplitude ($p = 0.042$). There was a decreased rightward amplitude following stimulation for all three groups in the older adults (left, $p = 0.005$; right, $p = 0.034$; sham, $p = 0.002$).

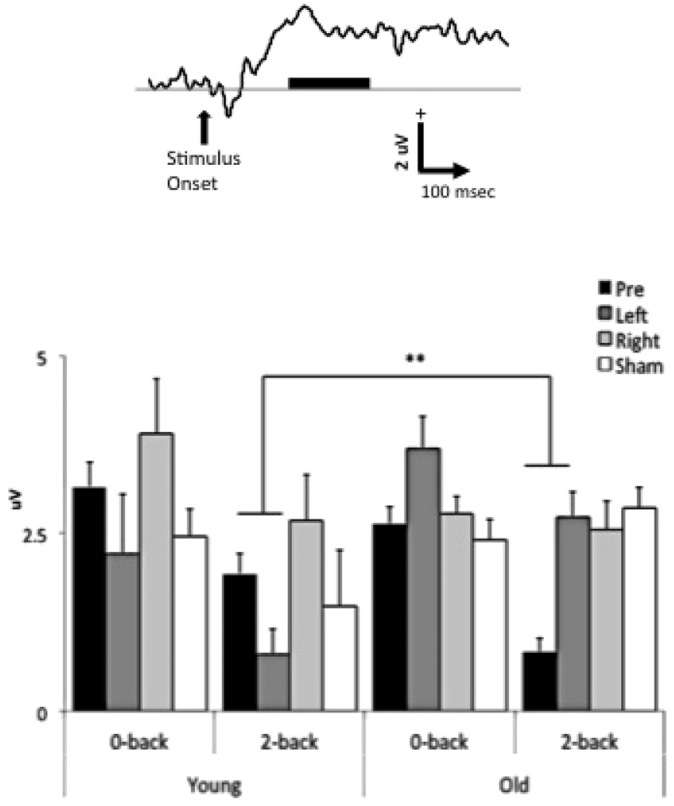

Fig. 4. Left stimulation decreased the P3 amplitude in younger adults and increased the amplitude in older adults. The top graph shows a representative sweep showing where the P3 amplitude time window (black bar). Older adults showed increased P3 amplitude following stimulation, while younger adults showed a decreased amplitude ($p = 0.045$).

task showed behavioral and physiologic changes to contralesional stimuli suggesting that disordered top-down control impacts the ipsilesional hemisphere [2]. rTMS to the right IFG during a working memory task disrupted accuracy and caused a reduction in P1 amplitude, similar to what was observed in the present study [64].

Magnetic stimulation activates neural networks in a method that has not been completely described. Sole-Padulles et al. [58] found that left PFC stimulation in memory impaired older adults caused improvement in memory ability corresponding with increased fMRI activity in the right frontal and bilateral posterior regions, however no comparison with younger adults was available and these individuals had baseline memory complaints. The current results suggest frontal stimulation has lateralized effects that differ between age groups, however it is still unknown the effects on the prefrontal networks (i.e. parietal cortex, deep cortical structures) that rTMS has and the differences in these networks with increasing age may underlie the differences in behavioral results seen with increasing age.

Older adults showed left hemispheric increased P3 amplitude following left stimulation. The changes in P3 may represent an adaptive mechanism through the use of increased resources to complete cognitive tasks [17]. Increased cortical activity has been hypothesized to represent a decrease in the integrity of neural circuitry [16], and alternatively represent a strategy that compensates for difficulty recruiting the necessary and/or most efficient neural networks to accurately complete a task [38]. Additionally, aging has been associated with a decline in the integrity of the corpus callosum [59], which may suggest that bilateral activity may be interpreted as a decline in hemispheric inhibition.

There are many other alternative hypotheses for the changes in neural activity observed with increasing age. Variations in strategies within and between age groups may also be responsible for differences between younger and older participants ([54], Daselaar et al., 2003, [1]) [46,62,57]. Increased prefrontal activity may also represent non-selective recruitment of additional regions or loss of integrity of the active brain circuitry [16,39].

We used the 10–20 EEG localization technique including the validated anatomical localization references for the dlPFC Fitzgerald et al. [19,21]. By utilizing this technique, we were not able to control for potential individual differences in anatomy that may account for some within-subject variability and provide information regarding accurate

targeting of the stimulation site. Controlling for these differences is especially important when examining populations of increasing age as brain anatomy is known to change due to atrophy [32]. Although our use of an offline rTMS design allowed us to record physiological data without induced artifacts from stimulation, there are some limitations to the use of offline rTMS as compared to online rTMS paradigms. First, with increased stimulation time the spread of cortical excitability from the stimulated region becomes increasingly likely. Therefore, we cannot be sure that our stimulation did not affect a wider cortical network than targeted. Additionally, rather than sham stimulation as a control, we could have used a control stimulation site (i.e. vertex) to control for overall stimulation effects and the ability to blind the subject to the treatment condition.

Finally, the effects of practice may also limit our results. Some studies show that practice effects cause different activity in younger and older adults [68]. Previous studies have examined the effects of practice on the ERP [4,41], however the physiological changes with practice are controversial.

The present study suggests rTMS can be used to study age-related changes in prefrontal networks. Our results support that there are differences in the lateralization of prefrontal networks in younger and older adults. A future direction may conduct bilateral prefrontal stimulation, which would further delineate the effect this had on older adults to further understand the meaning of this change in network with increasing age.

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