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Enhancing neural efficiency of cognitive processing speed via training and neurostimulation: An fNIRS and TMS study

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ABSTRACT

Speed of Processing (SoP) represents a fundamental limiting step in cognitive performance which may underlie General Intelligence. The measure of SoP is particularly sensitive to aging, neurological or cognitive diseases, and has become a benchmark for diagnosis, cognitive remediation, and enhancement. Neural efficiency of the Dorsolateral Prefrontal Cortex (DLPFC) is proposed to account for individual differences in SoP. However, the mechanisms by which DLPFC efficiency is shaped by training and whether it can be enhanced remain elusive. To address this, we monitored the brain activity of sixteen healthy participants using functional Near Infrared Spectroscopy (fNIRS) while practicing a common SoP task (Symbol Digit Substitution Task) across 4 sessions. Furthermore, in each session, participants received counterbalanced excitatory repetitive transcranial magnetic stimulation (rTMS) during mid-session breaks. Results indicate a significant involvement of the left-DLPFC in SoP, whose neural efficiency is consistently increased through task practice. Active neurostimulation, but not Sham, significantly enhanced the neural efficiency. These findings suggest a common mechanism by which neurostimulation may aid to accelerate learning.

1. Introduction

Classical psychological research has observed that an individual's performance across a wide range of tasks tends to depend on a limited set of underlying cognitive resources (Baddeley, 2003; Lehman et al., 2010; Sheppard and Vernon, 2008; Spearman, 1904; Vernon, 1983). In particular, the rate at which an individual is able to perform elementary cognitive operations has been proposed to predict performance on more complex cognitive tasks and contribute to measures of general intelligence (Kail and Salthouse, 1994; Vernon, 1983). This Speed of Processing (SoP) is conceptualized as a fundamental cognitive ability which underlies aspects of multiple cognitive domains (Fry and Hale, 1996; Sheppard and Vernon, 2008) and relate to the speed and efficiency of information transfer within the brain (Fry and Hale, 1996; Kail and Salthouse, 1994). Differences in processing speed are thought to explain cognitive changes observed in healthy developmental growth (Bryan and Luszcz, 1996), nonpathological declines observed during aging (Henninger et al., 2010), as well as neurological dysfunction caused by disease (Andreasen et al., 2010), fatigue (Pihlaja et al., 2014), and mental illness (Brsébion et al., 1998; Nebes et al., 2000). SoP has also been reported to contribute to measured Quality of Life in many disorders (Barker-Collo, 2006; Green, 1996; Ojeda et al., 2012) and in aged populations (Wolinsky et al., 2006), and as a result, is frequently a target of intervention and remediation (Ball et al., 2013; Edwards et al., 2013, 2002).

Behavioral measures of SoP can be assessed using tasks such as the Digit-Symbol and Symbol-Digit Substitution Test (DSST and SDST respectively), which are purported to measure the efficiency of elementary cognitive operations in a way which cannot be ascribed to purely sensorimotor measures (Kail and Salthouse, 1994). Developed as a way to study intelligence in children (Pyle, 1913), the method was quickly adopted as a cognitive screening battery for military recruits (Yerkes, 1921), and incorporated into multiple intelligence and neuropsychological screening tools such as the Wechsler Adult Intelligence Scale

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(WAIS) (Smith, 1982; Wechsler, 1981). Symbol coding tasks are among the most well-studied and widely used neurophysiological tests, in part, because of their brevity, accessibility, relative cultural immutability, and sensitivity to both acute and longitudinal changes (Jaeger, 2018). Findings using these methods have allowed researchers to gain insight into the nature of individual differences in SoP, neural substrates underlying these differences, and inform approaches seeking to enhance SoP or mitigate its deterioration.

1.1. Role of the Dorsolateral Prefrontal Cortex in rapid cognition

From adolescence into adulthood, the development of SoP and global cognition appears to be associated with the growth and maturation of the Prefrontal Cortex (PFC) (Ferrer et al., 2013; Kail and Miller, 2006). Moreover, lesions in this area can have catastrophic effects on processing speed while basic functions remain intact (Leskelä et al., 1999; Stuss and Levine, 2002). In particular, the Dorsolateral Prefrontal Cortex (DLPFC) has been identified as a critical structure in top-down executive functions (Banich, 2009) and the rapid cognition characterized by SoP (Takeuchi and Kawashima, 2012). In functional studies of healthy participants, faster processing speeds have been related to reduced directed functional connectivity and activation of the DLPFC (Biswal et al., 2010; Motes et al., 2018; Rypma et al., 2006; Sweet et al., 2005). The DLPFC is an associative cortical region that is often described as a functional hub enabling a host of higher-order processes including working memory (Gilbert et al., 2006; McKendrick et al., 2014), mentalizing (Burgess et al., 2007), attention (O'Reilly, 2010), and response inhibition (Rodrigo et al., 2014). Although DLPFC activation is commonly observed to increase in a parametric manner with workload (Ayaz et al., 2012; Callicott et al., 1999), increased DLPFC activation may also occur as a compensatory mechanism to reductions in available neural resources (Cabeza and Dennis, 2012) or alternatively, an inefficient utilization of neural resources (Haier et al., 1988; Neubauer and Fink, 2009a). These findings suggest that faster/more adept individuals may possess increased "neural efficiency" through the optimal use of structural/functional connections to engage in minimal neural processing and demonstrate reduced neural activity along with increased performance (Bennett et al., 2012; Di Domenico et al., 2015; Haler et al., 1992; Neubauer and Fink, 2009b).

Although differences in neural efficiency and task difficulty may account for performance differences, there is substantial evidence that practice allows the development of strategies through which complex tasks, initially cumbersome, become almost automatic in nature. The DLPFC is thought to manage the deliberate "general-purpose" networks which operate prior to this neural reorganization and optimization (Burke et al., 2010; Jonides, 2004). Development of task expertise is associated with decreased need for executive monitoring and subsequently decreased demands on the DLPFC resulting in increased regional neural efficiency (Ayaz et al., 2013; Curtin and Ayaz, 2019). This training effect has been proposed to be mediated by increased SoP (Dux et al., 2009). Interventions with the aim of restoring or optimizing the function of the DLPFC eventually may allow directed reinforcement of task-based networks by priming cortical activities during or prior to training. Such improvements may be able to impact direct measures of intelligence, improve performance, increase task capacity, or help consolidate the effects of training through improvements in neuroefficiency.

1.2. Neurostimulation to enhance neural efficiency

Noninvasive Brain Stimulation (NIBS) methods have been shown significant promise to restore or enhance cognition and a means by which skill acquisition can be accelerated (Bostrom and Sandberg, 2009; McKendrick et al., 2015; Parasuraman and McKinley, 2014). NIBS techniques such as transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES) are thought to modulate brain activity through the manipulation of neuroplasticity resulting in persistent changes in localized cortical excitability. Excitatory repetitive TMS (rTMS), increases in excitability are thought to be induced by short bursts of rapid stimulation in a mechanism similar to Long-Term Potentiation (LTP), whereas tES is thought to alter excitability by biasing currents and other indirect means (for review see (Knotkova et al., 2019; Strobach and Antonenko, 2017; Valero-Cabré et al., 2017)). A recent meta-analysis of tES has suggested that stimulation during or prior to learning may enhance learning (Simonsmeier et al., 2018) and more specifically, that tES to the left-DLPFC may increase SoP potentially by enhancing the efficiency of cognitive control (Pasqualotto, 2016; Plewnia et al., 2015). A recent study has suggested that tES to the left-DLPFC, when combined with SoP cognitive training can increase executive function as well as SDST task performance in patients with multiple sclerosis (MS) (Mattioli et al., 2016). rTMS offers a few advantages over tES by providing a more direct mechanism of activation and greater spatial precision (Dayan et al., 2013) and has similarly been shown to produce enhancement in cognitive tasks (Luber and Lisanby, 2014). Excitatory rTMS targeting the Left-DLPFC has been shown to both enhance reaction time and accuracy in working memory tasks (Brunoni and Vanderhasselt, 2014) and during selective attention tasks (Guse et al., 2010). While modest effects observed on SoP have been associated with rTMS (Lefaucheur et al., 2014; Martin et al., 2017; Xu et al., 2019), there is considerable conflicting evidence and the effects of rTMS on practice of SoP tasks have not been studied.

One substantial issue related to the evaluation of training and cognitive enhancement using NIBS is the common inability to evaluate changes apart from behavioral measures. Non-invasive neuroimaging techniques such as functional Near-Infrared Spectroscopy (fNIRS) offer one method of measuring changes in cortical activity related to training (Ayaz et al., 2013) and can be integrated with NIBS methods such as TMS for simultaneous use (for recent systematic review see (Curtin et al., 2019)). fNIRS measures relative changes in oxygenated hemoglobin [HbO] and deoxygenated hemoglobin [HbR] through changes in the relative absorption of backscattered light (Ferrari and Quaresima, 2012). Measurements made through fNIRS convey similar information offered by the blood-oxygen level dependent (BOLD) response observed in fMRI (Cui et al., 2011; Liu et al., 2017; Sato et al., 2012; Steinbrink et al., 2006), but can be acquired more practically for superficial cortical areas. An important advantage of fNIRS relies on its ability to be used conveniently for repeated measures and in naturalistic environments, providing a useful platform for the observation and assessment of workload and training in different settings (Causse et al., 2017; Curtin and Ayaz, 2018; McKendrick et al., 2016; Pinti et al., 2018).

In this study, we sought to investigate changes in neural efficiency in the DLPFC and behavioral improvement during practice of a common SoP task (i.e. the SDST). Additionally, we explored how noninvasive brain stimulation using excitatory TMS may affect metrics of neural efficiency using different types of rTMS paradigms: two excitatory (High Frequency (HF), intermittent Theta Burst Stimulation (iTBS)), one excitability-neutral (Single Pulses (SP)) and sham. In order to estimate neural efficiency in the DLPFC, we continuously monitored activity during task performance using fNIRS to investigate (1) how the involvement of the DLPFC evolves during SoP task-based training, and (2) whether rTMS-based neuromodulation can be used to facilitate enhanced neural efficiency. Based on prior literature, we hypothesized that task practice would reduce executive oversight required by the DLPFC, reducing relative task demands and improving behavioral performance, resulting in increased neural efficiency. Additionally, we hypothesized that increasing the DLPFC excitability through rTMS would improve task execution related efficiency.

2. Materials & methods

2.1. Subject demographics

16 healthy volunteers (8 M, 8 F; Age: Mean: 26.5 yrs, S.D.: 2.7 yrs) were recruited from the local community and gave written informed

Table 1
Subject demographics.

Subject	Gender	Age (yrs)	Resting Motor Threshold (RMT) (%)
1	F	28	43
2	F	24	41
3	F	25	30
4	M	34	47
5	F	25	34
6	F	25	38
7	F	27	27
8	M	23	34
9	M	27	40
10	F	26	41
11	M	25	32
12	M	28	43
13	M	27	34
14	M	25	26
15	F	25	34
16	M	30	39

consent prior to participation in this study. Participants all self-identified as right-handed and self-reported to have no history of mental illnesses, pregnancy, or drug abuse, and were compensated for their time. Participant demographic information is reported in Table 1. The study was run at the Shanghai Mental Health Center and conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Shanghai Mental Health Center.

2.2. Study design

A within-subjects design study was conducted to determine the influence of practice and different rTMS stimulation patterns on performance of the SDST. The study was conducted across four different sessions over two days (2 sessions/day) and sessions on the same day were separated by at least 1 h. Participants performed two trials of the SDST before and after a receiving randomized rTMS stimulation type consisting of one of four patterned rTMS conditions. During each trial of the SDST, cortical hemodynamic biomarkers were continuously monitored using an fNIRS headband placed over the DLPFC. The session protocol for a single session is detailed in Fig. 1.

2.3. Experimental task

Within each trial, subjects were asked to rest for 30 s and then perform a 90-s digitized version of SDST that had been built using a custom OpenGL engine. The SDST, (also called the symbol digit modalities test (SDMT) (Smith, 1982)), is a common symbol coding task and is similar to the Digit-Symbol Substitution Test (DSST) featured in the WAIS (Wechsler, 1981) except that participants are asked to match a digit to a novel symbol instead of a symbol to a digit. In the digitized version of this task (as seen in Fig. 2), subjects were given a Symbol-Digit key, serially presented with numbers (1–9) and asked to enter a number corresponding with the appropriate symbol for each task. When the symbol was correctly decoded, a soft beep was presented. Task performance was scored by the number of correct responses during the 90 s task. Furthermore, the Symbol-Digit key shown was pseudorandomly scrambled prior for each task to prevent memorization of Symbol-Digit associations. During each session, subjects performed the SDST twice prior to receiving TMS stimulation and twice after TMS stimulation for each of the four different sessions.

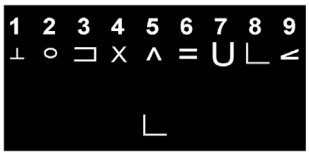

Fig. 2. Symbol Digit Substitution Task used for stimuli presentation with target symbol located on the bottom row and the symbol coding displayed on the top row. Following each response, the target symbol was changed.

2.4. fNIRS setup

Optical brain imaging was performed using the fNIRS1100 sensor (fNIR Devices Inc., Potomac, MD, USA) centered on the midline of the subject's forehead in line with Fp1-Fp2 and corresponding roughly with the location of the anterior PFC and DLPFC (Brodmann's area 10/46) as described by Ayaz et al. (2011). Probabilistic coregistration for optode locations and underlying anatomy has been described previously by Liu et al. (2017). Data was collected from 16 optodes continuously with a sampling frequency of 2 Hz using two wavelengths (730 nm and 850 nm). Raw light intensity was screened for excessively noisy and saturated signals. Motion artifacts were rejected automatically using a sliding motion artifact algorithm (SMAR) (Ayaz et al., 2010) and low-pass filtered with a cutoff frequency of 0.25 Hz. Raw light-intensities were converted to physiological measurements using the modified Beer-Lambert Law (Delpy et al., 1988) using the 10 s prior to task start as the baseline period. Measured biomarker values are reported as changes in relative oxygenated hemoglobin [HbO], deoxygenated hemoglobin [HbR], and the sum of these changes [HbTotal]. Parametric visualizations of fNIRS-measured biomarkers are projected onto a virtual brain model according to the methodology described in Ayaz et al. (2006).

2.5. rTMS procedure

After obtaining written informed consent, the participant was seated in a chair and had their resting motor threshold (RMT) estimated by an experienced physician (RMT: Mean 36.4%, Std 6.0%). TMS was delivered using a 75 mm outer diameter figure-of-8 coil and the MagPro stimulator (MCF-B65, MagVenture, Denmark). Patterned TMS stimulations were targeted to the Left-DLPFC at F3 using the 10–20 system, as this location has been reported to be a more accurate location than the commonly applied 5 cm rule (Lefaucheur et al., 2014). Stimulation occurred slightly ventral to the position of the fNIRS headband and typically was adjacent to Optode 3 on the fNIRS sensor.

TMS also allows the manipulation of cortical excitation based on the pattern of stimulation used, respectively allowing either excitation of cortical areas with high frequency stimulation (HF, >5 Hz) or inhibition when using low frequency stimulation (1 Hz). Other types of patterned stimulations have attempted to improve the effects of simple frequency-based patterns by using bio-inspired stimulation patterns such as Theta Burst Stimulation (TBS) which mimics the coupling of gamma and theta rhythms observed in hippocampal neurons during learning (Huang et al., 2005).

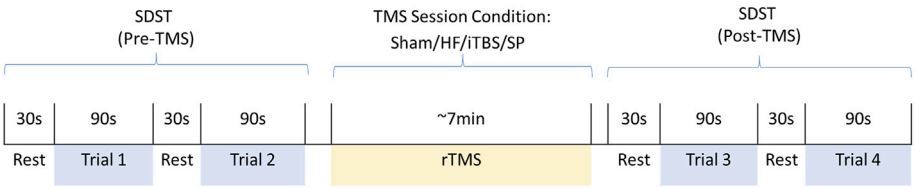

Fig. 1. Symbol-Digit Task and TMS session timeline.

During a resting break between the first two and last two trials of the SDST, participants received one of four rTMS stimulation paradigms which lasted approximately 7 min. In the Single Pulse (SP) stimulation paradigm, participants received one pulse of TMS stimulation at 110% RMT every 42 s. In the High Frequency (HF) paradigm, participants received 2 s of 15 Hz stimulation (30 pulses) at 110%RMT every 42 s. Intermittent Theta Burst Stimulation (iTBS) was delivered at 90% RMT for 2 s (3–50hz pulses delivered at 5 Hz, 30 pulses total). Sham stimulation was produced by reversing the coil and using a HF pattern to mimic the sounds and vibrations of stimulation without the corresponding magnetic flux. No adverse effects due to rTMS stimulation or fNIRS imaging were reported by any of the subjects in this study.

2.6. Statistical analysis

Measured fNIRS and behavioral data were preprocessed using Matlab (R2016a) and exported to R (v3.2.2) for statistical analysis. Correlations for continuous variables were conducted using the Spearman's rank correlation coefficients as a two-tailed test. Linear mixed-effects models were used to account for subject variability and repeated measures (Bates et al., 2015). Separate models were constructed to identify the impact of the fixed effects of interest on dependent measures of Score and respective biomarkers. Statistical significance of model fixed effects was assessed using the Satterthwaite approximation for degrees of freedom. Post-hoc tests were conducted using Tukey contrasts adjusted for Family-wise error rates using the Holm-Bonferroni correction. A criterion of $\alpha = 0.05$ was designated as the threshold for statistical significance. Optode-wise False Discovery Rate was performed on fixed-factors in addition to other Family-wise error corrections (Genovese et al., 2002) with $q = 0.05$.

Efficiency analysis was conducted as a way of providing a consolidated metric of neurobehavioral performance which relates mental effort to outcome (Tuovinen and Paas, 2004). In this study, outcome was described by changes in task score while mental effort was assessed based on the changes in fNIRS-measured biomarkers (HbO,HbR,HbT). Effort and Outcome metrics were converted into Z-scored measurements and then Efficiency was computed using the distance of the point from the zero-efficiency line (i.e. where Performance = Effort) and assessed as dependent measurements in statistical tests (Curtin and Ayaz, 2019).

3. Results

3.1. Task performance improved with each session

Subjects showed a session-on-session improvement in task performance (raw *Score*) as assessed by a linear mixed model using *Session* as a fixed effect and *Trial* as a random effect ($F_{(3,193.5)} = 114.6$, $p < 0.001, \eta^2 = 0.532$). Subjects also tended to improve trial-by-trial during a session ($F_{(3,21.8)} = 16.5$, $p < 0.001, \eta^2 = 0.077$) and there was a significant interaction between *Trial* and *Session* ($F_{(9,193.5)} = 4.13, p < 0.001, \eta^2 = 0.057$). Post-hoc tests also revealed that all *Sessions* were significantly different from each other ($p < 0.001$), and within a single session, the first trial was significantly different from all trials except trial 3 ($z > 4.2$, $p < 0.001$), and the fourth trial ($z > 2.76$, $p < 0.03$) was significantly different from all trials except for trial 2.

3.2. fNIRS measures an increase in neural efficiency due to practice

In order to study the relationship of fNIRS-based measures of cognitive task demand and learning prior to TMS, we constructed a linear mixed model using *Session* as a fixed factor, subject-normalized *Score*:

$$Rescaled\ Score = (Score - \min Score)/(\max Score - \min Score) \quad (1)$$

as a covariate and *Trial* as a within subject random factor. In order to assess learning only due to task practice and independent from TMS-related effects, we examined only the first two trials from each session (Pre-TMS). Following thresholding by FDR, subjects showed significant main effects for *Session* on [HbTotal] at Optode 3 ($F_{(3,104.4)} = 5.42$, $q_{(1/16)} = 0.027, \eta^2 = 0.117$), and for [HbO] in Optodes 1 ($F_{(3,90.443)} = 5.58$, $q_{(2/16)} = 0.012, \eta^2 = 0.133$) and 3 ($F_{(3,104.1)} = 4.687$, $q_{(2/16)} = 0.0329, \eta^2 = 0.104$). There were also significant interactions between *Score* and *Session* for [HbTotal] at Optode 1 ($F_{(3,91.4)} = 4.91$, $q_{(2/16)} = 0.0264, \eta^2 = 0.057$) and Optode 3 ($F_{(3,103.99)} = 5.93$, $q_{(2/16)} = 0.007, \eta^2 = 0.128$), and also for [HbO] in Optode 1 ($F_{(3,91.1)} = 5.85$, $q_{(3/16)} = 0.0057, \eta^2 = 0.139$), Optode 3 ($F_{(3,104.1)} = 5.547$, $q_{(3/16)} = 0.0076, \eta^2 = 0.124$) and Optode 4 ($F_{(3,106.9)} = 4.50$, $q_{(3/16)} = 0.027, \eta^2 = 0.103$). Post-hoc tests showed that for both biomarkers, on average, Optode 1, and 3, tended to decrease between sessions with significant differences observed between Session 3 and 4 ($z < -2.81, p < 0.024$). Parametric maps for *Session* and the interaction of *Session* with *Score* are presented in Fig. 3. No significant changes were observed for [HbR].

Next, we calculated the neural efficiency of optodes significantly responsive to task practice (Optodes 1 and 3) to present the trends of joint neural and behavioral data. First, we projected the normalized fNIRS measures ([HbO] or [HbTotal] as mental effort) and rescaled Score (as outcome) metrics into Efficiency coordinates. Then, we evaluated the effect of Session on Efficiency (pre-TMS) using Session as a fixed effect with Trial as a within-subject random effect. Both Optode 1 and 3 showed significant main effects for Session on Efficiency for [HbTotal] (Optode 1: $F_{(3,80.9)} = 27.25$, $p < 0.001, \eta^2 = 0.47$, Optode 3: $F_{(3,90.66)} = 29.57, p < 0.001, \eta^2 = 0.4316$) and [HbO] (Optode 1: $F_{(3,23.4)} = 81.6, p < 0.001, \eta^2 = 0.429$, Optode 3: $F_{(3,96.475)} = 26.4, p < 0.001, \eta^2 = 0.420$). Post-hoc tests suggested that for Optode 1, all sessions significantly differed from each other ($p<0.009$, $z>3.128$), except for the comparison between Sessions 2 and 3 which did not significantly differ from each other for either [HbO] or [HbTotal]. For [HbO] in Optode 3 all paired tests between sessions were significant ($p<0.047$, $z>2.59$) and for [HbTotal] all pairs were significant ($p<0.003$, $z>3.44$) except Session 3 and Session 4. Efficiency for [HbTotal] and *Score* is visualized in Fig. 4A and distance from E = 0 axis is projected in Fig. 4B.

3.3. rTMS reduces cognitive workload with maintained task performance

To determine whether TMS condition had any influence on performance or biomarker we evaluated Trials 3 and 4 (post-TMS trials) separately in an LME model with *Session* and *TMS-Type* as fixed factors and *Trial* as a within-subject random effect. When Raw *Score* and Rescaled *Score* were selected as the dependent variables of interest, TMS-type did not appear to be significantly related to behavioral performance following FDR correction. When we conducted an exploratory analysis examining the influence of TMS-type on subsequent cortical activity, significant changes in [HbTotal] were observed in Optode 3 ($F_{(3,103.17)} = 3.31, p = 0.023, \eta^2 = 0.079$), Optode 6 ($F_{(3,10.8)} = 3.06, p = 0.031, \eta^2 = 0.076$) and Optode 16 ($F_{(3,104.6)} = 3.77, p = 0.013, \eta^2 = 0.089$). In [HbO], changes were only significant for Optode 16 ($F_{(3,104.1)} = 3.59, p = 0.016, \eta^2 = 0.083$). Post-hoc differences showed that Task-evoked [HbTotal] after High Frequency Stimulation was significantly lower than Sham in Optode 3 ($z = -2.884$, $p = 0.02$) and Optode 6 ($z = -3.001$, $p = 0.014$). Further tests revealed that, at Optode 16, iTBS stimulation appeared to increase task-evoked measures compared to HF stimulation for both [HbO] ($z = 3.276$, $p = 0.0059$) and [HbTotal] ($z = 3.332$, $p = 0.044$). Other comparisons were not significant.

3.4. Active TMS methods, but not sham, enhance efficiency

Based on the overlap of observed involvement during task practice, changes in task-evoked activity related to TMS type, and proximity to the actual TMS stimulation location (see Fig. 5), we selected Optode 3 to examine the influence of TMS stimulation from the perspective of neuroefficiency. Results showed that the concordant decrease in cortical

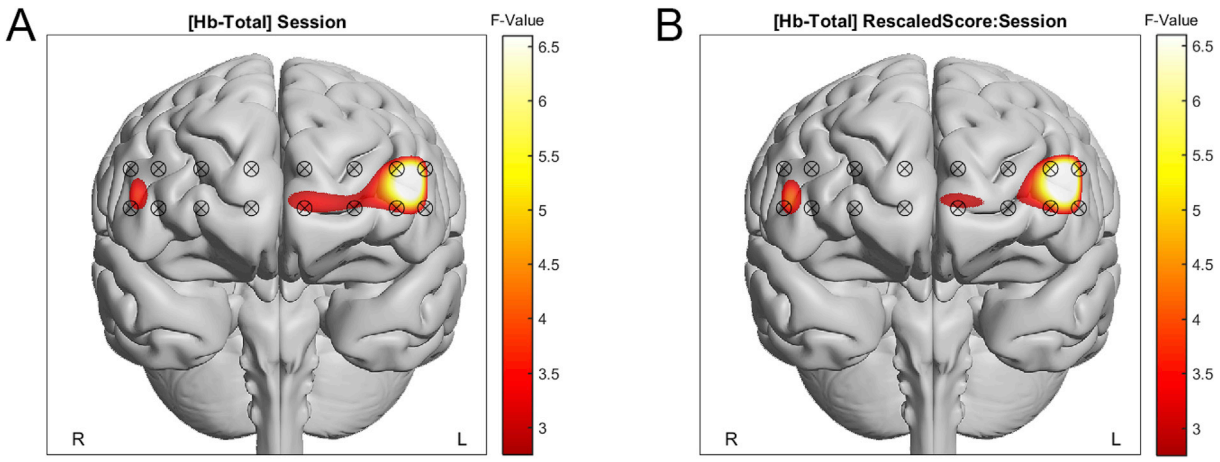

Fig. 3. Interpolated parametric map for [HbTotal] following thresholding via FDR for expression in pre-TMS fixed effect of Session (A) and interaction of Session with subject-normalized Score (B).

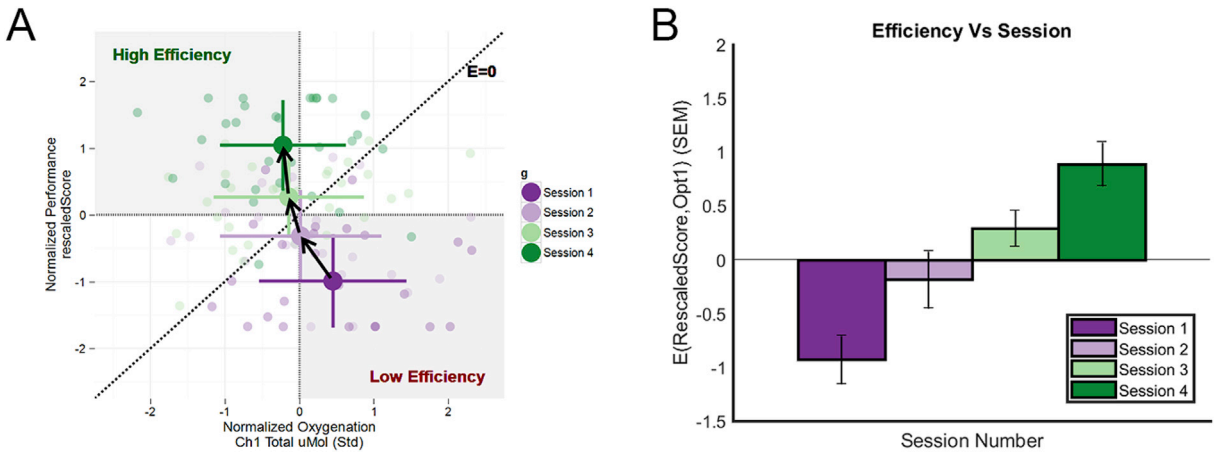

Fig. 4. Efficiency graph for Optode 1 [HbTotal] vs Subject-Normalized Score (A) and corresponding Efficiency vs Session (B), Error bars represent±Standard Deviation for normalized biomarkers and normalized performance, and Standard Error for efficiency metrics respectively.

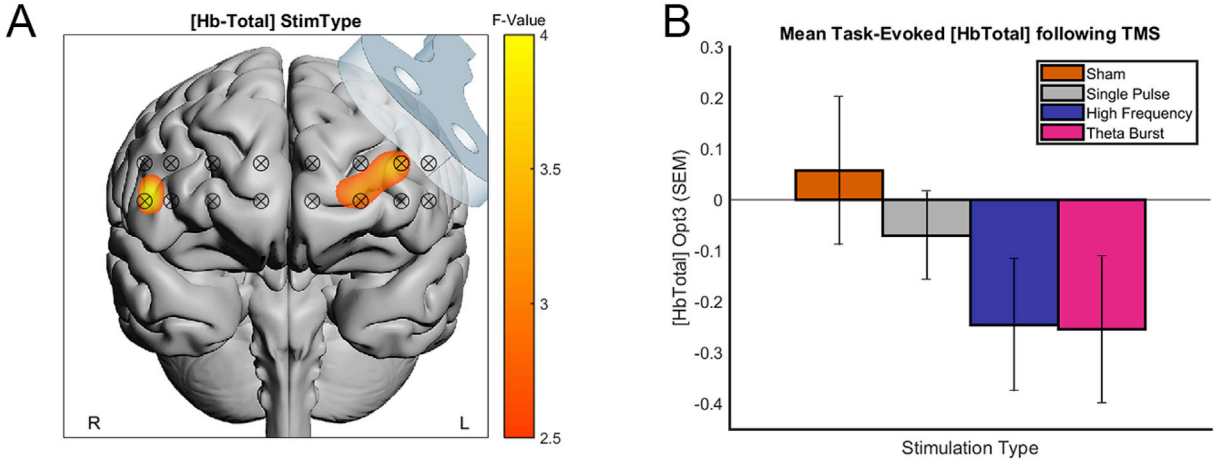

Fig. 5. Exploratory parametric map for main effect of TMS stimulation type on [HbTotal] (A) and mean changes in task-evoked activity in Optode 3 following TMS stimulation (B).

demand as measured by fNIRS, translated into corresponding increases in Efficiency. Efficiency increased relative to pre-TMS trials for Single Pulse ($t = -2.51$, $p = 0.0344$), High Frequency ($t = -4.79$, $p < 0.001$), and Theta Burst ($t = -2.72$, $p = 0.0315$) relative to pre-TMS trials as measured by paired t-tests with Holm's Bonferroni correction. Notably, while all subjects appeared to improve with practice, changes after trials using Sham stimulation appeared to move parallel to the zero-efficiency axis ($y = x$), suggesting an absence of change in Efficiency (Fig. 6). Behavioral performance changes from pre-TMS baseline were not statistically different between rTMS intervention types.

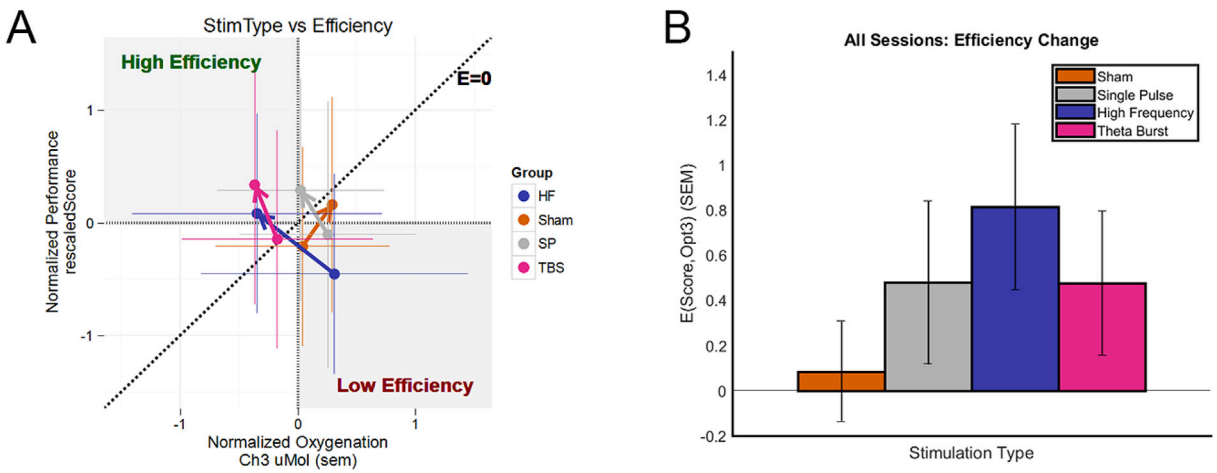

Fig. 6. Changes in neural efficiency from trials prior and post TMS stimulation (A) and relative differences in Efficiency as projected onto the efficiency line (B).

4. Discussion

Recent efforts to integrate routine cognitive testing as part of patient assessment have necessitated the understanding of how practice affects task performance as well as enhancing the test-retest reliability (Bartels et al., 2010; Gold et al., 1999). While the SDST (Symbol-Digit) and DSST (Digit-Symbol) tasks have both been validated and used extensively, independently and as part of comprehensive task batteries (see for review (Jaeger, 2018)), changes associated with learning which occur during task performance and repetition have not been studied with the aid of neuroimaging techniques. In the present work, we explored changes in prefrontal cortex activity during skill acquisition through practice of the SDST through a neuroefficiency perspective. Additionally, we explored how different forms of short rTMS stimulation may impact cognitive function underlying SoP. Our primary hypothesis was that practice of the SDST would result in increased behavioral performance and efficiency changes within the DLPFC, a key cortical area involved in the fronto-parietal network that is responsible for rapid information processing and the maintenance of working memory (Curtis and D'Esposito, 2003; Ramnani and Owen, 2004; Shaw et al., 2015). Specifically, we expected that cortical efficiency in the DLPFC may change with practice and may underlie individual differences in task performance.

4.1. Prefrontal involvement during practice of the SDST

Our results clearly demonstrate the expected effects of practice on SDST performance, i.e. subjects exhibiting increased performance across each session and often across trials as well. The general trend in performance and practice in this work mirrors findings from healthy participants in other published symbol coding studies which have reported and emphasized the presence of a learning effect in Symbol-Digit tasks (Bachman et al., 2010; Cornelis et al., 2015; Joy et al., 2003). Prefrontal involvement in the SDST was localized to left-DLPFC near Fp1 and F3 (encompassing Optodes 1, 3, and 4) as measured by task-evoked changes in [HbO] and [HbTotal]. In this region, task-evoked activation tended to decrease with practice across sessions, alongside aforementioned improvements in performance. The combination of decreases in cognitive demand and increases in performance resulted in significant session-on-session increases in neural efficiency consistent with expectations regarding task strategy consolidation (Sayala et al., 2006) and prior observations (Ayaz et al., 2013; Curtin and Ayaz, 2019).

The DLPFC has been described as a hub of executive function which is necessary to coordinate and integrate the outcomes of disparate cognitive processes in order to achieve higher order goals (Ramnani and Owen, 2004). Although the role played by the DLPFC is critical, it also may be cognitively expensive and relative inefficient when there are increased demands in executive control and task monitoring. These additional burdens may be reduced through the development of more efficient task-related strategies which enhance behavioral performance and reduce cognitive demand. In turn, regional metabolic requirements by moving task execution to more specific and automatic neural circuits. These increases in neural efficiency through training and task practice have been observed frequently during both routine behavioral tasks (Sayala et al., 2006), development of expert evaluations (Babiloni et al., 2010) and performance in complex environments (Ayaz et al., 2012).

Neuroimaging studies of Symbol-Digit tasks have previously identified a portion of the DLPFC near Brodmann's area 10 (BA10) as a primary source of individual variability in task performance. In an fNIRS imaging study of healthy individuals performing a written DSST task, Nakahachi et al. (2008) reported that DSST performance was correlated with increased prefrontal [HbO] which occurred most prominently in the left-DLPFC region in the vicinity of Fp1. Although several other more lateral optodes closer to Brodmann's Area 46 (BA46) showed prominent increases in [HbO] during task execution, these areas did not correlate strongly with behavioral performance and appeared to respond quicker and earlier than performance-dependent regions. In the performance of a modified SDST during fMRI, Rympa et al. observed that increased activation in the left DLPFC region (BA9/46) was associated with increases of RT (Rypma et al., 2006) while on the other hand, increased activation in the ventroparietal regions tended to correspond with improved task performance. The authors suggested that increased DLPFC activation reflected additional effort during the retrieval of information, citing evidence from similar responses during delayed-response memory tasks (Rypma et al., 1999). In a more recent study, the Motes et al. (2018) investigated the effect of cognitive training and exercise training on elderly participants longitudinally using fMRI. Using the same paced symbol-digit task, the authors observed that while all groups improved their response time in the symbol-digit task, cognitive training was associated more strongly with reduced Left-PFC involvement and increased neural efficiency.

Other fMRI studies have suggested a role for the left-DLPFC in the encoding of consistent working-memory associations which may occur during the initial mapping of Symbol-Digit associations. In one work, examining similar mapping during novel and practiced sets of a Sternberg task, Jansma et al. (2013) reported that novel sets evoked more left-DLPFC activity. A role for left-DLPFC was further established by the interruption of cortical activity via a mid-task rTMS burst which reduced accurate identification of targets from novel, but not known sets, replicating prior research disrupting verbal memory (Osaka et al., 2007). Together, these studies suggest that while the DLPFC is active and necessary during encoding of Symbol-Digit associations, it becomes less involved when associations are learned and activity has been

redistributed to posterior and parietal regions. Higher prefrontal involvement during Symbol-Digit performance may therefore reflect an inefficiency of functional transfer which then impedes task performance. Functional connectivity between the DLPFC and the parietal cortex and ventral PFC regions can in this sense effectively describe the differences between slower and faster symbol-digit performance as a balance between executive oversight and automaticity. Although the parietal cortex and lateral PFC regions were not measured in this study, reductions in DLPFC activity observed in this study observed during task practice are consistent with a relaxation of executive control by the DLPFC and delegation of task-related cognition to other cortical regions in order to optimize task performance.

4.2. Effects of rTMS stimulation on SDST performance

The second part of this study evaluated the effects of short (7 min) rTMS trains applied to the left-DLPFC (F3 in 10–20 system) on the performance of the SDST and evoked prefrontal activities as measured by fNIRS. While the left-DLPFC region's involvement in working memory and executive function has been demonstrated through the use of rTMS interference during delay periods within tasks (Bilek et al., 2013; Osaka et al., 2007), rTMS can also be used to enhance or reduce cortical excitability in a manner which may improve task performance. Usage of TMS for the purposes of cognitive enhancement represents an important non-pharmaceutical avenue for addressing cognitive deficits caused by disease, ageing, injury, or even promote the normal function in healthy individuals.

The neural effects of rTMS depend on the specific stimulus parameters employed, such as the timing and intensity of each burst. When stimulating while an individual is at-rest (i.e. offline, participant not currently engaged in a particular cognitive activity), the effects of rTMS are thought to be caused by changing the cortical excitability of the targeted region along with potentially other regions which are functionally or structurally associated. In this study, rTMS was applied offline after the first half of the SDST trials in each session with one of four different stimulation types (Sham, SP, HF, and iTBS). The use of excitatory rTMS types such as high frequency stimulation and iTBS may be expected increase the excitability of the underlying cortical region and facilitate cortical processing (Luber and Lisanby, 2014; Viejo-Sobera et al., 2017). However, TMS may also offer improvements in cognitive function through nonspecific effects such as sensory input caused by induced muscle movements, vibrations of the coil and the clicking sound of the coil. To account for this, Single Pulses of TMS were used as an active sham-like stimulation method which would be expected to not affect cortical excitability. Additionally, sham stimulation was used to reproduce vibration and auditory effects of rTMS without any magnetically induced neural effects. While behavioral performance improvements were observed across all sessions, increases in performance were not significantly different between any of the four TMS paradigms. This suggests that the primary driver of performance improvement is the practice effect. Although, the use of iTBS has been reported to improve behavioral performance in working memory tasks (Viejo-Sobera et al., 2017), for the most part, improvements in such tasks have not been observed when using offline stimulation (Martin et al., 2017; Preston et al., 2010). In a meta-analysis of the effects of daily rTMS for cognition enhancement of patients with MDD, Martin et al. reported data from 8 studies that daily stimulation using High Frequency rTMS at 5, 10 and 20 Hz, had not shown any significant effects on DSST performance although authors employed significantly higher rTMS dosages than the current study (300 vs 1000 + pulses) (Martin et al., 2017).

Despite the absence of behavioral improvements attributable to rTMS stimulation, neural efficiency was observed to increase for each of the three non-sham TMS methods employed but increased most strongly for 15 Hz HF stimulation. Similar results have been reported in the application of 10 Hz HF stimulation prior to performance of an N-Back task. Preston et al. (2010) measured changes associated with 250 pulses rTMS applied to the left-DLPFC in healthy individuals and observed that neither active nor sham conditions affected accuracy on the task, but that active stimulation decreased RT during the task. Together the authors reported that behavioral neural efficiency (as a measure of Accuracy and RT) was accordingly increased and speculated that active rTMS may have reduced the demands originating from the DLPFC.

The enhancement of prefrontal neural efficiency through practice as observed in this study and other works may be critical to proper task learning, adaptation and associated processes, but a firm interpretation of the observed reduction in neural efficiency due to rTMS is not yet clear. Reduction in prefrontal demands following cortical facilitation by active rTMS may represent changes due to multiple avenues including nonspecific changes which may "prime" functional networks in which the DLPFC may play coordinating roles (Rounis et al., 2007). Although in this study, 15 Hz stimulation was observed to have the largest increase in neural efficiency, iTBS and SP stimulation both showed positive but smaller effect sizes. However, sham TMS did not show any change in neural efficiency. While iTBS may be expected to promote similar increases in cortical excitability as 15 Hz HF stimulation despite the subthreshold intensity used in iTBS (Cárdenas-Morales et al., 2010; Curtin et al., 2017), the relatively slow SP paradigm (1 pulse every 42 s) used here was not expected to have an impact. Future works may wish to explore methods to control for the presence of nonspecific effects by including additional control conditions which feature active, but excitability-neutral effects such as intermediate TBS (imTBS).

4.3. Limitations and future directions

The SDST implemented in this study varies in several ways from paper-and-pencil variants, as well as other symbol-digit tests which have been used to study SoP. First and foremost, the simplification introduced by task digitization and keypad entry of responses compared with the necessity of physically writing the matching symbol or digit substantially decreases the total response time and in the case of the DSST, this eliminates the necessity to draw simple but otherwise unfamiliar characters. The pen and paper variant may also allow the participant to use this writing time to match the next symbol whereas in a sequential presentation of symbols (as implemented in this task) prevents such multitasking as the participant has no knowledge of the next symbol.

The task used in this study remains comparable to other referenced implementations of digitized Symbol-Digit tasks and there is evidence that absence of a writing component in the digitized SDST may actually enhance the utility of such tasks by eliciting more specifically cognitive domains of interest. Cornelis et al. (2015) examined learning across 3 sessions in a digitized-written version of the task which did not randomize the key. In their study which examined the effects of SDST learning in patients with Schizophrenia, the elderly, and healthy controls, matching time (time to start of writing) decreased consistently in all groups across sessions while writing time itself remained constant with no additional effect of learning. While writing time did not change across sessions, writing speed deficits in the elderly and clinical group would certainly contribute to decreased overall SDST performance as this specific deficit can be attributed largely to lower-level sensorimotor speed decreases rather than higher-level perceptual and coding processes.

In a deconstruction of DSST task components, Joy et al. (2003) compared the paper DSST to a Symbol-Copy task in which participants were only required to copy a given symbol and identified that the Symbol-Copy task shared 35% of the variance in performance with the written Digit Symbol task. When the authors pooled their results with prior works, they estimated that this contribution might be as high as 50% variance in the DSST. The authors additionally evaluated a Symbol-Scan task and a Name Copy task which were designed to be largely perceptual and largely graphomotor functions respectively. The Name Copy task again accounted for ~50% variance of the Symbol Copy Task, whereas the Symbol Scan task did not correlate significantly with the Name Copy task at all, but did correlate with visual memory, verbal

recall, executive function in the Trail-Making Task and Digit-Symbol score. Although differences between the Symbol Copy and Name Copy task suggest that novel digit writing still involves some perceptual cognition, removal of the written portion of the Symbol-Digit tasks through a digitized SDST can be expected to future reduce differences related to purely sensorimotor processes and instead include contributions more strongly associated with rapid higher-order perceptual coding processes such as working memory and executive functions of interest.

Other limitations of this study include the fact that subjects who were recruited were all right-handed. The left-hemispheric position of significant channels observed in this study may partially be due to a dominance and it may be difficult to describe how stimulation of the left-hemisphere may affect individuals who do not match the studied population. TMS targeting used during rTMS stimulation was based on the 10–20 system rather than the 5 cm rule which is often employed as targeting F3 has been shown to more accurately identify the location of the DLPFC (Lefaucheur et al., 2014). Despite this, the use of anatomical imaging to perform neuronavigated stimulation may have further decreased inter-subject variability in response to stimulation. In this protocol, the minimum time between sessions was set as 1 h, however, in practice, this time averaged 3.4 h (SD 0.6). Evidence from previous rTMS studies has suggested that effects of cortical excitability introduced by rTMS may persist for times ranging from the length of stimulation (Robertson et al., 2003) to up to an hour (Wischnewski and Schutter, 2015). Together with randomized stimulation order and the relatively short pulse doses used in this study (<=300), the length of the washout period prescribed seemed appropriate. Additionally, choice of sham stimulation method represents an important difficulty in TMS studies and no ideal approach has yet been established, especially in within-subject design experiments (Loo et al., 2000). While a sham control was used in this study which replicated auditory and tactile effects of rTMS, real TMS is often associated with a tingling sensation which occurs due to stimulation of superficial nerves and muscles which may have introduced a confounding factor by further increasing subject arousal. Additionally, the subject size in this study, although conducted in a within-subject design, could be larger. Also, the smaller effect sizes observed due to rTMS may in part be explained by the use of multiple paradigms instead of a single rTMS protocol across sessions. Future studies may wish to expand these findings in larger subject groups, higher number of sessions, longer rTMS durations and explore applications in clinical populations.

Finally, the use of continuous-wave fNIRS as an imaging technique presents several challenges including potential influence of extracerebral blood-flow changes, inability to measure absolute concentrations of cortical biomarkers, and contributions from systemic physiological influences and motion artifacts (Ferrari and Quaresima, 2012). While the contribution of extracerebral sources was not investigated in this study, future works may include the use of short-separation detectors to allow for the removal of superficial skin contributions and improve the signal to noise ratio of the cortical hemodynamic measures (Gagnon et al., 2011). The sensor used in this study was designed specifically to measure cortical activation over a subject's forehead, having the effect of restricting functional imaging to the PFC. The relevance of other cortical areas to Symbol-Digit task function may be expected given the importance of balance between prefrontal and parietal regions in effective task performance. Future studies may wish to explore the functional relationship between these areas to better understand and inform future neurostimulation approaches to cognitive enhancement.

5. Conclusion

In this study, we confirmed that fNIRS, as a wearable and accessible neuroimaging modality is well suited to monitor cortical changes associated with learning and neurostimulation. Studies exploring the capability of rTMS to enhance cognition are only beginning to uncover the potential of such stimulation methods to improve and promote cognition. Enhancement of SoP, a cognitive domain impaired in a wide range of disorders, represents one such potential use of this technique. Here, we observed the presence of increased neural efficiency during adaptation to a Symbol-Digit task and the presence of additional increases of this efficiency after the application of active rTMS. Our results in this setting suggest that the benefits of rTMS as a cognitive enhancement strategy for SoP may be more nuanced and could instead be refined through different stimulation paradigms. In particular, this work highlights the importance of neuroimaging as an additional perspective to both understanding the dynamics of cognitive function and illuminating otherwise unseen effects of noninvasive brain stimulation on cortical activities.

Disclosure

fNIR Devices, LLC manufactures the optical brain imaging instrument and licensed IP and know-how from Drexel University. HA was involved in the technology development and thus offered a minor share in the startup firm fNIR Devices, LLC. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Andreasen, A.K., Spliid, P.E., Andersen, H., Jakobsen, J., 2010. Fatigue and processing speed are related in multiple sclerosis. Eur. J. Neurol. 17, 212–218. https://doi.org/10.1111/j.1468-1331.2009.02776.x.

Ayaz, H., Izzetoglu, M., Platek, S.M., Bunce, S., Izzetoglu, K., Pourrezaei, K., Onaral, B., 2006. Registering fNIR data to brain surface image using MRI templates. Conf. Proc. IEEE Eng. Med. Biol. Soc. 1, 2671–2674. https://doi.org/10.1109/IEMBS.2006.260835.

Ayaz, H., Izzetoglu, M., Shewokis, P. a, Onaral, B., 2010. Sliding-window motion artifact rejection for functional near-infrared spectroscopy. Conf. Proc. IEEE Eng. Med. Biol. Soc. 6567–6570. https://doi.org/10.1109/IEMBS.2010.5627113, 2010.

Ayaz, H., Onaral, B., Izzetoglu, K., Shewokis, P.A., McKendrick, R., Parasuraman, R., 2013. Continuous monitoring of brain dynamics with functional near infrared spectroscopy as a tool for neuroergonomic research: empirical examples and a technological development. Front. Hum. Neurosci. 7, 871. https://doi.org/10.3389/fnhum.2013.00871.

Ayaz, H., Shewokis, P.A., Bunce, S., Izzetoglu, K., Willems, B., Onaral, B., 2012. Optical brain monitoring for operator training and mental workload assessment. Neuroimage 59, 36–47. https://doi.org/10.1016/j.neuroimage.2011.06.023.

Ayaz, H., Shewokis, P.A., Curtin, A., Izzetoglu, M., Izzetoglu, K., Onaral, B., 2011. Using MazeSuite and functional near infrared spectroscopy to study learning in spatial navigation. J. Vis. Exp. https://doi.org/10.3791/3443.

Babiloni, C., Marzano, N., Infarinato, F., Iacoboni, M., Rizza, G., Aschieri, P., Cibelli, G., Soricelli, A., Eusebi, F., Del Percio, C., 2010. "Neural efficiency" of experts' brain during judgment of actions: a high-resolution EEG study in elite and amateur karate athletes. Behav. Brain Res. 207, 466–475. https://doi.org/10.1016/j.bbr.2009.10.034.

Bachman, P., Reichenberg, A., Rice, P., Woolsey, M., Chaves, O., Martinez, D., Maples, N., Velligan, D.I., Glahn, D.C., 2010. Deconstructing processing speed deficits in schizophrenia: application of a parametric digit symbol coding test. Schizophr. Res. 118, 6–11. https://doi.org/10.1016/j.schres.2010.02.1029.

Baddeley, A., 2003. Working memory: looking back and looking forward. Nat. Rev. Neurosci. 4, 829–839. https://doi.org/10.1038/nrn1201.

Ball, K.K., Ross, L.A., Roth, D.L., Edwards, J.D., 2013. Speed of processing training in the ACTIVE study: how much is needed and who benefits? J. Aging Health 25, 65S. https://doi.org/10.1177/0898264312470167.

Banich, M.T., 2009. Executive function - the search for an integrated account. Curr. Dir. Psychol. Sci. 18, 89–94.

Barker-Collo, S.L., 2006. Quality of life in multiple sclerosis: does information-processing speed have an independent effect? Arch. Clin. Neuropsychol. 21, 167–174. https://doi.org/10.1016/j.acn.2005.08.008.

Bartels, C., Wegrzyn, M., Wiedl, A., Ackermann, V., Ehrenreich, H., 2010. Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. BMC Neurosci. 11, 118. https://doi.org/10.1186/1471-2202-11-118, 1471-2202-11-118.

Bates, D., Mächler, M., Bolker, B., Walker, S., 2015. Fitting linear mixed-effects models using lme4. J. Stat. Softw. 67, 251–264. https://doi.org/10.18637/jss.v067.i01.

Bennett, I.J., Motes, M.A., Rao, N.K., Rypma, B., 2012. White matter tract integrity predicts visual search performance in young and older adults. Neurobiol. Aging 33. https://doi.org/10.1016/j.neurobiolaging.2011.02.001, 433.e21-433.e31.
Bilek, E., Schafer, A., Ochs, E., Esslinger, C., Zangl, M., Plichta, M.M., Braun, U., Kirsch, P., Schulze, T.G., Rietschel, M., Meyer-Lindenberg, A., Tost, H., 2013. Application of high-frequency repetitive transcranial magnetic stimulation to the DLPFC alters human prefrontal-hippocampal functional interaction. J. Neurosci. 33, 7050–7056. https://doi.org/10.1523/JNEUROSCI.3081-12.2013.
Biswal, B.B., Eldreth, D.A., Motes, M.A., Rypma, B., 2010. Task-dependent individual differences in prefrontal connectivity. Cerebr. Cortex 20, 2188–2197. https://doi.org/10.1093/cercor/bhp284.
Bostrom, N., Sandberg, A., 2009. Cognitive enhancement: methods, ethics, regulatory challenges. Sci. Eng. Ethics 15, 311–341. https://doi.org/10.1007/s11948-009-9142-5.
Brébion, G., Amador, X., Smith, M.J., Gorman, J.M., 1998. Memory impairment and schizophrenia: the role of processing speed. Schizophr. Res. 30, 31–39.
Brunoni, A.R., Vanderhasselt, M.-A., 2014. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cogn. 86, 1–9. https://doi.org/10.1016/j.bandc.2014.01.008.
Bryan, J., Luszcz, M.A., 1996. Speed of information processing as a mediator between age and free-recall performance. Psychol. Aging 11, 3–9. https://doi.org/10.1037//0882-7974.11.1.3.
Burgess, P.W., Gilbert, S.J., Dumontheil, I., 2007. Function and localization within rostral prefrontal cortex (area 10). Philos. Trans. R. Soc. Lond. B Biol. Sci. 362, 887–899. https://doi.org/10.1098/rstb.2007.2095.
Burke, C.J., Tobler, P.N., Baddeley, M., Schultz, W., 2010. Neural mechanisms of observational learning. Proc. Natl. Acad. Sci. Unit. States Am. 107, 14431–14436. https://doi.org/10.1073/pnas.1003111107.
Cabeza, R., Dennis, N. a, 2012. Principles of frontal lobe function. Princ. Front. Lobe Funct. 628–652. https://doi.org/10.1093/acprof:oso/9780195134971.001.0001.
Callicott, J.H., Mattay, V.S., Bertolino, a, Finn, K., Coppola, R., Frank, J. a, Goldberg, T.E., Weinberger, D.R., 1999. Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. Cerebr. Cortex 9, 20–26.
Cárdenas-Morales, L., Nowak, D.A., Kammer, T., Wolf, R.C., Schönfeldt-Lecuona, C., 2010. Mechanisms and applications of theta-burst rTMS on the human motor cortex. Brain Topogr. https://doi.org/10.1007/s10548-009-0084-7.
Causse, M., Chua, Z., Peysakhovich, V., Del Campo, N., Matton, N., 2017. Mental workload and neural efficiency quantified in the prefrontal cortex using fNIRS. Sci. Rep. 7, 1–15. https://doi.org/10.1038/s41598-017-05378-x.
Cornelis, C., De Picker, L.J., Hulstijn, W., Dumont, G., Timmers, M., Janssens, L., Sabbe, B.G.C., Morrens, M., 2015. Preserved learning during the symbol-digit substitution test in patients with schizophrenia, age-matched controls, and elderly. Front. Psychiatry 6, 1–9. https://doi.org/10.3389/fpsyt.2014.00189.
Cui, X., Bray, S., Bryant, D.M., Glover, G.H., Reiss, A.L., 2011. A quantitative comparison of NIRS and fMRI across multiple cognitive tasks. Neuroimage 54, 2808–2821. https://doi.org/10.1016/j.neuroimage.2010.10.069.
Curtin, A., Ayaz, H., 2019. Neural efficiency metrics in neuroergonomics. In: Ayaz, H., Dehais, F. (Eds.), Neuroergonomics. Elsevier, pp. 133–140. https://doi.org/10.1016/B978-0-12-811926-6.00022-1.
Curtin, A., Ayaz, H., 2018. The age of neuroergonomics: towards ubiquitous and continuous measurement of brain function with fNIRS. Jpn. Psychol. Res. 60, 374–386. https://doi.org/10.1111/jpr.12227.
Curtin, A., Sun, J., Ayaz, H., Qian, Z., Onaral, B., Wang, J., Tong, S., 2017. Evaluation of evoked responses to pulse-matched high frequency and intermittent theta burst transcranial magnetic stimulation using simultaneous functional near-infrared spectroscopy. Neurophotonics 4, 041405. https://doi.org/10.1117/1.NPh.4.4.041405.
Curtin, A., Tong, S., Sun, J., Wang, J., Onaral, B., Ayaz, H., 2019. A systematic review of integrated functional near-infrared spectroscopy (fNIRS) and transcranial magnetic stimulation (TMS) studies. Front. Neurosci. 13 https://doi.org/10.3389/fnins.2019.00084.
Curtis, C.E., D'Esposito, M., 2003. Persistent activity in the prefrontal cortex during working memory. Trends Cognit. Sci. 7, 415–423. https://doi.org/10.1016/S1364-6613(03)00197-9.
Dayan, E., Censor, N., Buch, E.R., Sandrini, M., Cohen, L.G., 2013. Noninvasive brain stimulation: from physiology to network dynamics and back. Nat. Neurosci. 16, 838–844. https://doi.org/10.1038/nn.3422.
Delpy, D.T., Cope, M., Vanderzee, P., Arridge, S., Wray, S., Wyatt, J., 1988. Estimation of optical pathlength through tissue from direct time of flight measurement. Phys. Med. Biol. 33, 1433–1442.
Di Domenico, S.I., Rodrigo, A.H., Ayaz, H., Fournier, M.A., Ruocco, A.C., 2015. Decision-making conflict and the neural efficiency hypothesis of intelligence: a functional near-infrared spectroscopy investigation. Neuroimage 109, 307–317. https://doi.org/10.1016/j.neuroimage.2015.01.039.
Dux, P.E., Tombu, M.N., Harrison, S., Rogers, B.P., Tong, F., Marois, R., 2009. Training improves multitasking performance by increasing the speed of information processing in human prefrontal cortex. Neuron 63, 127–138. https://doi.org/10.1016/j.neuron.2009.06.005.
Edwards, J.D., Hauser, R.A., O'Connor, M.L., Valdes, E.G., Zesiewicz, T.A., Uc, E.Y., 2013. Randomized trial of cognitive speed of processing training in Parkinson disease. Neurology 81, 1284–1290. https://doi.org/10.1212/WNL.0b013e3182a823ba.
Edwards, J.D., Wadley, V.G., Myers, R.S., Roenker, D.L., Cissell, G.M., Ball, K.K., 2002. Transfer of a speed of processing intervention to near and far cognitive functions. Gerontology 48, 329–340. https://doi.org/10.1159/000065259.
Ferrari, M., Quaresima, V., 2012. A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. Neuroimage 63, 921–935. https://doi.org/10.1016/j.neuroimage.2012.03.049.
Ferrer, E., Whitaker, K.J., Steele, J.S., Green, C.T., Wendelken, C., Bunge, S.A., 2013. White matter maturation supports the development of reasoning ability through its influence on processing speed. Dev. Sci. 6 https://doi.org/10.1111/desc.12088 n/a-n/a.
Fry, A.F., Hale, S., 1996. Fluid intelligence: evidence for a developmental cascade. Psychol. Sci. 7, 237–241.
Gagnon, L., Perdue, K., Greve, D.N., Goldenholz, D., Kaskhedikar, G., Boas, D. a, 2011. Improved recovery of the hemodynamic response in diffuse optical imaging using short optode separations and state-space modeling. Neuroimage 56, 1362–1371. https://doi.org/10.1016/j.neuroimage.2011.03.001.
Genovese, C.R., Lazar, N. a, Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 15, 870–878. https://doi.org/10.1006/nimg.2001.1037.
Gilbert, S.J., Spengler, S., Simons, J.S., Steele, J.D., Lawrie, S.M., Frith, C.D., Burgess, P.W., 2006. Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. J. Cogn. Neurosci. 18, 932–948. https://doi.org/10.1162/jocn.2006.18.6.932.
Gold, J.M., Queern, C., Iannone, V.N., Buchanan, R.W., 1999. Repeatable battery for the assessment of neuropsychological status as a screening test in schizophrenia, I: sensitivity, reliability, and validity. Am. J. Psychiatry 156, 1944–1950.
Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatry 153, 321–330.
Guse, B., Falkai, P., Wobrock, T., 2010. Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review. J. Neural Transm. 117, 105–122. https://doi.org/10.1007/s00702-009-0333-7.
Haier, R.J., Siegel, B.V., Nuechterlein, K.H., Hazlett, E., Wu, J.C., Paek, J., Browning, H.L., Buchsbaum, M.S., 1988. Correlates of abstract reasoning and attention studied with positron emission tomography. Intelligence 12, 199–217.
Haler, R.J., Siegel, B., Tang, C., Abel, L., Buchsbaum, M.S., 1992. Intelligence and changes in regional cerebral glucose metabolic rate following learning. Intelligence 16, 415–426. https://doi.org/10.1016/0160-2896(92)90018-M.
Henninger, D.E., Madden, D.J., Huettel, S.A., 2010. Processing speed and memory mediate age-related differences in decision making. Psychol. Aging 25, 262–270. https://doi.org/10.1037/a0019096.
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, 201–206. https://doi.org/10.1016/j.neuron.2004.12.033.
Jaeger, J., 2018. Digit symbol substitution test. J. Clin. Psychopharmacol. 38, 513–519. https://doi.org/10.1097/JCP.0000000000000941.
Jansma, J.M., Van Raalten, T.R., Boessen, R., Neggers, S.F.W., Jacobs, R.H.A.H., Kahn, R.S., Ramsey, N.F., 2013. fMRI guided rTMS evidence for reduced left prefrontal involvement after task practice. PLoS One 8, 1–12. https://doi.org/10.1371/journal.pone.0080256.
Jonides, J., 2004. How does practice makes perfect? Nat. Neurosci. 7, 10–11. https://doi.org/10.1038/nn0104-10.
Joy, S., Fein, D., Kaplan, E., 2003. Decoding digit symbol: speed, memory, and visual scanning. Assessment 10, 56–65. https://doi.org/10.1177/0095399702250335.
Kail, R., Salthouse, T.A., 1994. Processing speed as a mental capacity. Acta Psychol. 86, 199–225. https://doi.org/10.1016/0001-6918(94)00021-8.
Kail, R.V., Miller, C.A., 2006. Developmental change in processing speed: domain specificity and stability during childhood and adolescence. J. Cogn. Dev. 7, 119–137. https://doi.org/10.1207/s15327647jcd0701_6.
Knotkova, H., Nitsche, M.A., Bikson, M., Woods, A.J. (Eds.), 2019. Practical Guide to Transcranial Direct Current Stimulation. Springer International Publishing, Cham. https://doi.org/10.1007/978-3-319-95948-1.
Lefaucheur, J.-P., André-Obadia, N., Antal, A., Ayache, S.S., Baeken, C., Benninger, D.H., Cantello, R.M., Cincotta, M., de Carvalho, M., De Ridder, D., Devanne, H., Di Lazzaro, V., Filipović, S.R., Hummel, F.C., Jääskeläinen, S.K., Kimiskidis, V.K., Koch, G., Langguth, B., Nyffeler, T., Oliviero, A., Padberg, F., Poulet, E., Rossi, S., Rossini, P.M., Rothwell, J.C., Schönfeldt-Lecuona, C., Siebner, H.R., Slotema, C.W., Stagg, C.J., Valls-Sole, J., Ziemann, U., Paulus, W., Garcia-Larrea, L., 2014. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin. Neurophysiol. 125, 1–57. https://doi.org/10.1016/j.clinph.2014.05.021.
Lehman, A., Lieberman, J., Dixon, L., 2010. Practice guideline for treatment of patients with schizophrenia second edition. Am. J. Psychiatry. https://doi.org/10.1176/appi.books.9780890423363.45859.
Leskelä, M., Hietanen, M., Kalska, H., Ylikoski, R., Pohjasvaara, T., Mäntylä, R., Erkinjuntti, T., 1999. Executive functions and speed of mental processing in elderly patients with frontal or nonfrontal ischemic stroke. Eur. J. Neurol. 6, 653–661.
Liu, Y., Piazza, E.A., Simony, E., Shewokis, P.A., Onaral, B., Hasson, U., Ayaz, H., 2017. Measuring speaker–listener neural coupling with functional near infrared spectroscopy. Sci. Rep. 7, 43293. https://doi.org/10.1038/srep43293.
Loo, C.K., Taylor, J.L., Gandevia, S.C., McDarmont, B.N., Mitchell, P.B., Sachdev, P.S., 2000. Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some "sham" forms active? Biol. Psychiatry 47, 325–331. https://doi.org/10.1016/S0006-3223(99)00285-1.
Luber, B., Lisanby, S.H., 2014. Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). Neuroimage 85, 961–970. https://doi.org/10.1016/j.neuroimage.2013.06.007.
Martin, D.M., Mcclintock, S.M., Forster, J.J., Lo, T.Y., Loo, C.K., 2017. Cognitive enhancing effects of rTMS administered to the prefrontal cortex in patients with

depression: a systematic review and meta-analysis of individual task effects. Depress. Anxiety 1–11. https://doi.org/10.1002/da.22658.
Mattioli, F., Bellomi, F., Stampatori, C., Capra, R., Miniussi, C., 2016. Neuroenhancement through cognitive training and anodal tDCS in multiple sclerosis. Mult. Scler. 22, 222–230. https://doi.org/10.1177/1352458515587597.
McKendrick, R., Ayaz, H., Olmstead, R., Parasuraman, R., 2014. Enhancing dual-task performance with verbal and spatial working memory training: continuous monitoring of cerebral hemodynamics with NIRS. Neuroimage 85, 1014–1026. https://doi.org/10.1016/j.neuroimage.2013.05.103.
McKendrick, R., Parasuraman, R., Ayaz, H., 2015. Wearable functional near infrared spectroscopy (fNIRS) and transcranial direct current stimulation (tDCS): expanding vistas for neurocognitive augmentation. Front. Syst. Neurosci. 9, 1–14. https://doi.org/10.3389/fnsys.2015.00027.
McKendrick, R., Parasuraman, R., Murtza, R., Formwalt, A., Baccus, W., Paczynski, M., Ayaz, H., 2016. Into the wild: neuroergonomic differentiation of hand-held and augmented reality wearable displays during outdoor navigation with functional near infrared spectroscopy. Front. Hum. Neurosci. 10, 216. https://doi.org/10.3389/fnhum.2016.00216.
Motes, M.A., Yezhuvath, U.S., Aslan, S., Spence, J.S., Rypma, B., Chapman, S.B., 2018. Higher-order cognitive training effects on processing speed–related neural activity: a randomized trial. Neurobiol. Aging 62, 72–81. https://doi.org/10.1016/j.neurobiolaging.2017.10.003.
Nakahachi, T., Ishii, R., Iwase, M., Canuet, L., Takahashi, H., Kurimoto, R., Ikezawa, K., Azechi, M., Sekiyama, R., Honaga, E., Uchiumi, C., Iwakiri, M., Motomura, N., Takeda, M., 2008. Frontal activity during the digit symbol substitution test determined by multichannel near-infrared spectroscopy. Neuropsychobiology 57, 151–158. https://doi.org/10.1159/000147467.
Nebes, R.D., Butters, M.A., Mulsant, B.H., Pollock, B.G., Zmuda, M.D., Houck, P.R., Reynolds Iii, C.F., 2000. Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. Psychol. Med. 30, 679–691. https://doi.org/10.1017/S0033291799001968.
Neubauer, A.C., Fink, A., 2009. Intelligence and neural efficiency. Neurosci. Biobehav. Rev. 33, 1004–1023. https://doi.org/10.1016/j.neubiorev.2009.04.001.
Neubauer, A.C., Fink, A., 2009. Intelligence and neural efficiency: measures of brain activation versus measures of functional connectivity in the brain. Intelligence 37, 223–229. https://doi.org/10.1016/j.intell.2008.10.008.
O'Reilly, R.C., 2010. The what and How of prefrontal cortical organization. Trends Neurosci. 33, 355–361. https://doi.org/10.1016/j.tins.2010.05.002.
Ojeda, N., , et al.Sánchez, P., Peña, J., Elizagárate, E., Yoller, A.B., Gutiérrez-Fraile, M., Ezcurra, J., Napal, O., 2012. An explanatory model of quality of life in schizophrenia: the role of processing speed and negative symptoms. Actas Esp. Psiquiatr. 40, 10–18.
Osaka, N., Otsuka, Y., Hirose, N., Ikeda, T., Mima, T., Fukuyama, H., Osaka, M., 2007. Transcranial magnetic stimulation (TMS) applied to left dorsolateral prefrontal cortex disrupts verbal working memory performance in humans. Neurosci. Lett. 418, 232–235. https://doi.org/10.1016/j.neulet.2007.01.087.
Parasuraman, R., McKinley, R.A., 2014. Using noninvasive brain stimulation to accelerate learning and enhance human performance. Hum. Factors 56, 816–824. https://doi.org/10.1177/0018720814538815.
Pasqualotto, A., 2016. Transcranial random noise stimulation benefits arithmetic skills. Neurobiol. Learn. Mem. 133, 7–12. https://doi.org/10.1016/j.nlm.2016.05.004.
Pihlaja, R., Uimonen, J., Mustanoja, S., Tatlisumak, T., Poutiainen, E., 2014. Post-stroke fatigue is associated with impaired processing speed and memory functions in first-ever stroke patients. J. Psychosom. Res. 77, 380–384. https://doi.org/10.1016/j.jpsychores.2014.08.011.
Pinti, P., Aichelburg, C., Gilbert, S., Hamilton, A., Hirsch, J., Burgess, P., Tachtsidis, I., 2018. A review on the use of wearable functional near-infrared spectroscopy in naturalistic environments. Jpn. Psychol. Res. 60, 347–373. https://doi.org/10.1111/jpr.12206.
Plewnia, C., Schroeder, P.A., Kunze, R., Faehling, F., Wolkenstein, L., 2015. Keep calm and carry on: improved frustration tolerance and processing speed by transcranial direct current stimulation (tDCS). PLoS One 10, 1–12. https://doi.org/10.1371/journal.pone.0122578.
Preston, G., Anderson, E., Silva, C., Goldberg, T., Wassermann, E.M., 2010. Effects of 10 Hz rTMS on the neural efficiency of working memory. J. Cogn. Neurosci. 22, 447–456. https://doi.org/10.1162/jocn.2009.21209.
Pyle, W.H., 1913. The Examination of School Children: A Manual of Directions and Norms. The Macmillan Company, New York.
Ramnani, N., Owen, A.M., 2004. Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. Nat. Rev. Neurosci. 5, 184–194. https://doi.org/10.1038/nrn1343.
Robertson, E.M., Théoret, H., Pascual-Leone, A., 2003. Studies in cognition: the problems solved and created by transcranial magnetic stimulation. J. Cogn. Neurosci. 15, 948–960. https://doi.org/10.1162/089892903770007344.
Rodrigo, A.H., Domenico, S.I., Di, Ayaz, H., Gulrajani, S., Lam, J., Ruocco, A.C., 2014. Differentiating functions of the lateral and medial prefrontal cortex in motor response inhibition. Neuroimage 85, 423–431. https://doi.org/10.1016/j.neuroimage.2013.01.059.
Rounis, E., Yarrow, K., Rothwell, J.C., 2007. Effects of rTMS conditioning over the fronto-parietal network on motor versus visual attention. J. Cogn. Neurosci. 19, 513–524. https://doi.org/10.1162/jocn.2007.19.3.513.
Rypma, B., Berger, J.S., Prabhakaran, V., Martin Bly, B., Kimberg, D.Y., Biswal, B.B., D'Esposito, M., 2006. Neural correlates of cognitive efficiency. Neuroimage 33, 969–979. https://doi.org/10.1016/j.neuroimage.2006.05.065.
Rypma, B., Prabhakaran, V., Desmond, J.E., Glover, G.H., Gabrieli, J.D.E., 1999. Load-dependent role of frontal brain regions in the maintenance of working memory. Neuroimage 9, 216–226.
Sato, Y., Oishi, M., Fukuda, M., Fujii, Y., 2012. Hemodynamic and electrophysiological connectivity in the language system: simultaneous near-infrared spectroscopy and electrocorticography recordings during cortical stimulation. Brain Lang. 123, 64–67. https://doi.org/10.1016/j.bandl.2012.07.006.
Sayala, S., Sala, J.B., Courtney, S.M., 2006. Increased neural efficiency with repeated performance of a working memory task is information-type dependent. Cerebr. Cortex 16, 609–617. https://doi.org/10.1093/cercor/bhj007.
Shaw, E.E., Schultz, A.P., Sperling, R.A., Hedden, T., 2015. Functional connectivity in multiple cortical networks is associated with performance across cognitive domains in older adults. Brain Connect. 5, 505–516. https://doi.org/10.1089/brain.2014.0327.
Sheppard, L.D., Vernon, P.A., 2008. Intelligence and speed of information-processing: a review of 50 years of research. Pers. Indiv. Differ. 44, 535–551. https://doi.org/10.1016/j.paid.2007.09.015.
Simonsmeier, B.A., Grabner, R.H., Hein, J., Krenz, U., Schneider, M., 2018. Electrical brain stimulation (tES) improves learning more than performance: a meta-analysis. Neurosci. Biobehav. Rev. 84, 171–181. https://doi.org/10.1016/j.neubiorev.2017.11.001.
Smith, A., 1982. Symbol Digit Modalities Test: Manual. Wester Psychological Services, Los Angeles.
Spearman, C., 1904. " general intelligence ," objectively determined and measured. Am. J. Psychol. 15, 201–292.
Steinbrink, J., Villringer, A., Kempf, F., Haux, D., Boden, S., Obrig, H., 2006. Illuminating the BOLD signal: combined fMRI-fNIRS studies. Magn. Reson. Imaging 24, 495–505. https://doi.org/10.1016/j.mri.2005.12.034.
Strobach, T., Antonenko, D., 2017. tDCS-induced effects on executive functioning and their cognitive mechanisms: a review. J. Cogn. Enhanc. 1, 49–64. https://doi.org/10.1007/s41465-016-0004-1.
Stuss, D.T., Levine, B., 2002. Adult clinical neuropsychology: lessons from studies of the frontal lobes. Annu. Rev. Psychol. 53, 401–433. https://doi.org/10.1146/annurev.psych.53.100901.135220.
Sweet, L.H., Paskavitz, J.F., O'connor, M.J., Browndyke, J.N., Wellen, J.W., Cohen, R.A., 2005. FMRI correlates of the WAIS–III Symbol Search subtest. J. Int. Neuropsychol. Soc. 11, 471–476. https://doi.org/10.1017/S1355617705050575.
Takeuchi, H., Kawashima, R., 2012. Effects of processing speed training on cognitive functions and neural systems. Rev. Neurosci. 23, 289–301. https://doi.org/10.1515/revneuro-2012-0035.
Tuovinen, J.E., Paas, F., 2004. Exploring multidimensional approaches to the efficiency of instructional conditions. Instr. Sci. 32, 133–152. https://doi.org/10.1023/b:truc.0000021813.24669.62.
Valero-Cabré, A., Amengual, J., Stengel, C., Pascual-Leone, A., Coubard, O.A., 2017. Transcranial Magnetic Stimulation in basic and clinical neuroscience: a comprehensive review of fundamental principles and novel insights. Neurosci. Biobehav. Rev. 83, 381–404. https://doi.org/10.1016/j.neubiorev.2017.10.006.
Vernon, P.A., 1983. Speed of information processing and general intelligence. Intelligence 7, 53–70. https://doi.org/10.1016/0160-2896(83)90006-5.
Viejo-Sobera, R., Redolar-Ripoll, D., Boixadós, M., Palaus, M., Valero-Cabré, A., Marron, E.M., 2017. Impact of prefrontal theta burst stimulation on clinical neuropsychological tasks. Front. Neurosci. 11, 1–15. https://doi.org/10.3389/fnins.2017.00462.
Wechsler, D., 1981. WAIS-R Manual: Wechsler Adult Intelligence Scale-Revised.
Wischnewski, M., Schutter, D.J.L.G., 2015. Efficacy and time course of theta burst stimulation in healthy humans. Brain Stimul 8, 685–692. https://doi.org/10.1016/j.brs.2015.03.004.
Wolinsky, F.D., Unverzagt, F.W., Smith, D.M., Jones, R., Wright, E., Tennstedt, S.L., 2006. The effects of the ACTIVE cognitive training trial on clinically relevant declines in health-related quality of life. J. Gerontol. Ser. B Psychol. Sci. Soc. Sci. 61, S281–S287. https://doi.org/10.1093/geronb/61.5.S281.
Xu, Y., Qiu, Z., Tao, J., Chen, L., Zhu, J., Liu, J., Wu, J., 2019. The modulation effect of non-invasive brain stimulation on cognitive function in patients with mild cognitive impairment: a systematic review and meta-analysis of randomized controlled trials. BMC Neurosci. 20, 1–11. https://doi.org/10.1186/s12868-018-0484-2.
Yerkes, R.M. (Ed.), 1921. Psychological Examining in the United States Army. Government Printing Office, Washington DC.