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What is difficult for you can be easy for me.
Effects of increasing individual task demand on prefrontal lateralization: a tDCS study.

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Abstract

1
2 Neuroimaging studies suggest that increment of the cognitive load associated with a specific
3 task may induce the recruitment of a more bilateral brain network. In most studies, however,
4 task **demand** has been manipulated in a static and pre-specified way, regardless of individual
5 cognitive resources.
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9 Here we implemented a new paradigm based on a pre-experimental assessment to set up
10 **subject-specific** levels of task demand and applied tDCS (transcranial direct current
11 stimulation) to assess each hemisphere involvement in task performance.
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14 24 young participants performed a digit span backward (DSB, complex cognitive function)
15 and a paced finger tapping task (pFT, basic motor function) at 3 levels of **subject-specific**
16 **task demand** ("low" 5/5 correct answers, "medium" 3/5, "high" 1/5). Anodal tDCS (20 min,
17 1.5 mA) was delivered through a target electrode (5x5cm) positioned to stimulate both the
18 inferior frontal gyrus and the primary motor area over left and right hemisphere and in sham
19 condition in three different days.
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25 A 3 (left, right, sham) x 3 (low, medium, high) mixed-model with random intercepts for
26 subjects was run with R software.
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29 As expected, in both tasks accuracy decreased with the increment of **subject-specific** task
30 demand. Moreover, a significant interaction between type of stimulation and **subject-specific**
31 task demand was found for the reaction times recorded during the DSB and for the accuracy
32 in the pFT: for the most demanding conditions, right anodal tDCS significantly interfered
33 with behavioral performance.
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38 Our results suggest that hemispheric lateralization is modulated by the **subject-specific** level
39 of task demand and this modulation is not task-specific.
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45 **Keywords:** **subject-specific** task demand, individual differences, functional lateralization,
46 tDCS.
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Working definitions of key concepts/glossary

Task demand: the concept of difficulty could seem trivial in the everyday life, but the lack of a shared and unambiguous definition has led researchers to conceive this construct in different ways.

An attempt to give a comprehensive classification of difficulty came from the field of motor learning, in which Guadagnoli & Lee (2004) distinguished between *Nominal* and *Functional* difficulty. *Nominal* difficulty refers to the absolute constraints of the task based on task features and on the effort that is necessary to be performed, while *Functional* difficulty refers to the challenges associated with the task when performed in specific conditions and with the performer's characteristics and abilities.

Similarly, in the present paper we distinguish between *objective* and **subject-specific task demand**. **Objective task demand** is fixed across participants and set by the experimenter in an a-priori way, regardless of participant intra-individual differences. **Subject-specific task demand** is built on the basis of individual performance. This latter is assessed before the experimental test session within the same task. In our theoretical framework, we assume the existence of an analogy between subject-specific task-demand and subject-specific difficulty.

Cognitive load: multidimensional construct representing the load that performing a particular task imposes on the learner's cognitive system (Paas & van Merriënboer, 1994). Cognitive load is determined by task characteristics, such as novelty, task complexity, time pressure etc., by the specific characteristics of the subject that is performing the task, such as expertise level and age, or by the interactions between both these factors.

Cognitive level of tasks: traditionally cognitive science has distinguished between higher and lower cognitive functions: low processes are said to be automatic and based on routines and scripts, while higher order processes typically contain a novel element and require

controlled strategic or executive processes (Shallice, 1988). Higher cognitive functions are also known as “executive functions” and are considered to be associated with the coordination of different processes to accomplish a particular goal in a flexible manner (Roberts et al., 1998).

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Introduction

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2 Although it is a common experience that walking on a paved road is easier than amble across
3 a tightrope, defining in what sense these two actions are differently difficult is more
4 complicated.
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7 Cognitive processes are defined by limited attentional resources (Kahneman, 1973; Craik &
8 Byrd, 1982) and working memory (WM) capacity; this latter, by definition, has the main
9 function to maintain and manipulate information online while performing a task (Baddeley &
10 Hitch, 1974; Baddeley, 2003).
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13 Many authors tried to investigate these limits and how our brain responds to challenging
14 requests provided by either ecological, or experimental conditions in which task **difficulty**
15 was manipulated. The idea of difficulty could seem trivial in the everyday use of the term, but
16 the lack of a shared definition has led researchers to approach this construct in different ways.
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18 The result is that at the operational level there is no consensus on what difficulty is and how it
19 should be **experimentally** manipulated, **especially in terms of task demand**.
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22 One of the possible strategies to manipulate task **demand** concerns the cognitive level of the
23 task (see the glossary for a definition): cognitive science distinguished between high and low
24 level cognitive functions. Low processes are generally described as automatic and based on
25 routines and scripts, while higher order processes typically contain a novel element and
26 require controlled strategic or executive processes (Shallice, 1988).
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29 If we consider cognitive resources, the employment of tasks belonging to different cognitive
30 domains is an experimental procedure typically adopted to manipulate *objective* task
31 **demand**. This methodological approach is based on the assumption that a specific task (for
32 example a WM task) might need more resources to be performed at an adequate behavioural
33 level than another (for example, a simple motor task). For example, Cabeza and colleagues
34 (2002) administered a source memory task and an episodic memory task to participants
35 during PET scanning to account for task load effect, **according to the** classical level of
36 processing assumption (Craik & Lockhart, 1972). In the category of “*objective* task **demand**
37 manipulation”, for example, we can also add those studies that explored the neurofunctional
38 patterns associated with the processing of syntactic **structures of different complexity**
39 (Meltzer et al., 2009; Newman et al., 2010). It is well known, indeed, that processing a simple
40 active sentence is “*objectively*” less **demanding** than processing a sentence including a
41 relative clause, **as this latter contains** a dependency between two discontinuous positions,
42 **which drives to a computational burden** (Grodner & Gibson, 2005).
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Another way to manipulate task **demand** is engaging people in one or more concurrent tasks (i.e. to adopt a classical dual-task paradigm) and comparing their performance with the one obtained in a single task condition (see Rice et al., 2012; **Nijboer et al., 2014**). In this case the *objective* **task demand** is associated with a competition between different processes and it is manipulated by varying the overlap degree of the employed resources.

A third possible way to manipulate task **demand** in an *objective* way is to change the cognitive load by varying only one parameter that characterizes the task, such as the number of items to be maintained in WM (Cappell et al., 2010; Mattay et al., 2006; Prakash et al., 2012), the degradation rate of visual stimuli (Grady et al., 1996), the sentence length in linguistic comprehension tasks (Papagno et al., 2007; Romero Lauro et al., 2010).

Despite the kind of manipulation imposed by authors, there is a general agreement for what concerns the task performance: as the level of task demand increases, the participants' performance decreases (Rice et al., 2012).

Neuroimaging studies also suggested a direct correlation between task-demand and blood oxygenation level dependent (BOLD) responses in healthy subjects (Berlingeri et al., 2013). In this regard Reuter-Lorenz and colleagues (1999) proposed that information processing resources can be theorized as neural units with a limited processing capacity. The complexity of the task may hence determine the extent of capacity required to accomplish it. Consequently, a more complex task should require more neural units, while less demanding conditions necessitate of fewer neural units.

Recently this idea has been implemented in two neurocognitive models that clearly account for task difficulty as a key factor for explaining changes in brain activations: **the CRUNCH and the STAC model.**

The CRUNCH model (*Compensation-related utilization of neural circuits hypothesis*, Reuter-Lorenz & Cappell, 2008) suggests that older adults engage more neural circuits at lower task demand compared to younger; as a consequence, this neurofunctional dynamic would be associated with less focal activations in older adults. However, as task demand increases, also younger adults may show either an overactivation, or a bilateral pattern, to suggest that their brain is “*working harder*” to face the new task demand (Cappell et al., 2010; Mattay et al., 2006; Schneider-Garces et al., 2010). The recruitment of additional neural resources seems to be linear until the reaching of a “resource ceiling” that is followed by a decrease of both performance and brain activations; this pattern of results can be pictured by an inverted-U curve (Nyberg et al., 2009; Schneider–Garces et al., 2010). Interestingly, the *plateau level* could be different from a person to another, depending on the

so-called inter-individual “neural reserve” (Stern 2009), namely the variability that leads to process information more efficiently and with greater capacity.

From the evidence described so far, it is clear that in the neurofunctional literature the recruitment of additional neural networks to face the increasing of task demand are typically associated with the concept of compensation. In this regard, the CRUNCH model postulates that neurofunctional signatures of compensatory processes may be detectable also in younger people, not only during the old-age. However, the most comprehensive neurocognitive model capable of merge the concept of compensation with the age-related changes across the entire life-span and the concept of task demand is the STAC model (*Scaffolding Theory of Aging and Cognition*, Park & Reuter Lorenz, 2009). This model employs the metaphor of scaffolding to indicate brain’s lifelong ability to recruit complementary and alternative neural circuits to reach a specific cognitive goal.

The key idea of STAC is that neurofunctional compensation is not a process that begins in older age, but it is present from childhood throughout the lifespan supporting, for example, the acquisition of new cognitive skills, on the one hand, and the possibility of facing challenging conditions, on the other hand (Petersen et al., 1998; Church et al., 2008).

Despite these models offer a possible explanation on how brain responds to the increase of task demand, it is still unclear which brain regions are implicated in this process. Neuroimaging studies suggested either an increased activation of the same brain regions usually activated by the task (Carlson et al., 1998; Jonides et al., 1997; Gould et al., 2003; Love et al., 2006), or the recruitment of additional areas (Dräger et al., 2004; Grady et al., 1996), in particular of homologous contralateral brain regions (Helton et al., 2010); other studies suggest, instead, the co-occurrence of both these patterns (Cappell et al., 2010; Just et al., 1996).

Although the conceptualization of task demand in terms of “recruitment of the contralateral homologue brain region” may seem simplistic, there is a number of empirical evidence hailing from both classical experimental psychology and neuroimaging studies to support this view. For example, visual field studies manipulating unilateral versus bilateral hemispheric engagement in task performance provided evidence of the benefits from engaging both hemispheres as task complexity increases (e.g. Guzzetti & Daini, 2014). This shift to bilateral activation could be coordinated by increased interhemispheric communication: a simple task could be performed by one hemisphere whereas a complex task would require the collaboration of both hemispheres (Banich, 1998; Luck et al., 1994; Scalf et al., 2007, 2009).

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Further, older adults exhibit greater bilateral activation compared to younger adults and this reduction in asymmetries has been suggested to reflect a compensation mechanism for decreased processing capacity due to aging (Cabeza et al., 2002).

It is worth noting that the conceptualization of compensatory processes as described by the CRUNCH (Reuter-Lorenz & Cappell, 2008) and the STAC (Park & Reuter Lorenz, 2009) models inevitably challenges the results of those studies that adopted an “objective” definition of task **demand**. According to these two models, the **subject-specific** level of cognitive and neural resources is something that cannot be neglected when dealing with the study of compensation and with the effect of task demand. This is to say that an *a priori* definition of the level of task **demand** may make the results of neuroimaging studies difficult to be interpreted, especially when the link between **the level of task demand** and neural units must be drawn. Indeed, these models stress the role of subject-specific characteristics, as what is “difficult” for a specific subject, may not be so challenging for another. Accordingly, assuming that a certain experimental condition is harder than another, leads to the risk of analyzing as a homogeneous group subjects that differently respond to a specific level of *objective* task **demand**. An *a priori* assumption, in which **task demand** levels remain fixed and static across participants, might be then weak: it is possible that different subjects might perceive load manipulation in different manners, with a consequent different urge for the employment of neural units supporting performance.

Reverberi et al. (2005) offered a critical example of how *a priori* expectations based on an estimation of the involved resources could be misleading: in a particular condition of a matchstick arithmetic task (in which the correct response was a tautology), patients with focal damage of dorsolateral prefrontal cortex (DLPFC) performed significantly better than the healthy control group, as patients were not sensitive to the “constraints” (Knoblich et al., 1999) that bound the responses of healthy subjects.

Sometimes, instead, the definition of task demand is given *a posteriori*, once the participant’s performance has been proved to be affected by a particular experimental condition. This, in turn, makes the definition circular. In an fMRI study of Vannini and colleagues (2004), **for example**, the reaction time (RT) patterns observed in the different conditions were correlated to brain activity to account for a difficulty effect in the superior parietal lobe, **under the assumption** that higher RTs corresponded to higher level of task demand.

To account for task difficulty without adopting an *a priori* assumption and taking into consideration subjects’ variability in cognitive resources and abilities, the best solution seems to be setting the **level of task demand** in an individual way for each subject.

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Actually, only few works tried to investigate brain activation by comparing subjects on subjectively equivalent cognitive load¹.

In an fMRI study (Sunaert et al., 2000) subjects had to make speed judgements by comparing random dots movement in a reference visual scene (moving 6 degrees per second) with five target scenes. Target conditions were built in order to allow each subject to reach – respectively- the 62, 74, 84, 90 and 95% of accuracy. Schneider-Garces et al. (2010), instead, proposed to account for individual differences by deriving a measure of individual WM span directly from the performance obtained within the Sternberg task: brain activity was considered as a function of the amount of information processed by each subject, with respect to his own memory span (a similar procedure was also used by Todd & Marois, 2005). They found two very different results: when all memory load conditions were combined together greater left hemisphere activations were observed, while when memory conditions were contrasted by using individual memory span, a bilateral recruitment was evident at high cognitive loads even for the younger group.

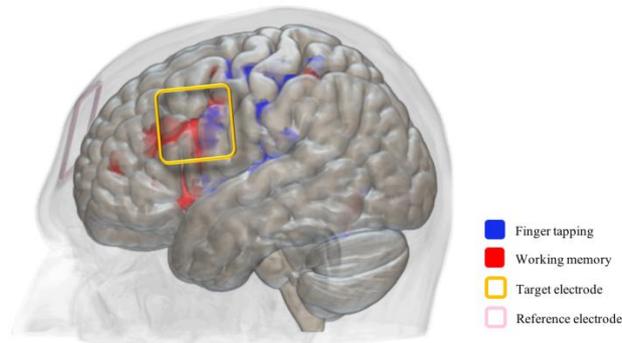
In the light of the evidence described so far, we developed an experimental paradigm capable of defining the level of task demand in a **subject-specific** manner, thus overtaking the limitations associated with an *a priori* definition of “*objective* task **demand**”. Moreover, by doing so, we were able to evaluate to what extent the behavioural performance can be supported and maintained at an optimal level also in relatively demanding conditions by the activation of bilateral brain regions. To this aim, we applied transcranial direct current stimulation (tDCS) over prefrontal (PFC) and motor cortex while participants were performing two different tasks, namely a digit backward task (DSB) and an externally paced finger-tapping task (pFT) at three different levels of **subject-specific task demand**.

DSB and pFT have been chosen because both show a left hemisphere specialization, but involve different cognitive functions. DSB involves repeating a series of digits of increasing length in reverse order². This task requires holding the digits in verbal short-term memory and performing a mental manipulation on them (Anderson & Grady, 2001; Halpern et al., 2003; Hedden & Gabrieli, 2004) in an un-paced condition (Dobbs & Rule, 1989). Finger tapping tasks involve simple motor coordination and are used for testing both normal control

¹ Here we do not consider “subjectively equivalent cognitive load” in terms of equivalence in the self-reported difficulty towards a given task, but rather the equivalence of behavioral outcome within the same task.

² Previous studies (Paulesu et al., 1993; Petersen et al., 1988; Romero Lauro et al., 2006) suggested that verbal rehearsal activated typically left inferior frontal gyrus.

1 participants and subjects with neural diseases affecting the motor system³. Finger tapping
2 tasks present a series of “methodological” advantages as they can be easily and flexibly
3 designed and modified to manipulate task difficulty (Witt et al., 2008).
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22 **Figure 1:** Results from [Neurosynth.org](https://neurosynth.org) (Yarkoni et al., 2011) for the research terms “wm” (red) and “finger
23 tapping” (blue). The automated meta-analyses were run respectively on 275 and 60 studies (forward inference
24 only), with a statistical threshold of 0.01 FDR-corrected. The rectangles show the positioning of the electrodes
25 for the left stimulation condition.
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28 By means of this experimental tasks we aimed at addressing a number of issues associated
29 with the concept of task **demand** and with its neurofunctional counterpart. First of all, we
30 wanted to test the feasibility of our subject-**specific** manipulation of task demand. Second, by
31 applying tDCS over both right and left hemisphere, we wanted to explore whether the
32 stimulation of the left or right PFC may contribute to the maintenance of an adequate level of
33 performance and whether this effect may be moderated by the subject-**specific** level of task
34 **demand**. Lastly, by using two different types of task, we tried to disentangle whether the
35 compensatory mechanism associated with the stimulation of the PFC can occur only in the
36 case of higher cognitive functions, such as WM, or also in the case of lower level cognitive
37 functions, such as motor planning, according to the distinction made by Cabeza (2002).
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57 ³ Previous neuroimaging studies suggested that simple repetitive finger movements involve contralateral
58 primary sensorimotor and premotor cortex, supplementary motor area and ipsilateral cerebellum (Roland et
59 al., 1980; Fox et al., 1985; Hutchinson et al., 2002).
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Materials and methods

Participants

Eighteen (9 male; mean age= 22 ± 2.96; educational level=13.8 ± 1.55) healthy participants were recruited for the pilot study, while twenty-four healthy participants (10 male and 14 female; mean age= 21.83 ± 1.46; educational level=13.6 ± 1.24) took part in the experimental study. Participants were right-handed according to Edinburgh Handedness Inventory (Oldfield, 1971) with a mean laterality coefficient of 0.77 (range 0.6-1).

All participants were Italian native speakers and were naïve to the experimental procedure. The study was approved by the local Ethical Committee (protocol number: 163) and it was carried out in accordance with the ethical standards of the revised Helsinki Declaration.

Experimental tasks

Participants performed two experimental tasks: a verbal WM task, namely DSB, and a simple motor task, namely pFT. Both tasks were performed on a pc with E-prime software 1.2 (Psychology Software Tools Inc., Pittsburgh, PA).

In the DSB, subjects listened to recorded number sequences with increasing series of digits (3 to 9). Subjects were instructed to repeat each sequence backwards through a microphone connected to a response-box to record the reaction times. The experimenter pressed “1” for correct answers or “0” for wrong answers. Participants sat with the pc monitor behind their back, so they could not see the keys pressed by the experimenter, thus they were not receiving any feedback about their performance.

In the pFT we used a simple version of a tapping task in which subjects had to press five keys on the keyboard that were chosen on the basis of a natural hand position (“X-5-6-7-I”, Italian keyboard). The target keys were covered by disks of rough material to be easily distinguished from the others. For each sequence, participants had to tap from thumb to little finger and back, twice. To manipulate task demand, we used a paced version of the pFT: auditory stimuli, produced by a metronome, were used to manipulate the task demand by increasing the rate. Participants started at 1 Hz and every 5 trials the rhythm increase of 0.5 Hz up to 7 Hz. At every pace increment subjects listened to the rhythm before performing the task.

The tapping accuracy was calculated in order to measure each subject’s adherence to the superimposed rhythm: participants could press the selected key during the sound presentation (14 ms) or in a temporal range, before or after the sound constrained by each trial’s pace.

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2 To calculate the temporal range we first converted frequency units from hertz to milliseconds,
3 then we applied the following formula

$$4 \quad \text{Temporal range} = (\text{ms} - \text{sound presentation})/2$$

5 For example, when the rhythm was 1 Hz (1000 ms), participants could press the key 493 ms
6 before the sound, during the 14 ms of the sound or 493 ms after.
7

8 Accurate performance thus required not only pressing the correct key sequence but also
9 pressing each keys at the right timing.
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12 *Pre-experimental and experimental procedure*

13 During the pre-experimental session, each participant performed the DSB and the pFT in
14 order to identify the subject-specific levels of task demand for each task.
15

16 The two tasks were organized in mini-blocks. Each mini-block corresponded to 5 trials with a
17 specific demand. For example, in the DSB there were 5 trials with 3 digits to be maintained
18 in the WM, 5 trials with 4 digits and so on. In the pFT there were 5 trials to be performed at 1
19 Hz, 5 trials at 1.5 Hz and so on.
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22 Participants executed the two tasks starting from the lower level of task demand to the level
23 at which they were no longer able to perform any trial correctly. This procedure allowed us to
24 obtain a complete spectrum of the subject-specific performance and to use it to determine,
25 for each participant, three different levels of subject-specific task demand: low, medium and
26 high, as follows:
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- 28 1) Low subject-specific task demand, which corresponded to the level at which each
29 participant made 5 correct answers out of 5;
- 30 2) Medium subject-specific task demand, i.e the level at which the participant correctly
31 performed 3 trials out of 5;
- 32 3) High subject-specific task demand, which corresponded 1 correct answer out of 5.

33 Once the three levels of subject-specific task demand were determined, participants
34 performed the experimental DSB and pFT tasks while stimulated by sham only (pilot study)
35 or anodal and sham (main experiment) tDCS. In the experimental session, 15 trials for each
36 of the subject-specific levels were administered and the order of the two tasks and of the
37 three subject-specific task demand was counterbalanced between participants.
38

39 For the DSB task, both accuracy and reaction times (RTs) were calculated, while for the pFT
40 only the accuracy was considered, since RTs were directly manipulated in the experimental
41 design: the faster the rhythm of the metronome, the faster the participants' responses.
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Pilot experiment

Before the main experiment we ran a pilot experiment to check the effectiveness of our approach of setting **subject-specific** levels of **task demand** to manipulate task **difficulty**. 18 healthy right-handed subjects participated. After the pre-experimental session, participants underwent one single experimental session with a placebo stimulation. Anode was placed on either the left or right PFC cortex and the cathode was placed on the supraorbital contralateral area. tDCS turned off automatically after 30 seconds from the beginning of the stimulation.

Analyses were performed in the statistical programming environment R (R Development Core Team, 2008): the accuracy dichotomous variable of both tasks was analysed using general mixed effects models (Baayen et al., 2008), fitted using the GLMER function of the lme4 package (Bates, Maechler, Bolker, Walker, 2015).

«**Subject-specific** task demand» (factorial, 3 levels: low, medium, high) was entered into the model as fixed factor. Concerning the random effect structure, a by-subjects random intercept was included to account for participant-specific variability. For the pFT task a nested random structure was preferred in order to take into account also the effect of sequences, i.e. in the pFT each trial was actually composed by a sequence of key-presses, as a consequence the random effect was computed to obtain a subject-by-sequence structure.

Significant effects were explored using the R package “phia” (De Rosario – Martinez, 2015) applying FDR correction for multiple comparisons.

In the DSB data from one participant were eliminated because of a program failure during the experiment.

Results showed that the expected linear trend indicating that for both tasks our manipulation of **subject-specific** task demand was effective: performance linearly decreased as task demand increased.

Particularly, in DSB the effect of **subject-specific** task demand was significant ($\chi^2_{(2)} = 148.12$, $p < .001$): participants made more errors in the medium compared to the low condition ($\chi^2_{(1)} = 37.22$, $p < .001$) and in the high compared to the low ($\chi^2_{(1)} = 140.98$, $p < .001$) and medium condition ($\chi^2_{(1)} = 60.88$, $p < .001$).

In the pFT the effect of **subject-specific** task demand was significant ($\chi^2_{(2)} = 581.55$, $p < .001$) with more errors for the high level compared to the low ($\chi^2_{(1)} = 572.57$, $p < .001$) and medium ones ($\chi^2_{(1)} = 144.44$, $p < .001$) and for the medium compared to the low ($\chi^2_{(1)} = 180.27$, $p < .001$).

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These empirical evidence suggest that at baseline the experimental settings and the designed experimental conditions are suitable to detect differential effects associated with the preliminary evaluation and setting of **subject-specific** task demand.

Here it is worthy to remember that we did not aim at studying the effect of tDCS in moderating task-performance, as the only condition was the sham one. Rather we aimed at testing the experimental paradigm, namely whether the preliminary identification of **subject-specific** cognitive load could be an effective and reliable approach to manipulate the level of **subject-specific task demand** (i.e. subject-specific **difficulty**).

Main experiment

tDCS procedure

TDCS is a non-invasive neuromodulatory technique that uses a weak constant direct current to modify the spontaneous firing rate of neurons in a polarity-dependent way: anodal tDCS depolarizes membrane potential, while cathodal tDCS reduces it (Bindman et al., 1964; Purpura & McMurtry, 1965).

Anodal tDCS has been reported to affect performance of healthy subjects in a broad range of cognitive, motor and perceptive domains such as WM (Fregni et al., 2005), attention (for a recent review see Reteig et al., 2017), linguistic abilities such as verbal fluency and sentence comprehension (Pisoni et al., 2017; Giustolisi et al., *in press*), motor learning (Reis et al., 2009).

In our experiment participants received three tDCS sessions on three different days, with an intersession interval of 48 hours to avoid long-lasting after-effects of the stimulation (Nitsche et al., 2008): two real sessions (one with the anode placed on the right hemisphere, one on the homologue area of the left hemisphere) and a sham/placebo condition.

tDCS was delivered by a BrainSTIM stimulator (EMS) through 2 electrodes: the anode was placed over the PFC of either the left or right hemisphere, while the cathode was placed over the contralateral supraorbital area (see Figure 2 for electrode montage and the simulated tDCS-induced electrical field distribution). To find the optimal site of stimulation we used a frameless stereotactic neuronavigation system (Nextim Ltd., Helsinki, Finland) on three individual MRIs and we chose the optimal position for the anode, such to simultaneously stimulate the primary motor cortex and the inferior frontal gyrus, corresponding to FC3 (left PFC) and FC4 (right PFC) positions according to the international 10-20 system for electroencephalogram (EEG) electrode placement.

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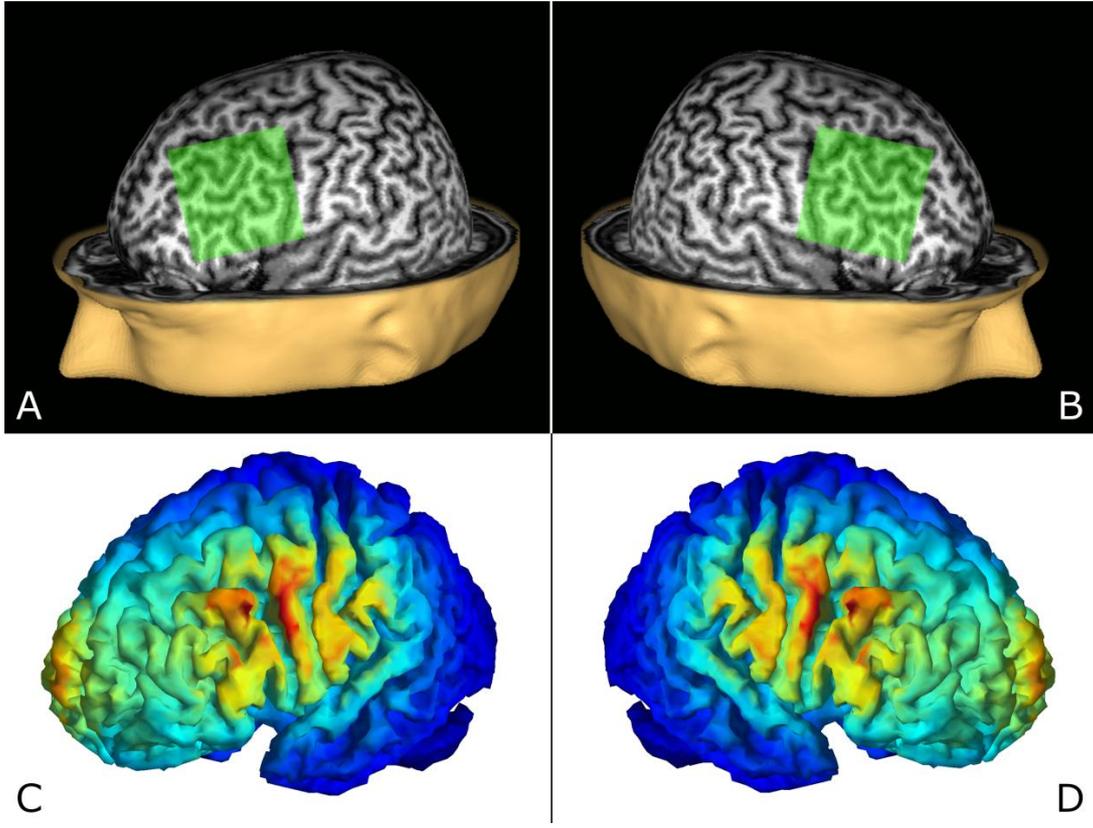


Figure 2 shows electrode montage over left (A) and right (B) prefrontal cortices and the simulated tDCS-induced electrical field distribution for each hemisphere (C & D).

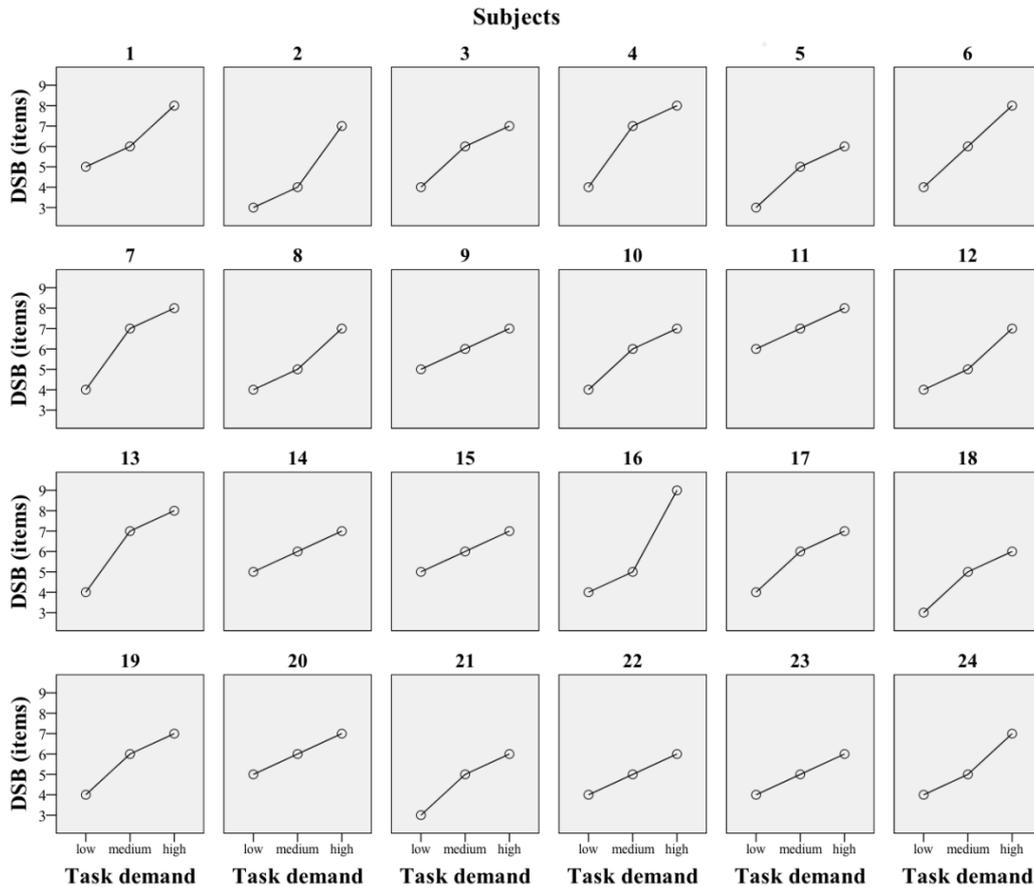
In the two real conditions tDCS was delivered for 20 minutes at 1.5 mA; the anode was 25 cm², whereas the cathode was 35cm², in order to increase the focality of the stimulation (Nitsche et al., 2008). In the sham condition half of the participants received the placebo stimulation over the left hemisphere and the other half over the right. In order to give the same skin sensations of real tDCS, the stimulator was on at the beginning and then turned off automatically after 30 seconds, as consequence participants were unable to distinguish between real and sham stimulation (Gandiga et al., 2006).

Each participant completed the Adult Safety Screening Questionnaire (Keel et al., 2001) and gave informed written consent prior to study procedures. Participants with any contraindication, such as brain injury or surgery, heart attack or stroke and use of medications known to alter cortical excitability (e.g., anti-depressant medication), were excluded (Rossi et al., 2009).

Pre-experimental and experimental procedure

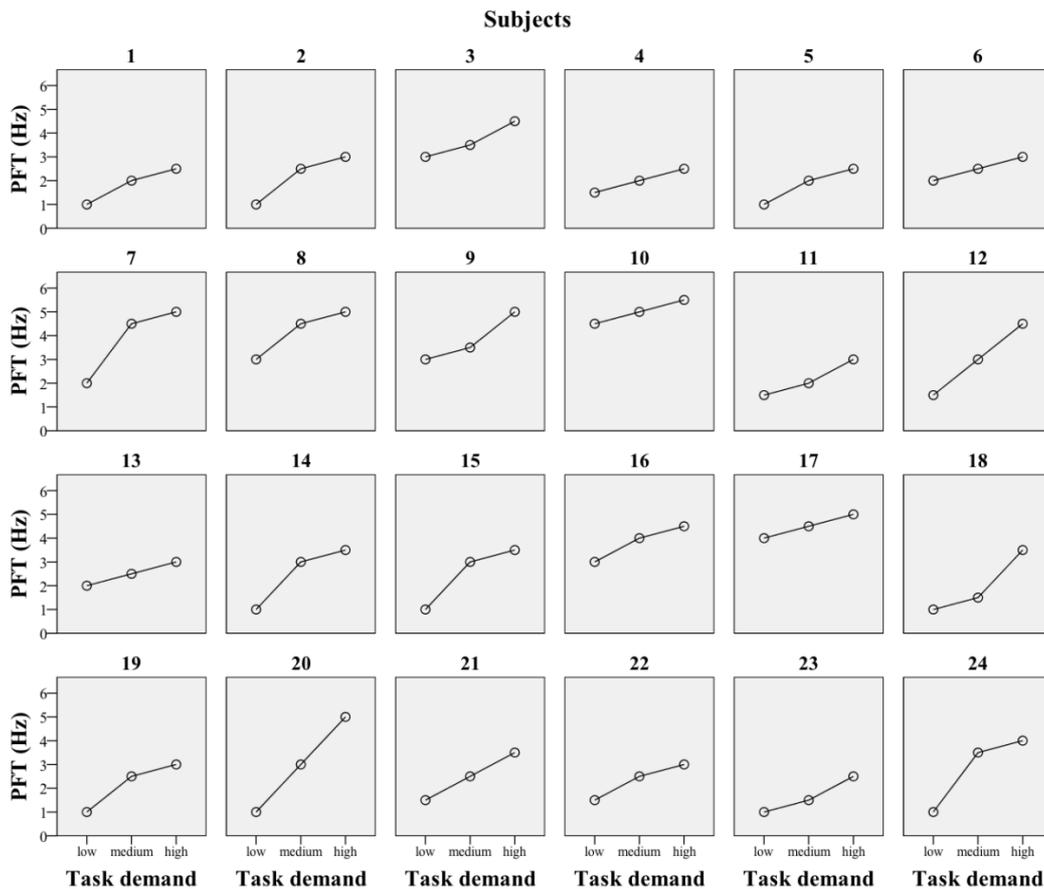
The first day participants performed the pre-experimental tasks in order to allow us to define the three different levels of **subject-specific task demand**.

Graphs 1 and 2 represent the distribution of the three level of subject-specific cognitive load in the entire sample for the DBT and the pFT respectively.



Graph 1 shows Cognitive load spectrum for each participant in DSB. Dots represent the number of digits that corresponds to the three **task demand** conditions.

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Graph 2 shows Cognitive load spectrum for each participant in pFT. Dots represent the frequency rate at which participants performed the three task demand conditions.

Once the three levels of subject-specific task demand were determined, participants performed the experimental tasks while stimulated by tDCS. The order of the three subject-specific task demand was counterbalanced between participants. As in the pilot experiment, each level of subject-specific task demand included 15 trials.

The order of the stimulation and of the two tasks were counterbalanced across participants.

Statistical analyses

Statistical analyses were performed in the statistical programming environment R (R Development Core Team, 2008). The accuracy dichotomous variable of both tasks was analysed using general mixed effects models (Baayen et al., 2008), fitted using the GLMER function of the lme4 package (Bates, Maechler, Bolker, Walker, 2015). In the DSB squared

1 root transformed RT values were analysed according to linear mixed effects regression using
 2 the LMER procedure available in the “lme4” R package (version 1.1-5, Bates, Maechler and
 3 Bolker, 2014).
 4

5 Fixed effects inclusion in the final models have been tested with a series of likelihood ratio
 6 tests by progressively including each effect that significantly increased the overall model’s
 7 goodness of fit (Gelman and Hill, 2006). The results of this procedure are summarized in
 8 table 1.
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14 **Task Analysis _ Model selection**

DSB	Accuracy	AIC	Chi2	p
	accuracy ~ (1 Subject)	3869.0		
	accuracy ~ Task demand + (1 Subject)	3038.2	834.8	<.001
	accuracy ~ Task demand + Stimulation condition + (1 Subject)	3042.0	0.19	.9
	accuracy ~ Task demand * Stimulation condition + (1 Subject)	3043.0	6.94	.14
<u>Reaction Times</u>				
	RT ~ (1 Subject)	16734		
	RT ~ Task demand + (1 Subject)	16418	320.44	<.001
	RT ~ Task demand + Stimulation condition + (1 Subject)	16418	3.48	.18
	RT ~ Task demand * Stimulation condition + (1 Subject)	16415	11.49	.02
<u>pFT Accuracy</u>				
	accuracy ~ (1 Subject:sequence)	33039		
	accuracy ~ Task demand + (1 Subject:sequence)	31861	1181.8	<.001
	accuracy ~ Task demand + Stimulation + (1 Subject:sequence)	31822	43.4	<.001
	accuracy ~ Task demand * Stimulation + (1 Subject:sequence)	31802	27.8	<.001

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 40 **Table 1** shows the analysis for the model selection for the DSB and pFT task

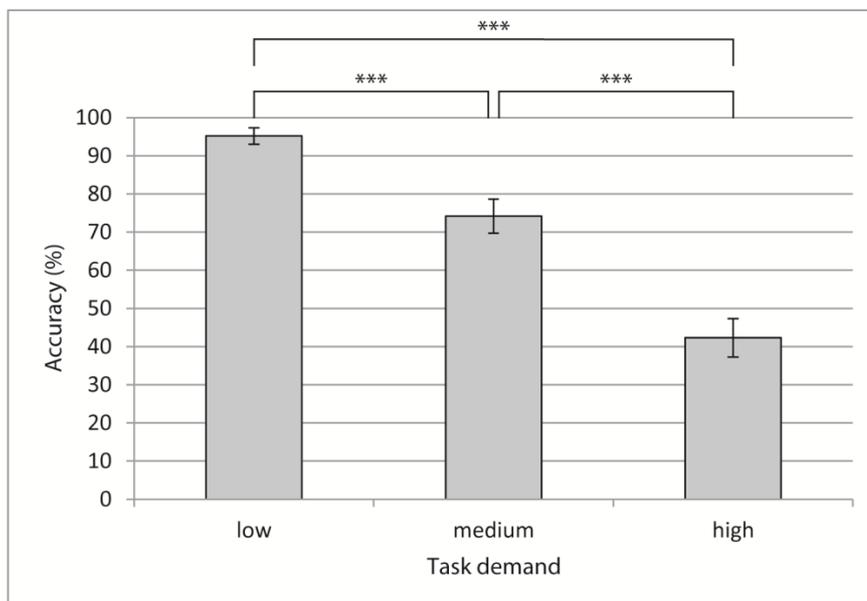
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 43 «**Subject-specific** task demand» (factorial, 3 levels: low, medium, high) and «Type of
 44 stimulation» (factorial, 3 levels: left, right, sham/placebo) were entered into the model as
 45 fixed factors. Concerning the random effect structure, a by-subjects random intercept was
 46 included to account for participant-specific variability. For the pFT task a nested random
 47 structure was preferred in order to take into account also the effect of sequences, i.e. in the
 48 pFT each trial was actually composed by a sequence of key-presses, as a consequence the
 49 random effect was computed to obtain a subject-by-sequence structure.
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56 Significant interactions were explored using the R package “phia” (De Rosario – Martinez,
 57 2015) applying FDR correction for multiple comparisons.
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Results

Digit span backward task

For what concerns the accuracy level, the best model was that with only **subject-specific** task demand as fixed factor (see Table 1). Participants made more errors in the medium compared to the low condition ($\chi^2_{(1)} = 154.21, p < .001$) and in the high compared to the low ($\chi^2_{(1)} = 469.57, p < .001$) and medium ($\chi^2_{(1)} = 224.49, p < .001$) conditions.



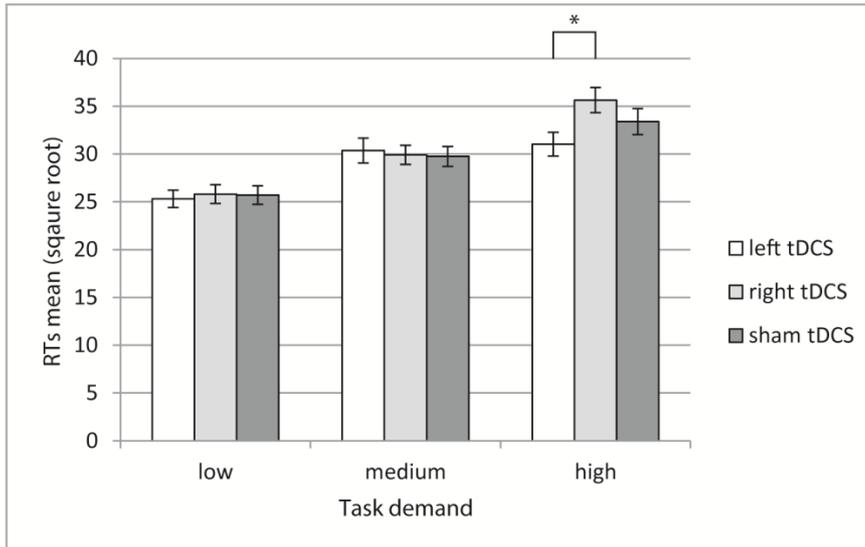
Graph 3 shows estimated accuracy mean for the DSB in the three **task demand** conditions. Stars indicate significant differences $*=p < .05$, $**=p < .01$, $***=p < .001$. **Error bars represent mean standard error.**

For the RT the best model was the one with **subject-specific** task demand -by-type of stimulation condition interaction (see Table 1).

The main effect of **subject-specific** task demand was significant ($\chi^2_{(2)} = 346.27, p < .001$): RTs were slower in the high compared to the low ($\chi^2_{(1)} = 324.79, p < .001$) and medium **levels** ($\chi^2_{(1)} = 70.41, p < .001$) and in the medium compared to the low **level** ($\chi^2_{(1)} = 124.86, p < .001$).

The main effect type of stimulation was not significant ($\chi^2_{(2)} = 3.48, p = .175$). Crucially, the **subject-specific** task demand-by-type of stimulation interaction effect was significant ($\chi^2_{(4)}$

= 11.48, $p = .022$): for the high **level of subject-specific task demand** RTs were slower during the right anodal stimulation compared to the left ($\chi^2_{(1)} = 12.99, p = .003$) one.



Graph 4 shows the interaction between **task demand** and type of stimulation in squared root normalized RT in the DSB task. Stars indicate significant differences $* = p < .05$, $** = p < .01$, $*** = p < .001$. **Error bars represent mean standard error.**

Paced finger tapping task

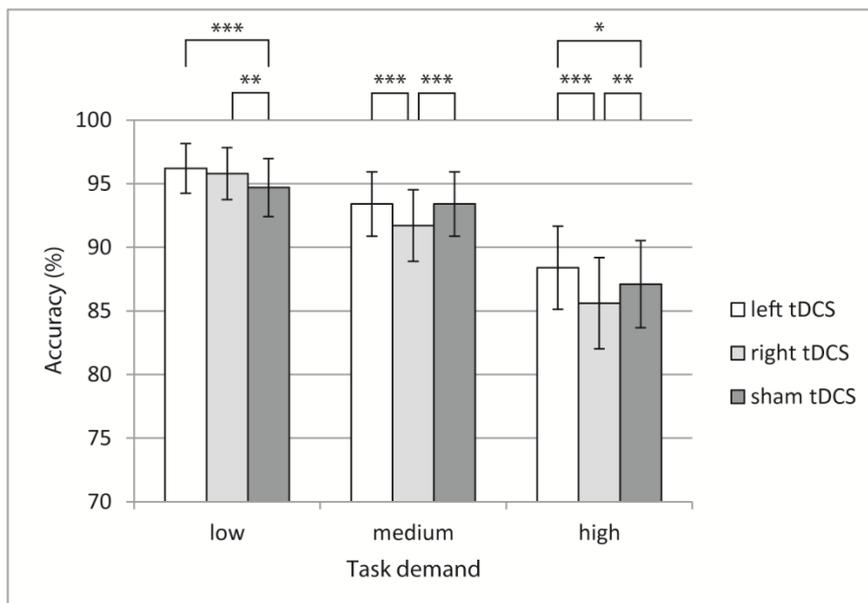
The best fitting model was that with **subject-specific** task demand-by-type of stimulation interaction (see table 1).

The main effect of **subject-specific** task demand was significant ($\chi^2_{(2)} = 1125.94, p < .001$), with more errors for the high level compared to the low ($\chi^2_{(1)} = 1012.71, p < .001$) and medium ones ($\chi^2_{(1)} = 445.52, p < .001$) and for the medium compared to the low ($\chi^2_{(1)} = 157.35, p < .001$).

The main effect of type of stimulation was also significant ($\chi^2_{(2)} = 44.83, p < .001$), with less errors for the left stimulation compared to the right ($\chi^2_{(1)} = 29.22, p < .001$) and to the sham ($\chi^2_{(1)} = 17.31, p < .001$) conditions.

The **subject-specific** task demand-by-type of stimulation interaction effect was also significant ($\chi^2_{(4)} = 28.42, p < .001$): at the low level participants made more errors in the sham compared to the left anodal ($\chi^2_{(1)} = 18.84, p < .001$) and right ($\chi^2_{(1)} = 10.36, p = .002$)

1 stimulations; at the medium level performance was significantly impaired in the right anodal
 2 compared to both left ($\chi^2_{(1)} = 16.48, p < .001$) and sham ($\chi^2_{(1)} = 16.2, p < .001$) conditions,
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 4 and at the high level participants committed more errors in the right compared to the left ($\chi^2_{(1)} = 29.76, p < .001$) and sham ($\chi^2_{(1)} = 8.12, p = .006$) conditions, and in the sham compared
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 6 to the left anodal ($\chi^2_{(1)} = 6.84, p = .011$) condition.
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36 Graph 5 shows the interaction between **task demand** and type of stimulation in accuracy in the pFT task. Stars
 37 indicate significant differences $*=p<.05$, $**= p<.01$, $***= p < .001$. **Error bars represent mean standard**
 38 **error.**
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Discussion

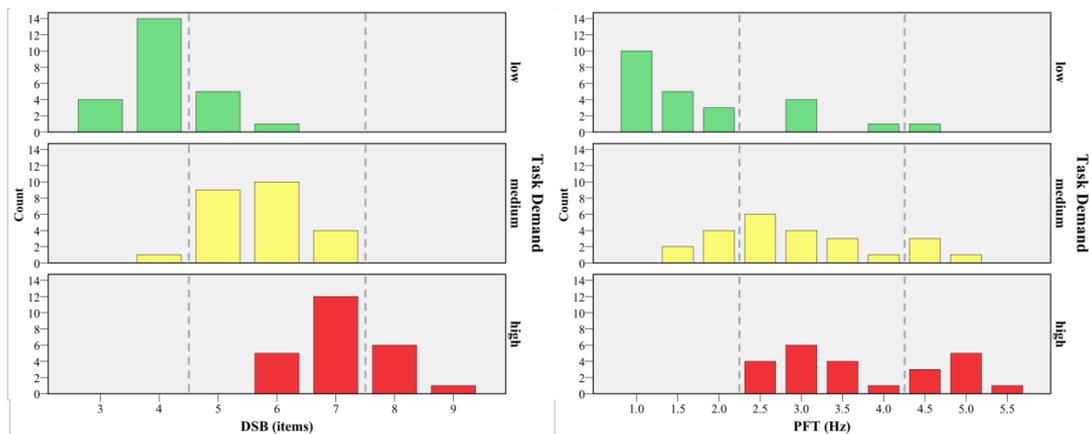
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3 In the present study we used an empirically-based method to explore the relationship between
4 **subject-specific** levels of task **demand** and bilateral involvement of the PFC. In other words,
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6 we wanted to create an experimental paradigm capable of explicitly testing the functional
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8 laterality dynamics⁴ associated with increasing task **difficulty**, without using either a fixed *a*
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10 *priori objective* level of task **demand** (like, for example in Cappell et al., 2010; Mattay et al.,
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12 2006), or an *a-posteriori* classification of task demand based on the level of obtained task-
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14 performances (like, for example, in the study by Cabeza 2002 and Berlingeri et al., 2013).
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18 Moreover, we were interested in testing whether the contribution of the right PFC is
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20 necessary for maintaining a good level of performance in predominantly left-lateralized tasks
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22 (DSB, pFT) and if so, which characteristics of the experimental task (cognitive level vs task
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24 demand) may trigger the recruitment of bilateral neurofunctional networks, thus causing a
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26 decrement of the functional hemispheric lateralization.
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30 To address these issues we first manipulated the cognitive level of the task by adopting two
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32 different experimental tasks: one associated with high level cognitive functions (WM: DSB),
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34 one associated with low level cognitive functions (motor execution: pFT). As a second step,
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36 we created an experimental procedure capable of setting, for each participant, subjectively
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38 defined levels of task demand (low, medium and high) for each experimental task. Once the
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40 subject-specific levels of task demands were set up, each participant performed the two
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42 paradigms in the three task demand conditions during three tDCS sessions (left PFC
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44 stimulation, right PFC stimulation, sham/placebo condition).
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57 ⁴ It is worthy to remember that the spatial resolution of the technique adopted here is definitely low, but the
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59 reader has to consider that the aim of the present study was not to address the regional neuro-functional correlate
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61 of the task-demand effect, but rather to describe the laterality changes associated with **subject-specific** level of
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63 task **demand**.
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Graph 6 shows the variability among individual thresholds in DSB and pFT tasks.

The first result we want to discuss is the feasibility of task difficulty manipulation at a *subject-specific* level. For both tasks we found a main effect of **task demand**: performance decreased when task demand increased, in line with literature studies (Rice et al., 2012). We found a significant difference between the three levels of **subject-specific task demand** for both accuracy and RTs in DSB and for accuracy in pFT. This result confirms that our subject-specific manipulation was effective.

The large variability found among individual thresholds (see figure 6), together with the coefficient of variation (a statistical measure of the variability of data points around the mean computed as the ratio between the standard deviation and the average of the collected data; $CV_{\text{DSB}} = 0.29$, $CV_{\text{pFT}} = 0.56$) suggest that actually it would be misleading to compare subjects on the basis of static and a priori *objective* levels of task **demand**.

Regarding the bilateral involvement of PFC according the **subject-specific** level of task demand and/or task cognitive level (i.e. whether the task tackled high vs low level cognitive functions), crucially, we found a significant stimulation -by- **subject-specific** level of task **demand** interaction effect in both tasks. In particular, right anodal stimulation disrupted performance when tasks demand increased: RTs were slower in the DBS at the hardest level

1 of **subject-specific** difficulty and accuracy decreased at the pFT in the medium and high level
2 of **demand** compared to both left and sham stimulation.
3

4 Inconsistently with previous neuroimaging studies (Schneider-Garces et al., 2010; Mattay et
5 al., 2006; Cappell et al., 2010), our results suggest that the stimulation of the right PFC does
6 neither improve, nor help in keeping adequate the level of performance at WM and motor
7 tasks when task demand increases. On the contrary, for both DSB and pFT we found a
8 stimulation-by-cognitive load interaction effect that was due to the detrimental effect of the
9 right stimulation for the most demanding conditions.
10

11 Taken together, our results do not support the “Inter-Hemispheric Interaction” (IHI)
12 hypothesis (Passarotti et al, 2002). According to this hypothesis, IHI would be a basic
13 mechanism of the brain to increase its information processing efficiency: in particularly
14 demanding conditions, the brain would split the task demands between the two hemispheres
15 in order to count on parallel information processing. This would be particularly true in highly
16 demanding conditions in which the benefits associated with the greater computational power
17 brought by the bi-hemispheric activation outweighs the neural/cognitive costs triggered by
18 the integration of information processing between the two hemispheres (Guzzetti & Daini,
19 2014; Passarotti et al., 2002; Banich et al., 1998, 2002; Weissman & Banich, 2000).
20

21 Our stimulation-by-**task demand** interaction effect seems to better fit with the inhibitory
22 interhemispheric hypothesis (Kinsbourne 1975, 1982): i.e. the activation in one hemisphere
23 tends to decrease the activation of the other. According to Kinsbourne (1982), hemispheric
24 functional lateralization would provide the necessary neural distance between complementary
25 processes that, under specific task conditions, can be combined to obtain an adequate level of
26 behavioural performance. This neurofunctional specialization/integration would be mediated
27 by the corpus callosum and it’s meant to prevent maladaptive cross-talk between the
28 hemispheres for which a given function is dominant (Kinsbourne & Hiscock, 1977). A
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change in excitability in one hemisphere, also caused by an exogenous stimulation, can produce indirect excitability effects in the other by the means of interhemispheric projections (e.g. Gilio et al., 2003; Vines et al., 2006; Smirni et al., 2015; Rosso et al., 2014). This mechanism is at the basis of the paradoxical functional facilitation effect, which was first described in brain-damaged patients who performed better than healthy subjects in certain tasks (Kapur et al., 1996) and that can be defined as the “behavioural improvement occurring as a consequence of altered competitive opponent processing” (Bestmann et al., 2015).

Mangano et al. (2014), for example, suggested that patients with lesions in the right posterior parietal cortex performed better than healthy controls in a visual search task; Morgan et al. (2012) reported the cases of patients with bilateral basolateral amygdala calcification who performed better than the control group in WM span.

Paradoxical facilitation can be induced in healthy subject also through the application of non-invasive brain stimulation techniques (especially low rTMS and cathodal tDCS) to inhibit a targeted region. The mechanism at the basis of such improvement seems to be the “release of a secondary and functionally connected neural site from the suppressive control [of the stimulated region] thereby generating a behavioural gain” (Pascual-Leone et al., 2012). In a recent study, Smirni and colleagues (2015) engaged participants in a recognition memory task that typically rely on left DLPFC. The authors did not find an effect for anodal tDCS over both left and right DLPFC and for cathodal stimulation over left DLPFC. Conversely, cathodal tDCS over the right DLPFC significantly improved participant performance.

Our result can be considered as the other side of the coin for this effect: the stimulation through anodal tDCS of the contralateral homologous region (i.e of the right PFC) leads to a detrimental effect by increasing the competition between the two hemispheres.

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Crucially, in our study this effect was specific for the most demanding conditions, suggesting that for lower **task demand**, the increase of excitability in the contralateral region does not influence behavioural performance.

Another possible explanation of the current results refers to the hypothesis of limited information processing resources in the brain (Kahneman, 1973; Craik & Byrd 1982) and the ability to distribute these resources within different neural substrates. This idea has recently been re-elaborated in the so called zero-sum theory (see Pascual-Leone et al., 2012; Bestmann et al., 2015) which states that our brain has a limited amount of processing power and that for either each function, or process that has to be enhanced, the processing power must be ‘stolen’ from another neurocognitive source. The authors also suggest that since ‘discrete neural regions interact to form functional neural networks, it is possible that finite processing power is network-specific and that noninvasive electromagnetic stimulation serves to distribute this power within a given network’. This theory can be also adopted to bridge the gap between our empirical results and the CRUNCH (Reuter-Lorenz & Cappell, 2008) and STAC (Park & Reuter-Lorenz, 2009) models predictions. Indeed, the two models predicts that the manipulation of the **subject-specific** task demand can modify the allocation of the neural resources, but these re-allocations are always described in terms of activation of additional brain regions that, according to the HAROLD model, could be the homologues regions of the other hemisphere. Our results challenge this assumption and suggest that, in line with CRUNCH and STAC, the task demand may trigger a neurofunctional re-organization and the activation of scaffolding networks to support the behavioural performance, but these re-allocations should occur only if really needed (i.e. if they are really necessary to maintain an adequate level of performance). This is to say that, an exogenous stimulation of a scaffolding brain region (in our case right PFC), although potentially useful in particularly challenging conditions, may be detrimental if resource ceiling (Reuter-Lorenz

1 & Cappell, 2008) of the left PFC is not reached yet as, according to the zero-sum theory, this
2 exogenous stimulation would subtract important neural resources to a task-specific neural
3 network that is still “working for us” (Luber, 2014).
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7 It is also worthy to note that our experimental manipulation implicitly assumed that the right
8 anodal stimulation coupled with increasing cognitive load would have caused a switch from a
9 left-lateralized brain activity to a bilateral pattern and that within such a bilateral pattern the
10 two homologue regions would have had a synergic (or “temporally-correlated”) activity. This
11 particular statement, which might be associated with the concept of “connectivity” (Friston,
12 2011), however, is apparently inconsistent with our findings. We say apparently because this
13 is the case if one thinks about connectivity only in terms of excitatory connections that
14 mediate a positive behavioural outcome. However, it is well known that network connections
15 can be both excitatory, both inhibitory and that they can combine their local effects to support
16 the manifestation of complex behaviors (Park & Friston, 2013). For example, Fu et al., 2006,
17 found a significant switch from positive to negative effective connectivity between the left
18 middle frontal gyrus and the precuneus during a phonemic fluency task and this polarity
19 switching was triggered by the increment of the cognitive load.
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Aside the effect of right tDCS at the hardest task demand, we found other results which were
somehow unexpected.

The DSB accuracy analysis did not show a significant main effect of stimulation condition,
nor a stimulation condition-by-**subject-specific** task demand interaction. The lack of a
moderation effect of tDCS on accuracy could be due either to our experimental setting, or to
tDCS characteristics. Participants had to perform the task three times, in three different days,
as a consequence it is possible that the learning effect was higher than the effect of the tDCS.
Another possible explanation is the absence of a temporal constraint for this task: participants
could take all the time they needed to repeat the digits in the reverse order. Together, these

1 two limitations may have triggered a change in the kind of cognitive strategy adopted to
2 perform the task. This, in turn may have caused a switch in the recruited neural networks that
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4 our experimental setting and technique was not capable of capturing.
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7 Our result is inconsistent with previous studies that describe an improvement of verbal WM
8 after anodal tDCS (Smith & Jonides, 1999; Postle, 2006; Wilde et al., 2004). However, the
9 effect of tDCS in WM tasks are controversial: Jeon & Han (2012) found an effect over
10 accuracy after anodal tDCS, while Andrews and colleagues (2011) found an improvement for
11 the performance at the digit span forward (and not for the DSB).
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18 Two recent meta-analyses on WM tasks (Brunoni & Vanderhasselt, 2014; Hill et al., 2015)
19 suggested that tDCS may have an effect only on RTs, without causing a noticeable change in
20 the level of response accuracy.
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26 In our study, however, left tDCS did not influence RTs, neither the accuracy index at any
27 level of task demand. Such widespread scenario across studies might be due to differences in
28 the stimulation protocols (online vs offline tDCS, differences in montage/duration/intensity
29 of the stimulation), participants inter and intra-individual differences and task features such
30 as the paradigm and the method adopted to define and manipulate the level of task difficulty
31 (Jantz et al., 2016).
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41 Another unexpected result regards the pFT, in which tDCS affected performance at lower
42 task demand: compared to sham condition, participants' performance improved in both right
43 and left anodal stimulation conditions (see Graph 5). According to our initial hypothesis,
44 indeed, we did not expect to find an effect for low **levels** task demand, but only for higher
45 **ones**. However, this result per se is not surprising: it is well known that the cortical motor
46 system of each hemisphere engaged primarily the contralateral side of the body, by means of
47 crossed cortico-spinal fibers (for a meta-analytical review see Witt et al., 2008); moreover,
48 also the ipsilateral primary motor cortex is involved in hand movements. An interesting
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example comes from the TMS study by Davare and colleagues (2007), in which the ipsilateral primary motor cortex was stimulated while healthy subjects were performing different movements with their right dominant hand. The results showed that, irrespective of the type of movement, TMS over this region altered the behavioural performance, by modifying the timing of muscles recruitment during task execution.

It could be hard to explain how the involvement of ipsilateral M1 resulted reduced during medium- and high-level conditions, where we found a detrimental effect during right tDCS. This could be partially explained by the results of an fMRI experiment conducted by Newton and colleagues (2005), who studied the effects of movements duration on BOLD signal in bilateral M1. The results showed a significant signal decrease in ipsilateral M1, in parallel with greater task-related increases in contralateral M1, associated with movements duration: the greater the duration of the movement, the lower the contribution of the ipsilateral M1.

Our speculative explanation for our result points to the method adopted to manipulate **subject-specific** task **demand** in our pFT task. The low task demand was characterized by a slower rhythm and therefore might be seen as a set of different single movements, recruiting also the ipsilateral M1. On the contrary, the medium and high **levels** were characterized by an increased speed of the rhythm, such to represent a longer “unique” movement, involving only the contralateral motor area.

Our last question addressed to a possible difference in neurofunctional lateralization triggered by the specific cognitive level of the task, that is higher vs lower level cognitive functions. Our results show that similar mechanisms seem to explain DSB and pFT performance, suggesting that cognitive load could be empirically manipulated by varying the **subject-specific** level of task **demand** rather than varying the cognitive level of the task per se.

1 **To conclude, in the present study we combined current-flow modeling with**
2 **neuroimaging meta-analysis in order to build an appropriate intracefalic tDCS**
3 **montage. Further studies could deeper investigate our issue by applying a high-**
4 **definition tDCS montage (Datta et al., 2009), to help increasing focal current flow to the**
5 **region of interest and removing potential influence due to the reference electrode.**
6
7 **Moreover, we could not assess whether other brain regions are involved in the psycho-**
8 **physiological dynamics associated with increasing subject-specific level of task demand.**
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10 **Further studies based on imaging techniques such as fMRI, allowing to study**
11 **activations all over the brain, should further address this issue.**
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25
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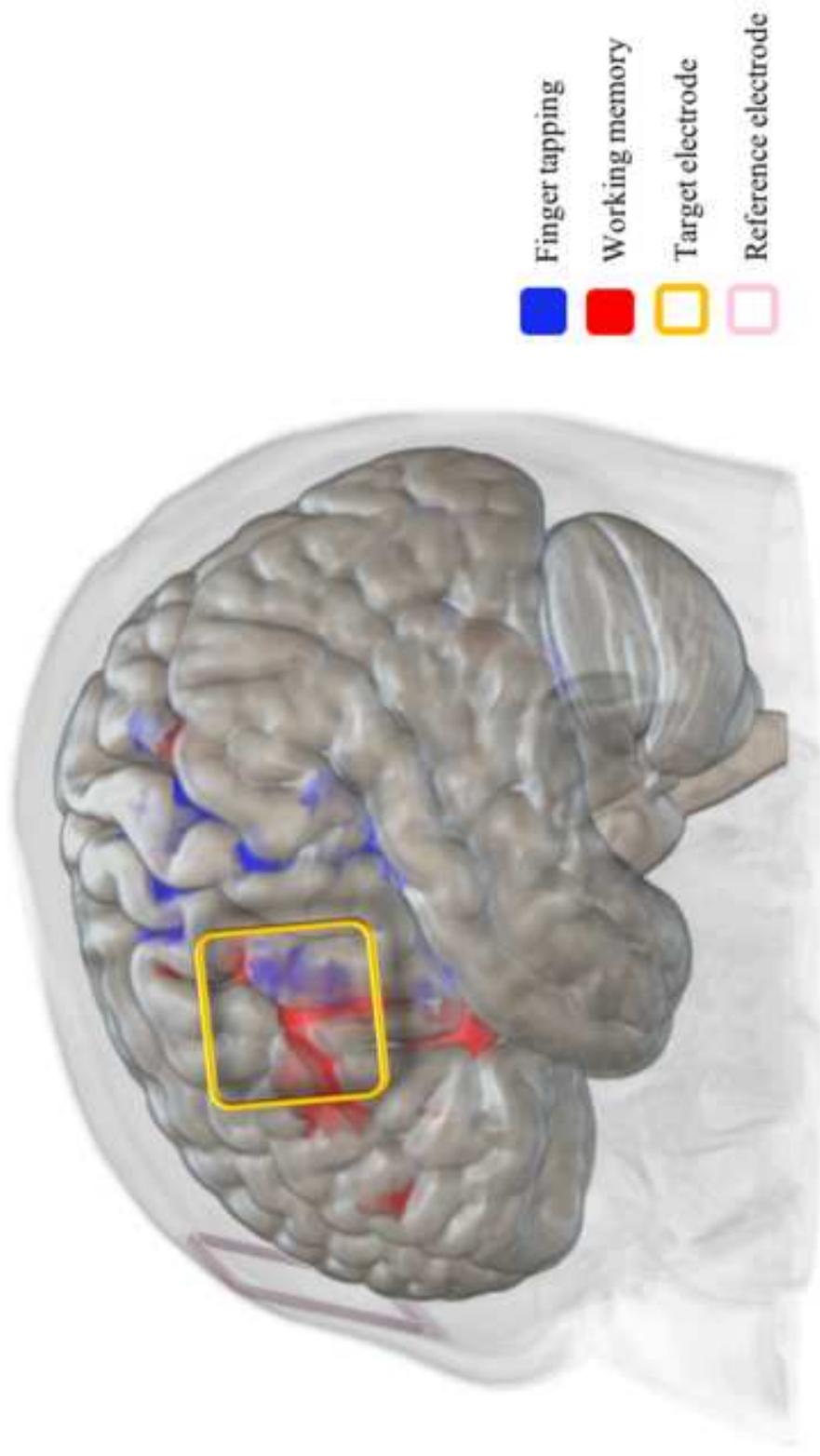
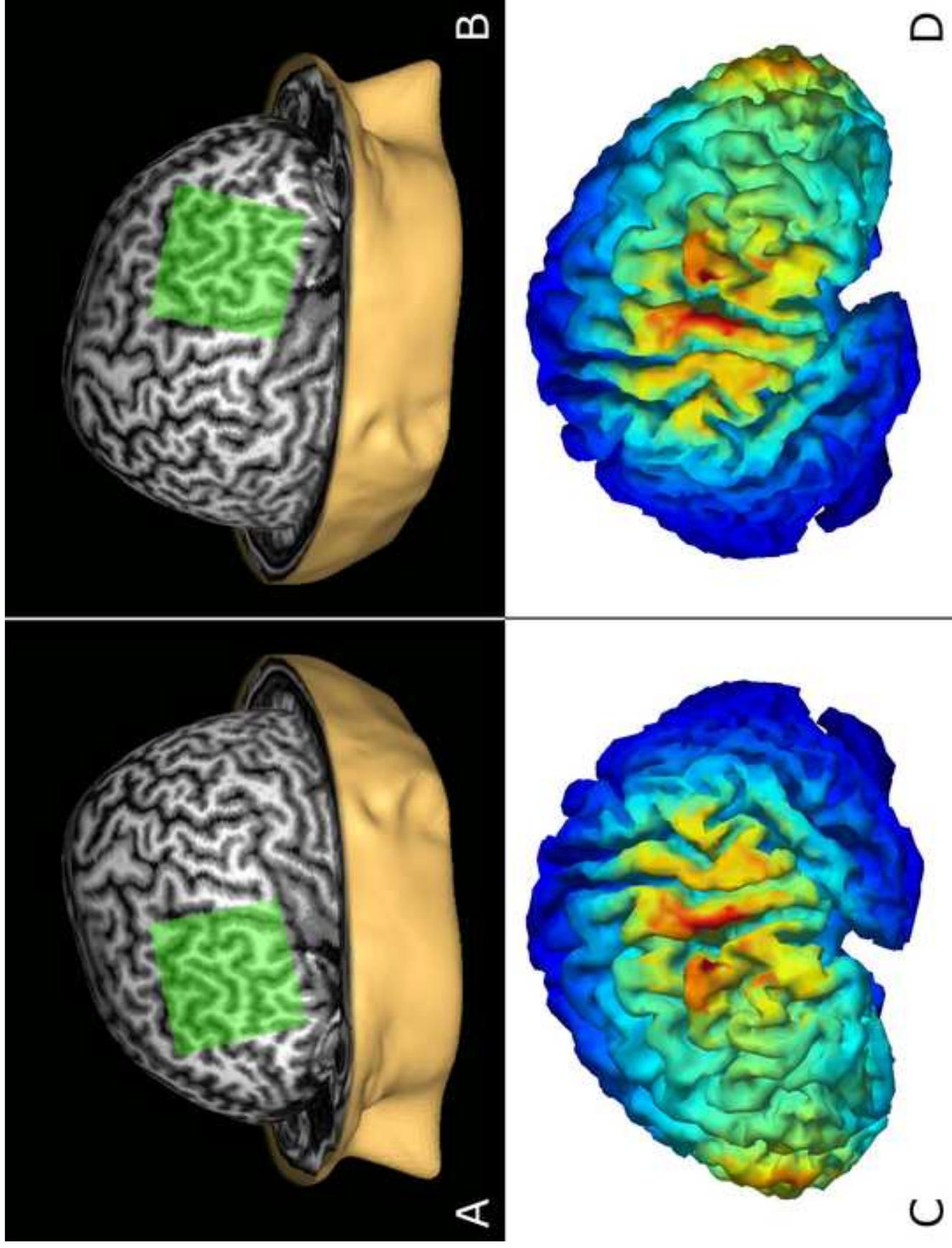
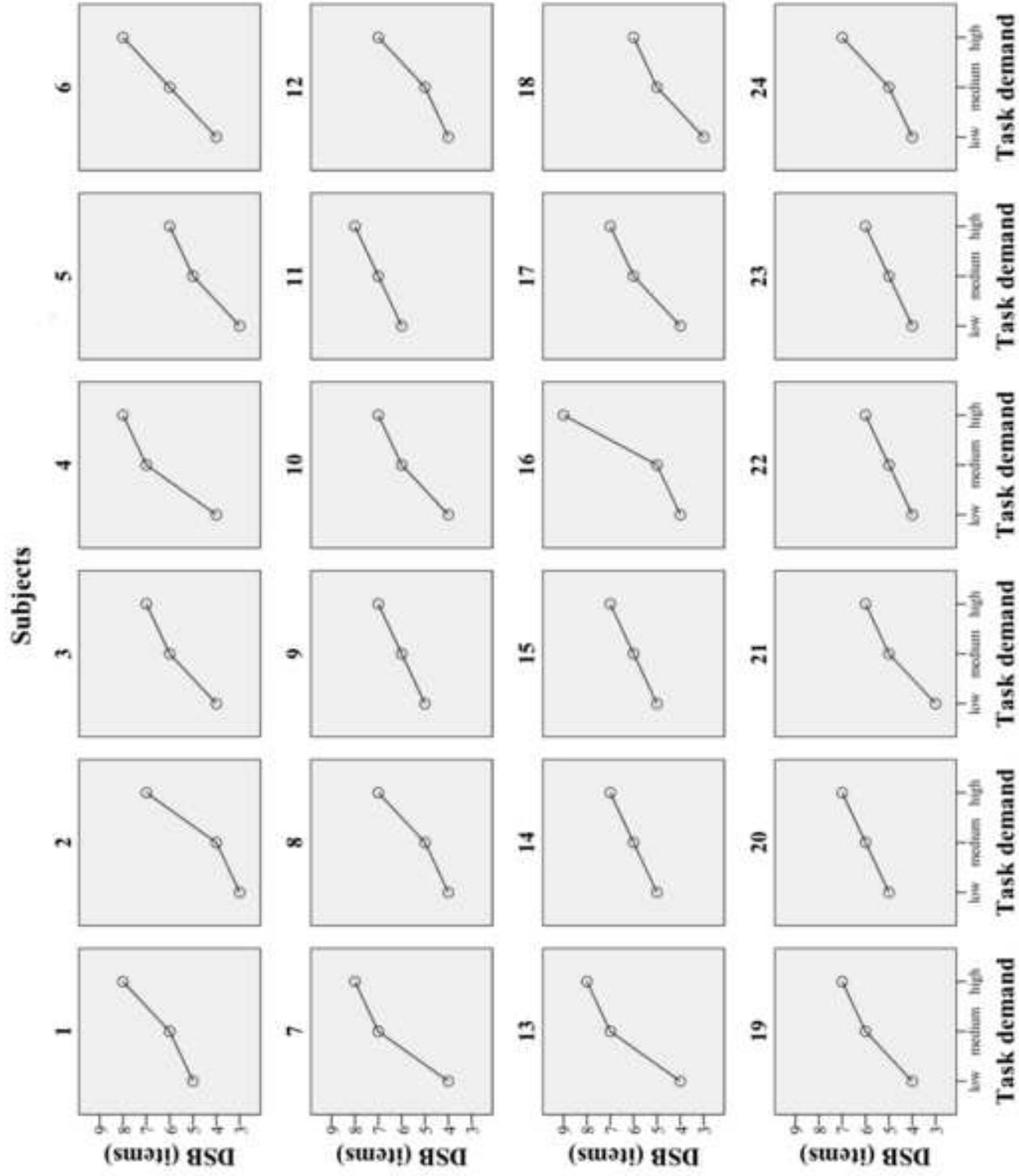
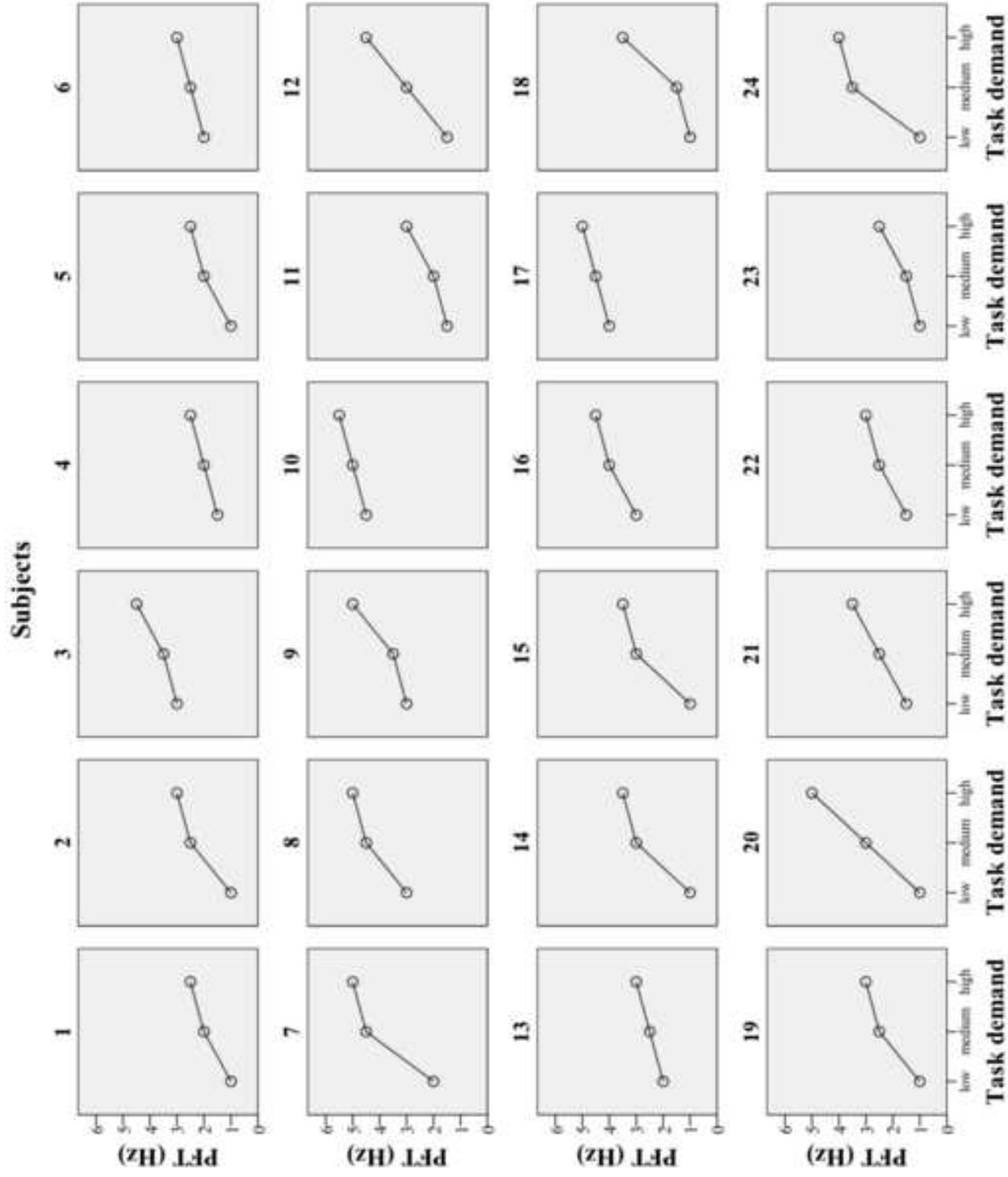


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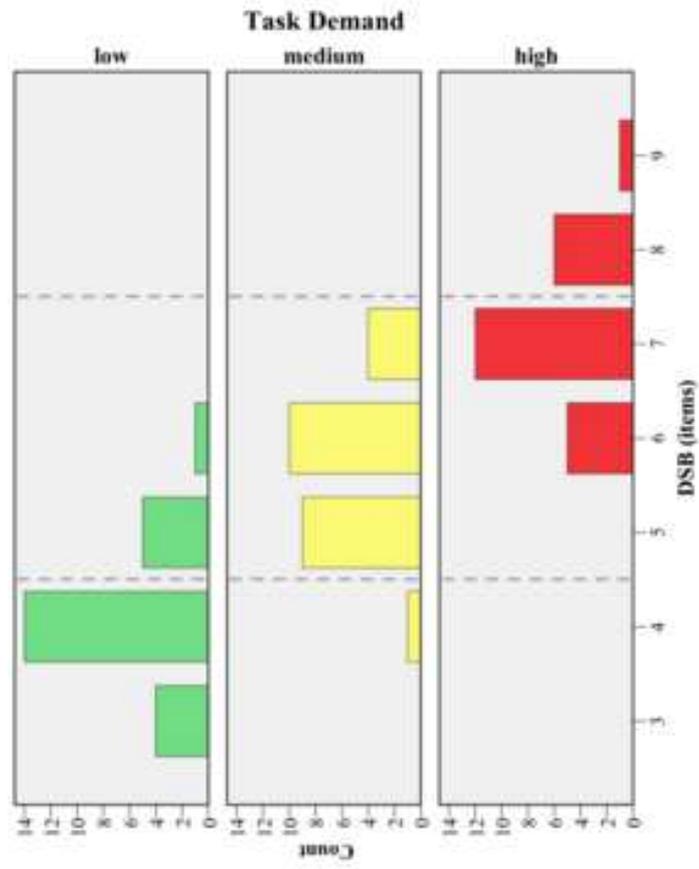
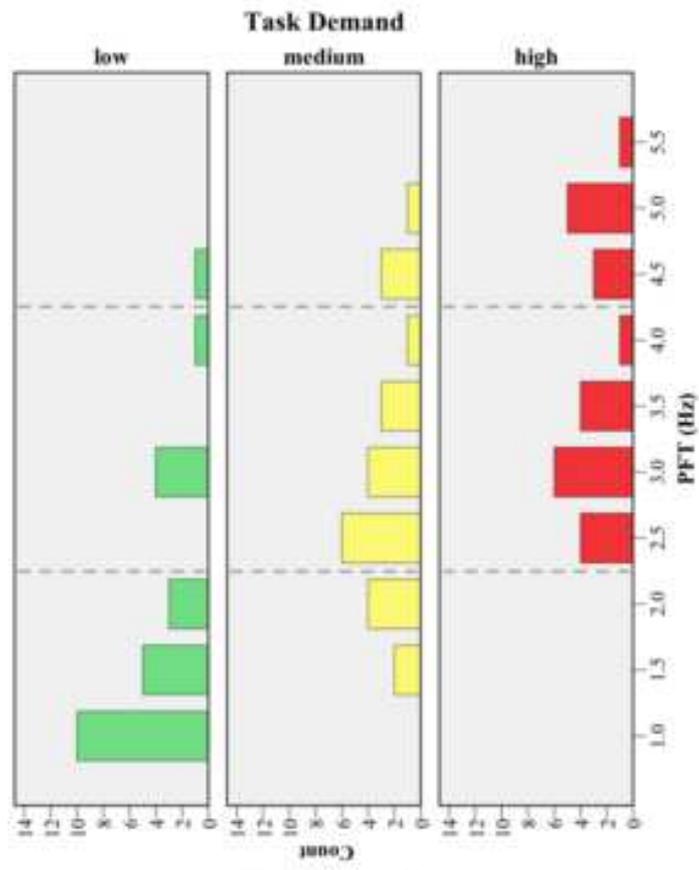


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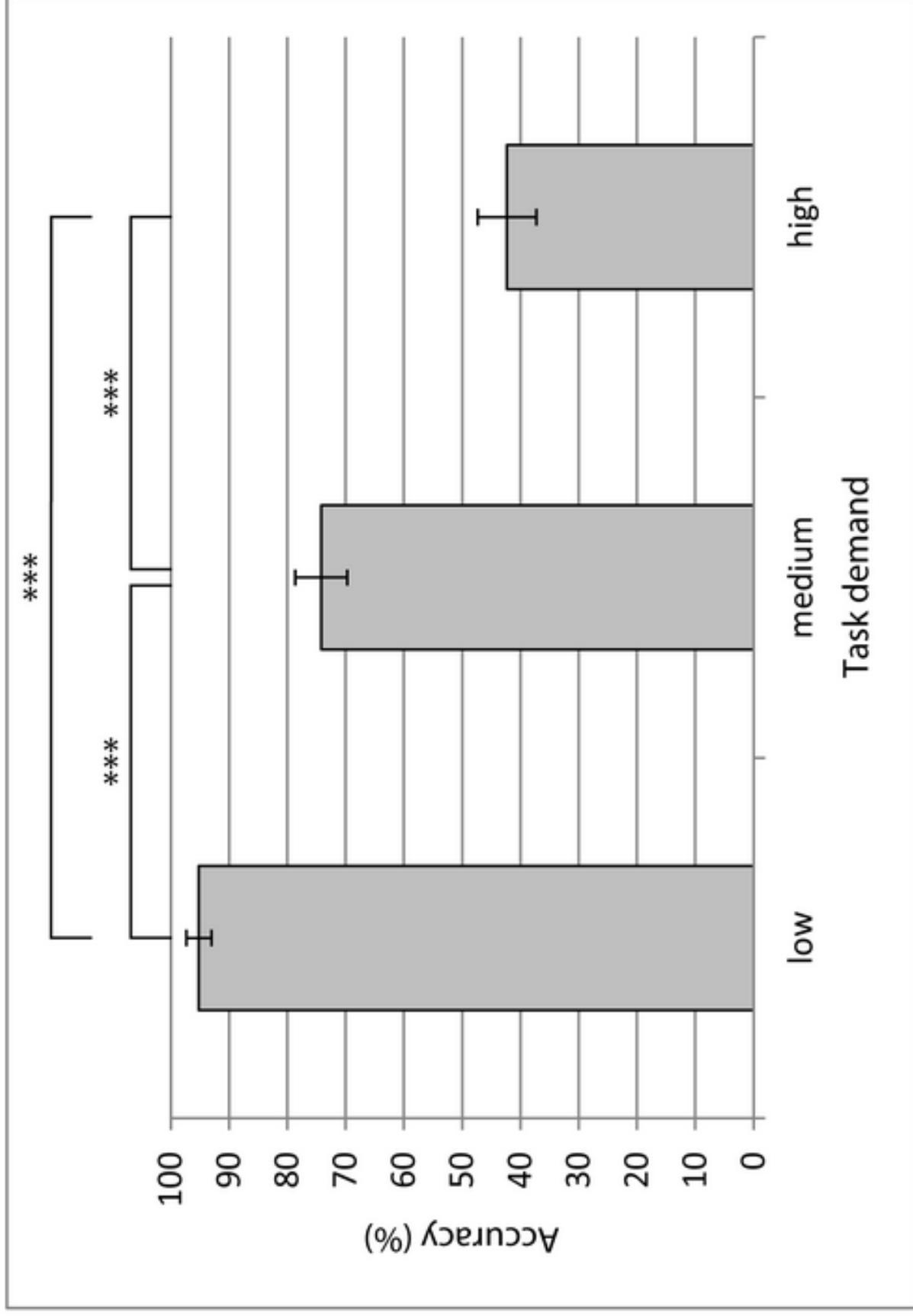


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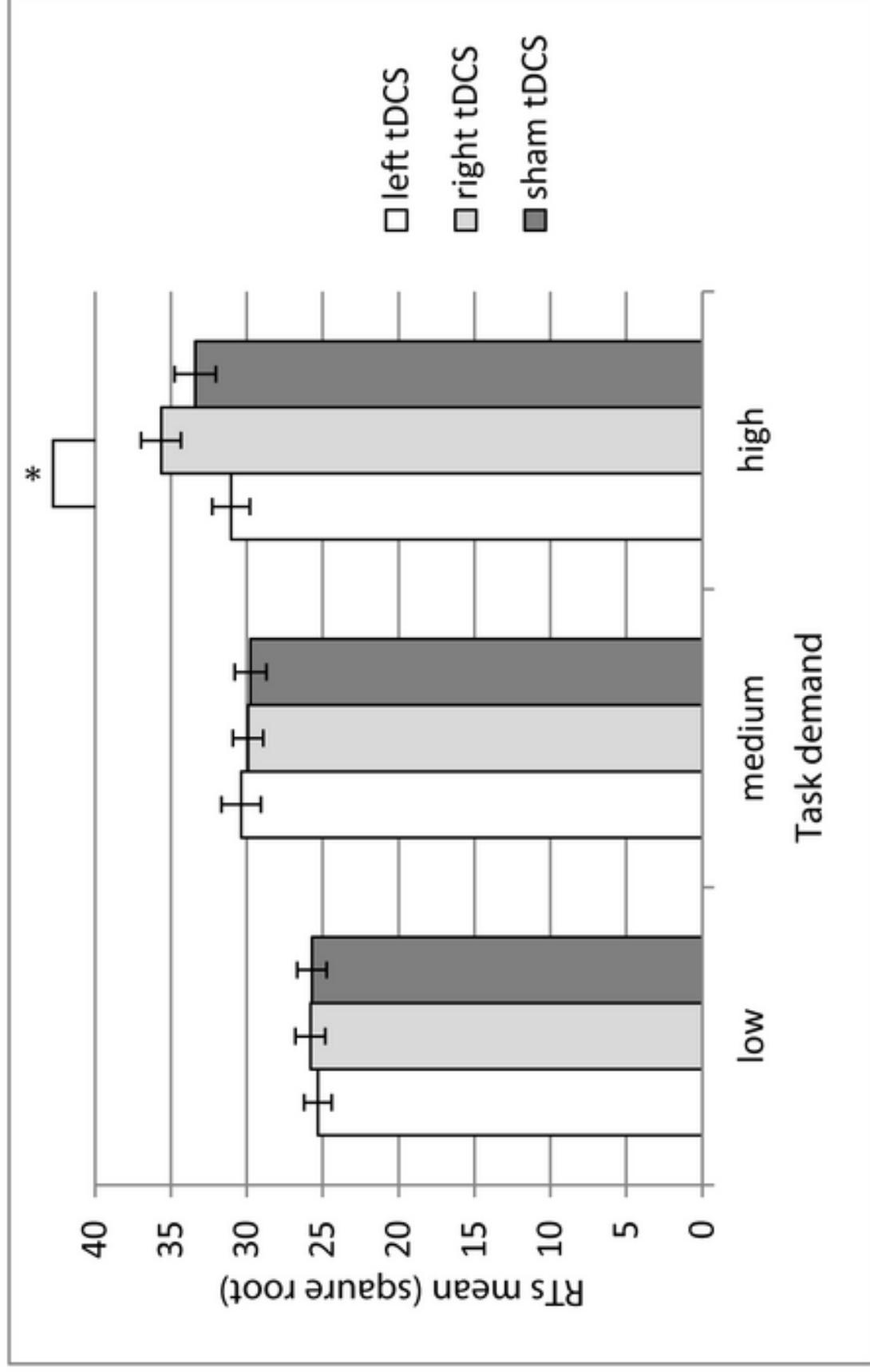
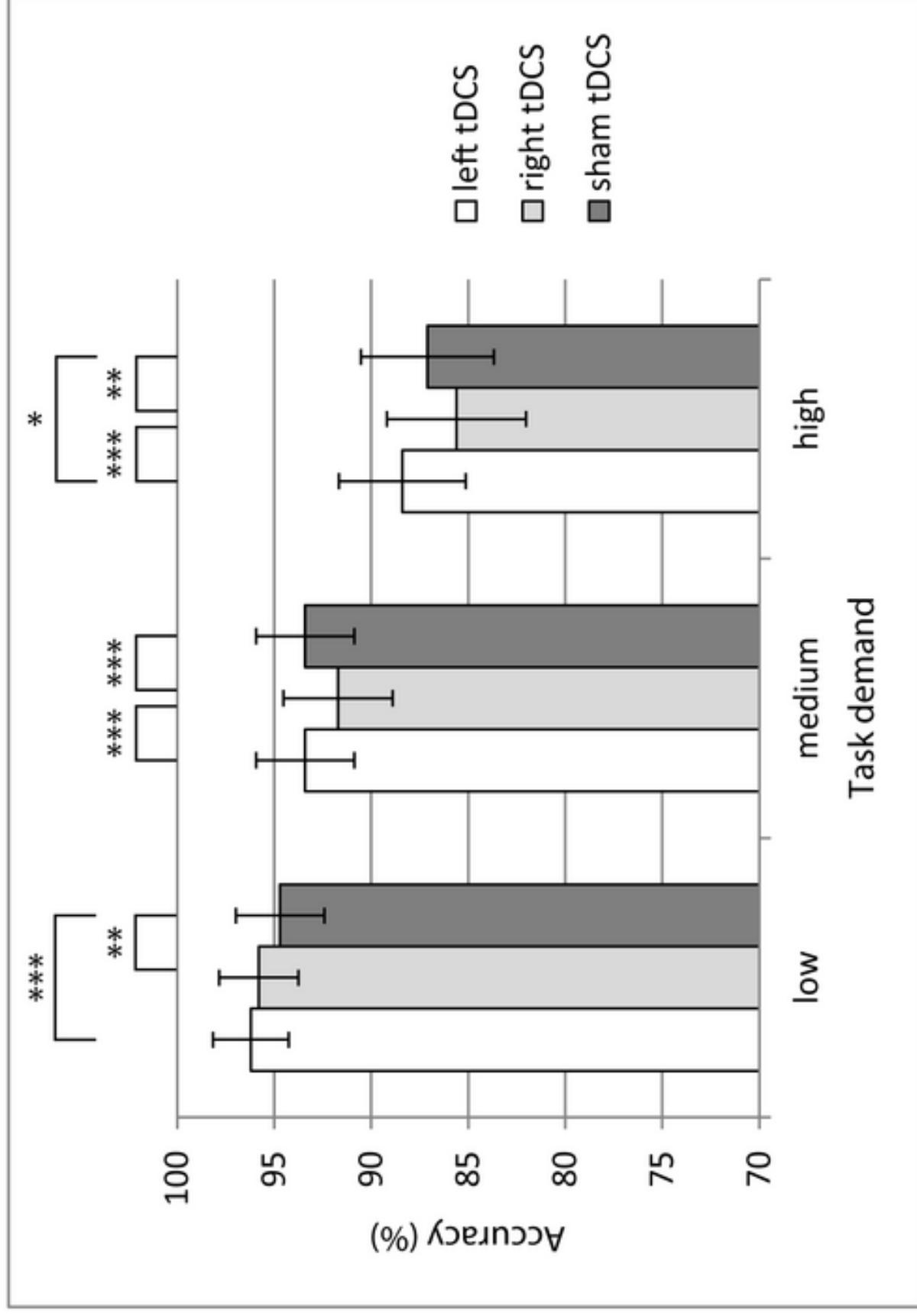


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