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BRIEF COMMUNICATION

Motor threshold predicts working memory performance in healthy humans

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Abstract

Cognitive functions, such as working memory, depend on neuronal excitability in a distributed network of cortical regions. It is not known, however, if inter-individual differences in cortical excitability are related to differences in working memory performance. In the present transcranial magnetic stimulation study, which included 188 healthy young subjects, we show that participants with lower resting motor threshold, which is related to higher corticospinal excitability, had increased 2-back working memory performance. The findings may help to better understand the link between cortical excitability and cognitive functions and may also have important clinical implications with regard to conditions of altered cortical excitability.

Introduction

Resting motor threshold (rMT), assessed by transcranial magnetic stimulation (TMS) correlates with the excitability of neurons activated by TMS, and is mediated by ion channel conductivity, as well as the excitability of synaptic connections at both the cortical and the spinal level.[1] It is commonly defined as the minimum TMS intensity necessary to produce a motor evoked potential (MEP) or visually detectable twitch on 50% of pulses.[2] rMT varies widely between subjects, but has a high test–retest reliability,[3] which may result partly from relatively stable biological differences in corticospinal excitability between individuals.[4] Additionally, individual scalp-cortex distance, subject-specific gyral folding pattern, the location of cortical motor neurons in the primary motor cortex and the relative orientation of the axonal projections may also contribute to between-subject variation in rMT.[5–7] Besides these anatomical differences, ovarian hormone levels have been shown to modulate neuronal excitability.[8,9] rMT is not only used for motor cortical excitability estimation but also for TMS intensity calibration over non-motor areas, as advised in the TMS safety guidelines.[10] The underlying assumption is a relation between the excitabilities of different systems. Indeed, motor threshold as a measure of motor cortex excitability has been found to be correlated with phosphene threshold, a measure of visual cortex excitability.[5,11] Furthermore, rMT predicts the effect size of TMS in a cognitive task when subjects were stimulated with a fixed intensity.[12] Moreover, TMS has been used together with electroencephalography to relate cortical excitability and connectivity during different states of consciousness,[13] to study task-dependent changes in cortical excitability and effective

connectivity[14] and to link cortical activity to distinct states of cortical excitability.[15]

Working memory is a dynamic process allowing the temporary storage and manipulation of information. Studies in animals have shown that working memory processes depend on the excitability and sustained firing of neurons in the prefrontal cortex and other cortical regions.[16] Pharmacological studies in humans indicate that antiepileptic drugs can decrease motor cortical excitability and can decrease cognitive performance, in particular working memory, possibly by enhancing inhibitory neurotransmission leading to reduced neuronal excitability.[1,17] Furthermore, there is evidence indicating that the stimulating antidepressant bupropion – a dopamine and norepinephrine reuptake inhibitor – decreases rMT, increases motor cortical excitability,[18] and improves working memory performance during tobacco abstinence.[19]

Cognitive functions, such as working memory, depend on neuronal excitability in a distributed network of cortical regions.[16] Moreover, there is evidence that corticospinal excitability might be correlated with excitability in other cortical regions. We therefore aimed at investigating if interindividual rMT differences are related to measures of cognitive performance in healthy subjects. Because ovarian hormones have been shown to modulate neuronal excitability[8,9] and previous studies report gender-specific TMS results,[20] we considered possible gender differences.

Methods

Participants

Overall, 140 healthy, right-handed participants (72 men, mean age 25.03 ± 5.38 [SD]; 68 women, mean age 22.71 ± 3.3 [SD]) were included in sample 1 and 48 healthy, right-handed participants (19 men, mean age 23.58 ± 4.94 [SD]; 29 women, mean age 24.31 ± 4.86 [SD]) in sample 2 (see below). Handedness was assessed by the Edinburgh inventory.[21] Participants were free of any psychiatric and physiological disease and did not report any cases of epilepsy among first-degree relatives. Local Ethics Committee approved this study and all participants gave written informed consent and received 25CHF/h compensation.

Procedure

In sample 1, the N-back task was preceding rMT measurement. In sample 2, the order was reversed to investigate the possibility that the preceding N-back task influenced rMT measurement. Before starting the N-back task, participants were instructed and then trained on the task. If the performance of the 0- and 2-back training was at least 75% the N-back main task was started.

rMT measurement

Stimulation was performed with a biphasic magstim Rapid2 stimulator (The MAGSTIM® Company Ltd, Whitland, U.K.) and a 70-mm figure-of-eight coil. As in previous studies[22] rMT was determined by visual inspection that is highly correlated with rMT as measured by MEP[23] and represents a reliable method for determining rMT.[24] For a detailed description on rMT measurement, see supplementary information.

Behavioral tasks and questionnaires

The 0-, 2-, and 3-back version of the N-back letter task[25] was used and consisted of six blocks. For a detailed description see supplementary information. Variables of interest were accuracy (hits plus correct rejections divided by the total number of letters shown) and D-prime analysis (d') (z-transformed values of hit- minus false alarm-rates),[26] two widely used measures of working memory performance.

Daily intake of nicotine, caffeine, and alcohol was assessed with a screening questionnaire as well as motivation by means of a 5-point Likert scale. Furthermore, to measure state anxiety in the context of rMT measurement, Spielberger State Anxiety Inventory (STAI)[27] and a visual analogue scale (VAS) with a range from 0 (no anxiety at all) to 100 (highest anxiety imaginable) were used in sample 1.

Statistical analysis

We specified univariate analyses of variance (ANOVA) for each variable of interest, using sum of square type II, leading to an increased power for main effects in case of nonsignificant interactions. In case of a significant main effect of rMT, we report the standardized β's of the linear model, which underlays the ANOVA. N-back performance was taken as (quantitative) dependent variable. Independent variables were rMT as quantitative variable, gender as factor and the interaction terms of rMT and gender. In the case of a significant interaction effect, we applied post hoc analysis separately for both gender groups by calculating bivariate Pearson's correlations to further investigate the effect. For significant post hoc effects we additionally regressed out the 0-back performance, age, VAS for anxiety, STAI, daily intake of stimulants (caffeine, nicotine, alcohol), motivation, degree of dexterity or daytime of experiment separately to control for an influence of these variables on the correlation by using partial correlations.

Gender differences in rMT were analyzed using an independent *t*-test. A nominal alpha level of 0.05 was chosen for all statistical tests. For multiple comparison correction we used Bonferroni correction by controlling for six independent tests. All analyses were done using SPSS20 (Armonk, NY, USA).

Results

Sample 1 (N-back before rMT): There was no significant difference in rMT between men and women ($t(138) = 0.23$, $P = 0.82$). The results of our univariate ANOVAs for 0-back-and 3-back-accuracy or -d' performance indicated no significant main effects of rMT or gender and no significant interaction between rMT and gender. However, we found significant interactions of rMT and gender on 2-back-accuracy ($F(1,136) = 8.85$, $P = 0.003$) as well as 2-back-d' ($F(1,135) = 11.36$, $P = 0.001$), which survived Bonferroni correction (six comparisons, see Table 1). Therefore, in post hoc analyses, 2-back correlations with rMT were calculated separately for men and women. In women, no significant correlations were found between any of the 2-back performance measures and rMT (2-back-accuracy $r(66) = 0.17$, $P = 0.16$; 2-back-d': $r(66) = 0.21$, $P = 0.1$). In men, rMT was negatively correlated with 2-back-accuracy ($r(70) = -0.31$, $P = 0.008$) as well as 2-back-d' ($r(69) = -0.34$, $P = 0.003$, see Fig. 1), meaning that men with lower rMT showed a higher N-back performance. Moreover, regressing out mean N-back reaction times, 0-back performance, age, VAS for anxiety, STAI, daily intake of stimulants (caffeine, nicotine, alcohol), motivation, degree of dexterity or daytime of experiment, each separately, did not affect these negative correlations between rMT and 2-back performance in men.

Potential smaller variances within the 0-back or 3-back condition compared to 2-back condition may obscure the detection of significant correlations with rMT. Comparison of variance indicated a trend toward less variance for 0-back-d' compared with 2-back-d' ($F(1,140) = 3.2$, $P = 0.07$), as well as for 3-back-d' compared with 2-back-d' ($F(1,140) = 2.93$, $P = 0.09$, see Fig. S1). Furthermore, 2-back performance shared only little variance with 0-back performance ($r^2 \leq 0.15$) and only a moderate variance with 3-back performance ($r^2 \leq 0.35$) (see Table S1).

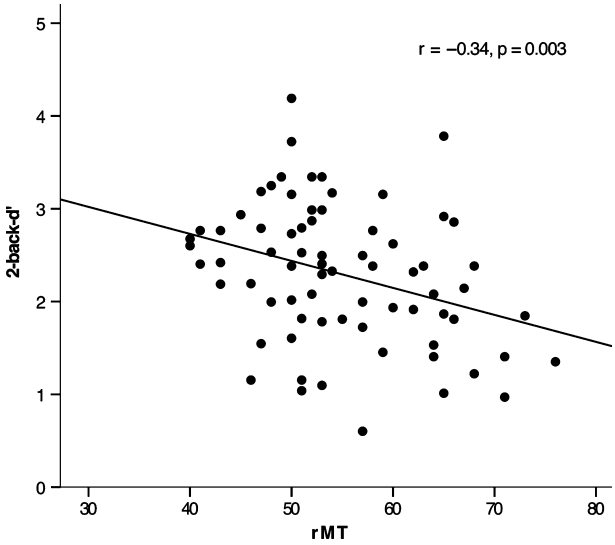

Figure 1. Correlation between working memory and motor threshold in men (Sample 1). 2-back-d': difference between the Z-transformed values of hit minus false alarm-rates in the 2-back condition; rMT, resting motor threshold.

Sample 2 (rMT before N-back): To investigate the possibility that the observed negative correlation between rMT and 2-back performance was due to the procedure of sample 1, meaning that working memory performance affects the subsequent measurement of the rMT, we also assessed rMT before the working memory task in an additional sample. The results of our univariate ANOVAs indicated no significant interactions between rMT and sex on N-back performances ($P > 0.24$). But we observed a significant main effect of rMT on 2-back performance (accuracy: $F(1,45) = 4.2$, $P = 0.047$, $\beta = -0.29$; d': $F(1,44) = 6.49$, $P = 0.013$, $\beta = -0.36$, see Table S2) indicating also in this sample a negative correlation between rMT and 2-back

Table 1. Accuracy and d' correlations with rMT in sample 1.

				Gender-specific correlations	
Variable of interest	Main effect gender	Main effect rMT	Gender by rMT interaction	Men ($n = 72$)	Women ($n = 68$)
Accuracy 0-back	$P = 0.69$	$P = 0.11$	$P = 0.67$		
Accuracy 2-back	$P = 0.002$	$P = 0.28$	$P = 0.003$**	$r = -0.31$, $P = 0.008$**	$r = 0.17$, $P = 0.16$
Accuracy 3-back	$P = 0.45$	$P = 0.29$	$P = 0.54$		
d' 0-back	$P = 0.74$	$P = 0.18$	$P = 0.82$		
d' 2-back	$P = 0.0003$	$P = 0.25$	$P = 0.001$**	$r = -0.34$, $P = 0.003$**	$r = 0.20$, $P = 0.10$
d' 3-back	$P = 0.92$	$P = 0.18$	$P = 0.91$		

**$P < 0.0083$ representing Bonferroni corrected α level. The relationship between rMT and 2-back performance differed across gender. rMT was Bonferroni corrected significantly correlated with 2-back performance in men.

performances (see Fig. S2). Comparison of variance indicated significantly less variance for 3-back-d' compared with 2-back-d' ($F(1,94) = 7.36$, $P = 0.008$ see Fig. S3). Furthermore, 2-back performance shared only little variance with 0-back performance ($r^2 \leq 0.05$) and only a moderate variance with 3-back performance ($r^2 \leq 0.37$).

Discussion

In this study, we found a significant negative correlation between rMT and working memory: a lower rMT predicted a better performance in a medium load working memory task (2-back-d', 2-back-accuracy). The correlation explained variance of about 12%. These findings suggest that rMT not only correlates with corticospinal excitability, but might be also related to a broader state of cortical activity. To our knowledge, these results are the first to indicate a direct association between motor cortex excitability and cognitive performance.

We did not find significant correlations between rMT and 0-back or 3-back. We cannot exclude, however, that the smaller variances in these conditions may have obscured the detection of significant correlations in the 0-back or the 3-back condition. In sample 1, no correlation was detected in women. Animal as well as human studies indicate an influence of ovarian hormones on neuronal excitability[8,9] and on working memory.[28] Therefore, it is possible that an inhomogeneous distribution regarding ovarian hormone levels across the samples may have led to different TMS findings between sample 1 and sample 2. Clearly, more studies are needed to investigate the relation of rMT and cognitive functions and to assess possible gender differences. At this stage, the conclusion regarding the relation between rMT and 2-back performance should to be restricted to men.

Importantly, we found a significant negative correlation between rMT and 2-back working memory independent of rMT application order. This finding suggests that the observed correlation was not due to working memory performance effects on rMT or due to TMS effects over M1 on working memory.

In conclusion, the present findings suggest that motor cortical excitability in men correlates with working memory performance, which depends on cortical areas beyond the motor cortex. The correlation found between corticospinal excitability and working memory may add to the understanding of human cognitive processes and has potentially important clinical implications, as working memory deficits are a key component of neuropsychiatric disorders, such as schizophrenia,[29] bipolar disorder,[30] and attention deficit hyperactivity disorder.[31] Moreover, the findings may have important clinical implications with regard to conditions of altered cortical excitability. For instance, TMS could prove useful to probe and monitor drug treatments with known effects on cortical excitability and working memory.

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Author Contributions

D. J.-F. d.Q., K. S., and A. P. designed the study and wrote the manuscript. N. S. designed and conducted the study, analyzed the results and wrote the manuscript. T. N. wrote the manuscript. M. F., K. Sp. and A. M. analyzed the results and wrote the manuscript.

Conflict of Interest

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. d' N-back performance in men of sample 1. Comparison of variance indicated a trend toward less variance for 0-back-d' compared with 2-back-d' ($F(1,140) = 3.2$, $P = 0.07$), as well as for 3-back-d' compared with 2-back-d' ($F(1,140) = 2.9$, $P = 0.09$).

Figure S2. Correlation between working memory and motor threshold (Sample 2). 2-back-d': difference between the Z-transformation of hit- minus false alarm-rates in the 2-back condition; rMT, resting motor threshold.

Figure S3. d' N-back performance in sample 2. Comparison of variance indicated significantly less variance for 3-back-d' compared with 2-back-d' ($F(1,94) = 7.36$, $P = 0.008$), but not for 0-back-d' compared with 2-back-d' ($F(1,94) = 0.05$, $P = 0.48$).

Table S1. Shared variances between 0-, 2-, and 3-back performances in men of sample 1.

Table S2. Accuracy and d' correlations with rMT in sample 2.

