

The effect of response frequency on cognitive brain activity during an alertness task

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A required response forces the brain to react overtly on a stimulus. This may be a factor that influences cognitive activity during a task, as it could facilitate for instance alertness, especially in tasks that are relatively easy. In the current article, we therefore tested the hypothesis that response frequency affects cognitive brain activity in an alertness task. In this 3T functional MRI study, healthy volunteers performed a continuous performance task with three conditions with increasing response frequency. Only scans during presentation of non-targets were analyzed, to exclude activity related to the change in frequency in response selection and motor responses between conditions. To evaluate changes in cognitive brain activity, a network analysis was performed based on two main networks including regions with task-induced activation and task-induced deactivation. We tested for differences in brain activity as an effect of target frequency. Performance results indicated no effect of target frequency on accuracy or reaction time. During non-targets, we found significant signal changes in TID for all three conditions, whereas TIA showed no significant signal changes in any condition.

Introduction

Being able to adjust alertness is important in daily life. We are all aware that task performance can be improved by increasing our level of alertness. Alertness appears to be influenced by various factors. A lack of sleep or tiredness can for instance lead to a lower level of alertness, which makes cognitive performance more challenging. Apparently, alertness is a function of the brain that can be modulated. Another important external factor that may influence cognitive brain activity is the demand for action. There is, however, almost no literature available from imaging research that examines this question. The goal of the current study is therefore to examine how the response frequency affects cognitive brain activity. This knowledge may aid in understanding the role of the demand for overt action on brain activity.

Target frequency did not have a significant effect on the level of signal change at network level, as well as at individual region level. Our study showed predominantly deactivation during non-responses in all three task conditions. Furthermore, our results indicate that response frequency does not influence brain activity during an alertness task. Our results provide additional information relevant for the understanding of the neurophysiological implementation of cognitive control or alertness. *NeuroReport* 30: 1166–1171 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

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Arguably one of the most important discoveries that has been made using neuroimaging research is that performance of cognitive tasks does not only increase activity in specific brain regions, but also reduces activity in a large set of other brain regions [1,2]. The network of regions that reduce their activity during performance of many cognitive tasks is called the default mode network (DMN). In this study, we will focus on the effect of target frequency on both activated as well as deactivated regions of the brain.

Target detection depends on many processes other than alertness, such as visual perception, decoding, target detection, response selection and response execution. Our assumption is that the target frequency will affect the overall level of alertness during a task, and thus can be measured during presentation of targets as well as non-targets. In order to focus as much as possible on activity associated with alertness, and exclude activity related to successful target detection and motor responses, we focused on activation associated with the presentation of non-targets which did not require a response. In our experiment, we used three conditions with an increasing

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frequency in targets and tested for effects of target frequency in two networks, with one consisting of regions showing task-induced activation (TIA), and one of regions showing task-induced deactivation (TID).

Methods

Participants

Eighteen healthy right-handed volunteers participated in this 3T functional MRI (fMRI) study [M/F: 5/13; mean age: 28.7 years (SEM: 1.7)]. Participants were recruited through online advertisement. Exclusion criteria included: left-handedness, diagnosed neurological or psychiatric disorders, severe concussion of the brain with loss of consciousness in the past, or contraindications for the MRI-scan (such as pregnancy, magnetic elements in the body and claustrophobia). All participants gave written informed consent before the scan session. This study was approved by the Independent Ethical Committee (protocol number: NL51147.028.14).

Task design

We used a short alertness task, based on a continuous performance task (CPT) paradigm. The CPT is widely used in neuroscience research and fMRI experiments to investigate sustained attention [3–5]. In our version, participants were instructed to pay attention to a fast, sequential display of consonants. Participants were instructed only to respond if the consonant was the target letter 'X'. In order to examine whether brain activity will be influenced by response frequency, three task conditions with an increasing number of targets were presented: low (LO) with four targets, medium (MD) with 18 targets and high (HI) with 39 targets per condition. Targets were pseudo-randomly presented such that each stimulus category had varying intervals. Each condition was presented in two 30-second blocks with 39 trials (i.e. target and non-target stimuli) within each block. The total duration of one trial was 750 ms in which the stimulus was presented for 400 ms. The task blocks were separated by 15-second rest conditions, except for the middle rest condition, which was 30 seconds. The participants were not informed about the variation in target frequency but were only instructed to respond to the target letter 'X'.

A video projector displayed the visual stimuli on a screen placed behind the scanner, which the participants saw through a mirror attached to the head coil. The participants responded to a target by pushing a button on a button box with their right hand.

Performance

The response accuracy and reaction time were used as performance measurements. We calculated the mean accuracy and reaction time for each condition separately. To test for performance differences between the three conditions, we used two separate repeated-measures analysis of variance (ANOVA) with condition as

within-subject factor for response accuracy and reaction time, respectively.

Image acquisition

Scans were performed on a 3T Philips Achieva scanner (Philips Medical Systems, Best, the Netherlands) using a 32-channel SENSE head coil, which enables parallel imaging. A 3D T1-weighted structural image was acquired for anatomical registration purposes [scan parameters: TR/TE: 8.4/3.8 ms, FOV: 254 × 254 × 158 mm, flip angle: 8°, voxel size 1 mm isotropic, 158 slices (sagittal orientation)]. fMRI images were obtained using a 3D PRESTO pulse sequence [6,7] [scan parameters: scan time 1.5 seconds, TR/TE: 19/27 ms, FOV: 256 × 256 × 160 mm, flip angle: 10°, voxel size 4 mm isotropic, 40 slices (sagittal orientation), 201 volumes].

Functional MRI preprocessing

Functional MRI data were preprocessed and analyzed using SPM12. All scans were registered to the first scan to correct for subject movement during the experiment. Subsequently, the images were co-registered to the anatomical image and spatially normalized into standard Montreal Neurological Institute (MNI) space, using parameters derived from the spatial normalization of the anatomical image. Individual scans were spatially smoothed with a 3D Gaussian filter (full-width at half-maximum: 8 mm) to minimize effects of functional anatomical differences between subjects.

Functional MRI analysis

For the evaluation of the fMRI data, we performed an event-related general linear model (GLM) regression analysis with separate regressors for targets and non-targets in each condition, estimating the signal change compared to rest. To examine the effect of target frequency on brain activity without confounding effects of successful target detection or motor responses, we focused on results associated with the activation during non-targets. The tolerance values (which indicate the independence of regressors) were 0.53, 0.25 and 0.32 for the non-target regressor in the LO, MD and HI condition, respectively. A blocked GLM regression analysis that combined targets and non-targets for each condition was also performed in order to specify task-related activity which was used to select the regions of interest (ROIs).

Region of interest selection

A ROI analysis was performed for the group evaluation of signal changes, due to its superior statistical power over a whole-brain voxel analysis [8,9], as well as the possibility to statistically compare signal changes in different networks and regions, and because it allows for quantitative replication of the findings of our study [10].

A second level voxel-wise whole-brain analysis of the HI condition with targets and non-targets combined was

used to determine the ROIs. Areas in which the brain activity exceeded the threshold value of $|t| \geq 3.09$ were used to select ROIs. For the positive activity, we focused on activity within the central executive network [11,12], and excluded areas from our analyses that are known to be primarily related to motor-responses, such as the primary motor and premotor cortex, and excluded primary visual regions and non-cortical regions such as the thalamus. Cubic ROIs with a dimension of $15 \times 15 \times 15$ mm were placed over the activity of these activated or deactivated brain areas (Fig. 1a). Two networks were formed with the

selected ROIs, namely: TIA and TID. The average brain activity was calculated for each network. The location of the selected ROIs is presented in Fig. 1. MNI coordinates of the center point of the ROIs and the corresponding automated anatomical labeling (AAL) atlas labels [13] and Brodmann areas [14] are indicated in Table 1.

Statistical testing

All statistical hypothesis tests were performed using SPSS 24 using the results based on activation during non-targets. We applied a repeated-measures ANOVA with the

Fig. 1

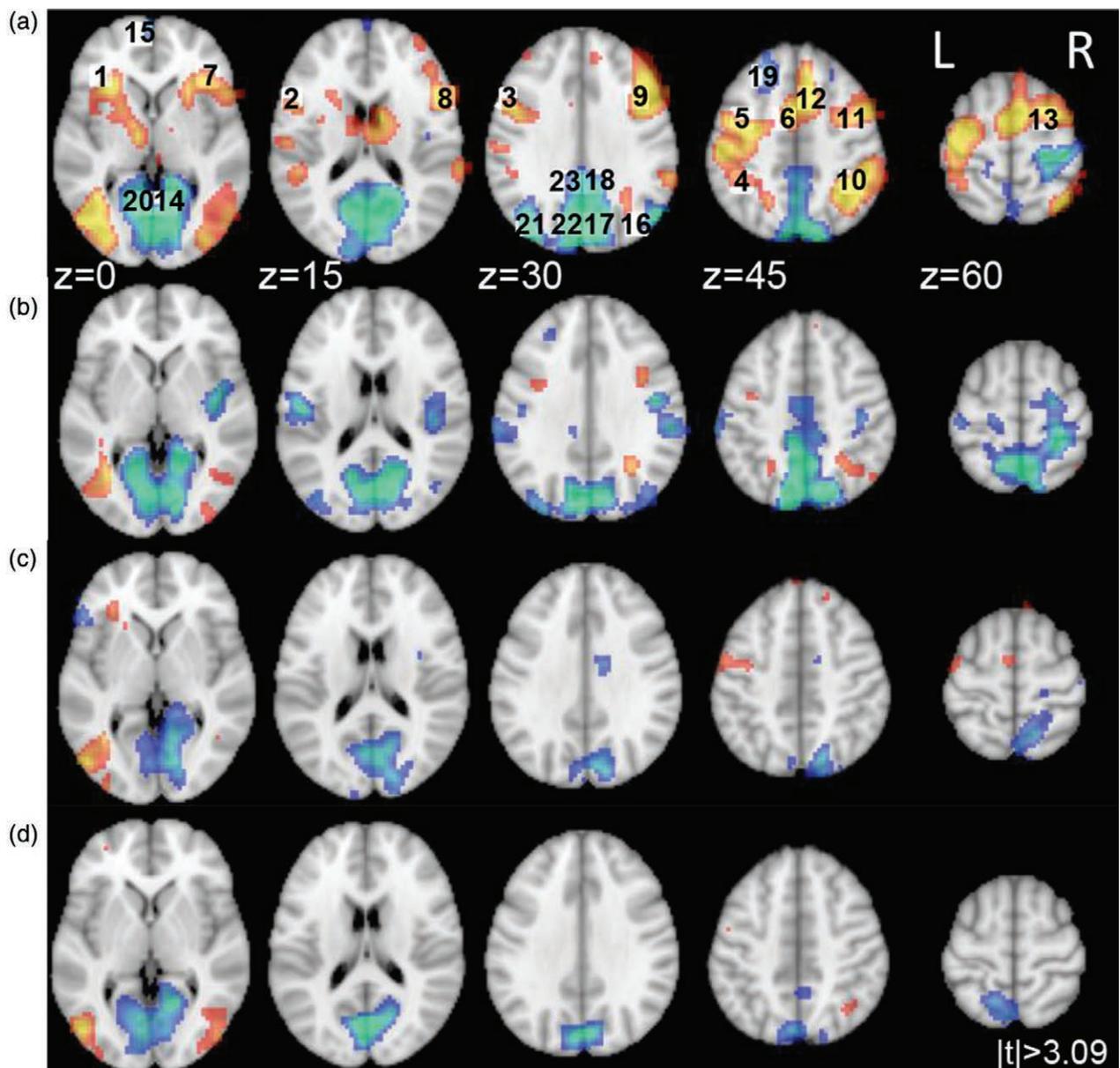


Illustration of the activation patterns ($|t| > 3.09$) and regions of interest (ROIs, see Table 1 for abbreviations and descriptions of the numbered ROIs). Task-induced activation is indicated in orange, task-induced deactivation is indicated in blue. (a) activation during HI condition used for ROI selection (targets and non-targets combined); (b) activation during non-targets in LO condition; (c) activation during non-targets in MD condition; (d) activation during non-targets in HI condition. HI, high; LO, low; MD, medium.

Table 1 Description of regions of interest and statistical results per region

TIA	AAL	ACRO	BA	NV	MNIx	MNIy	MNIz	INT		LOAD	
								F	P value	F	P value
ROI1	Left inferior frontal gyrus (triangular)	LIFGtri	47	125	-39	30	0	1.61	0.22	0.00	0.95
ROI2	Left inferior frontal gyrus (opercular)	LIFGop	44	124	-54	15	15	0.22	0.65	0.20	0.66
ROI3	Left inferior frontal gyrus (triangular)	LIFGtri	44	106	-54	15	30	1.33	0.27	0.35	0.56
ROI4	Left inferior parietal gyrus	LIPG	40	125	-39	-45	45	0.47	0.50	1.42	0.25
ROI5	Left precentral gyrus	LPreCG	6	125	-39	0	45	6.49	0.02	2.64	0.12
ROI6	Left median cingulate gyrus	LMCG	24	125	-9	0	45	0.14	0.71	0.17	0.69
ROI7	Right inferior frontal gyrus (orbital)	RIFGor	47	125	39	30	0	2.56	0.13	0.15	0.71
ROI8	Right inferior frontal gyrus (opercular)	RIFGop	44	125	54	15	15	0.48	0.50	0.52	0.48
ROI9	Right inferior frontal gyrus (opercular)	RIFGop	44	125	39	15	30	3.98	0.06	0.38	0.54
ROI10	Right inferior parietal gyrus	RIPG	40	125	39	-45	45	0.35	0.56	1.59	0.22
ROI11	Right precentral gyrus	RPreCG	6	125	39	0	45	2.94	0.10	3.49	0.08
ROI12	Right median cingulate gyrus	RMCG	32	125	9	15	45	1.05	0.32	0.89	0.36
ROI13	Right superior frontal gyrus (dorsolateral)	RSFGdl	6	125	24	0	60	4.65	0.05	2.23	0.15

TID	AAL	ACRO	BA	NV	MNIx	MNIy	MNIz	INT		LOAD	
								F	P value	F	P value
ROI14	Left lingual gyrus	LLING	18	125	-9	-60	0	37.83	0.00	0.25	0.62
ROI15	Left superior frontal gyrus (medial orbital)	LSFGmo	10	125	-9	60	0	1.22	0.29	0.71	0.41
ROI16	Left middle occipital gyrus	LMOG	39	118	-39	-75	30	6.49	0.02	0.00	1.00
ROI17	Left cuneus	LCUN	18	125	-9	-75	30	36.52	0.00	0.02	0.89
ROI18	Left posterior cingulate gyrus	LPCG	23	125	-9	-45	30	0.16	0.70	0.67	0.43
ROI19	Left middle frontal gyrus	LMFG	9	123	-24	30	45	0.61	0.45	0.69	0.42
ROI20	Right lingual gyrus	RLING	18	125	9	-60	0	54.23	0.00	0.05	0.83
ROI21	Right middle occipital gyrus	RMOG	39	123	39	-75	30	6.76	0.02	3.20	0.09
ROI22	Right cuneus	RCUN	18	125	9	-75	30	52.80	0.00	0.33	0.57
ROI23	Right posterior cingulate gyrus	RPCG	23	125	9	-45	30	5.15	0.04	0.05	0.83

The numbers of the individual ROIs correspond to the ROIs presented in Fig. 1. The Montreal Neurological Institute (MNI) coordinates of the center point of the ROIs and the corresponding AAL-atlas labels and Brodmann areas (BA) are indicated. We performed a repeated-measures ANOVA intercept test (INT) to identify regions that are (de)activated during non-targets. A linear contrast repeated measures ANOVA was performed to test for the effect of target frequency (LOAD). Significant results are indicated in bold ($P < 0.05$). Since the network results were not significant in TIA (both tests) and TID (LOAD test), Bonferroni correction was applied to correct the results of the individual ROIs for multiple comparisons in these three tests.

AAL, automated anatomical labeling atlas; ACRO, acronym; ANOVA, analysis of variance; BA, Brodmann area; INT, repeated measures intercept test; MNI, Montreal Neurological Institute; NV, number of voxels; ROI, region of interest; TIA, task-induced activation; TID, task-induced deactivation.

three task conditions as repeated measures for TIA and TID separately. We used the intercept test (which tests if the average signal of the conditions differs from zero) to identify if TIA or TID showed significant signal changes during non-targets. In order to test the hypothesis that the TIA or TID networks were affected by response frequency, we tested for a linear effect of target frequency in TIA and TID using a repeated measures linear contrast ANOVA. For follow-up analysis, the intercept as well as the linear contrast test were repeated for each individual ROI. Bonferroni corrections were not applied if the omnibus test of the network to which the ROI belonged was already significant.

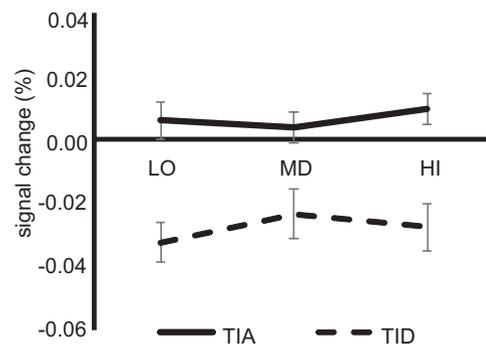
Results

Performance

The accuracy (mean \pm SEM) was 99.8 ± 0.1 , 99.6 ± 0.1 and 98.6 ± 0.4 for LO, MD and HI respectively. Reaction times (mean \pm SEM) were 407 ± 10 , 385 ± 9 and 400 ± 11 ms for LO, MD and HI respectively. There was no significant difference between conditions in accuracy ($F = 3.28$, $P = 0.06$) nor reaction times ($F = 0.52$, $P = 0.48$).

Region of interest analysis

Detailed results from the analyses are presented in Fig. 1 and 2 and Table 1. The TID network showed significant

Fig. 2

Network activation during non-targets: signal change (\pm SEM) for the LO, MD and HI condition within the TIA (solid line) and TID (dashed line) networks: the TID showed deactivation in all conditions during non-targets. There was no significant activation within the TIA network over conditions during non-targets. The level of signal change was not affected by target frequency in TIA as well as TID. HI, high; LO, low; MD, medium; TIA, task-induced activation; TID, task-induced deactivation.

deactivation during non-targets compared to rest, as indicated by the significant repeated measures intercept test ($F = 35.10$, $P < 0.001$). The level of deactivation in the TID network was not affected by the target frequency, as indicated by a strongly non-significant linear contrast

ANOVA test ($F = 0.23$; $P = 0.62$) (Fig. 2). Follow-up tests for the individual ROIs of the TID network confirmed these results, as all individual ROIs of the TID showed significant deactivation except for LSFGmo, LPCG and LMFG, and none of the ROIs showed a significant linear contrast (Table 1).

The TIA network did not show a significant signal change during non-targets compared to rest, as reflected by the repeated measures intercept test ($F = 2.72$, $P = 0.12$). There was also no significant signal change in the TIA network as a function of target frequency, as reflected by the linear contrast ($F = 0.28$, $P = 0.61$) (Fig. 2). Follow-up analyses on individual ROIs indicated that within the TIA network, none of the regions showed a significant signal change after correction for multiple comparisons. Furthermore, none of the individual regions showed a significant linear change with the target frequency (Table 1).

Discussion

The main goal of this study was to examine if response frequency can affect cognitive brain activity. For this purpose, we designed a task based on a continuous performance paradigm, with three conditions with varying target frequency. In order to minimize the direct motor effects of the varying response frequency, we analyzed activation during non-targets that did not require a response.

Our results indicated significant changes in brain activation during non-targets in all three conditions, indicating sufficient power to potentially detect an effect of target frequency. These signal changes included predominantly deactivation. More importantly, the level of deactivation was not affected by target frequency. Our results indicate that response frequency does not affect the level of cognitive brain activity during an alertness task.

Our results may be relevant for further understanding of how the brain interacts with environmental requirements. Although it may appear intuitive that increasing the response frequency could be an adequate method to facilitate a high level of alertness, our study did not show evidence for this concept, at least not in level of brain activity. However, even if there is not a direct effect of target frequency on the level of brain activity, it may still be possible that a high response frequency has a positive effect on task performance, as it may facilitate to direct attention to relevant stimuli and not to distracting stimuli.

Our study also indicated that, apart from higher visual regions, there was only consistent deactivation during non-responses in all three conditions, but no activated regions. This deactivation is likely associated with functions that need to be inhibited to optimize performance. This finding replicates previous findings of Jansma *et al.*

[15] who also did not report any increase in activation during automatic processing of non-targets. Thus, these studies suggest that concepts like attention and alertness that need to be at a high level both during targets as well as non-targets, is not reflected in increases in activation, but possibly with decreases in activation compared to rest.

An interesting finding in our study, although unrelated to our main hypotheses, was the fact that the medial frontal DMN regions were not deactivated during non-targets, despite the fact that our task required a continuous high level of alertness and goal-oriented behavior. Some previous studies have shown that the level of deactivation in the medial frontal regions is correlated with the difficulty of a task [15–18]. As the task that was used in our study was relatively simple, our results are in line with these previous findings.

Some limitations have to be taken into account while interpreting the results of this study. First, our task did not require maintenance or manipulation of information, and thus had a low level of cognitive processing. Possibly, cognitive brain activity may be affected by the response frequency in a task that requires a high level of cognitive processing. Second, while our results suggest that the deactivation plays an important role in alertness, we were not able to examine the possible involvement in performance, due to the near-perfect performance in all conditions.

To conclude, our study showed predominantly deactivation during non-responses in all three task conditions. The target frequency did not have an effect on brain activity in activated or deactivated regions during non-responses in our alertness task. This indicates that response frequency does not influence brain activity during an alertness task. Our results provide additional information relevant for the understanding of the neurophysiological implementation of cognitive control or alertness.

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Conflicts of interest

There are no conflicts of interest.

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