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The use of fMRI to detect neural responses to cognitive interference and planning: Evidence for a contribution of task related changes in heart rate?

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HIGHLIGHTS

- We examine the impact of heart rate variation on fMRI during the Stroop and ToL task.
- Both tasks show significant task-related changes in heart rate.
- The fMRI BOLD signal shows significant sensitivity to these changes in heart rate.
- However, fMRI main task effects are marginally influenced by the heart rate changes.
- We conclude that heart rate changes do not impact strongly on fMRI task effects.

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ABSTRACT

fMRI signals during rest are strongly correlated with heart rate variations. These heart rate/fMRI associations may influence the results of brain activation studies, particularly if heart rate is affected by the task. To assess the contribution of task-related heart rate changes on fMRI brain activation related to executive processing, we co-registered the electrocardiogram with fMRI in 91 subjects during an interference task (color-word Stroop) and during a planning task (Tower of London; ToL). We found that both Stroop interference and ToL planning significantly increased heart rate in the scanner and confirmed significant main effects of heart rate regressors on the fMRI signals. Nevertheless, statistical contrasts that test for increased fMRI during Stroop interference and ToL planning were not significantly influenced by inclusion of heart rate regressors. We conclude therefore that fMRI changes associated with heart rate changes do not impact strongly on higher-order fMRI effects in these commonly used executive function tasks, but routinely adding a correction seems prudent.

1. Introduction

The applicability of functional Magnetic Resonance Imaging (fMRI) as a neuroimaging tool rests on the assumption that fMRI signal changes include a Blood Oxygenation Level Dependent (BOLD) mechanism (Ogawa et al., 1992). This implies that regional brain activations result in local excess of oxy-hemoglobin supply, which leads to an increase in the homogeneity of magnetic susceptibility, an increase in T2*, and hence increased fMRI signal (Buxton, 2009). Obviously, fMRI is only a very indirect measure of brain activity and, apart from the BOLD-effect, T2* is also influenced by hemodynamic and metabolic fluctuations due to other physiological factors such as respiratory and cardiac cycles which modulate blood oxygen levels and microvessel diameters (Triantafyllou et al., 2011, 2005; Glover et al., 2000; Windischberger et al., 2002; Birn et al., 2006; van Houdt et al., 2010; Bhattacharyya and Lowe, 2004; Katura et al., 2006; Tong et al., 2011). Indeed, it has recently been demonstrated for recordings during resting state conditions that fMRI signals over large parts of the brain are correlated with changes in heart rate (Shmueli et al., 2007; de Munck et al., 2008; Chang et al., 2009).

If there are no systematic differences in cardiac activity between task conditions, one could argue that the effects of this physiological noise can always be compensated by recording a sufficient number of trials. However, in paradigms where heart rate is modulated by

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the task, there may well be contributions of fMRI signal changes correlated with cardiac activity to the statistical parametric maps (SPMs). Statistically significant differences between task conditions may then not be caused by the BOLD-effect alone, but also by non-neuronal responses of the vascular bed to heart rate variations.

An important domain of neuroimaging research where task related heart rate variation may occur is the measurement of brain activation during executive control. Executive control paradigms are well known (and often used as) cognitive stressors that influence cardiovascular reactivity (e.g., Willmann et al., 2012; Sheu et al., 2012; Gianaros and Sheu, 2009). Therefore, we focused in this study on the influence of fMRI signal changes correlated with cardiac activity during executive processes. Specifically, we performed simultaneous electrocardiogram (ECG) and BOLD fMRI recordings during the color-word Stroop task and a Tower of London (ToL) planning task. We selected these paradigms because, jointly, they cover a broad spectrum of executive functions, i.e., performance monitoring and top down inhibition, working memory, planning and problem solving. In addition, assessment of the influence of heart rate variation on measured brain activity for these tasks is very important given that they have evolved as common work horses to test for cognitive control and computerized versions of these tasks are very popular for fMRI studies on executive control related brain activity. The designs of the paradigms were also such that they covered the two basic experimental setups for BOLD fMRI assessment; the Stroop task was administered in a blocked paradigm and the ToL in an event-related paradigm. The subjects in our study are monozygotic twins, selected from a large twin cohort established to assess genetic and environmental influences on fMRI signals from the brain (den Braber et al., 2010, 2012). Here, we exploited the advantage of having recordings from monozygotic twins specifically to investigate the stability of our findings. That is, we first computed our results using an initial sample composed by randomly selecting one member of each twin pair, and then repeated the analyses in the set of the remaining identical co-twins. In this way an exact replication of the experiment is achieved, without the confounder of learning effects. fMRI Task effects due to heart rate modulation were assessed by computing task related fMRI changes using a general linear model (GLM) that includes estimation of heart rate effects by adding heart rate regressors, and comparing the results with the fMRI signal changes from a GLM without inclusion of heart rate information, as is standard practice in BOLD fMRI research on the effect of executive function tasks.

2. Materials and methods

2.1. Subjects

From the Netherlands Twin Registry (Boomsma et al., 2002) we recruited a 'Test sample' of 46 subjects. All subjects (13M/33F: mean age 36.9 ± 8.9 yrs) were twins from monozygotic pairs, but by selecting only one of the members from each pair, shared family backgrounds were avoided. To investigate the stability of our findings, we repeated our analyses in the set of co-twins of the subjects in the test sample, which we will refer to as the 'Repetition sample'. However, for one of the co-twins (F: 35 yrs) no MRI data was available, leaving 45 subjects in the repetition set. None of the twins in both samples had a history of neurological illness as assessed from self-report surveys, and all twins provided written informed consent. The study was approved by the VU university ethical review board.

2.2. Tasks

The Stroop task of this study consisted of standard color-word stimuli as well as words with emotional content. For our purpose we investigated only the results pertaining to color-word interference, because it had the largest effect on task performance and heart rate. During the Stroop color-word task, subjects had to report the ink color of written color words. Dutch translations of the words "red", "yellow", "blue" and "green" were used that could be written in any of these four colors. Word meaning and ink color could be either congruent (e.g. the word "green" written in green) or incongruent (e.g. the word "red" written in blue). The correct answer had to be indicated by pressing buttons: left middle finger for ink color yellow, left forefinger for green, right forefinger for red and right middle finger for blue. The task was administered in a block design with 18 blocks in total. Of these, 3 blocks contained congruent (C_COL) and 3 blocks contained incongruent color-word stimuli (I_COL). The remaining blocks were filled with words that convey general emotional content (NEG: 3 blocks, e.g., cancer, suffocate, etc.), words with content related to obsessions/compulsions (OCD: 3 blocks, e.g., guilty, dirty, etc.), and neutral words with similar linguistic parameters (e.g. word length and frequency of occurrence) as the words with emotional content (N_NEG: 3 blocks) and neutral words with similar linguistics as the words conveying obsession/compulsion related content (N_OCD: 3 blocks). The order of the 18 blocks was held constant between subjects: [I_COL; N_OCD; OCD; N_OCD; NEG; N_OCD; I_COL; C_COL; N_NEG; I_COL; NEG; C_COL; OCD; C_COL; N_NEG; NEG; OCD; N_NEG]. In each individual block of 35 s, 16 words were presented for 2 s and separated by small intervals of 200 ms. The subjects were asked to respond to the stimuli as quickly and accurately as possible. Total task duration was 10.5 min.

Stimuli for the ToL task consisted of images of colored beads (red, blue, yellow), placed on three vertical rods of decreasing height (Fig. 1). On each trial a start configuration and final target configuration were simultaneously depicted at the bottom and top of the screen, respectively. Subjects were requested to count the number of steps from the starting configuration to reach the target configuration. Five planning difficulty levels were included that corresponded with the minimal number of moves (1–5) actually needed to achieve the target. As a baseline condition, similar stimuli were presented but this time the subject only had to count the number of beads with specified colors. Each time, two possible answers (one correct and one incorrect) were presented at the bottom left and right of the screen, from which the correct one had to be indicated by pressing a corresponding left or right hand button. No feedback was provided during the task. The stimuli were presented in an event related design with self-paced stimulus timing, i.e., a subsequent trial was presented on the screen with a delay of 32 ms after the response on a previous trial. For all subjects the stimulus presentation order was the same, but the total number of trials depended on the subject's reaction times. Total task duration was 17 min. Here we will focus on the comparison of 4-steps planning versus baseline, because it showed the largest modulation of heart rate. The heart rate effect for 5-steps planning was less pronounced and not statistically significant (Test sample: $p = 0.148$: Repetition sample: $p = 0.859$). This is likely because several of our subjects experienced this condition as very difficult and reported that they had given up on a number of trials. On average subjects completed 16 ± 3 trials with 4-steps planning stimuli (~9% of the total number of trials) versus 62 ± 15 trials with baseline stimuli (~36%).

For both the Stroop and ToL, stimuli were projected on a screen at the end of the MRI scanner table, viewed by the participants through a mirror. Two magnetic compatible response boxes were used to record the subject's performance. Before the experiment, the subjects practiced a number of trials on a computer outside the scanner and again inside the scanner, prior to the actual start of the session.

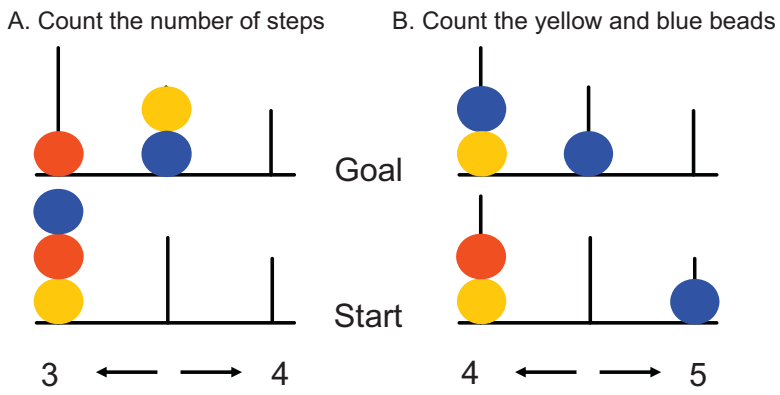

Fig. 1. Examples of Tower of London stimuli. (A) 4-Steps planning condition; (B) baseline condition. Adapted from van den Heuvel et al. (2005).

2.3. MRI and ECG

MR scans were made on a 3.0 T Intera MR system (Philips, Medical Systems, Best) with an 8-channel standard SENSE receiver head coil. Of each subject a three-dimensional T1-weighted gradient-echo sequence anatomical scan was made consisting of 182 coronal slices of 256 × 256 pixels; voxel size was 1.0 mm × 1.0 mm × 1.2 mm). For fMRI, an echo planar imaging sequence (flip angle 80°; repetition time = 2300 ms; echo time = 30 ms, matrix, 96 × 96 pixels; field of view 220 mm × 220 mm) was used, covering the whole brain (40 axial slices; 2.29 mm × 2.29 mm in-plane resolution; 3.0 mm slice thickness; no gap between slices). For the Stroop task a total of 260 and for the ToL a total of 440 EPI volumes were scanned per subject in one single run. During fMRI scanning a four-lead electrocardiogram (ECG) was recorded using the ECG system provided with the MR scanner, and sampled at 500 Hz. The ECG was stored in an ASCII log file and time aligned to the fMRI scanning using information from the additionally stored MRI field gradient onsets.

2.4. Inter heart Beat Interval (IBI) regressors

Inter heart Beat Interval (IBI) regressors were constructed similarly as described by de Munck et al. (2008). In brief, first the R-peaks of the QRS complex in the ECG were detected automatically and large changes (>30%) in consecutive RR intervals, i.e., the time between R-peaks of successive heart beats, were flagged and if necessary manually corrected after visual inspection. Subsequently, the ECG time series were subdivided into epochs corresponding to each of the fMRI scans (a single volume was acquired in 2.3 s). Since the RR interval times are irregularly sampled over time they cannot be directly used as IBI regressor. To compute an IBI value per fMRI epoch, all RR intervals were averaged having at least one point of overlap with that epoch. Since the effect of time varying heart beats on the fMRI signal does not follow the standard hemodynamic response function used for neuroimaging, IBI-regressors were shifted in time over multiple time steps of the MRI volume repetition time (TR), to account for possible delayed responses of the fMRI-signal to heart beat variations. In this way, the effect of heart beat on fMRI is described with a general impulse response model, where the optimal response shape is a priori unknown and is extracted from the data. In this study we used 7 IBI-regressors corresponding to time shifts of [−2, −1, 0, 1, 2, 3, 4] × TR, i.e., from −4.6 to +9.2 s. The IBI time series were either considered as effects of interest, or as 7 additional nuisance regressors in the GLM for statistical testing, or ignored.

We also used the ECG data to test if heart rate changed with task difficulty. To compute a mean IBI value per stimulus type for the Stroop task in each individual we took the mean of all RR interval times that overlapped each individual stimulus block and then averaged these mean RR times separately across the 3 blocks with congruent and incongruent color-word stimuli, respectively. For the ToL we first computed, for each stimulus, the mean of all RR times that overlapped the interval between stimulus onset and the subject's response and then averaged the mean RR times per stimulus type. Similar to the computation of IBI values per fMRI epoch, all RR times were included having at least one point of overlap with the relevant epoch (i.e., stimulus block for the Stroop task and interval between stimulus onset and the subject's response for the ToL task).

2.5. Statistical analyses

MRI data were analyzed using Statistical Parametric Mapping version 5 (SPM5: Wellcome Department of Imaging Neuroscience, London, UK). Echo planar imaging scans were slice time corrected, realigned and normalized to the standard Montreal Neurological Institute (MNI) brain of SPM. Subsequently, data were re-sliced to 3 mm × 3 mm × 3 mm voxels and spatially smoothed using an 8 mm isotropic Gaussian kernel. After high-pass filtering with cut-off at 128 s (0.0078125 Hz), functional scans were analyzed in the context of the general linear model using delta functions convolved with a canonical hemodynamic response function. For the ToL task, event duration, computed as the time between stimulus and response onset, was included in the GLM to account for hemodynamic responses of varying lengths to each type of stimulus. Error trials and head-movement parameters were modeled as regressors of no interest. For the Stroop task, a 'color-word interference' main effect was computed in which brain activation during trials with color-word incongruent stimuli was compared with brain activation during trials with color-word congruent stimuli. For the ToL task, we applied a 'planning versus baseline' contrast to compare brain activation during 4-steps planning with brain activation during baseline. The 1st-level results for each individual were computed twice; once with and once without taking into account all 7 IBI-regressors. The influence of including IBI-regressors in the GLM was assessed statistically by means of a paired *t*-test that compared the 1st level results of each subject with and without inclusion of the 7 IBI-regressors. Task main effects across subjects are reported after correction for multiple comparisons using a false discovery rate of 5% and a minimal cluster size of 10 voxels.

Table 1
Task performance and IBI changes.

Task	Condition	Test sample			Repetition sample			Test versus Repetition		
		Reaction time (ms)	Accuracy (%)	IBI (ms)	Reaction time (ms)	Accuracy (%)	IBI (ms)	Reaction time	Accuracy	IBI
Stroop	Congruent	808.7 ± 145.5	95.2 ± 6.0	836.3 ± 137.1	792.5 ± 129.8	96.3 ± 5.0	820.2 ± 129.4	.416	.226	.449
	Incongruent	956.9 ± 168.4	82.6 ± 12.9	827.7 ± 132.9	967.7 ± 157.9	83.4 ± 10.9	815.3 ± 121.0	.536	.687	.533
ToL	Baseline	3566.1 ± 874.8	93.2 ± 4.3	825.1 ± 125.8	3636.6 ± 995.6	94.2 ± 2.6	814.5 ± 121.6	.456	.124	.563
	Planning	11,580.0 ± 5229.7	75.1 ± 13.1	817.3 ± 124.8	11,830.8 ± 4716.1	77.9 ± 13.5	809.2 ± 120.1	.402	.334	.652

Mean reaction times (ms ± sd), mean reaction accuracies (ms ± sd) and mean Inter heart Beat Intervals (IBIs: ms ± sd) for the twins in the Test and Repetition sample on color-word congruent and incongruent trials for the Stroop task and on baseline and 4-steps planning trials for the ToL task. The column Test versus Repetition indicates statistical *p*-values from paired *t*-tests between the twins in the Test sample and their co-twins in the Repetition sample (the paired tests included 45 pairs composed of twins from the Test sample and their MZ co-twins from the Repetition sample; for one additional twin in the test sample, data of the co-twin was missing).

3. Results

3.1. Task performance and Inter heart Beat Intervals

Table 1 shows mean reaction times, mean reaction accuracies and mean Inter heart Beat Intervals (IBIs) on color-word congruent and incongruent trials for the Stroop task and on baseline and 4-steps planning trials for the ToL task. Task performance and heart beat intervals were similar in the Test sample and Repetition sample (see column Test versus Repetition). Differences in task performance and IBIs between the two trial types of both tasks are highlighted in Fig. 2. Both Stroop color word interference (Fig. 2: left) and ToL planning (Fig. 2: right) were associated with significantly reduced reaction accuracies and significantly increased reaction times. Furthermore, reduced performance in both tasks was accompanied by shorter IBIs (=increased heart rate) which were all significant, except for Stroop performance in the Repetition sample. These task related IBI changes create the potential for an influence on the computed fMRI responses.

3.2. Main effects of IBI regressors

Fig. 3 shows fMRI main effects for the Stroop and ToL task of the 7 individual IBI regressors included in the GLM, corresponding to time delays between fMRI signal changes and heart rate changes ranging from $-2 \times TR = -4.6$ s to $+4 \times TR = +9.2$ s. Results are shown separately for tests of positive statistical contrast (*t*-test contrast +1: hot colors) and negative statistical contrast (*t*-test contrast −1: cold colors). Since decreased IBIs indicate increased heart rate and vice versa, the positive contrast tests for an inverse relation between heart rate and fMRI changes, whereas the negative contrast tests for co-variation between heart rate and fMRI signal changes. Fig. 4 additionally shows fMRI effect sizes at the different time delays for a selected voxel in the occipital cortex. As can be clearly appreciated from both Figs. 3 and 4, the correlation patterns across the different time delays are highly equivalent in the Test sample and Repetition sample and also appear similar for the Stroop task and ToL task, although the patterns are most robust for recordings during the ToL task. For time shifts of 0 and 2.3 s, co-variations between heart rate and fMRI signal changes

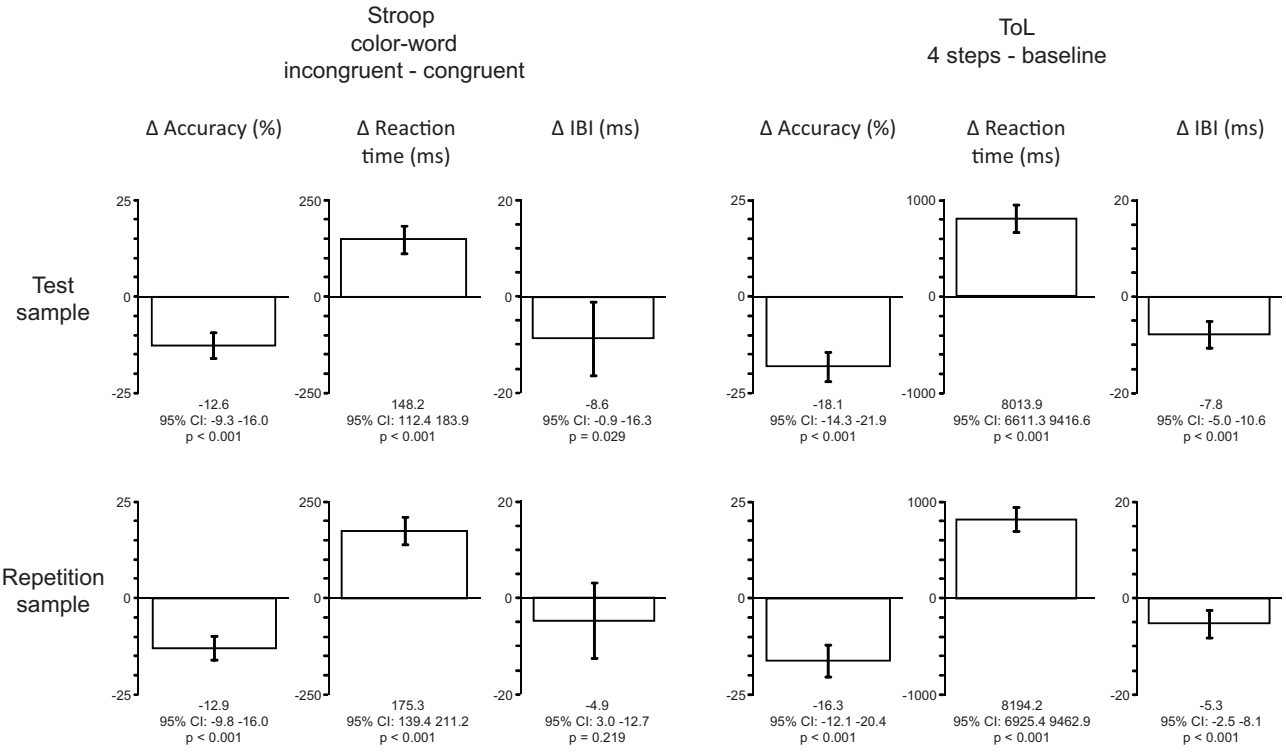

Fig. 2. Means of within subject differences in task performance (accuracy and reaction time) and Inter heart Beat Intervals (IBIs) on color-word incongruent compared to congruent trials for the Stroop task (left) and on 4-steps planning compared to baseline trials for the ToL task (right). Results of between condition paired *t*-test comparisons, for the Test sample (top) and Repetition sample (bottom), are indicated by 95% confidence intervals of the differences (CI: error bars) and *p*-values.

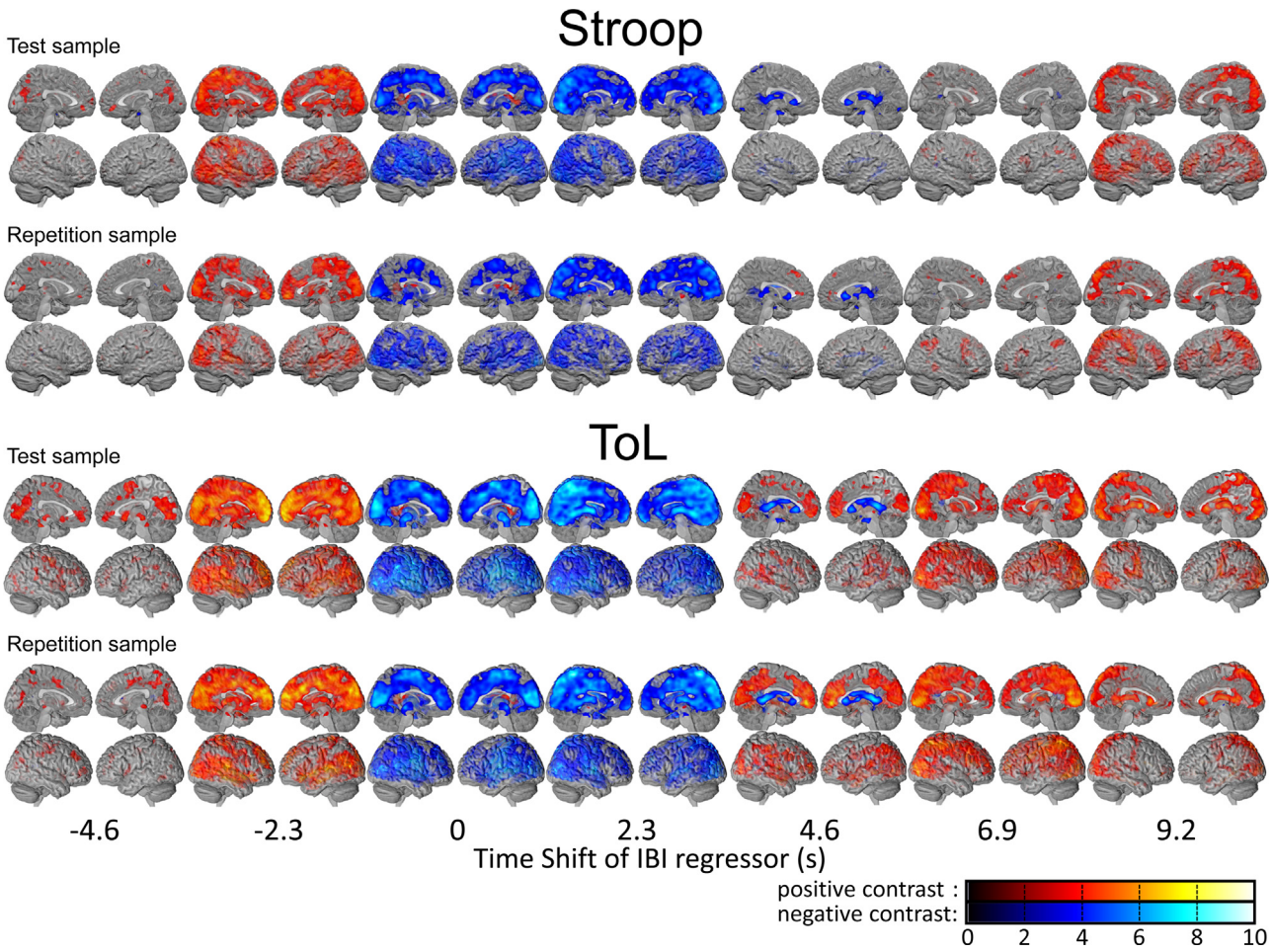

Fig. 3. Stroop task main effects (top) and ToL task main effects (bottom) of the 7 individual IBI regressors included in the GLM, corresponding to time shifts relative to the recorded fMRI signals of [−2, −1, 0, 1, 2, 3, 4] × TR (−4.6 to 9.2 s), for the Test sample and Repetition sample. Since decreased IBIs indicate increased heart rate and vice versa, the tests for positive contrast between IBI and fMRI changes (indicated by hot colors) indicate voxels where heart rate and fMRI are inversely related, whereas the test for negative contrast (cold colors) indicate voxels with co-variation between heart rate and fMRI modulations. The color bar indicates the statistical *t*-value mapping. (For interpretation of the references to color in figure legend, the reader is referred to the web version of the article.)

(suprathreshold voxels for negative statistical contrast) are evident across the whole brain, with posterior dominance. In contrast for larger positive time shifts of 4.6, 6.9 and 9.2 s, heart rate and fMRI are inversely related (suprathreshold voxels for positive statistical contrast). Similar inverse heart rate versus fMRI associations are observed for shifts of the IBI regressor back in time, in particular for a shift of −2.3 s.

3.3. *Influence of IBI variation on fMRI task effects*

Next, we examined the extent to which the higher heart rates (decreased IBIs) after Stroop color-word incongruent stimuli and after ToL planning stimuli contributed to the fMRI main effects obtained using the color-word incongruent versus congruent contrast for the Stroop task and 4-steps planning versus baseline contrast for the ToL task. Fig. 5 shows glass brain projections of SPMs for Stroop color-word interference (left panels) and ToL planning (right) in the Test sample (top) and Repetition sample (bottom). Lists of significant clusters for both tasks and samples are depicted in Tables 2 and 3 (direct statistical comparison did not reveal any significant differences between SPM activation maps from the Test sample and Repetition sample). In both samples, the SPMs computed without IBI-regressors were highly similar to the SPMs obtained with the 7 IBI-regressors. To statistically assess the influence of including IBI-data in the GLM, we applied paired *t*-tests that compared the 1st level results of each subject with and without accounting for the 7 IBI-regressors. Despite this highly sensitive test, we found no significant differences at our statistical threshold of $p < 0.05$, FDR corrected. For further post hoc analysis, to explore the possibility that there may be differences at some locations that failed our a priori threshold but however do show physiologically meaningful and reproducible spatial patterns, we lowered the threshold to a more lenient value of $p < 0.005$, uncorrected, with no cluster extend limit. The results for the Stroop and ToL task, depicted in Figs. 6 and 7, revealed a general tendency to find more clusters when testing for larger fMRI activations when using a GLM without heart beat regressors. However, as can be observed by comparing the glass brain projections as well as the MRI slice overlays which indicate the voxel with highest statistical *T*-value, the results for both tasks and for the Test and Repetition samples did not reveal a consistent pattern of differences at specific brain locations. Furthermore, the effect sizes of the difference contrast at the voxel with highest *T*-value, as indicated by the bar graph inserts on the slice overlays, were very small (<0.2).

Finally, we investigated if the impact of heart rate related fMRI changes on computed brain activations was larger in individuals with strong versus weak task related heart rate variation. Voxel by voxel correlation of differences between task related heart rate change in each subject and differences in 1st level results with and without accounting for the 7 IBI-regressors did not reveal any

clusters with significant association for both tasks and samples. In addition, we computed correlations between task related heart rate change in each subject and the difference in activated number of voxels (at $p < 0.005$, uncorrected) as well as maximum statistical T scores as derived from a GLM with versus without heart rate regressors. The correlation values for both samples are listed in Table 4. For the Stroop task, there were close to significant positive correlations for number of activated voxels and maximum T scores, indicating a tendency for a higher reduction in number of activated voxels and maximum T scores after inclusion of IBI regressors in individuals with a stronger task related heart rate increase, but this was true only in the Repetition sample. For the ToL task there was a close to significant negative correlation for activated number of voxels, indicating a tendency for an increase in number of suprathreshold voxels after inclusion of IBI regressors in individuals with a stronger task related heart rate increase, but this was found only in the Test sample.

4. Discussion

In this study we found that heart rate was influenced by task difficulty. This is in line with previous evidence for substantial momentary variation in heart rate both at rest and during conditions of mild cognitive load, assumed to reflect a complex set of hormonal, thermoregulatory, hemodynamic and respiratory effects on neural control over the heart (Berntson et al., 1997). The increase in heart rate to ToL planning stimuli was quantitatively similar to the heart rate change noted after color-word incongruent Stroop stimuli, despite the fact that the ToL task was administered in an event-related design, rather than a blocked design as used for the Stroop. It must be emphasized however that the inter-stimulus time windows in the present ToL task were determined by the planning reaction times of the subjects which amounted to about 12 s for the 4-steps condition. These relatively long trial spacings

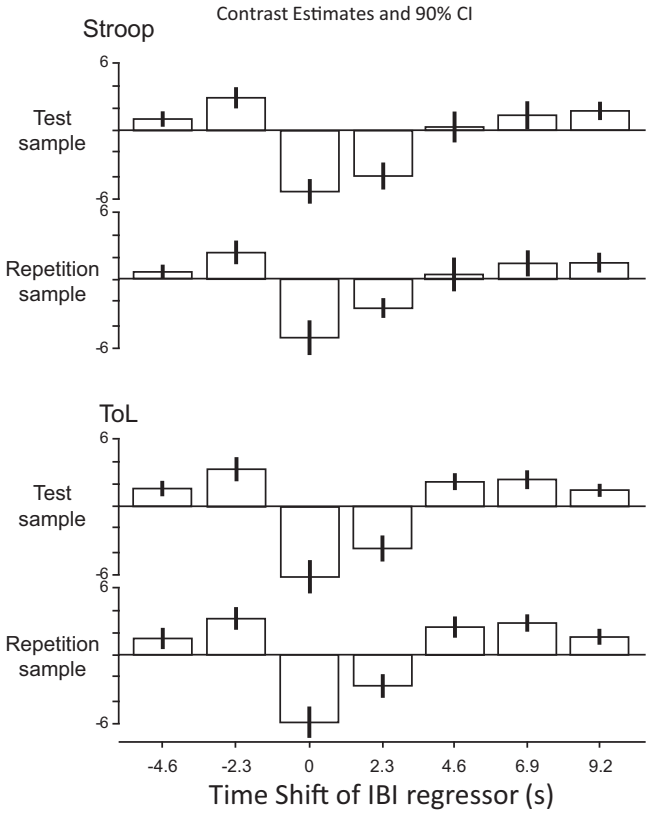

Fig. 4. Effect sizes (in arbitrary units) and 90% Confidence Intervals (CI) of the 7 IBI regressors for a single voxel in the occipital cortex (MNI coordinates $x = 6$ mm, $y = -78$ mm, $z = 6$ mm). We selected this location because it showed the largest IBI regressor effect in the Test sample group analysis for fMRI recorded during the Stroop task (for the contrast estimate of the unshifted IBI regressor: $0 \times TR = 0$ s). For each of the 7 time delays we selected the results of either the positive or the negative contrast between IBI and fMRI changes, depending on which one was largest.

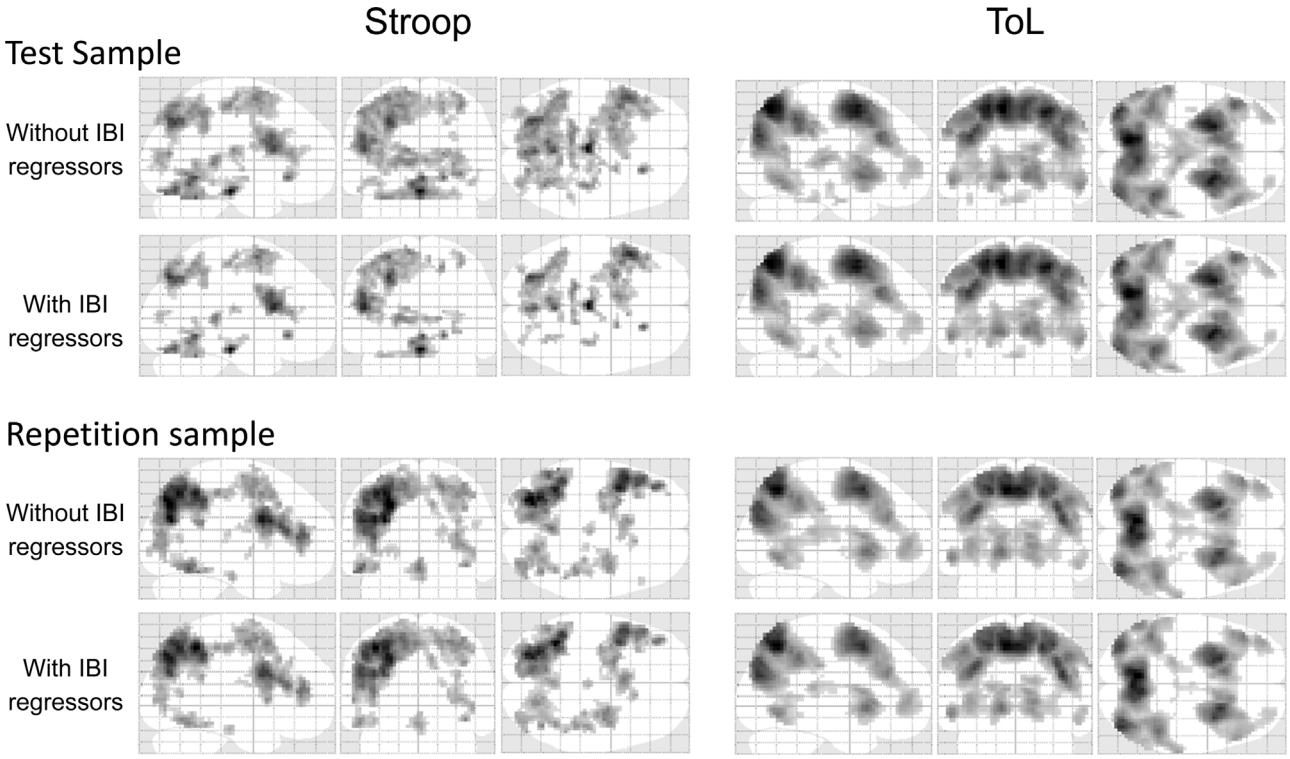

Fig. 5. Glass brain projections of SPMs for Stroop color-word interference (left) and ToL planning versus baseline (right) in the Test and Repetition samples. In each pane, top row projections indicate results without the IBI-regressors as confounders; bottom row projections results obtained with the 7 IBI-regressors as nuisance effects.

Table 2
Significant clusters from the SPMs for Stroop color-word interference.

Anatomical location		Test sample									Repetition sample								
		Without IBI regressors					With IBI regressors				Without IBI regressors					With IBI regressors			
		MNI coordinates			*T* score	# voxels	MNI coordinates			*T* score	# voxels	MNI coordinates			*T* score	# voxels	MNI coordinates			*T* score	# voxels
		x	*y*	*z*			*x*	*y*	*z*			*x*	*y*	*z*			*x*	*y*	*z*		
L./R.	Brainstem	0	−21	−18	7.06	925	0	−21	−18	6.69	96	3	−18	−24	3.95	31	3	−21	−21	3.96	21
L./R.	Cerebellum	–	–	–	–	–	3	−51	−6	5.34	347	0	−54	−15	5.13	86	0	−54	−15	4.37	74
L.	Caudate/Glob. Pall.	−21	0	21	3.69	21	–	–	–	–	–	−18	−3	0	3.34	12	–	–	–	–	–
R.	Caudate	21	30	−6	5.03	39	21	30	−6	5.06	22	21	−3	18	3.47	14	21	−9	21	3.27	12
L.	Thalamus	–	–	–	–	–	−12	−18	18	3.98	25	–	–	–	–	–	–	–	–	–	–
R.	Thalamus	–	–	–	–	–	–	–	–	–	–	18	−21	15	3.33	13	–	–	–	–	–
L.	Parahippocampus	−9	−36	6	4.71	453	−18	−33	9	4.66	103	–	–	–	–	–	–	–	–	–	–
R.	Parahippocampus	–	–	–	–	–	30	−57	−3	3.83	34	–	–	–	–	–	–	–	–	–	–
L.	Occipital/Parietal	−27	−69	42	5.76	928	−27	−75	45	5.78	532	−27	−75	42	7.47	1365	−36	−51	51	7.63	2089
		–	–	–	–	–	−33	−81	12	3.72	21	−27	−93	0	3.56	18	–	–	–	–	–
R.	Occipital	21	−75	15	4.57	101	21	−75	15	3.65	24	33	−84	15	4.54	162	48	−78	0	4.14	132
R.	Parietal	21	−66	60	4.14	133	21	−66	60	3.45	10	21	−69	57	4.90	413	36	−75	27	3.72	22
		24	−60	42	3.56	19	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
		30	−72	33	3.28	14	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
L.	Temporal	−42	−45	−9	3.65	41	–	–	–	–	–	−51	−57	−15	3.65	41	−51	−57	−15	4.69	128
R.	Temporal	45	−36	−12	3.54	20	–	–	–	–	–	42	−63	−12	3.54	20	42	−63	−12	4.61	15
R.	Precentral	36	−21	57	4.60	88	36	−21	57	4.20	40	42	−30	51	4.57	264	42	−30	51	4.37	88
L.	Frontal	−48	18	18	5.62	1188	−48	18	18	5.97	418	−39	9	27	6.90	785	−39	9	27	6.25	690
		–	–	–	–	–	−27	3	63	4.98	376	−30	6	51	4.65	404	−3	12	54	4.86	487
R.	Frontal	21	6	54	4.13	39	21	6	54	4.33	16	48	27	24	3.25	13	–	–	–	–	–

Lists of significant clusters from the SPMs for Stroop color-word interference in the Test sample (left) and Repetition sample (right). Left columns indicate results without the IBI-regressors as confounders; right columns the results obtained with the 7 IBI-regressors as nuisance effects. MNI coordinates and *T*-score are listed for the voxels with largest effect size in each cluster.

Table 3
Significant clusters for ToI 4-steps planning versus baseline.

Anatomical location		Test sample								Repetition sample							
		Without IBI regressors				With IBI regressors				Without IBI regressors				With IBI regressors			
		MNI coordinates			*T* score	# voxels	MNI coordinates			*T* score	# voxels	MNI coordinates			*T* score	# voxels	MNI coordinates			*T* score	# voxels
		x	*y*	*z*			*x*	*y*	*z*			*x*	*y*	*z*			*x*	*y*	*z*		
L./R.	Par./Occ./Temp./	−9	−72	57	13.70	4686	−12	−72	60	13.64	4563	−6	−63	54	14.82	5552	−6	−63	54	14.13	3778
	Thalamus/Caudate	−15	9	−3	8.27	1466	−15	9	−3	8.01	1335	–	–	–	–	–	−12	15	0	8.37	855
		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	−21	−33	18	5.18	80
		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	18	−57	21	5.14	81
		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	54	−57	−12	4.91	81
L./R.	Frontal/Cingulate	27	6	54	12.61	2897	27	6	54	12.64	2843	−24	12	54	12.26	2562	−24	12	54	11.44	1172
		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	24	12	51	11.28	1263
L.	Frontal	−33	57	9	4.83	142	−33	57	9	4.70	138	−39	51	6	6.17	198	−39	51	6	5.96	173
L.	Precuneus	−21	−57	21	3.66	24	−21	−57	21	3.50	15	–	–	–	–	–	–	–	–	–	–
L.	Temporal	−39	−12	−24	3.72	14	−39	−12	−24	3.17	11	–	–	–	–	–	–	–	–	–	–
	Brainstem	0	−33	−24	4.08	59	3	−33	−24	4.52	48	–	–	–	–	–	–	–	–	–	–
		−15	−18	−12	4.00	24	−15	−18	−12	3.59	13	–	–	–	–	–	–	–	–	–	–

Lists of significant clusters from the SPMs for ToL planning versus baseline in the Test sample (left) and Repetition sample (right). Left columns indicate results without the IBI-regressors as confounders; right columns the results obtained with the 7 IBI-regressors as nuisance effects. MNI coordinates and *T*-score are listed for the voxels with largest effect size in each cluster.

provide a substantial amount of time to allow for significant heart rate changes.

The spontaneous variations in heart rate were highly correlated with the fMRI modulations during our paradigms. Similar correlations across large parts of the brain, but most robust over posterior regions, have been noted for functional recordings during rest (Shmueli et al., 2007; de Munck et al., 2008; Chang et al., 2009). Furthermore, the pattern of correlations across the 7 heart rate regressors in this study is highly consistent with the response function between heart rate and fMRI modulations during the resting state condition as reported by de Munck et al. (cf. Fig. 4 in de Munck et al., 2008). For the IBI regressor aligned in time with the fMRI data (0 × TR) and a regressor delayed by 1 × TR, positive associations between heart rate and fMRI changes were observed, while for larger delays of 2, 3 and 4 × TR, there were inverse associations. This essentially indicates that heart rate increases are initially followed, between 0 and 4.6 s, by enhanced fMRI signal, and thereafter, between 4.6 and 9.2 s, by reduced fMRI signal (and vice versa). Similar inverse relations were observed for the IBI regressors advanced in time by −2 × TR, and in particular −1 × TR. This would mean that fMRI signal increases (decreases) are generally followed up to 4.6 s later by decreased (increased) heart rate.

It should be kept in mind that the associations between heart rate and fMRI modulations observed in this study do not necessarily imply causal relations. For example, the possibility that shifting the IBI regressor backward or forward in time just results in bringing the low frequency component of the IBI changes either in or out of phase with respect to the low frequency component of the fMRI modulations may play a role. These low frequency fluctuations in IBI and fMRI signals may for example be caused by respiratory effects that were not evaluated. However, the fact that the correlation pattern across the 7 heart beat regressors was similar during both tasks of this study, in particular for the unshifted regressor and the regressor delayed by 2.3 s, and that IBI-fMRI response functions comparable to the present ones have been observed in the resting state study by de Munck et al. (2008), indicates that the observed heart rate-fMRI relations, at least partly, represent systematic effects. In addition to indirect changes in blood oxygenation and microvessel diameter, these heart rate-fMRI relations may also, partly, indicate the control and monitoring of the cardiovascular system by the brain (Critchley et al., 2004; Critchley, 2005; Thayer et al., 2012; Gianaros and Sheu, 2009).

Irrespective of the exact biological background, the presence of associations between heart rate and fMRI changes together with our finding that heart rate was influenced by task demands creates a theoretical potential for a contribution of heart rate variation to computed fMRI group effects. In the paradigms and control subjects we explored, however, this contribution was small and not statistically significant. For both Stroop color-word interference and ToL planning, comparison of fMRI main effects after ignoring IBI information in the GLM with the main effects obtained after inclusion of IBI time series revealed the same general neurocircuitry engaged. In this context, it should be noted that the reduction of inter beat times after incongruent compared to congruent color-word stimuli for the Stroop and 4-steps planning versus baseline for the ToL were both in the order of about 8 ms. Although statistically significant, these changes are only marginal relative to the standard deviations of IBI times in this study which were in the order of 130 ms. With regard to the small effect size, it should be noticed that we compared conditions within a performed task (Stroop color-word incongruent versus congruent blocks; ToL planning versus baseline, i.e., counting colored beads trials), rather than equating heart rate between performing and not performing a task. Furthermore, we did not apply experimental manipulations to further increase stress, such as reducing Inter Trial Intervals to maintain a certain response error rate (Sheu et al., 2012). Overall, SPMs from the GLM

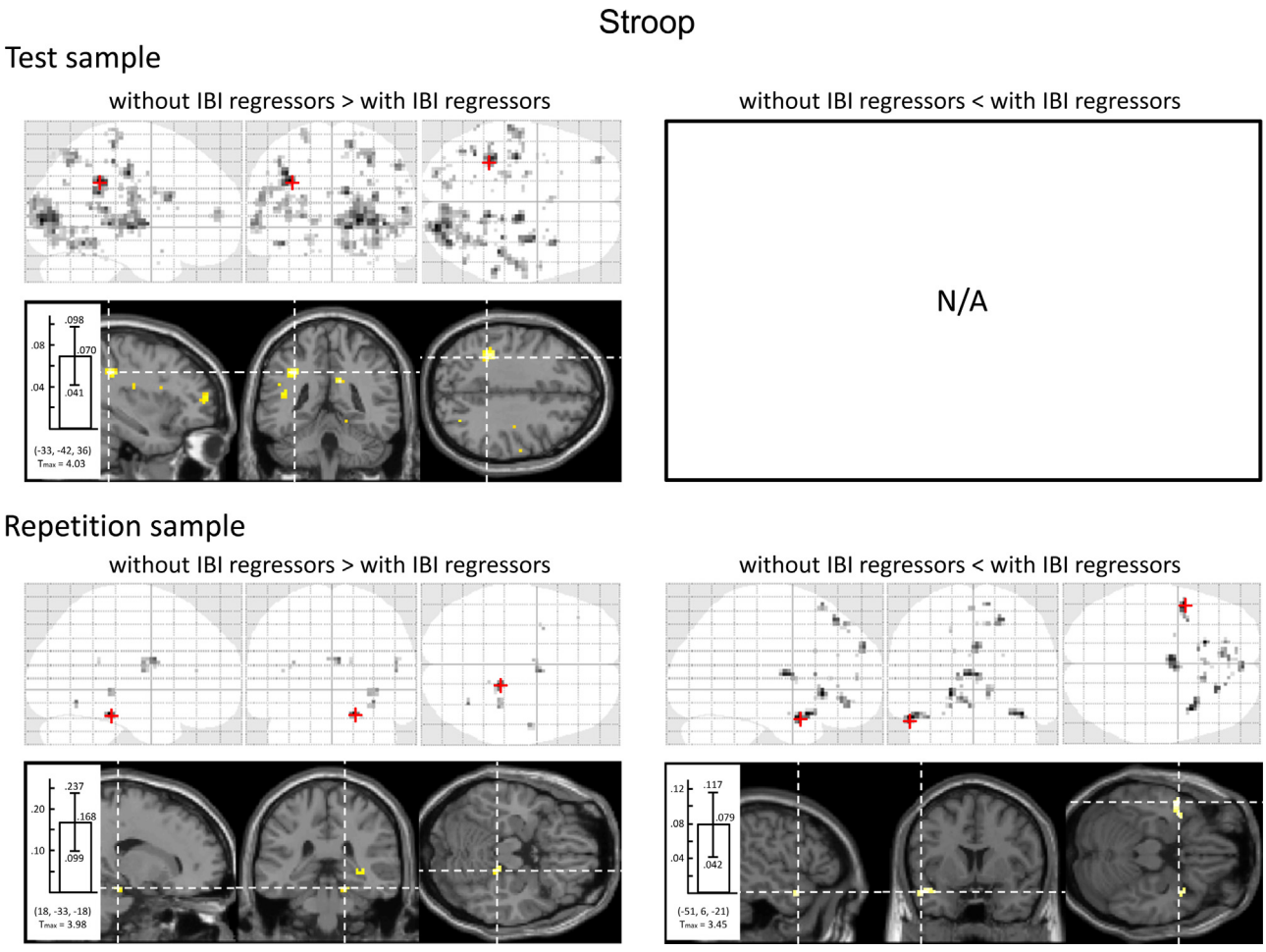

Fig. 6. Post hoc results of paired *t*-tests, at lowered statistical threshold, for the Test sample (top) and Repetition sample (bottom) that compare brain activations during Stroop color-word interference in each individual as estimated with versus without accounting for the 7 IBI-regressors in the GLM. On the left, tests for regions with higher activation when IBI-regressors were not included; on the right, tests for regions with higher activation when IBI-regressors were included. Glass brain projections in each panel indicate the overall distribution of the observed clusters. MRI slice overlays show the voxel with largest *T*-value, with bar graph inserts on each sagittal slice depicting the contrasts estimate and 90% confidence interval for this individual voxel (numbers within brackets below each bar indicate the MNI coordinates of the voxel and *T*max the maximum statistical *T*-value).

with regressors did show a tendency toward small reductions in voxel *T*-scores and number of suprathreshold voxels compared to the SPMs obtained without heart beat regressors. This effect of heart rate regressors on the SPMs, although not statistically significant, does imply that their inclusion in the GLM can potentially influence final conclusions, in particular in studies dealing with weak-to-detect fMRI signal changes and/or limited numbers of subjects.

Instead of our present approach based on inclusion of IBI regressors to account for an influence of heart rate, a cardiac response function as proposed by Chang et al. (2009) and RETROICOR (Glover et al., 2000) could also be applied (Brooks et al., 2008; van Buuren et al., 2010; Khalili-Mahani et al., 2013; Jo et al., 2010). However, modeling the effect of heart beat on fMRI without a-prior assumptions on the shape of the cardiac response function using a general impulse response model is more flexible and allows for modeling cardiac responses that deviate more from the standard and taking into account possible delayed responses of the fMRI-signal to heart beat variations. If a fixed and a priori known cardiac response would have been applied, our main results, i.e. that stimulus induced heart rate variations do not explain fMRI responses, could have been much more susceptible for the critique that a wrong cardiac response model was taken. In RETROICOR the heart beat artifact is described as a non-linear function of the instantaneous phase of the heart beat, whereas our IBI-regression model is based on the heart rate and time delays thereof. After applying RETROICOR together with the present IBI-regression model, de Munck et al. (2008) showed that the instantaneous phase model (RETROICOR) is too restricted for a complete description of the heart beat effect.

Our final conclusion is that there are substantial correlations between heart rate and fMRI signal changes across large parts of the brain during performance of the present executive control tasks. However, the fMRI signals associated with heart rate variations only marginally influenced higher-order fMRI task effects. This conclusion is based on heart rate and fMRI data recorded during commonly used cognitive control tasks administered in a block design as well as an event-related design, with relatively wide trial spacing. However, we expect similar results for test paradigms with closer trial spacing, in particular since smaller trial-to-trial onset times allow less time for significant heart rate changes. The absolute values of the observed IBI changes between task conditions in this study were relatively small (around 8 ms). During tasks with higher emotional valence, stress or in specific patient samples, heart rate changes and their effect on fMRI signals may be more pronounced. We therefore recommend to routinely include cardiac response data to fMRI analyses, also considering the small effort of deriving regressors from the ECG.

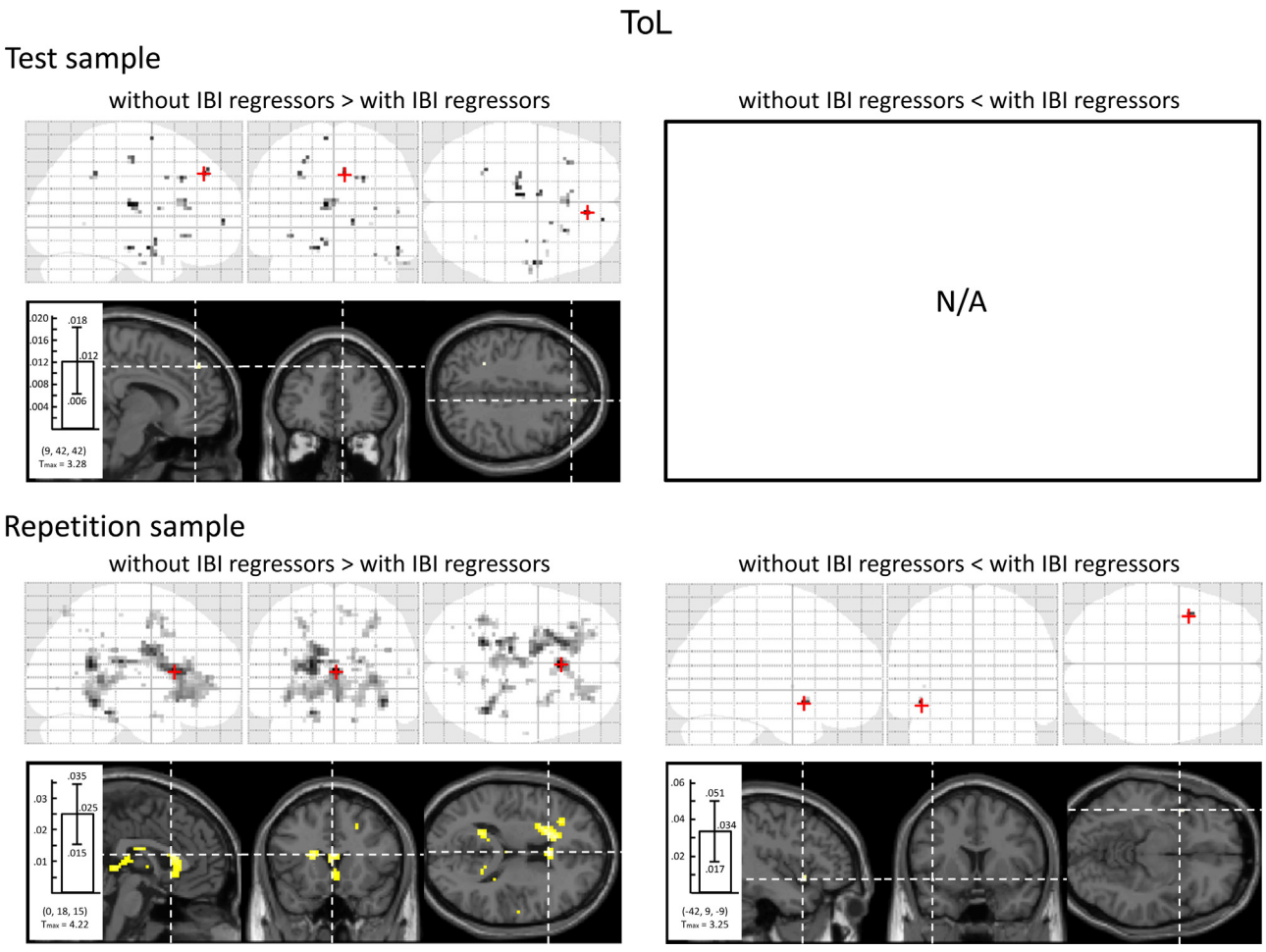

Fig. 7. Post hoc results of paired *t*-tests, at lowered threshold, for the Test sample (top) and Repetition sample (bottom), that compare brain activations for ToL planning versus baseline in each individual as estimated with versus without accounting for the 7 IBI-regressors in the GLM.

Table 4
Correlations of 1st level results with task related IBI changes.

Task	Test sample						Repetition sample					
	# activated voxels			Maximum *T* score			# activated voxels			Maximum T score		
	N	*p*	Pearson *r*	*N*	*p*	Pearson r	*N*	*p*	Pearson r	*N*	*p*	Pearson r
Stroop	46	0.665	0.066	46	0.563	−0.088	45	0.083	0.261	45	0.077	0.266
Tol	46	0.067	−0.273	46	0.305	−0.155	45	0.485	0.114	45	0.238	0.180

Correlations between the task related heart rate change in each subject and the difference in number of suprathreshold voxels (# activated voxels: at $p < 0.005$, uncorrected) and maximum statistical *T* scores (Maximum *T* score) as derived from a GLM with versus without heart rate regressors. Left columns: results for the Test sample; right columns: results for the Repetition sample. *N*: number of subjects; Pearson *r*: Pearson's bivariate correlation coefficient; *p*: statistical significance of correlation. Significant positive correlations would indicate that inclusion of heart rate regressors results in a relatively larger reduction in number of activated voxels/maximum *T* scores for subjects with stronger task related heart rate increases and vice versa. Significant negative correlations would indicate a weaker reduction (or an increase) in number of activated voxels/maximum *T* scores after inclusion of heart rate regressors in subjects with stronger increases in heart rate and vice versa.

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