Journal of Neuroscience Methods 229 (2014) 97–107

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

Computational Neuroscience

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.

ARTICLE INFO

Article history:
Received 19 February 2013
Received in revised form 21 January 2014
Accepted 11 April 2014

Keywords:
Heart rate
Confound
fMRI
Cognitive tasks
Stroop
ToL

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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http://dx.doi.org/10.1016/j.jneumeth.2014.04.013

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.