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Ethanol modulates the neurovascular coupling

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ABSTRACT

Despite some evidence of the underlying molecular mechanisms the neuronal basis of ethanol-induced effects on the neurovascular coupling that forms the BOLD (blood oxygenation level dependent) signal is poorly understood. In a recent fMRI (functional magnetic resonance imaging) study monitoring ethanol-induced changes of the BOLD signal a reduction of the amplitude and a prolongation of the BOLD signal were observed. However, the BOLD signal is assumed to consist of a complex superposition of different underlying signals. To gain insight how ethanol influences stimulus efficacy, oxygen extraction, transit time and vessel-related parameters the fMRI time series from the sensori-motor and the visual cortex were analyzed using the balloon model. The results show a region-dependent decrease of the stimulus efficacy to trigger a post-stimulus neurovascular response as well as a prolongation of the transit time through the venous compartment. Oxygen extraction, feedback mechanisms and other vessel-related parameters were not affected. The results may be interpreted as follows: the overall mechanisms of the neurovascular coupling are still acting well at the moderate ethanol level of about 0.8‰ (in particular the vessel-related parts), but the potency to evoke a neurovascular response is already compromised most obviously in the supplementary motor area responsible for complex synchronizing and planning processes.

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1. Introduction

The influence of ethanol on the brain metabolism, particularly on the neurovascular coupling, is still not fully understood. A variety of physiological mechanisms are believed to be responsible for the manifold physiological effects in the brain. Over the last few years pharmacological magnetic resonance imaging (phMRI) has been established as a powerful tool to observe pharmacological effects of drugs on neuronal activity on human as well as on animals (Honey and Bullmore, 2004; Matthews et al., 2006; Matthews, 2009; Steward et al., 2005). Thus, several groups investigated alcohol-induced effects on the neuronal activity using BOLD (blood oxygen level dependent) imaging techniques. Yoon et al. (2009) found region-dependent alterations of brain activation using memory encoding tasks. Seifritz et al. (2000) reported a BOLD signal decrease in the primary auditory cortex between 12% and 27%, depending on the definition of region of interest for signal quantitation. In order to determine the contribution of the vasodilatating effects of ethanol to potential BOLD signal changes a model calculation was performed with the conclusion that BOLD imaging should be feasible if after moderate ethanol intake the cerebral vessels have still the capacity to react appropriately on increased cerebral activity with a net increase large enough to be detected by BOLD imaging techniques. Levin et al. (1998) found that the BOLD signal amplitude was significantly reduced up to 33% in the visual cortex (VC) after ethanol application and photic stimulation. Other studies found more complex pattern of ethanol induced activation changes, depending on the brain region and the task (Calhoun et al., 2004a,b). Van Horn et al. (2006) examined the acute effects of alcohol in the context of goal-directed visuomotor performance. Sripada et al. (2011) observed the impact of ethanol regarding to fear processing. Both groups found region-dependent alterations of neuronal activity.

The underlying functional magnetic resonance imaging (fMRI) technique is based on the well known BOLD effect that provides a high temporal and spatial resolution making it ideally suited to

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investigate drug-induced effects on brain activity (Tank et al., 1992). BOLD fMRI is based on indirect measures of changes in regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV) as well as from alterations in the relative amount of deoxygenated hemoglobin (Ogawa et al., 1990). While it is clear that rCBF is tightly coupled to neuronal activation, the underlying coupling transduction mechanisms are still debated (Giove et al., 2003; Uludag et al., 2004). The *neurogenic hypothesis* proposes a mechanism consisting of direct innervations of blood vessels by neurons or glial cells (Iadecola, 1998; Kuschinsky and Wahl, 1978). In comparison the *metabolic hypothesis* assumes that the rCBF is changed by a release of diffusible coupling factors following the neuronal activation (Mraovitch et al., 1993; Villringer, 1997). Although the underlying physiological mechanisms are not entirely revealed, BOLD signal increases have been hypothesized to result from increased rCBF, rCBV and changes of local concentrations of deoxyhemoglobin (cerebral metabolic rate of oxygen consumption – $CMRO_2$). Furthermore it is well known that the increased rCBF following neuronal activity is much larger than the activity-induced extraction of oxygen from hemoglobin. Oxyhemoglobin and deoxyhemoglobin differ in the property to generate an extraneous magnetic field when placed in an external magnetic field. The decrease of paramagnetic deoxyhemoglobin results in greater local field homogeneities and leads to an increased MRI signal (Buxton et al., 1998). Directly after the onset of a neuronal activation the consumption of oxygen leads to a higher concentration of deoxyhemoglobin, which reduces the BOLD signal, resulting in the initial dip. The following increased rCBF and rCBV caused by neurovascular coupling lead to the above-mentioned decreased concentration of deoxyhemoglobin and thus to the typical positive BOLD response. After about 10 s following short stimulus oxygen consumption and rCBF return to their initial level. The decline of rCBF is slower. For a certain time the relative amount of deoxyhemoglobin is increased by a higher blood volume, resulting in a BOLD signal undershoot. The shape of the BOLD response following stimulation appears to be similar across early sensory and motor regions (Boynton et al., 1996; Josephs et al., 1997).

Thus, the measured BOLD signal is the sum of several signals that unfortunately cancel each other to a large extent. The effect how the individual time courses of the single components contribute to the overall BOLD signal can be seen well by simulating the curves with the balloon model (Buxton et al., 1998), which was later modified by other authors (Friston et al., 2000; Obata et al., 2004; Stephan et al., 2007; Uludag et al., 2009). Buxton et al. (1998) showed that the balloon model reproduces well the experimental BOLD data, particularly the initial dip and the post-stimulus undershoot. Friston et al. (2000) demonstrated that the balloon model is sufficient in reproducing main non-linearities observed in evoked BOLD responses. Based on the experimental work of Mandeville et al. (1999) the dynamics of the neurovascular coupling is modeled by a set of coupled non-linear differential equations describing the interaction between different physiological parameters such as neuronal activation, vessel properties, rCBF/rCBV as well as the magnetic properties of oxygenized and de-oxygenized hemoglobin that finally lead to the observable fMRI signal. The balloon model is based on two main physiological assumptions: first, the post-capillary venous compartment reacts to an increase of rCBF and rCBV like an inflating balloon. Second, the oxygen extraction is tightly coupled with the regional cerebral blood flow (Stephan et al., 2007). Although the balloon model may be over-simplistic it nevertheless may serve as a guide to analyze potential underlying processes that couple neuronal activity with vascular responses (Buxton, 2012).

However, only little is known how ethanol as one of the most prominent vessel-active drug acts on the hemodynamic response. Ethanol, which is assumed to interact with a variety of receptor systems, causes local as well as global effects (Howes and Reid, 1985; Mathew and Wilson, 1986; Stendel et al., 2006). Ethanol is also known to change the cerebral metabolism and to directly cause cerebral vasodilatation (Nicoletti et al., 2008) as well as vasoconstriction (Gordon et al., 1995).

We used the balloon model implemented in SPM8 (Stephan et al., 2007) to analyze the fMRI time series of the sensori-motor cortex and the visual cortex before and after application of moderate doses of ethanol. However, the original balloon model was customized to BOLD signals at 1.5 T magnet field strength that required adapting inherent field-dependent model parameters to 3 T (Mildner et al., 2001; Uludag et al., 2009)

To validate the results a forward simulation how parameters changes affect the BOLD-signal was performed. The analysis is based on data of a previously published study (Luchtmann et al., 2010).

2. Materials and methods

2.1. Subjects

Fourteen healthy right-handed volunteers (7 male, 7 female, aged between 21 and 29 years) were observed in a test/re-test design before and after administration of ethanol. All participants gave their written informed consent to the presented study that was approved by the Local Ethics Committee of the University of Magdeburg in compliance with national legislation and the Code of Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association (Declaration of Helsinki). All volunteers were social drinkers and had experience with beverages containing high concentrations of alcohol. None of them had any self-reported history of neurological disease, major psychiatric disturbance, substance abuse, or medication usage.

2.2. Study protocol

Prior to the MRI examination the volunteers were asked to refrain from eating for 6 h and to refrain from drinking alcoholic beverages for at least 24 h. Sobriety prior to the experiment has been tested using a breath alcohol test device. All subjects were observed within an MRI scanner using BOLD imaging procedures with identical tasks prior to and after ethanol application. Ethanol-induced effects were observed using a test/re-test design. The task-framework consisted of an identical set of on/off task before and after the administration of ethanol. Therefore the time course of the BOLD signal measured under sober conditions served as baseline for potential individual ethanol effect. Between the runs under sober and alcoholic conditions all subjects had ingested a beverage containing pure ethanol mixed with 400 ml orange juice. The applied amount of ethanol to reach a blood alcohol concentration of 1.0‰ (C_o) was estimated using modified Widmark's equation:

$$C_o = \frac{a}{p \times r} \quad (1)$$

where p denotes the body weight in kg and r denotes the individual correction factor according to the equations developed by Seidl et al. (2000).

To estimate the blood alcohol concentration (BAC) the breath alcohol level (BAL) was repeatedly measured until the BAL reached about 0.8‰. For the BAL measurement a legally certified breath alcohol test device (Draeger 7110 Evidential MK III, Germany) was used. Additional blood samples were collected every 10 min. The BAC based on blood samples was measured according to the guidelines for determining blood alcohol concentration for forensic

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