Alcohol xxx (2013) 1–8

Contents lists available at SciVerse ScienceDirect

Alcohol

journal homepage: http://www.alcoholjournal.org/

Decreased effective connectivity in the visuomotor system after alcohol consumption

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ARTICLE INFO

Article history:
Received 11 October 2012
Received in revised form
8 January 2013
Accepted 9 January 2013

Keywords:
Ethanol
Alcohol
Functional magnetic resonance imaging (fMRI)
Psychophysiological interaction (PPI)
Effective connectivity

ABSTRACT

Functional magnetic resonance imaging (fMRI) allows observing cerebral activity not only in separated cortical regions but also in functionally coupled cortical networks. Although moderate doses of ethanol slowdown the neurovascular coupling, the functions of the primary sensorimotor and the visual system remain intact. Yet little is known about how more complex interactions between cortical regions are affected even at moderate doses of alcohol. Therefore the method of psychophysiological interaction (PPI) was applied to analyze ethanol-induced effects on the effective connectivity in the visuomotor system. Fourteen healthy social drinkers with no personal history of neurological disorders or substance abuse were examined. In a test/re-test design they served as their own controls by participating in both the sober and the ethanol condition. All participants were scanned in a 3 T MR scanner before and after ingestion of a body-weight-dependent amount of ethanol calculated to achieve a blood alcohol concentration of 1.0‰. PPIs were calculated for the primary visual cortex, the supplementary motor area, and the left and right primary motor cortex using the statistical software package SPM. The PPI analysis showed selective disturbance of the effective connectivity between different cortical areas. The regression analysis revealed the influence of the supplementary motor area on connected regions like the primary motor cortex to be decreased yet preserved. However, the connection between the primary visual cortex and the posterior parietal cortex was more severely impaired by the influence of ethanol, leading to an uncoupled regression between these regions. The decreased effective connectivity in the visuomotor system suggests that complex tasks requiring interaction or synchronization between different brain areas are affected even at moderate levels of alcohol. This finding may have important consequences for determining which components of demanding tasks such as driving a car might be compromised earlier than the functions of the main cortical motor and visual areas.

Introduction

The neurological short- and long-term effects of alcohol, especially on the visuomotor system, are well known. Depending on the amount of ethanol administered, all cognitive abilities are affected although the impact on the regions differs. Ethanol may lead to coordination disturbances of the eyes even at moderate blood alcohol concentration (BAC) (Honegger, Kampschulte, & Klein, 1970). Additionally, the muscle coordination is impaired in terms of slower and less accurate movements finally resulting in decreased fine motor performance (Solomon & Malloy, 1992; Zhu, Volkow, Ma, Fowler, & Wang, 2004) and in increased response time (Jennings, Wood, & Lawrence, 1976; Rauschke, 1954). The underlying physiological mechanisms in the brain metabolism may be clarified using functional magnetic resonance imaging (fMRI). The blood oxygen level dependent (BOLD) signal measured by fMRI relies on neurovascular coupling (Ogawa, Lee, Kay, & Tank, 1990), which may change due to potential effects of ethanol on underlying coupling transduction mechanisms. Many psychopharmacological agents may have a direct or indirect potential impact on the underlying neurovascular coupling. Leithner et al. (2010) observed that pharmacologically induced reductions in cerebral blood flow could abolish the BOLD signal without affecting the neuronal

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http://dx.doi.org/10.1016/j.alcohol.2013.01.002

activity (uncoupling). Thus, it may be possible that the BOLD signal is merely being affected by changes in the vascular mechanisms without any alteration of neuronal function. But since a large body of evidence shows that $GABA_A$ receptors (Davies, 2003) and several other molecular targets (Lovinger & Roberto, 2013) are responsible for short and long-term effects of ethanol, it is highly unlikely that the observed ethanol-induced changes in the BOLD signal time course were mediated only by the vascular part of the neurovascular coupling while neuronal activity remained unaffected by ethanol. Previous fMRI studies showed that the hemodynamic responses were preserved but that their time course had changed after moderate alcohol intake (Seifritz et al., 2000; Sripada, Angstadt, McNamara, King, & Phan, 2011). In a recent study we analyzed the time course and the baseline of the hemodynamic response with respect to ethanol-induced changes (Luchtmann, Jachau, Tempelmann, & Bernarding, 2010). Averaged over the group, no significant alterations of the BOLD signal baseline were obtained after ethanol ingestion, indicating an unchanged rCBF and rCBV during the resting condition. The analysis of the BOLD time course revealed a region-dependent alteration of the hemodynamic response while the HRF time course was still well detectable, proving that the vascular reserve was sti ll intact. The magnitude of the HRF signal was reduced and the time-to-peak was prolonged, showing an overall slowdown of the neurovascular coupling. To analyze these findings in more detail, we used the hemodynamic model within SPM and a self-implemented version of the balloon model (Stephan et al. 2007) to investigate and simulate the impact of ethanol on the neurovascular coupling and the BOLD signal. We obtained evidence of decreased neuronal efficacy and increased transit time through the venous compartment, indicating a slowdown of the dynamics of the neurovascular system with respect to the flow changes (Luchtmann et al., 2013).

Other studies have also demonstrated the impact of ethanol on the BOLD effect. Calhoun et al. (2004) found dose-dependent effects on the visuomotor system using a visual perception task. The application of alcohol resulted in a decreased activation amplitude across the entire visual cortex. Additionally, dose-dependent activation decreases were found in precentral regions. Data was analyzed using the general linear model (GLM). Based on a GLM analysis Van Horn, Yanos, Schmitt, and Grafton (2006) reported a fronto-parietal network that was identified as most affected by the acute consumption of alcohol, suggesting a region-dependent sensitivity. In previous studies, we also demonstrated region-dependent alterations of cerebral activity following the consumption of ethanol (Luchtmann et al., 2010). It was not only demonstrated that ethanol reduces the amplitude of the hemodynamic response, but also that ethanol prolongs the time course of the BOLD signal depending on the region observed. The supplementary motor area (SMA) was found to be more affected than the primary motor and visual cortical areas.

The principle of functional segregation in the cerebral cortex is well established (Zeki et al., 1991). In recent years an increasing number of functional neuroimaging studies have been used to infer modulation of different areas by cognitive processes (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1991; O'Craven, Rosen, Kwong, Treisman, & Savoy, 1997). In neuroimaging studies functional connectivity refers to the simple temporal correlation between two separate cortical areas. No information is provided as to how these correlations are mediated. Effective connectivity extends the concept of functional connectivity in terms of inferences about the influence that one neuronal system exerts over another (Friston et al., 1997). To explain the hemodynamic response in a brain region in terms of an interaction between the prevalence of a modulating process and the activity in another region, Friston et al. (1997) and Büchel and Friston (1997) introduced the model of psychophysiological interaction (PPI). PPI is a special kind of regression analysis demonstrating how the contribution of one region to another is altered by the experimental context. In our case, the psychophysiological effects of ethanol modulated the experimental context.

Despite the above-mentioned studies, many questions about the influence of alcohol on cognitive networks like the visuomotor system remain still open. In this study we present an approach to investigating the impact of ethanol on the effective connectivity in parts of the visuomotor system using the method of PPI. For this purpose volunteers served as their own controls by participating in both the sober and the ethanol condition. Thus, all participants were scanned before and after the ingestion of a body-weight-dependent amount of ethanol within a 3-T MRI scanner. A simple visuomotor pathway containing the primary visual cortex (V1), the supplementary motor area (SMA) and the left and right primary motor cortex (lM1 and rM1) was studied. Although connections between different brain areas are usually reciprocal for mathematical reasons (to decrease the number of known and unknown variables), the observed model (Fig. 1) comprised only unidirectional paths. Higher functional regions like V2 and V5 were excluded in the interest of the simplicity and stability of the model.

To investigate how ethanol modulates the connections within this simple pathway model, two areas were selected as source region for the PPI analysis: first, the primary visual cortex (V1) as starting point for the processing of visual information, and second, the supplementary motor area (SMA) as region for the preparation and execution of controlled movements. For the statistical analysis individual PPIs were calculated for the regions modulated by the effect of ethanol. Put simply, PPI was used to estimate significant ethanol-induced alterations of the regression between the seed

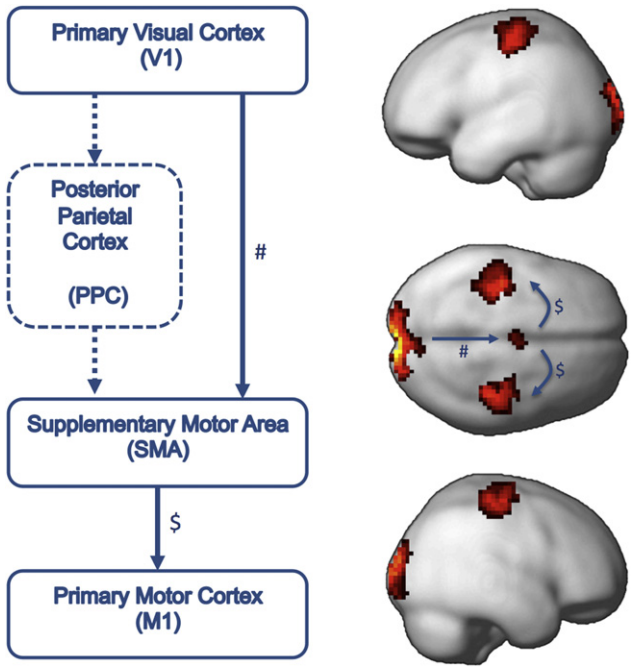

Fig. 1. Linear structural model of the simple visuomotor pathways examined. Four regions (V1, SMA, left and right M1) were reliably evoked using a simple fMRI paradigm across all subjects (Luchtmann et al., 2010) and a GLM-based design matrix with a canonical hemodynamic response function (solid lines). The modulatory effects of ethanol on the effective connectivity between these regions were evaluated based on a PPI-analysis. Our results showed that the posterior parietal cortex (PPC) was not directly evoked by the visuomotor paradigm and therefore did not appear in the GLM analysis but showed a strong sensitivity to the psychophysiological effects of ethanol (dashed line).

regions (independent variables) and the rest of the brain (dependent variables).

Methods

The study 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).

Functional MRI data were obtained from a previously reported study (Luchtmann et al., 2010). The initial purpose was to measure the changes of the individual hemodynamic response in parts of the visuomotor system following the acute influence of ethanol.

Subjects

Fourteen healthy, right-handed participants (7 male, 7 female, 21–29 years, mean 23.2 ± 1.9 years) were recruited from a pool of fMRI volunteers. All subjects were social drinkers, well experienced in dealing with alcoholic beverages, had no history of alcohol abuse or neurological disorders and were not using psychoactive medications at the time. Subjects were asked to refrain from drinking alcoholic beverages for at least 24 h and from eating for at least 6 h. Participants gave their written informed consent to the study.

Experimental design

All volunteers served as their own controls by participating in both the sober and the ethanol condition. For this, subjects were scanned before and after ingestion of a body-weight-dependent amount of ethanol. The amount required to achieve the intended blood alcohol concentration (BAC) of 1.0‰ was estimated according the modified Widmark's equation by Seidl, Jensen, and Alt (2000). Participants had to drink the mix of ethanol and orange juice within 15 min. After alcohol intake all subjects waited until their BAC reached 0.8‰. The BAC was estimated using a legally certified breath alcohol level test device (Dräger 7110 Evidential MK III, Germany).

Additionally, blood samples were taken frequently to determine the BAC according to the guidelines for determining blood alcohol concentration for forensic purposes using the alcohol dehydrogenase based enzyme assay and the gas chromatography method (Aderjan et al., 2011).

Experimental paradigm

In order to evoke cortical activations a visually paced task paradigm was used. A flickering checkerboard served as a visual stimulus as well as the starting signal for a finger-tapping task. The checkerboard inverted the color with a frequency of 8 Hz for duration of 1 s. Once the volunteer perceived the visual stimulus, he had to touch sequentially all four fingers with the opposing thumb as fast as possible for 1 s. The stimulus was presented using an event-related design with a fixed rest condition of 19 s. Since placebo-controlled alcohol studies are only reliable if the observed BAC is < 0.4‰ (Glautier, Remington, & Taylor, 1992; Hammersley, Finnigan, & Millar, 1992) all subjects served as their own controls. To recognize training or habituation effects, all participants had to perform the paradigm outside the scanner prior to the MR session. To account for order effects the subjects had to perform the task twice both in the pre-ethanol and post-ethanol condition. For the statistical data analysis, this resulted in 4 runs (2 runs for sober, and 2 runs for ethanol condition), each of the runs containing 30 blocks of 20 s duration.

A small red centrally located fixation cross was presented throughout the complete block of 20 s. To minimize eye movement subjects had to fixate the cross. The color of this fixation cross altered randomly to blue for half a second. To focus their attention, volunteers had to count the number of the color changes and report this number after the complete run to the investigator. Additionally, to allow for the problem of decreased compliance the participants had to perform a simple "button press task" between both runs of each condition. All subjects had to follow a visually paced paradigm by pressing buttons within the MR scanner. For this purpose, the words "both," "left," and "right" blinked with a frequency of 1 Hz, 2 Hz and 3 Hz. The participants had to press the corresponding buttons while the paradigm was presented.

MR imaging

All anatomical and functional datasets were acquired using a 3 T Magnetom Trio whole body scanner from Siemens (Erlangen, Germany) equipped with an 8-channel head volume coil. The functional T2*-weighted images were obtained using an echo-planar imaging sequence (TE 30 ms, repetition time 500 ms, 7 slices, slice thickness 6 mm, axial slice orientation, field of view (FOV) = 192 × 192 mm, matrix size = 64 × 64 with a resulting voxel size of 3 × 3 × 6 mm = 54 mm^3). The volume acquired covered both hemispheres except for parts of the temporal lobes and the cerebellum.

Image processing and statistical analysis

All functional data were preprocessed and analyzed using SPM8 (Wellcome Trust Centre for Neuroimaging – SPM8, http://www.fil.ion.ucl.ac.uk/spm/) running on Matlab 2009b (MathWorks, Version 2009b; http://www.mathworks.com/). All images were realigned to the first saturated image of the fMRI data set to minimize motion artifacts. Additionally, all images were spatially normalized into a standard space defined by the ICBM NIH P-20 project. A high-pass cut-off (128 s) and the autoregressive model AR(1) were applied to reduce time drifts and to account for serial correlations due to aliased biorhythms and unmodeled neuronal activity. The data was smoothed using a 6 mm full width at half maximum isotropic Gaussian kernel to suppress noise and effects due to residual differences in functional and gyral anatomy resulting from inter-subject averaging.

As reported in a previous study (Luchtmann et al., 2010) a design matrix containing both the sober and the ethanol condition was modeled by convolving the stimulus with the standard canonical hemodynamic response function (HRF). To take into account the prolongation of the HRF, the design matrix was extended by the derivatives of the HRF with respect to time and dispersion. Contrasts for the different conditions (sober and ethanol) were calculated and analyzed using a random effects group analysis.

The effective connectivity of the evoked areas involved in visuomotor processing was assessed using psychophysiological interaction analysis (Friston et al., 1997). Spheres with a radius of 6 mm (volume = 905 mm^3), modeled as regions of interest (ROI) around the peak voxel in the above mentioned random effects analysis in the right and left primary visual cortex V1 ($x = 6$, $y = -90$, $z = -65$ and $x = -4$, $y = -89$, $z = -65$) and the supplementary motor area ($x = 0$, $y = -9$, $z = 57$), served as source regions for extracting the eigenvariate of the fMRI signal. For each individual subject the PPI variable including the psychophysiological interaction term was calculated for the contrast matrix *sober vs. ethanol*. Subsequently, these terms were used to model a GLM for each subject. At the group level, contrast images of the PPIs were analyzed using one-sample *t*-tests. Finally, individual PPI variables

for all significant clusters of the group analysis were calculated separately for the conditions *sober* and *ethanol*.

However, the results of the PPI analyses, illustrated as statistical brain maps, do not show the slope of the regression. Therefore, the modulatory effects of ethanol and its psychophysiological impact were illustrated using a regression analysis described by Büchel and Friston (1997). The modulatory influence of an ROI over another ROI was visualized by splitting the observations into two sets. The first set contained the observations that were not subject to the modulatory effects of ethanol. The second set contained those that included the modulatory effects of ethanol. Standardized as well as unstandardized regression coefficients were estimated (Allen, 1997). The unstandardized beta was used for actually making the prediction, using the independent regional BOLD signal as it was measured. Standardized coefficients were calculated to compare the strength of both different independent conditions (sober and ethanol).

All reported coordinates correspond to the anatomical MNI space. In order to assign the cytoarchitectonic reference, the anatomical SPM toolbox (Forschungszentrum Jülich, Version 18, http://www2.fz-juelich.de/inm/index.php?index=194) by Eickhoff et al. (2005) was used.

Results

Behavioral data

The mean amount of ethanol consumed was 58.9 ± 6.4 g. The mean BAC of the participating volunteers was 0.82 ± 0.07‰ and varied from 0.72 to 0.92‰. All subjects reported the correct number of color changes in the sober condition as well as in the ethanol condition. Additionally, no significant changes of the accuracy of the "button press task" were observed (1 Hz: $p = 0.625$, 2 Hz: $p = 0.580$, 3 Hz: $p = 0.340$).

Analysis of effective connectivity

Statistical parametric maps of the general linear model including the psychophysiological interaction term of the SMA as source region are shown in Fig. 2. The activities in the left and the right primary motor cortex (M1) as well as in parts of the occipital lobe including the right and left primary visual cortex (V1 and parts of V2) were significantly altered due to modulatory effects of ethanol. This is consistent with altered influence of the SMA over M1 and V1. Thus, the analysis revealed significantly decreased effective connectivity between the SMA and M1 and V1.

Fig. 3 shows the results using V1 as source region. Clusters in the right portion of the SMA and the right PPC were significantly changed in the group analysis. These observations revealed decreased coupling between the areas V1 and the SMA as well as between the areas V1 and PPC. Parametric maps that display the cerebral activations for the conditions sober and ethanol separately were provided in a recent publication (Luchtmann et al., 2013).

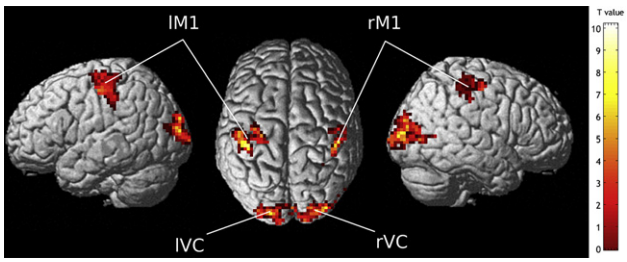

Fig. 2. Psychophysiological interaction analysis using the SMA as source region. The interaction term revealed a significant ethanol-induced change of the effective connectivity as an uncoupling between the SMA and the bilateral regions M1 (lM1 – left primary motor cortex, rM1 – right primary motor cortex) and VC (lVC – left visual cortex, rVC – right visual cortex) [Group level analysis; $p < 0.001$ uncorr., cluster threshold of 5 voxel].

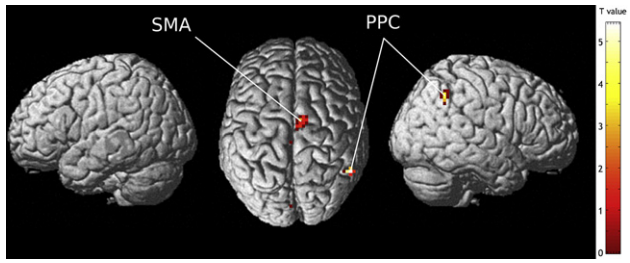

Fig. 3. Psychophysiological interaction analysis using the right V1 as source region. The interaction term revealed selective disruption of the effective connectivity between the primary visual cortex V1 and the right portion of the supplementary motor area (SMA) and parts of the posterior parietal cortex (PPC) [Group level analysis; $p < 0.001$ uncorr., cluster threshold of 3 voxel]. The PPI analysis using the left V1 as source region exhibited no significant effects.

Table 1 shows the corresponding statistical values of the local maximum within clusters of significantly activated voxels.

Fig. 4 displays the modulating effects of alcohol on the observed brain regions. The ethanol consumption causes a decrease in the effective connectivity between the supplementary motor area and the left (Fig. 4A) and right (Fig. 4B) primary motor cortex M1. Thus, the positive response of the primary motor cortex to the activation in the SMA was lower under ethanol conditions than under sober conditions resulting in a decreased regression (Table 2). Similar results were seen between the primary visual cortex V1 and the SMA (Fig. 4C). The positive BOLD response in the supplementary motor area following activation in the visual cortex was lower as well. The ethanol-induced changes in the effective connectivity between the primary visual cortex and the posterior parietal cortex were shown somewhat differently (Fig. 4D). In the sober condition the PPC responded to activation in the V1 with negative BOLD response. The modulating effects of ethanol led to complete disruption of the regression between these two areas.

Discussion

To our knowledge this is the first study to evaluate the impact of ethanol on the effective connectivity in the human brain. In contrast to *functional connectivity*, which is usually a simple correlation between distinct areas, the term *effective connectivity* describes the influence that one neuronal system exerts over another (Büchel & Friston, 1997). Psychophysiological interaction is a statistical model for estimating the effective connectivity of a brain region and the rest of the brain relating to different psychological contexts. The pathways of a simple visuomotor model were observed for ethanol-induced effects, which reduce the influence that one region exerts over another. Our analysis strongly suggests that ethanol selectively reduces the effective connectivity between regions that are involved in the planning and control of voluntary movement. The supplementary motor area showed a pronounced impairment of the effective connectivity to both the left and right primary motor cortex. In the regression analysis the influence of the SMA on the primary motor cortices was observed to be decreased yet preserved. These results are in line with recent studies. Van Horn et al. (2006) found that alcohol significantly affects fronto-parietal networks including the supplementary motor area. In a recent study we also showed that the SMA is particularly sensitive to ethanol-induced alterations of the

Table 1
Statistical values of activated areas of Figs. 2 and 3.

Seed region	Activated area	Hemisphere	MNI coordinates			*T*-value	Vol. (cm^3)
			x	*y*	*z*		
Supplementary motor area (Fig. 2)	Primary motor cortex	R	39	−36	39	6.21	4.13
		L	−48	−21	54	6.95	8.26
	Primary visual cortex	R	18	−87	3	10.15	18.41
		L	−15	−93	6	7.12	13.55
Primary visual cortex (Fig. 3)	Supplementary motor area	R	6	−18	51	4.28	1.65
	Posterior parietal cortex	R	54	−54	45	5.41	0.43

hemodynamic response on fMRI (Luchtmann et al., 2010). Additionally, Meda et al. (2009) found dose-related spatio-temporal disruptions in regions that are involved in visuomotor control including the SMA. In each of these studies the motor abilities were affected only slightly or not at all after ingestion of moderate alcohol doses. Interestingly, we also found decreased effective connectivity with the posterior parietal cortex using the primary visual cortex as source region for the PPI analysis. Since the BOLD response of the PPC to activity in the primary visual cortex is negative (Fig. 4B) a usual GLM based fMRI analysis using the usual canonical basis function in SPM is not sufficient to visualize negative cerebral activity based on the paradigm used. However, recent studies of visually guided, goal-directed movements presented a variety of cerebral circuits that are believed to be involved in visuomotor control (Desmurget & Grafton, 2000; Jeannerod, 1999; Ogawa, Inui, & Sugio, 2006; Vesia & Crawford, 2012). The posterior parietal cortex is assumed to be critically involved in controlling goal-directed movements like grasping and reaching. Desmurget et al. (2001) described a crucial role of the PPC for feedback loops that allow corrections of ongoing movements. The PPC may be involved in both transformation of visual information into a motor plan for a new movement (Crawford, Henriques, & Medendorp, 2011) and the use of a visual feedback for the control of ongoing movements (Iacoboni, 2006). Additionally, parts of the posterior parietal cortex are also involved in the control of eye movements and saccades. These hypotheses were supported by lesion studies showing that bilateral PPC lesions could lead to deficits in grasping movements (Gréa et al., 2002). Lesions in the posterior parietal cortex disrupt the online adjustment during aiming movements. Our results support these hypotheses. The regression analysis of the effective connectivity exhibits a significant influence of the neuronal activity for V1 on the cerebral activation in the posterior parietal cortex in the sober condition, resulting in a negative BOLD response. It may be interpreted as a correlate of a feedback control mechanism, which was discussed by Desmergut et al. (2000) and (2001). After moderate alcohol ingestion the effective connectivity between V1 and PPC was severely impaired. The regression analysis failed to reveal any preserved influence of the primary visual cortex on the posterior parietal cortex (Table 2). In general, alcohol consumption leads to impaired eye control, slower and less accurate muscle coordination, and decreased fine motor performance of goal-directed movements even at moderate BAC (Honegger et al., 1970; Solomon & Malloy, 1992; Zhu et al., 2004). Critical parts of these abilities are controlled by the PPC. Thus, the reduction of the effective connectivity between the V1 region and the PPC under alcohol indicates an important role of the posterior parietal cortex in mediating ethanol-induced impairment of motor skills. However, a number of neuroimaging studies have identified more regions that are functionally affected by the influence of alcohol. The cerebellum has an important function in the control of voluntary movements. Recent studies have shown strong evidence for a crucial role of the cerebellum in affecting the control of visuomotor movements. Van Horn et al. (2006) demonstrate alcohol dose dependent effects of cortico-cerebellar circuits. The fMRI analyses relied on the use of a general linear model. Conclusions about interregional influences and dependencies are based on simple activation maps. A reliable connectivity analysis of cerebral circuits was not conducted. Rogers, Parks, Nickel, Katwal, and Martin (2012) recently presented the first study of alcohol-induced effects on the connectivity of distinct brain areas, focusing on fronto-cerebellar regions in patients who suffered from the ramifications of chronic alcohol consumption. They showed specific patterns of deficits in functional connectivity and recruitment of additional brain regions for the performance of a simple finger-tapping task. In principle, functional connectivity refers to the ordinary temporal correlation between two distinct areas. No information about the origin of these correlations is provided. Temporal correlations of neuronal activity in spatially distinct areas can arise from many sources that do not reflect real interactions between neuronal populations (Friston et al., 1997). Our study shows for the first time that the effective connectivity between different brain areas is altered after ingestion of ethanol. However, the reduction of the effective connections between the primary visual cortex and the posterior parietal cortex was demonstrated only for the right non-dominant hemisphere. Conclusions about the potential causes are rather speculative, but some groups reported dominant effects of ethanol on the right hemisphere (Levin et al., 1998; Rhodes, Obitz, & Creel, 1975; Seifritz et al., 2000; Wendt, Risberg, Stenberg, Rosén, & Ingvar, 1994). Additionally, neurotransmitters are distributed asymmetrically (Davies, 2003; Little, 1999; Yeh & Kolb, 1997) indicating an asymmetrical susceptibility to ethanol. The examinations of Eidelberg and Galaburda (1984) yielded cytoarchitectonic differences of the parietal lobes toward a right lateralization. Inferences about the underlying molecular mechanisms of ethanol based on the presented PPI analysis are also speculative. Nevertheless, the disturbances of effective connectivity in the visuomotor system demonstrated by the present study are in line with the assumption that the inhibition of $GABA_A$ receptors plays a crucial role in meditating ethanol-induced short-term effects. Hanchar, Dodson, Olsen, Otis, and Wallner (2005) showed an alcohol-induced motor impairment caused by increased extrasynaptic $GABA_A$ receptor activity. A large body of evidence supports this hypothesis (Meera, Olsen, Otis, & Wallner, 2010; Olsen, Hanchar, Meera, & Wallner, 2007; Santhakumar, Wallner, & Otis, 2007).

However, there are certain limitations to the method applied. First, BOLD imaging relies on the indirect measurement of neuronal activity. Neuronal activation increases the regional cerebral blood flow (rCBF) and the regional cerebral blood volume (rCBV) as a result of the neurovascular coupling. The complex interplay between the inflow and outflow of oxygenated and deoxygenated hemoglobin leads to changes in magnetic susceptibility in the underlying brain tissue. The resulting hemodynamic response is an indirect but highly correlated measure of neuronal activity (Ogawa et al., 1990). In order to measure both conditions on the same day it was necessary to observe the ethanol-induced effects after the run

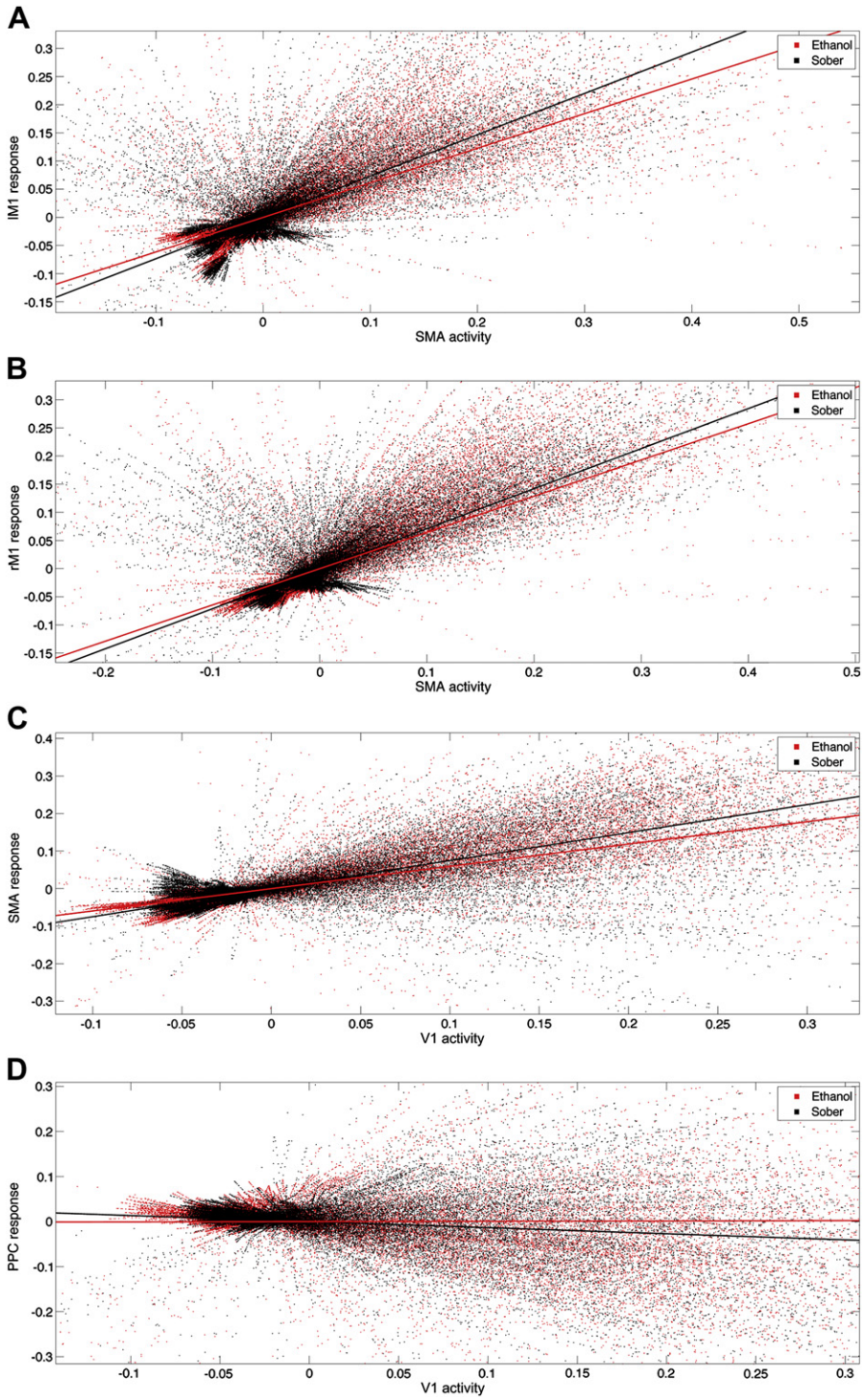

Fig. 4. Regressions between distinct brain regions as a function of the modulating effects of ethanol. The figure shows the corresponding mean relative changes of the BOLD signal within the observed regions. All observations were divided into two sets: The first set contains the observations that are not subject to the modulatory effects of ethanol (red). The *X* axis encodes for the values of the seed region. The *Y* axis displays the values of the regions whose connectivity is significantly modulated by ethanol. The second set contains the modulatory effects of ethanol (black). Table 2 shows the corresponding statistical values of regression. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in the sober condition. This could lead to order effects due to training and habituation. To allow for this problem all subjects were required to perform the visuomotor task twice prior to the session in the ethanol condition. No habituation effects were found between these runs. This indicates a stable, reliable, and unchanged intra-individual BOLD response to this rather simple visuomotor task as has been described by Aguirre, Zarahn, and D'Esposito (1998). However, the possibility that small order effects may still play a role cannot be fully excluded.

While V1 and M1 showed decreased but preserved regression to activity in the supplementary motor area, the effective connectivity between V1 and the PPC seems to be reduced to a high degree as

Table 2
Results of the regression analysis of the effective-connectivity modulating effects of ethanol.

Independent	Dependent	Condition	Regression coefficient beta		*p*-value	R^2
			Unstandardized	Standardized		
SMA	lM1	Sober	0.502	0.706	<0.001	0.498
SMA	lM1	Ethanol	0.432	0.549	<0.001	0.302
SMA	rM1	Sober	0.571	0.715	<0.001	0.511
SMA	rM1	Ethanol	0.516	0.612	<0.001	0.374
V1	SMA	Sober	0.747	0.754	<0.001	0.568
V1	SMA	Ethanol	0.594	0.669	<0.001	0.447
V1	PPC	Sober	−0.132	−0.162	<0.001	0.026
V1	PPC	Ethanol	0.004	0.005	0.230	<0.001

shown by the low value of the regression line in the ethanol condition (Table 2 and Fig. 4). We cannot fully exclude a partial ethanol-induced uncoupling/decoupling of the BOLD signal solely on the basis of the study data. Further studies are necessary to determine the degree of this potential uncoupling. Nevertheless, under the condition of preserved neurovascular coupling we argue that PPI analyses of the modulating effects of psychoactive drugs may not only be reliable but may provide additional important information about mutual effects in a brain network.

Nevertheless, the results presented here, particularly the decrease of the visuomotor connectivity, are very consistent with the results of other recent studies. Vesia and Crawford (2012) proposed a functional framework for the human PPC that is integrated within broader cortical networks for reach, grasp, and eye-hand coordination.

In conclusion, the PPI analysis of ethanol-induced effects on the visuomotor system in the human brain showed strong evidence for a selective reduction of the effective connectivity in brain regions involved in the control of voluntary movements. Connections to and from the supplementary motor area and particularly with the posterior parietal cortex are affected even at the moderate doses of ethanol applied. Our findings are consistent with other studies and independent neurological observations and suggest that reduced interactions in the networks including the PPC and the SMA may be particularly relevant for the understanding of the acute pathophysiological mechanism of ethanol. This finding may also have important consequences for determining which components of demanding tasks such as driving a car or handling engines may be compromised more earlier than the functions of the main cortical motor and visual areas. However, a word of caution applies. Since the effect of ethanol on the different constituents of the neurovascular coupling are not yet fully understood, a potential decoupling of neuronal activation and neurovascular coupling cannot fully be excluded.

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