Effect of alcohol on the sense of agency in healthy humans

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Title: **Effect of alcohol on the sense of agency in healthy humans**

Running Title: **Alcohol and agency**

Silvana De Pirro[1,2], Peter Lush[1,2,3], Jim Parkinson[3], Theodora Duka[1,2], Hugo D. Critchley[1,2,3], Aldo Badiani[1,2,4]

[1]Sussex Addiction Research and Intervention Centre (SARIC), School of Psychology, University of Sussex, Brighton, United Kingdom; [2]Sussex Neuroscience, University of Sussex, Brighton, United Kingdom; [3]Sackler Centre for Consciousness Science, University of Sussex, Brighton, United Kingdom; [4]Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy

*Correspondence should be addressed to:

Aldo Badiani,
SARIC, School of Psychology, and Sussex Neuroscience,
University of Sussex, Falmer,
BN1 9QH Brighton, United Kingdom.
Email: Aldo.Badiani@sussex.ac.uk
Phone: +44 (0)7447 528760

or

Silvana De Pirro
SARIC, School of Psychology, and Sussex Neuroscience,
University of Sussex, Falmer,
BN1 9QH, United Kingdom,
Email: S.DePirro@sussex.ac.uk
Phone: +44 (0)7463 798574

Abstract

Even at low to moderate doses, ingestion of the widely-used recreational drug alcohol (ethanol) can impact cognitive and emotional processing. Recent studies show that the Sense of Agency (SoA; i.e. the subjective experience of voluntary control over actions) can be modulated by specific pharmacological manipulations. The SoA, as quantified by the Intentional Binding (IB) paradigm, is enhanced by direct or indirect dopaminergic agonists in patients with Parkinson's Disease and by ketamine (an NMDA receptor antagonist) in healthy individuals. These findings implicate dopaminergic and glutamatergic neurotransmission in mechanisms underlying SoA. Alcohol has a complex set of actions, including disinhibition of dopaminergic neurotransmission and allosteric antagonism at NMDA receptors. Here, we tested the hypothesis that low to moderate doses of alcohol would enhance SoA, and impact impulsivity and subjective emotional state.

We conducted two experiments in 59 healthy male and female social drinkers, who ingested either a placebo 'vehicle', or one of two doses of ethanol: 0.4 and 0.6 g/kg. In both experiments we observed increased SoA/IB at both doses of alcohol exposure, relative to the placebo condition. We found no correlation between the effects of alcohol on IB and on impulsivity or subjective emotional state.

Our findings might have implications for social and legal responsibility related to alcohol use, particularly in states prior to overt intoxication. Further studies are necessary to investigate the effects of alcohol and other addictive substances on the SoA.

Keywords: ethanol, alcohol, affect, impulsivity, intoxication, sense of agency

Introduction

The cognitive and physiological effects of alcohol (ethanol) are both time- and dose-dependent (Hendler, Ramchandani, Gilman & Hommer 2011). Research has mostly focused on the loss of inhibitory control produced by alcohol intoxication (Loeber & Duka 2009a; Field, Wiers, Christiansen, Fillmore & Verster 2010; Potenza & de Wit 2010), characterized by increased impulsivity, aggressivity, and risky behaviour (Rose & Duka 2007; de Wit 2009; Field *et al.* 2010; Potenza & de Wit 2010; Nutt, King, Phillips & Independent Scientific Committee on Drugs 2010; McMurran 2012; Nikolaou, Field, Critchley & Duka 2013; Miczek, DeBold, Hwa, Newman & de Almeida 2015; Berry & Johnson 2017). The effects of low to moderate doses of alcohol, i.e. levels that are commonly consumed during social drinking, have received less attention (Cui & Koob 2017). At these doses, alcohol can produce a pleasant state of euphoria, stimulation, disinhibition, loss of social anxiety, and relaxation, yet can also have a negative impact on cognition and emotional processing (Breitmeier, Seeland-Schulze, Hecker & Schneider 2007; Bisby, Leitz, Morgan & Curran 2010; Dry, Burns, Nettelbeck, Farquharson & White 2012; Kamboj, Joye, Bisby, Das, Platt & Curran 2013). These effects forewarn potential societal consequences even following consumption of moderate-to-low doses (Dimock 2011; Husak 2012; Cui & Koob 2017; Law & Sociology 2018). In this context, it would be important to investigate directly the effects of alcohol on an implicit measure of the Sense of Agency (SoA).

The SoA refers to the subjective experience of voluntary control over one's own actions, and thus, the sense of ownership of the effects of these actions on the external environment (Moore & Obhi 2012; Wolpe & Rowe 2014; Haggard 2017). Explicit quantitative measures as proxy of the SoA, are affected by a number of biases (Ebert & Wegner 2010). Thus, in the last two decades, neuroscientists have focused on implicit procedures (for reviews see (Moore & Obhi 2012; Wolpe & Rowe 2014; Haggard 2017). In

particular, the Intentional Binding (IB) paradigm, which evolved from Libet's experiments on the neurophysiological basis of human volition (Libet, Gleason, Wright & Pearl 1983), is a chronometric quantitative approach to investigate the association between one's voluntary action and an external sensory effect (Haggard, Clark & Kalogeras 2002). In healthy humans, a voluntary action followed by presentation of an external stimulus evokes a systematic subjective distortion of time-perception when linked to a voluntary action. By using a 'Libet's clock' participants report the time of either a voluntary action (e.g. pressing a button) or of a sensory event (e.g. hearing a tone). When the voluntary action and the sensory event are predictably coupled, humans tend to judge their action as occurring later in time and the sensory event as occurring earlier in time, relative to when both events occur separately. This biased perception of time indicates the 'intentional binding' of the voluntary action and sensory percept, an effect that is not produced for involuntary actions evoked by TMS or reflex (Haggard *et al.* 2002; see also Buehner 2015).

   Abnormalities of the SoA have been observed in several neurological and psychiatric conditions (Moore, Schneider, Schwingenschuh, Moretto, Bhatia & Haggard 2010/3; Haggard, Martin, Taylor-Clarke, Jeannerod & Franck 2003; Synofzik, Thier, Leube, Schlotterbeck & Lindner 2010; Voss, Moore, Hauser, Gallinat, Heinz & Haggard 2010), but very little research has been conducted on the effects of pharmacological manipulations (Moore *et al.* 2010/3; Moore, Turner, Corlett, Arana, Morgan, Absalom, Adapa, de Wit, Everitt, Gardner, Pigott, Haggard & Fletcher 2011), and no information at all is available on the effect of alcohol. Interestingly, facilitation of IB has been observed after administration of drugs that increase dopaminergic transmission, such as L-DOPA and dopamine receptor agonists (Moore *et al.* 2010/3). Given that a great deal of attention has been placed on the ability of alcohol to indirectly increase dopamine levels in terminal regions of the

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mesostriatal system (Morikawa & Morrisett 2010), we hypothesize that alcohol might affect IB in the same manner of dopaminergic medications.

In the present study, we report on the effect of moderate to low doses of ethanol on healthy social drinkers, using a standard IB paradigm. The doses of ethanol used here produced blood alcohol concentration (BAC) within the legal limits for driving in most European and North-American countries (0.05 to 0.08 g/dl), corresponding to breath alcohol concentrations (BrAC) of 0.25-0.35 mg/l.

Methods and Materials

Participants

Fifty-nine healthy social drinkers (30 females and 29 males) participated in this study, receiving one of the following doses of ethanol: 0.0 (N=19), 0.4 (N=20), or 0.6 (N=20) g/kg. Sample size was estimated on the basis on previous studies (see Supplementary Information). Demographic characteristics are illustrated in Table 1. Exclusion criteria included: i) allergic reactions to alcohol; ii) alcohol flush reaction, iii) diabetes, iv) psychotropic medications, v) medications that might interact with alcohol, vi) self-reported pregnancy, possible pregnancy, and breastfeeding. Inclusion criteria included a weekly alcohol consumption of at least 4-5 UK units (1 unit = 8 g of ethanol) and a body mass index (BMI) between 18 and 30 (which was verified before testing).

The participants were recruited via advertisements and posters within the University of Sussex. The study was described in detail to each participant before written informed consent was obtained. Procedures and methods were in accordance with the Declaration of Helsinki and were approved by the University of Sussex C-REC. All participants received a modest monetary compensation for their participation in the study.

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Procedures

The participants were instructed to follow the pretest requirements before testing (see Supplementary Information). At their arrival at the testing facilities, the participants' BrAC was measured using a breathalyser (Lion Alcolmeter SD-400, Lion Laboratories Ltd, Barry, UK) to ensure a value of 0.0 mg/l at baseline (T0).

Experiment 1. Thirty participants (mean age = 21.53, SD=1.94), received one of the following doses of ethanol: 0.0 (N=10, 5 females), 0.4 (N=10, 5 females), or 0.6 (N=10, 5 females) g/kg. Testing took place after 11:30 am, starting with a training phase during which the participants practiced the IB task.

Administration of ethanol followed previously described procedures (Loeber & Duka 2009b). Both doses were diluted in a flavoured solution to a total of 300 ml (see Supplementary Information), which was then divided into six drinks of 50 ml each. The drinks were consumed at the rate of one every 2 min. Ten minutes after the last drink (T1), BrAC was recorded again. The testing session started 30 min after the first drink and lasted 25-32 min. After completion of the task, BrAC was recorded for the third time (T2).

Experiment 2. The results of Experiment 1 indicated that low to moderate doses of alcohol may affect IB. The main goal of Experiment 2 was to replicate the finding of Experiment 1 using a slightly different alcohol administration procedure. Since the IB paradigm has been linked to the SoA and because the SoA has been hypothesized to be related to affect (Takahata, Takahashi, Maeda, Umeda, Suhara, Mimura & Kato 2012; Yoshie & Haggard 2013, 2017; Christensen, Yoshie, Di Costa & Haggard 2016), and impulsivity (Moore *et al.* 2010/3), we also collected measures of subjective affective state and action inhibition using the Stop Signal Task (SST) (Logan 1994), for an initial test of these hypotheses. Detailed information concerning the procedures for the SST, questionnaires, and scales is reported in the Supplementary Information section.

Twenty-nine participants (mean age = 22, SD=1.98), received one of the following doses of ethanol: 0.0 (N=9, 5 females), 0.4 (N=10, 5 females), or 0.6 (N=10, 5 females) g/kg. In this experiment instead of adjusting for body weight by keeping the volume of drinks constant and changing alcohol concentration (as in Experiment 1), we kept the concentrations constant (10.6% and 15.8% v/v, respectively, for the doses of 0.4 g/kg dose and 0.6 g/kg) and changed the volume of drinks accordingly (see Supplementary Information).

In Experiment 2, the participants attended two different sessions. During the pre-session the participants used a PC to complete the following questionnaires: i) Alcohol Use Disorder Identification Test (AUDIT, Saunders, Aasland, Babor, de la Fuente & Grant 1993); ii) Drug Use Questionnaire (Townshend & Duka 2005), iii) Positive and Negative Affective Scale (PANAS, Watson, Clark & Tellegen 1988); iv), Barrat Impulsivity Scale (BIS-11, Patton & Stanford 1995).

The testing sessions took place 3-8 days after the pre-session, after 11:30 am. At baseline (T0), pre-test (T1), and post-SST (T3), the participants completed the following computerised scales concerning their affective state: (i) *Affective GRID* (Russell, Anna & Mendelsohn 1989), a graphic two-dimensional single-item scale, with arousal on the vertical axis and pleasure, on the horizontal axis, both dimensions ranging from 1 (lowest) to 9 (highest); (ii) *Biphasic Alcohol Effects Scale* (BAES) (Martin, Earleywine, Musty, Perrine & Swift 1993), designed to measure both the stimulant and the sedative effects of alcohol (associated to the rising and declining limbs, respectively, of the BrAC curve), including seven items for each dimension ranging from 1 to 10. At T3, the participants also completed VASs (Visual Analogue Scales) probing the subjective perception of being under the influence of alcohol.

All other procedures (including debriefing) were identical to those of Experiment 1, except that, after the recording of BrAC post-IB (T2), the participants performed the SST, at the end of which (T3) BrAC was measured again.

Intentional Binding (IB) Task

The IB task instantiated an independently published protocol (Haggard *et al.* 2002). The participants were asked to sit in front of a computer screen (Figure 1a) where a red dot appeared at a pseudo-randomised position at each trial and rotated around a clock face at a constant rate of 2560 ms per revolution (Libet *et al.* 1983). The clock face was marked with conventional 5-min interval ticks. A fixation cross was displayed at the center of the clock. The task consisted of four distinct blocks of 30 trials each.

During two of these blocks (baseline conditions, Figures 1b and 1c), the participant either performed a voluntary action or perceived an auditory tone, respectively, then estimated the timing of these two physical events. During the other two blocks (agency conditions, Figures 1d and 1e), the two physical events were predictably coupled to each other: i.e. a *voluntary action* was always followed by the *sensorial outcome* after a fixed period of 250 ms. The blocks were separated by a 30-s resting period. The trial time limit for the blocks involving voluntary action was fixed at a maximum of six full revolutions of the dot on the clock's face (15360 ms). Each trial was initiated when the participant decided to press the key. They were instructed to not use the ticks on the clock face as external cues to perform the action, but instead to press the key whenever they felt the urge to do so, and to use the clock only as an external metric to gauge the onset of their subjective experience. The participants were encouraged to be as precise as possible in judging the timing of the events. Additional information about the IB task is provided in the Supplementary Information section.

Data Analysis

Demographic data were analysed using one-way analysis of variance (ANOVA). The frequency of drug use was analysed using the Fisher's Exact test.

The BrAC data were analysed separately for the two experiments using two-way ANOVAs on between-subject factor *alcohol* (0.0, 0.4, and 0.6 g/kg) and within-subject factor *time* (T0, T1, and T2 for Experiment 1; T0, T1, T2, and T3 for Experiment 2), followed by appropriate post-hoc pair-wise comparisons.

Intentional Binding data were obtained as described in previous studies (Moore *et al.* 2010/3, 2011; Haggard *et al.* 2002; Christensen *et al.* 2016; Lush, Parkinson & Dienes 2016). First, we calculated distinct values for the action shift and the tone shift. The former was obtained by subtracting the estimated time of voluntary action in the Baseline condition from that of the Action Agency condition. Similarly, the tone shift was calculated by subtracting the estimated time of tone perception in the Baseline condition from that of the Tone Agency condition. We then calculated IB by subtracting the action shift from the tone shift. This measure is thought to provide an implicit, quantitative measure of the SoA. The action shift, tone shift and IB data were analysed in two ways. First, we used a planned one-tailed One Sample t-test (as the direction of the effect was predicted) to verify the occurrence of IB in each of the three groups. Second, group differences were assessed with a two-way ANOVAs on between-subject factors *experiment* (experiment 1 and experiment 2) and *alcohol* (0.0, 0.4, and 0.6 g/kg), followed by appropriate post-hoc pair-wise comparisons.

Detailed information concerning the analysis of SST, questionnaires, and scales data is reported in the Supplementary Information section. A summary of the main results is provided in Table 2.

Effect size was estimated by calculating partial eta-squared (η^2), with critical values: 0.01-0.059=small effect size, 0.06-0.13=medium effect size, and >0.14=large effect size (Cohen 1988).

Results

Demographics characteristics

The demographics of the participants are summarized in Table 1. There were no significative between-group differences in age, BMI, and use of alcohol, cigarettes, cannabis, or other recreational drugs.

BrAC

As shown in Figure 2, alcohol increased BrAC levels to same extent in Experiment 1 ($F[4, 54]=82.62$, $p<0.001$, $\eta^2=0.860$) and Experiment 2 ($F[6,78]=54.209$, $p<0.001$, $\eta^2=0.870$). The increase was greater after administration of 0.6 mg/kg than after 0.4 mg/kg at T1, T2, and T3 (all p's<0.05).

Intentional Binding task

As expected, in all groups manifested a significant (p's≤0.004) shift in estimating the time of voluntary action, relative to the actual physical event, and a significant (p's≤0.004) IB effect (see Figures 3, 4a, and 4c, and Supplementary Information, Table S1). In contrast, there was a much greater shift in estimating the time of tone perception after administration of alcohol than after vehicle (Figures 3 and 4b), leading to a compression in the estimated delay between action and tone perception (Figure 3). As a result, overall IB was much greater under the influence of the alcohol than in controls (Figure 4c). The ANOVAs, indicated a main effect of *alcohol* for IB ($F[2,53]=0.649$, $p=0.003$, $\eta^2=0.194$) and tone shift ($F[2,53]=0.647$, $p=0.003$,

η^2=0.196) but not for action shift (p=0.97). As shown in the insets of Figure 3, the results were almost identical in the two experiments, with no effect of *experiment* and no *alcohol* x *experiment* interaction for action shift, tone shift, or IB (p's>0.25). Post-hoc LSD tests showed significant differences in IB between the vehicle group and both alcohol groups (p=0.004 and p=0.002 for the 0.4 g/kg and 0.6 g/kg group, respectively; p<0.05 and p<0.01, respectively, after Bonferroni's correction), which did not differ from each other (p=0.82). Also for tone shift there were significant differences between the vehicle group and both alcohol groups (p=0.003 and p=0.002 for the 0.4 g/kg and 0.6 g/kg group, respectively; p<0.01 for both groups after Bonferroni's correction), which did not differ from each other (p=0.9). Additional information about the IB task is reported in the Supplementary Information section (Tables S1 and S2).

Measures of impulsivity and affect

Detailed information concerning the results of the SST, questionnaires, and scales is reported in the Supplementary Information section. A summary of the main results is provided in Table 2. As shown in Table S3 (Supplementary Information section), there was no significant correlation between the effects of alcohol on IB and those on SSRT, arousal, pleasure, on stimulation/sedation.

Discussion

To the best of our knowledge, this is the first study to investigate the effects of alcohol on Intentional Binding (IB). We found that at low to moderate doses (0.4-0.6 g/kg) of ethanol, producing BrAC within the driving limits of most European and North American countries (0.25-0.35 mg/l), alcohol enhanced IB, indicating a tighter linkage between voluntary action

and external sensory events. These same doses of alcohol did not affect impulsivity, as indicated by the SST, nor the affective state of participants.

Effects of alcohol on IB

The mechanisms responsible for the effect of alcohol on IB are not obvious, as this drug has a variety of actions in addition to its well know allosteric agonism at GABA-A receptors (Stephens, King, Lambert, Belelli & Duka 2017). Previous studies suggest the possible involvement of at least two of these mechanisms. The first one is represented by the ability of alcohol to increase dopamine levels in the terminal regions of the mesostriatal dopamine system by inhibiting (via GABA-A receptors) GABAergic interneurons projecting onto dopaminergic neurons, effectively disinhibiting the latter (Morikawa & Morrisett 2010). Indeed, enhanced IB occurs in individuals with Parkinson's Disease (PD) treated with L-DOPA and/or dopamine D2 receptor agonists (Moore *et al.* 2010/3). The second potential mechanism is represented by allosteric antagonism at ionotropic glutamatergic receptors (Möykkynen & Korpi 2012). Increased IB has been, in fact, observed in healthy individuals treated with the non-competitive NMDA antagonist ketamine (Moore *et al.* 2011). Interestingly, in addition to its action on NMDA receptors, ketamine has also direct agonist effects on dopamine D2 receptors (Kapur & Seeman 2002).

However, it is important to point out that the effects of ketamine and dopaminergic medications on IB are not identical. Ketamine increases the binding of the action towards the tone (Moore *et al.* 2011) whereas L-DOPA and dopaminergic agonists increase the binding of the tone towards the action (Moore *et al.* 2010/3). The dissociation in judgment shift for action versus tone (see Wolpe, Haggard, Siebner & Rowe 2013) point to distinct mechanisms of action for the two classes of drug. The effects of alcohol reported here are similar to those of dopaminergic medications, consistent with our working hypothesis.

It is not clear how increased dopaminergic transmission strengthens IB relative to placebo. It is unlikely that this effect depended on the transient slowing on a hypothetical internal clock after the voluntary action (Moore & Obhi 2012), because drugs that increase dopaminergic transmission, such as amphetamine and cocaine actually speed up the clock (Badiani & Stewart 1999; Cheng, Ali & Meck 2007). Alternatively, it has been suggested, building on the role of dopamine in prediction error learning (Schultz 1998), that the "exaggerated action–effect binding" of dopaminergic medications may be "caused by modulation of phasic dopamine prediction error signals" (Moore *et al.* 2010/3). Lastly, since dopamine has been implicated in the attribution of incentive salience (Berridge & Robinson 1998), it is possible that dopaminergic hyperactivity increases the incentive-salience of the tone in relation to the voluntary action, thus 'attracting' the former towards the latter.

A potential limitation of the present study is intrinsic to the IB task. Previous studies show stronger binding between voluntary actions and outcomes than between pairs of sensory stimuli (Haggard *et al.* 2003; see also Buehner 2012; Suzuki *et al.* 2019). Thus, we focused here on the effects of alcohol on a task that can reflect sense of agency, as previously done in studies with dopaminergic medications (Moore *et al.* 2010/3). Further research is necessary to determine whether dopaminergic agonists and alcohol would facilitate also the binding of sensory events in the absence of voluntary action.

It has been hypothesized that the facilitation of IB in individuals with PD treated with dopaminergic medications might be related to impulsivity (Moore *et al.* 2010/3), which is thought to depend on dopaminergic transmission (Jentsch, Ashenhurst, Cervantes, Groman, James & Pennington 2014). The fact that impulse control disorders (e.g. pathological gambling, hypersexuality, compulsive shopping and eating) often develops in PD patients receiving dopaminergic medications, especially dopamine agonists, is a convincing rationale for this interpretation (Voon, Hassan, Zurowski, de Souza, Thomsen, Fox, Lang & Miyasaki

2006; Dagher & Robbins 2009). However, the results presented here suggest that abnormalities in IB might develop independently of impulsivity, as we found no correlation between the effects of alcohol on IB and performance on the SSRT (see Supplementary Information section, Table S3). Although the sample size in Experiment 2 was relatively small, these findings are also consistent with the results of a previous study with 0.4 g/kg ethanol (Caswell *et al.* 2013) and findings of an additional smaller study with 0.6 g/kg ethanol (unpublished data). Both indicate that alcohol had no significant effect on the performance in a visual SST. Nevertheless, others have observed that the same doses of alcohol can produce impaired inhibitory control in the SST (Mulvihill, Skilling & Vogel-Sprott 1997; de Wit, Crean & Richards 2000). It is possible that these inconsistent effects of alcohol on inhibitory control might reflect different alcohol administration procedures resulting in different absorption rates.

Previous studies exploring the emotional modulation of IB in healthy volunteers focused on assessing the valence of the outcome, showing that binding is reduced when one's voluntary actions cause negative outcomes, compared to positive or neutral outcomes (Takahata *et al.* 2012; Yoshie & Haggard 2013, 2017; Christensen *et al.* 2016). Indeed, low to moderate doses of ethanol typically increase positive emotions and prosocial behaviours, which is thought to represent a motivating factor for alcohol consumption among non-dependent individuals (Kamboj *et al.* 2013; Müller & Schumann 2011), whereas at higher doses ethanol can produce aversive effects, including dysphoria and aggression (Ito, Miller & Pollock 1996). However, our results show that at doses that altered IB, alcohol had no significant effects on the affective state of participants (see Table 2 and Table S3 in Supplementary Information). These findings deserve particular attention, especially in the context of future neuropharmacological investigations of IB under the effect of alcohol, as discussed in the following section.

Alcohol, IB, and Legal Responsibility

The major aim of our study was to fill a gap in our understanding of the effects of moderate doses of alcohol. However, it is not inappropriate to observe that, to the extent that IB reflects the SoA, our study might have significant implications for important aspects of human social behaviour that are underpinned by the SoA. In law, for example, criminal responsibility requires not only that an agent perform a specific motor action (*actus reus*) but also that the agent "knows the nature and quality of the act" (*mens rea*) (Child, Child & Ormerod 2015), with obvious implications for liability and sentencing in cases of intoxication. Indeed, alcohol intoxication, by altering partially or totally the capacity of a person to form *means rea*, is a commonly invoked defence in alcohol-related accidents or crimes (Dimock 2011; Husak 2012; Law & Sociology 2018). Quite surprisingly, we found here that at concentrations within legal limits for driving (that is, in the absence of overt intoxication usually associated to impulsive and aggressive behaviour) alcohol does not decrease but facilitates IB. This finding challenges simplified notion of alcohol intoxication, suggesting that the degree of intoxication matters not only quantitatively but also qualitatively.

Intentional Binding as an index of SoA

While IB is sensitive to experiences of agency (Lush *et al.* 2017), temporal binding also occurs between events believed to be causally related (Buehner & Humphries 2009; Buehner 2012) and the magnitude of IB can be the same for both intentional and causal binding when conditions are well matched (Suzuki, Lush, Seth & Roseboom 2019). It has recently been claimed that IB is unrelated to action intention, because binding is driven by the relative precision of action and outcome cues (Kirsch, Kunde & Herbort, 2019). However, because

motor intentions are likely to influence the variability of action timing judgements, and therefore the extent of binding (Lush, Roseboom, Scott, Seth, Cleermans & Dienes 2019), IB is perhaps best understood as causal binding arising from intentional action. To the extent that motor intentions support the SoA, changes in IB may to reflect changes in the availability of motor intentions to higher order processes, including both the generation of SoA and the timing of sensory events.

Finally, although we agree with Moore and Obhi (2012) that "whilst it is yet to be fully explicated, the link between intentional binding and the sense of agency is compelling", it is fair to note that our study presents two limitations. First, in the absence of a control task, we cannot rule out the possibility that binding here is attributable to differences in causal beliefs. However, we have no theoretical reason to anticipate alcohol-related influences on beliefs about causation. Hence, such a chain of phenomena is not required for a parsimonious interpretation of our results. Second, although the IB task represents an indirect, albeit objective, measure of SoA, it does not necessarily index the higher-level explicit experience of agency. Thus, it would be important to verify whether the effect of alcohol on an implicit measure of SoA extends to explicit (metacognitive) measures (Ebert & Wegner 2010).

Conclusions

On the assumption that changes in IB reflect SoA here, our study suggests important implications which could be explored in future work. First, it might help update the conceptualization of addiction and other impulse control disorders as disorders of 'free-will' (Heyman 2013). Second, although there is no agreement on whether "the sense of agency is either necessary or sufficient for consciousness of the kind that the law takes to be involved in voluntary action" (Maoz & Yaffe 2016), our study might have some bearing on forensic

aspects of substance use (Yoshie & Haggard 2013; Haggard 2017). Thus, further

investigation of the influence of alcohol and other addictive substances on the SoA may

foster the refinement of neuroscientific models of motivation and volitional self-control, and

provide a more useful framework for both therapeutic and legal applications (Pierre 2014).

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Authors Contribution

SD was responsible for the study concept. All authors made an active contribution to the study design. SD recruited the participants and acquired the data. SD, PL, and AB analysed the data. SD and AB drafted the original version of the manuscript. All authors critically reviewed and edited content, and approved the final version for publication.

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Table 1. Demographics, BrAC, and drug use. Values are expressed as means (SD) or percentage of use.

Variable	Ethanol dose (g/kg)			Group Comparisons
	0.0 **N=19**	**0.4** **N=20**	**0.6** **N=20**	
Age	21.58 (1.98)	21.65 (1.79)	22.05 (2.16)	$F_{(2,56)}=0.32$, $p=0.73$
Gender	9M, 10F	10M, 10F	10M, 10F	
BMI	23.55 (3.21)	23.24 (2.09)	22.79 (2.35)	$F_{(2,56)}=0.42$, $p=0.66$
Alcohol intake (units per week)	8.26 (6.05)	11.7 (7.18)	8.60 (7.18)	$F_{(2,56)}=1.51$, $p=0.23$
Number of cigarettes per day[a]	1.42 (3.42)	1.00 (2.10)	0.23 (0.57)	$F_{(2,56)}=1.34$, $p=0.27$
Recreational Cannabis use[b]	48%	35%	55%	$p=0.80$ (two-tailed Fisher Exact Probability test)
Other recreational drugs[c]	21%	20%	20%	$p=0.99$ (two-tailed Fisher Exact Probability test)

Abbreviations: BMI, body mass index; BrAC, breath alcohol concentration.

[a] Cigarettes: All smokers smoked <11 cigarettes a day.

[b] Cannabis: Participants reported a temporal pattern ranging from 'weekly' to 'less than once a month'.

[c] Other recreational drugs: Participants reported a frequency of use of 'less than once a month'

Table 2. Questionnaires, scales, and SST. (A) Barrat Impulsivity Scale (BIS-11), Positive and Negative Affective Scale (PANAS), and Alcohol Use Disorder Identification Test (AUDIT) collected during the pre-session; (B) Stop Signal task (SST); (C) Affective Scales at T0 (baseline), T1 (pre-test) and T3 (post-test); (D) Visual Analogue Scales (VASs) at T3. Values indicates mean±SEM. See text and Supplementary Information for details.

	Vehicle		Ethanol 0.4g/kg		Ethanol 0.6 g/kg		F		p		η^2	
A) Pre-session scales												
BIS - 11	65.78±4.06		58.10±3.20		67.50±3.60		1.97		0.16		0.13	
PANAS Positive	32.89±2.50		37.20±1.72		30.20±1.82		3.20		0.057		0.20	
PANAS Negative	18.67±1.89		19.90±1.59		17.20±0.80		0.88		0.43		0.06	
AUDIT	8.67±1.80		8.80±1.02		6.10±0.63		1.61		0.22		0.11	
B) SST												
Go accuracy %	97.41±1.03		96.66±1.11		96.67±1.03		0.17		0.84		0.01	
Go reaction time (ms)	457.61±28.25		506.42±43.63		491.96±31.77		0.48		0.63		0.04	
Stop accuracy %	49.4±2.27		52.5±2.14		52±1.07		0.67		0.55		0.05	
SSRT (ms)	226.9±11.39		239.05±12.66		246.46±15.29		0.62		0.546		0.04	
Mean SOA stop	230.69±36.30		267.38±42.68		245.50±27.72		0.26		0.78		0.02	
C) Affective Scales												
Affective Grid	Ar	Pl	Ar	Pl	Ar	Pl	Ar	Pl	Ar	Pl	Ar	Pl
• T0	4.89 ±0.75	6.67 ±0.75	4.70 ±0.62	7.20 ±0.42	4.60 ±0.54	6.40 ±0.64	0.87	0.21	0.49	0.93	0.06	0.02
• T1	6.22 ±0.60	7.22 ±0.46	6.40 ±0.72	8.10 ±0.31	5.40 ±0.67	6.90 ±0.55						
• T3	4.33 ±0.97	6.44 ±.58	4.90 ±0.77	6.90 ±0.31	5.15 ±0.48	6.40 ±0.27						
BAES	Stim	Sed	Stim	Sed	Stim	Sed	Stim	Sed	Stim	Sed	Stim	Sed
• T0	31.67 ±5.21	19.56 ±5.19	38.90 ±3.34	14.40 ±2.92	27.70 ±3.96	22.30 ±3.80	0.78	0.12	0.54	0.98	0.06	0.01
• T1	36.22 ±3.66	16.33 ±4.48	47.60 ±3.80	10.90 ±2.79	39.50 ±4.21	21.00 ±4.96						
• T3	26.11 ±5.56	26.22 ±6.10	30.80 ±4.72	17.80 ±4.47	27.50 ±2.74	27.60 ±5.66						
D) post-test VASs												
"Feeling the effect of alcohol"	1.67±0.44		4.40±0.62		4.90±0.64		8.61		0.001		0.40	
"Feeling high"	1.89±0.81		3.60±0.76		5.20±0.73		4.60		0.02		0.26	
"Liking the effect"	2.78±0.88		5.00±0.70		5.00±0.52		3.22		0.056		0.20	
"Wanting more drink"	1.44±0.67		4.00±0.82		3.70±0.96		2.71		0.08		0.17	
"Liking the taste of the drink"	4.33±0.78		5.10±0.82		4.30±0.92		0.29		0.75		0.02	

Abbreviations: SSRT (Stop Signal Reaction Time), SOA (stimulus onset asynchronies). BAES (Biphasic Alcohol Effects Scale), Stim (Stimulant), Sed (Sedative), Ar (Arousal), Pl (Pleasure).

Figure Legends

Figure 1. Schematic representation of the Intentional Binding Task. Participants were seated in front of a computer screen where a red dot was rotating around a clock's face at the constant speed of 2560 ms (a). The task included two Baseline and two Agency blocks. In the Baseline-Action block (b) participants make a voluntary action (key press) at the time of their own free choice and then estimated the point on the clock when they made that action. In the Baseline-Tone (c) an outcome (tone) was delivered at a random time and participants estimated the perception of that event. In the Agency conditions, voluntary actions were always followed by an outcome (a tone) after a constant delay of 250 ms (d, e). In the Agency-Action block (d) participants estimated the time at which they made the voluntary action whereas in the Agency-Tone (e) block they estimated the time at which they heard the tone.

Figure 2. Mean (±SEM) BrAC following ethanol administration in Experiment 1 and Experiment 2 at T1, T2, and T3 (only for Experiment 2) for the participants who received 0.4 g/kg or 0.6 g/kg ethanol (see text for details). Asterisks indicate a difference at $p<0.05$ (*) and $p<0.001$ (****) relative to T0.

Figure 3. Schematic representation of the timing of actual events for the three groups. When voluntary actions and the sensory events are coupled, humans tend to judge the action as occurring later in time (action shift, indicated by the blue dotted arrow) and the sensory event as occurring earlier in time (tone shift, indicated by the red dotted arrow), relative to when the events occur separately. This results in a compression of the estimated delay (green arrow), that is, in the 'binding' of the two processes. See text and Supplementary Information for details.

Figure 4. Summary of the results from the Intentional Binding task. (a) Action shift in estimating the time of voluntary action, relative to the actual phyisical event, in all groups. (b) In contrast, there was a much greater shift in estimating the time of tone leading to a compression in the estimated delay between action and tone perception in the alcohol groups comapred to placebo (sign-reversed for illustration purpose). As a result, the overall IB (c) was much greater under the influence of the alcohol than in controls. Data are presented as Mean (±SEM). Asterisks indicate a difference at $p<0.005$ (**) relative to vehicle group (0.0

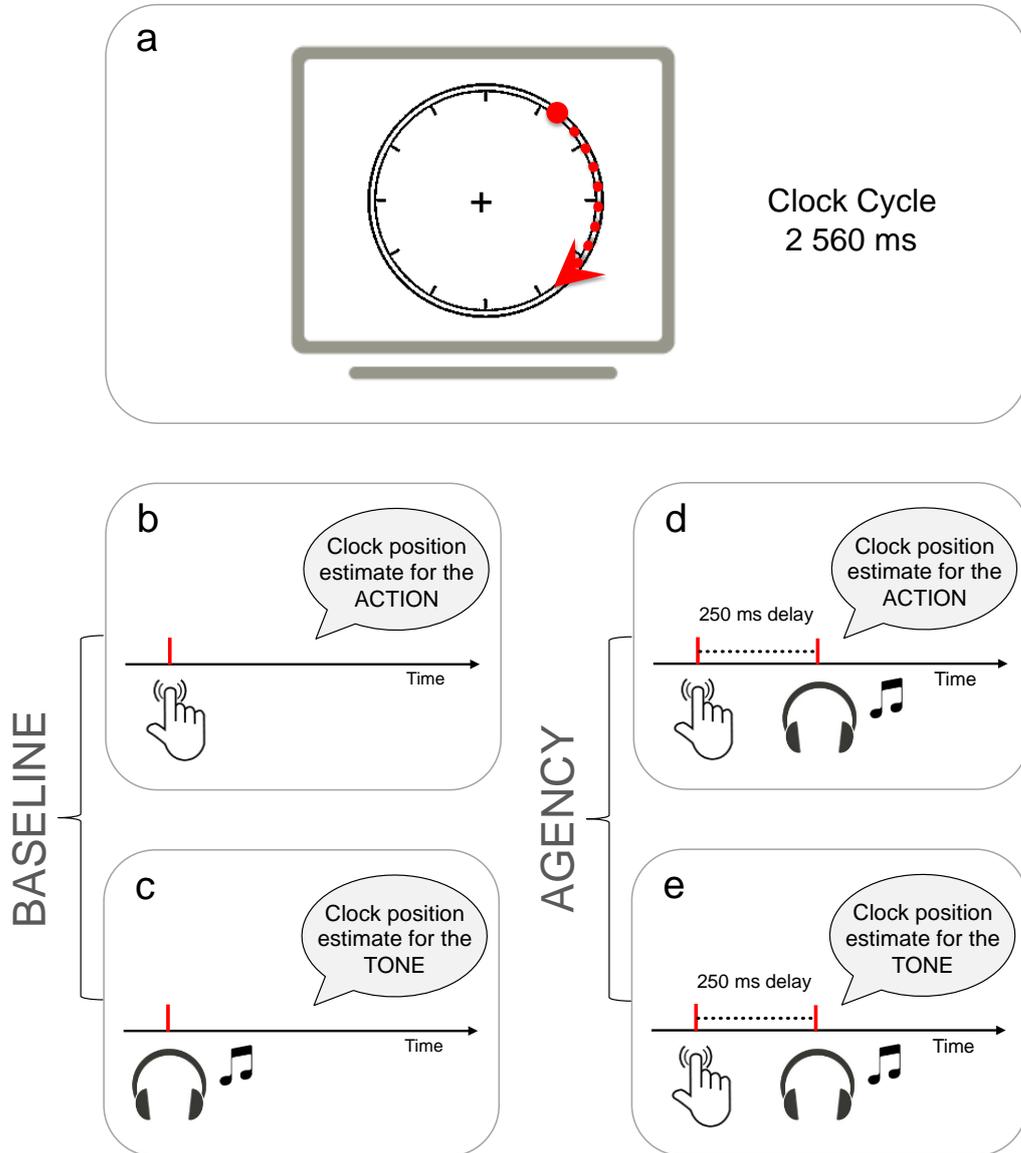mg/kg). The insets show the results for the two experiments separately, with no effect of *experiment* and no *alcohol* x *experiment* interaction for action shift, tone shift, or IB (p's>0.25).
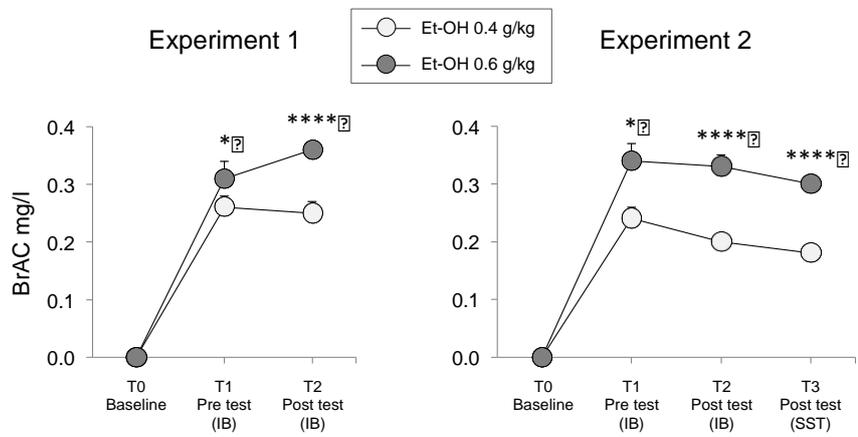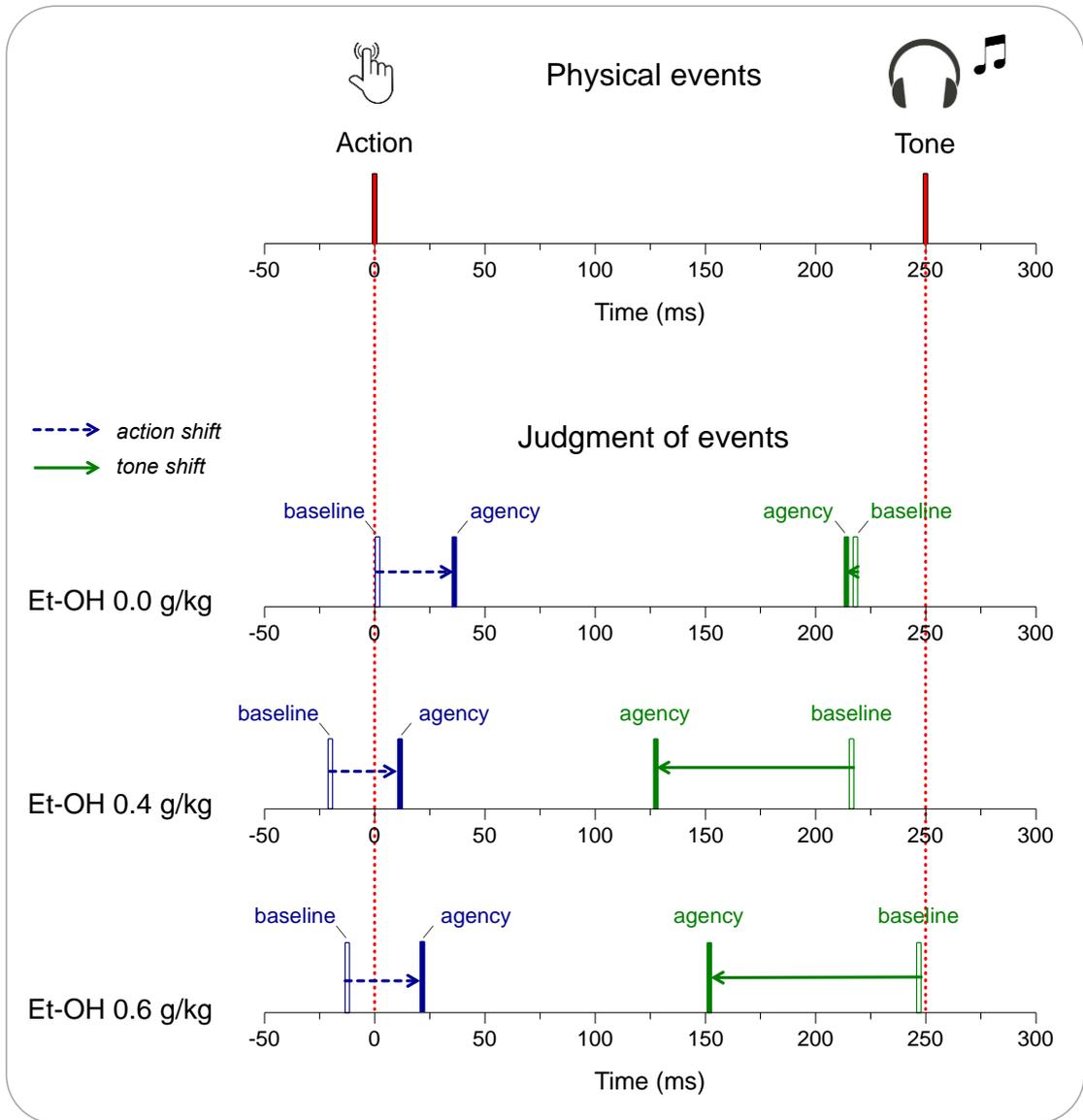
Figure 1

Figure 2

Figure 3

Figure 4