Stimulus-driven and intentional inhibition: Perspectives on loss of control in substance use and misuse

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Yang LIU (刘 洋) was born on 17th August in Henan, China. She obtained her B.Sc. degree in Applied Psychology with distinction and awarded the 'China National Scholarship' in 2012. In the same year, she carried out her graduate study at the Key Laboratory of Cognition and Personality of the Ministry of Education in Southwest University (China). In 2015, she received her master's degree in Experimental Psychology, focusing on substance use and decision making, interventions in promoting self-control. She then joined the developmental psychology department of the University of Amsterdam as a Ph.D. student. Until her graduation in 2019, she worked under the supervision of Prof. dr. Richard Ridderinkhof, Prof. dr. Reinout Wiers and Dr. Wery van den Wildenberg. Her research focused on the association between substance use (e.g., poly-substance use, acute & chronic alcohol use, binge drinking) and (stimulus-driven, intentional) inhibition, following a holistic approach—questionnaires, behavioral measures and neuroimaging (e.g., EEG).

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aan de Universiteit van Amsterdam

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"If an alcoholic takes a drink, he can never be sure he will be able to stop before he loses control and starts on a bout."

—Mark Keller

Contents

Chapter 1

General introduction

Why it is important to investigate 'loss-of-control' behavior amongst substance users

Derived from the Latin verb addicere (i.e., 'to enslave'), addiction is characterized by an apparent loss of control or autonomy over one's behavior. Substance addiction develops from voluntary, recreational consumption to automized and compulsive consumption patterns (Everitt et al., 2008; Everitt & Robbins, 2005). This loss of control of behavior was proposed to play important roles in several steps in the addiction circle: 1) initial use of substance; 2) transition from recreational use to heavier use and abuse; 3) continuation of heavy use despite growing problems; 4) relapse after abstinence (e.g., Garavan, Potter, Brennan, & Foxe, 2015; Koob & Volkow, 2010). Regarding the loss-of-control over substance use, three criteria of alcohol use disorder (similar to other substances) from the DSM-5 are relevant to this loss-of-control: "alcohol is often taken in larger amounts or over a longer period than was intended; there is a persistent desire or unsuccessful efforts to cut down or control alcohol use; continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol" (American Psychiatric Association [APA], 2013).

Furthermore, most addiction models emphasize the role of impaired response inhibition. For instance, the I-RISA model (impaired response inhibition and salience attribution) suggests that impaired response inhibition and increased salience of the reward-associated drug cues are two key components of the vicious circle of drug addiction (Goldstein & Volkow, 2002). Dual process models posit that addiction develops as the imbalance between a hyper-sensitized impulsive system and a compromised reflective or control system (Bechara, 2005; Gladwin, Figner, Crone, & Wiers, 2011; Volkow, Fowler, Wang, & Swanson, 2004; Volkow, Koob, Mental, Parity, & Act, 2015; Wiers & Stacy, 2006). In the recently proposed Research Domain Criteria (RDoC, Yücel et al., 2018), response inhibition is one of the seven primary constructs underpinning addictive behaviors (substance addiction and behavioral addiction).

Loss-of-control could be expressed either as an *impulsive choice* or as an *impulsive response*. Impulsive choices may be driven by the preference for a smaller more immediate reward over a larger more delayed reward (see meta-analysis: Amlung, Vedelago, Acker, Balodis, & MacKillop, 2017). Impulsive responses, on the other hand, refer to the inability to withhold an inappropriate response to prepotent stimuli (de Wit, 2009). Subtypes of impulsivity (e.g., impulsive choice, impulsive response, and trait impulsivity) were found to be only weakly inter-correlated (MacKillop et al., 2016). For the purpose of the thesis, we focused on *impulsive responding and its relationship with alcohol use (long-term & acute)*.

Globally speaking, current drinkers' daily alcohol consumption is averaged at

32.8 grams of pure alcohol (cf, 3.3 standard drinks in the Netherlands); the highest levels of *per capita* are observed in WHO European countries (World Health Organisation & Management of Substance Abuse Team, 2018). Worldwide, the harmful use of alcohol resulted in about 3 million deaths (5.3% of all deaths) and 132.6 million disability-adjusted life years (5.1% of all) in 2016 (World Health Organisation & Management of Substance Abuse Team, 2018). In the same year, 28.7% of all deaths attributable to alcohol consumption were due to *injuries* worldwide, which is the first contributor (World Health Organisation & Management of Substance Abuse Team, 2018). This also reflected the hazardous effect of impulsive behavior after drinking.

Research paradigms used to measure response inhibition

The stop-signal task (SST, Logan & Cowan, 1984) and go/no-go task (GNG, Donders, 1969) are most commonly used to measure inhibitory control. In the GNG, participants are asked to respond as fast and as accurate as possible to one set of stimuli (i.e., frequent go stimuli), whereas they should inhibit responding to another set of stimuli (i.e., infrequent no-go stimuli). The proportion of failed inhibition (commission errors) on no-go trials reflects disinhibition. In the SST, on a subset of the trials, the go signal is followed by a stop signal after a variable delay (stop-signal delay or SSD), indicating the participants to withhold their response. Therefore, unlike the GNG, the SST tests one's capability of inhibiting *already initiated* responses. The SST is unique in providing the latency of the stop process (stop-signal response time or SSRT) in addition to the inhibition rate. As the SST was used more often in this thesis, we introduce it here in more detail.

The SST is based on a horse-race model of stopping, where independent go and stop processes are modeled as racing against each. The outcome of the race (which process wins) decides whether a response is successfully inhibited or not (Band, van der Molen, & Logan, 2003; Logan, 1994; Logan & Cowan, 1984). If the go process finished before the stop process (e.g., the left side of the dashed line in **Figure 1**), then the faster go process wins the race and the inhibition fails. Otherwise, if the stop process wins, inhibition is successful (the right side of the dashed line in **Figure 1**). There are several ways of calculating SSRT, and **Figure 1** depicts the *integration*/*quantile* method (Band et al., 2003). Using the *integration* method, SSRT is calculated as follows: 1) RTs for go trials are rank-ordered ascendingly, 2) the go RT corresponding to the percentage of failed inhibition is selected (*n*th RT), 3) SSRT is calculated by subtracting SSD from the *n*th RT (Verbruggen & Logan, 2009). SSRT can be calculated for each SSD or averaged SSD. Alternative methods include the *median* method (a variant of the integration method that assumes that inhibition rate is always exactly .50) and the *mean* method (the mean of the inhibition function is subtracted from the mean of the

RT distribution, Verbruggen & Logan, 2009). If the distribution of go RT is symmetrical, the mean and median methods yield the same result. It was suggested that the mean and median methods should be abandoned in favor of the integration methods as these methods are susceptible to the positive-skewed distribution of RTs and gradual slowing of RTs (Verbruggen, Chambers, & Logan, 2013).

Variants of the SST include stop-signal modality (visual or auditory), stop-signal probability (usually 25%), number of experimental trials (a minimum of 50 stop trials was suggested, Verbruggen et al., 2019), and SSD setting (fixed SSD or adaptive staircase tracking procedure). In the fixed SSD, a broad range of SSDs was suggested to prevent waiting for the stop signals (e.g., 100 ms, 150 ms, 200 ms, 250 ms, and 300 ms). In the tracking procedure, the SSD is set to an initial value (e.g., 200 ms). SSD decreases by 50 ms after failed inhibition (rendering stopping on the next stop trial easier) and increases by 50 ms after successful inhibition (rendering stopping on the next stop trial more difficult). In this way, the inhibition rate is adjusted around 50%. For a reliable SSRT, fewer stop-signal trials are needed with the tracking procedure than the fixed-SSDs procedure (Verbruggen et al., 2019).

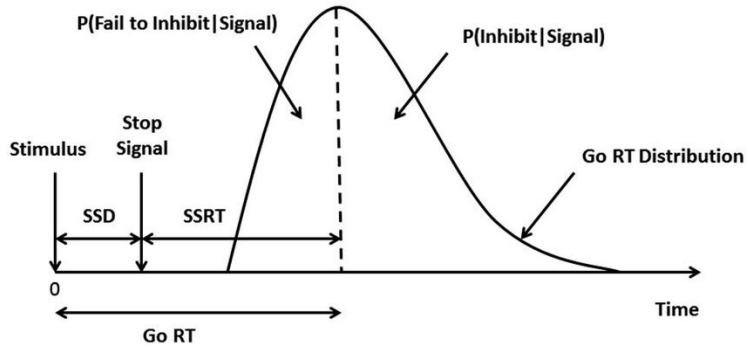

Figure 1. Graphic representation of SSRT calculation, based on the assumptions of the independent horse-race model of Logan & Cowan (1984).

Chronic alcohol use and response inhibition

The relationship between response inhibition and alcohol use has evoked broad research interests in the past decades. Regarding long-term alcohol use, the results are mixed. Some studies found that heavy drinkers/people diagnosed with alcohol use disorder showed longer SSRT in the SST or made more commission errors in GNG than light drinkers/healthy controls (e.g., Christiansen, Cole, Goudie, & Field, 2012; Houston et al., 2014; Murphy & Garavan, 2011; meta-analysis: Smith, Mattick, Jamadar, & Iredale, 2014). Alternatively, many other studies documented comparable inhibition performance between light and heavy drinkers (Courtney et al., 2012; Papachristou, Nederkoorn, Havermans, van der Horst, & Jansen, 2012), some identifying even better

performance among heavier users (Bø & Landrø, 2017). Possible reasons underlying this inconsistency include 1) tasks with different parameters were used (e.g., alcohol-related images were used in a modified GNG task: Kreusch, Vilenne, & Quertemont, 2013 vs. a conventional GNG); 2) sample characteristics (e.g., adolescents vs. adults, variants of alcohol use severity); 3) data analysis procedure (e.g., how outliers were dealt with, how dependent variables were calculated); and 4) statistical power (e.g., whether the sample size was large enough). This also relates to the test-retest reliability of the SST which has been questioned (intra-class correlation of 0.03, Wöstmann et al., 2013). As no study has specifically examined the reliability of the SST or GNG within substance/alcohol users, how the above significant or null findings might be replicated in multi-site studies is yet unknown.

Meanwhile, this inconsistency indicates the possibility that long-term recreational substance use (without a diagnosis of substance use disorder) may not necessarily be associated with general inhibition deficits, but only when it is related to the substance-intake behavior. Specifically, response inhibition is not a stable trait but could change in response to internal and external events (de Wit, 2009). Exposure to appetitive cues is one potential external event that may negatively influence inhibitory control. According to the incentive sensitization theory of addiction, substance-related cues take on the motivational properties of the drug itself and elicit the automatic approach tendencies and even consummatory behaviors (Berridge & Robinson, 2003; Robinson & Berridge, 1993, 2000). In order to examine this assumption, substance-related stimuli have been embedded into the GNG and SST, either response-related (e.g., respond to pictures of soft-drink bottles and inhibit response to alcoholic bottles, Ames et al., 2014) or response-irrelevant (e.g., background pictures are substance-(un)related, Luijten, Littel, & Franken, 2011; Petit, Kornreich, Noël, Verbanck, & Campanella, 2012). In a recent meta-analysis, it was found that alcohol-related cues negatively influenced response inhibition for heavy drinkers and alcohol-dependent patients but not for light drinkers (Jones, Duckworth, Kersbergen, Clarke, & Field, 2018). What's more, cue modality (pictorial, olfactory, and lexical cues) was not a moderator of these findings.

Acute alcohol use and response inhibition

Compared to chronic alcohol use, the impairment of acute alcohol use on response inhibition is more consistently reported. It was found that moderate to high doses of alcohol (0.4g/kg to 0.8g/kg) lead to worse performance on the GNG and SST (Field, Wiers, Christiansen, Fillmore, & Verster, 2010; Gan et al., 2014; Loeber & Duka, 2009; Marczinski & Fillmore, 2003; Nikolaou, Critchley, & Duka, 2013; Ridderinkhof et al., 2002; Rose & Duka, 2007; Rose & Duka, 2008), although some inconsistent

findings exist (e.g., Guillot, Fanning, Bullock, McCloskey, & Berman, 2010; McCarthy, Niculete, Treloar, Morris, & Bartholow, 2012). Interestingly, such alcohol dosage did not affect the ability to execute a response (e.g., no influence on go RT, Field, Wiers, Christiansen, Fillmore, & Verster, 2010), denoting that the alcohol-seeking behavior (i.e., go process) remained intact. There are several important methodological factors that varied between studies. First, whether a control condition is included in addition to the alcohol and the placebo condition. A balanced placebo design with a control group is suggested to separate the pharmacological and expectancy effect of alcohol (Rohsenow & Marlatt, 1981). Second, whether alcohol administration is a between- (Loeber & Duka, 2009b) or within-subject factor (Gan et al., 2014). Third, whether there is a pre-drink baseline assessment due to the day-to-day individual variance of inhibition capacity (with: Bartholow et al., 2018; without: Caswell, Morgan, & Duka, 2013).

Taken together, a 'snowball effect' exists between acute alcohol intake and inhibitory control. That is, acute alcohol use leads to impaired response inhibition, which leads to further consumption, which in turn contributes to further deterioration of the inhibition system (López-Caneda, Holguín, Cadaveira, Corral, & Doallo, 2014). Empirical studies confirmed that alcohol-induced inhibitory control impairment was positively correlated with ad-lib beer consumption (Weafer & Fillmore, 2008). Using a within-subject design, participants performed the cued GNG task under both alcohol and placebo. It was found that the variance in inhibitory impairment accounted for 20% variance of ad-lib consumption. However, the amount of alcohol consumed was tested when participants were sober. Therefore, this finding could not answer whether alcohol 'priming' leads to an increased craving for and self-administration of alcohol (de Wit, 1996) via insufficient inhibitory control. More studies are needed to replicate this finding and explore it further.

Interventions for reducing alcohol/substance use

It is widely known that alcohol use causes serious individual (e.g., increased morbidity and mortality, Rehm et al., 2009) and social problems (e.g., medical cost, Williams et al., 2018). Therefore, effective interventions aimed at reducing alcohol use and the relapse rate are of particular need. Given the fact that alcohol misuse is associated with inhibitory control deterioration, training inhibition capability provides a promising avenue. One relevant method is termed the inhibitory control training (ICT), which functions by repetitively associating appetitive-cues (e.g., alcohol-related stimuli) with stop signals (see review: Jones & Field, 2013). It was recently found that ICT works by devaluating alcohol-related stimuli rather than strengthening the top-down control over alcohol-related stimuli or creating an automatic bottom-up association

between alcohol stimuli and the stopping process (Houben, Havermans, Nederkoorn, & Jansen, 2012; Veling, Lawrence, Chen, van Koningsbruggen, & Holland, 2017). An alternative brief intervention currently gathering popularity is the implementation intentions (Gollwitzer, 1999). It is proposed that successful goal achievement is facilitated by furnishing the intention with an if-then plan specifying when, where, and how the person will activate responses that promote goal realization (Gollwitzer, 1999; Gollwitzer & Sheeran, 2006). Implementation intentions work by formulating if-then plans, e.g., 'if I am in situation X, then I will do Y' (Gollwitzer, 1999). In this way, the unwanted behavior (e.g., drinking) is replaced by behavior X (e.g., order a soda instead) in a critical situation Y (e.g., being encouraged by friends to keep up drinking with them). It was supposed to be especially effective amongst people with self-control deficits (Gollwitzer, 1999; Toli, Webb, & Hardy, 2016), based on the presumed generation of a prepared reflex (proactive control): once an implementation intention is formulated, action initiation becomes instantaneous, efficient, and requiring no conscious intent (Gollwitzer, 1999). Regarding its role in reducing alcohol use, it was proved to be effective for the general population (Armitage, 2009) as well as those at high risks (Moody, Tegge, Poe, Koffarnus, & Bickel, 2018).

Research gaps and research needs

Poly-substance use

Poly-substance use is defined as using more than one substance over a certain period, either simultaneously or concurrently (i.e., co-use in a given period such as 12 months, but not simultaneously, Connor, Gullo, White, & Kelly, 2014; Subbaraman & Kerr, 2015). Poly-substance use is common according to the recent epidemiological and clinical studies (Carter et al., 2013; Staines, Magura, Foote, Deluca, & Kosanke, 2001). Among alcoholics, for example, two-thirds reported having used other substances in the past three months as well (Staines et al., 2001), for which the prevalence rate would probably increase if a longer period of time was traced back. With regard to the profile of poly-substance use, the latent-class analysis revealed that the most prevalent category of poly use included alcohol, tobacco, and cannabis (Connor et al., 2014).

Although prevalent, poly-substance use has not been addressed sufficiently in the existing literature on long-term substance use and response inhibition. In most cases, except for the main substance of interest, other substance use (excluding tobacco) was either not recorded at all or not reported. In other cases, as long as between-group differences of other substance use did not reach significance, it was not controlled in the main analysis. This is a serious issue when the effects of different substances do not work in parallel but interact with each in their relationship with cognitive functions. Indeed, greater-than-additive effects (alcohol and cocaine: Abé et al., 2013; Pennings,

Leccese, & Wolff, 2002; alcohol and tobacco: Moallem & Ray, 2012) and/or protective effects (tobacco mitigated the effect of cannabis on recall memory: Hindocha, Freeman, Xia, Shaban, & Curran, 2017) were confirmed. Poly-substance use and its relationship with response inhibition appear worthy of systematical analysis, as we did in **Chapter 2**.

Intentional inhibition

Most likely, people who ever successfully went through *dry January* or a diet, have the experience of having to literally withdraw their hands as they approached the wine bottle or junk food on the shelf. In such cases, there is no warning on the package or any stop signals from the outside world signaling the stop; it all depends on one's prior resolve. This kind of volition often referred to as free will (or rather, in this case, free won't), does not come out of thin air. It can be thought of as one's ultimate goal or self-encouragement, e.g., I could survive without drinking/eating it right now. What matters is that the decision to inhibit was made endogenously, rather than triggered exogenously. Theoretically, response inhibition can be categorized into stimulus-driven inhibition and intentional inhibition based on the degree of endogenous volition involved (Ridderinkhof, van den Wildenberg, & Brass, 2014). In daily life, deciding on one's own when and whether to withdraw an action plays a more important role than externally triggered stopping (Aron, 2011). Paradigms such as the GNG and SST are informative in explaining uncontrolled driving under intoxication, but not for failed control over alcohol-seeking behavior. The alcohol addiction cycle/cascade is characterized by drinking more than planned on a typical drinking occasion, development from recreational to hazardous drinking and so on, which appears to reflect dysfunctional intentional inhibition rather than stimulus-driven inhibition.

Although its importance has been recognized, intentional inhibition is largely under-investigated, with methodological difficulty possibly being the primary reason. Specifically, there is no external cue triggering the inhibition, and if the behavior is successfully inhibited, there is no behavioral output. In that way, inhibited actions cannot be differentiated from the ones that are never initiated. Up to now, there are three commonly used research paradigms, called the variants of the Libet task (Brass & Haggard, 2007; Walsh, Kühn, Brass, Wenke, & Haggard, 2010), the Marble task (Kühn, Haggard, & Brass, 2009) and the modified GNG (Parkinson, Garfinkel, Critchley, Dienes, & Seth, 2017). In these tasks, a free-choice condition was added to quantify intentional inhibition. Participants were encouraged to choose between go and stop with approximately equal frequency. Such free-choice design is suboptimal in terms of 1) incentive: nothing hinges on whether participants decide to go or stop. In that regard, is it more like a selective choice task rather than an inhibition task, as the go response is not predominant; 2) participants are under substantial time pressure to make the

decision, which conflicts with the time-consuming nature of intentional inhibition; 3) the possibility of pre-decision cannot be excluded.

In order to remedy these limitations, the Chasing Memo task has been developed (Rigoni, Brass, van den Wildenberg, & Ridderinkhof, *unpublished manuscript*), to measure stimulus-driven inhibition and intentional inhibition within the same task format, and we adapted it for the present purpose. The main task is to move the computer mouse in order to track a fish that is swimming against the background of a sea world. In a stimulus-driven condition, the time to stop and disengage from tracking is signified by a change in stimulus color. Alternatively, in an intentional condition, the time of disengagement is self-determined. To simulate the motivational aspects that play a role during drinking, incentive strategies were borrowed from the delay discounting task (Richards, Zhang, Mitchell, & de Wit, 1999). That is, continued tracking produced more immediate reward (cf. instant pleasure from drinking), whereas disengagement from tracking stops the immediate reward in favor of larger delayed reward (cf. staying sober for an important meeting later on, or for long-term physical health). Inspired by the 3-W model (*what*, *when* and *whether*) of intentional action, intentional inhibition should have three corresponding components: *what* action to inhibit, *when* to inhibit and *whether* to inhibit (Brass & Haggard, 2008). Different components might present dissimilar responses to the effect of alcohol, and this was examined step by step (**Chapter 3** and **Chapter 4**).

As it is hard to capture the behavioral output of intentional inhibition, the majority of existing literature employed neuroimaging techniques to assist their understanding of the mechanisms. Except for the overlapping brain areas with stimulus-driven inhibition (bilateral parietal and lateral prefrontal cortex and pre-supplementary motor area), intentional inhibition produced distinct fMRI activations in the medial prefrontal cortex (Kühn et al., 2009; Schel et al., 2014). Though fMRI has a superior spatial resolution, its temporal resolution is inferior to EEG. And with regard to intentional inhibition, it is also important to figure out neural precursors other than the brain areas engaged. Over the past decade, there have been a few EEG studies on intentional inhibition (Bianco, Berchicci, Perri, Spinelli, & Di Russo, 2017; Parkinson et al., 2017; Parkinson & Haggard, 2015; Walsh et al., 2010; Xu, Fan, Li, Qi, & Yang, 2019). In most cases, components such as N2 and P3 that were associated with stimulus-driven inhibition were analyzed. Unlike these studies, the current thesis focused on the neural activities *preceding* intentional inhibition, and one related key component is the readiness potential (RP) or Bereitschaftspotential. The classical RP is characterized by a negative-going ramp-like form, which was first recorded by Kornhuber and Deecke (1964) and attracted broad attention after Libet and colleagues' striking work in 1983. They found that the self-reported urge to move preceded the actual movement by 200

ms, but the RP already built up 500 ms prior to this awareness (Libet, Gleason, Wright, & Pearl, 1983). This was explained as follows: "the brain resolves to start certain actions at a time before there is any reportable subjective awareness" (Libet et al., 1983). This elucidation incurred a great many criticisms, including that the RP does not reflect voluntary intention nor consciousness intention as it was also found in motor-unrelated process (such as decision making: Alexander et al., 2014). Others proposed that the RP simply represented the averaged fluctuations of spontaneous neural activity. If the fluctuation is sufficient to cross a threshold, a movement will be triggered; otherwise, there is no behavioral output (Schurger, Sitt, & Dehaene, 2012). Our concern here is not so much with the interpretation but with the development and time course of the processes associated with intentional inhibition and how this might be influenced by acute alcohol use (**Chapter 3)**.

Reducing alcohol intake in a naturalistic environment

People with an alcohol restriction goal might not want to avoid visiting high-risk situations (e.g., bar) completely, either for social purposes or being over-confident about their ability to control substance-seeking behavior (restraint bias, see Jones, Cole, Goudie, & Field, 2012). However, exposure to high-risk situations may likely launch a chain of reactions. A highly appealing environment might induce an initial drink, which elicits craving for further consumption and in turn impairs inhibitory control, and so forth. If that happens, one typical drinking occasion would probably develop into a hazardous drinking episode. In this way, it is practically meaningful to examine how interventions might work during such *hot* state (**Chapter 5**). As this has rarely been tested before, whether laboratory findings (e.g., the effectiveness of interventions) can be translated into out-of-lab settings is yet unknown. Implementation intentions were selected as the intervention, instead of the ICT, as it is more feasibly available for a naturalistic environment for being brief and (probably) also less vulnerable to the noisy background. One side effect from this naturalistic approach is that it provides an initial idea about how reduced drinking on signal episodes (rather than reduced frequency) contributes to the total consumption that was usually recorded by the Timeline Followback (i.e., a tool for retrospective estimation of substance use up to 2 years prior to the interview: Sobell & Sobell, 1992; see studies: Armitage, 2009; Armitage & Arden, 2012).

Aim of the thesis

The primary aim of this dissertation was to investigate the association between alcohol use (both long-term and acute) and intentional inhibition. Previous studies in this field exclusively focused on stimulus-driven inhibition. This is meaningful in explaining real-life phenomena such as uncontrolled driving after drinking, but cannot

clarify the loss-of-control over drinking itself. This thesis provides a first step in bridging this gap by using a novel intentional inhibition task to test the chronic and short-term effect of alcohol on intentional inhibition. Meanwhile, we were also interested in how acute alcohol use influences the unfolding of the neural activities related to and preceding the implementation of intentional inhibition (RP). The secondary aim was to examine how different substances interact with each in their relationship with stimulus-driven inhibition while controlling for demographics and task parameters. Though the prevalence of poly-substance use is well recognized, it has not been handled properly. This phenomenon should be taken seriously as drugs may interact in their effects on cognitive functions. Specifically, greater-than-additive as well as protective effects have been reported. We explored the possible interactive effects by merging individual raw data from many published studies included in a mega-analysis (i.e., participant-level mega-analysis). As a third purpose, we examined whether a brief intervention could strengthen transient inhibitory control over drinking in a field study. It is challenging but potentially quite meaningful to explore if people's capability to reduce alcohol use can be enhanced in a *hot* state.

To address these research questions, we conducted four experimental studies and one mega-analysis, reported in four chapters.

Chapter 2 presents an individual-level mega-analysis of 43 studies (3610 participants) that investigated substance use and response inhibition assessed with the GNG or SST. Multilevel regression was used to control study-level and individual-level variances. Demographics (e.g., age, sex, education years) and task parameters (e.g., substance-related, no-go density) were controlled for while investigating the substance-related two-way interactions and their three-way interaction with sex.

Chapter 3 contained two experiments. In experiment 1, we focused on the long-term effect of alcohol use on intentional as well as stimulus-driven inhibition in undergraduates. Using an adapted version of the recently-developed *Chasing Memo task*, we compared light versus heavy drinkers' intentional stopping latency. A classic SST was administered to examine the criterion validity of the cued inhibition condition in the Chasing Memo task. Experiment 2 investigated how acute alcohol use affects the neural activity underlying intentional inhibition. The same computer task was used while EEG signals were recorded. The component of primary interest was the RP, a negative-going, ramp-like potential that develops slowly before voluntary action.

Chapter 4 was an extended study based on Chapter 3. We further explored the acute effect of alcohol by 1) employing a balanced placebo design (a control condition was

added); 2) replacing the small fish used in the Chasing Memo task with (non)alcoholic bottles to increase the ecological validity; 3) the effect of appetitive cues were examined by comparing performance under the alcoholic condition versus the neutral condition; 4) both the *when* and the *whether* components of intentional inhibition were examined; 5) a substantially larger sample than in Chapter 3 was recruited.

Chapter 5 was a field study where a brief intervention was implemented when people were drinking in the bar. This intervention aimed at bridging the gap between intention and goal achievement by linking specific cues with alternative behaviors. This provides the possibility to transiently strengthen self-control when drinking is in progress.

Chapter 2

Is (poly-) substance use associated with impaired inhibitory control? A mega-analysis controlling for confounders

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ABSTRACT

Many studies have reported that heavy substance use is associated with impaired response inhibition. Studies typically focused on associations with a single substance, while polysubstance use is common. Further, most studies compared heavy users with light/non-users, though substance use occurs along a continuum. The current mega-analysis accounted for these issues by aggregating individual data from 43 studies (3610 adult participants) that used the Go/No-Go (GNG) or Stop-signal task (SST) to assess inhibition among mostly "recreational" substance users (i.e., the rate of substance use disorders was low). Main and interaction effects of substance use, demographics, and task-characteristics were entered in a linear mixed model. Contrary to many studies and reviews in the field, we found that only lifetime cannabis use was associated with impaired response inhibition in the SST. An interaction effect was also observed: the relationship between tobacco use and response inhibition (in the SST) differed between cannabis users and non-users, with a negative association between tobacco use and inhibition in the cannabis non-users. In addition, participants' age, education level, and some task characteristics influenced inhibition outcomes. Overall, we found limited support for impaired inhibition among substance users when controlling for demographics and task-characteristics.

Introduction

Substance use and response inhibition

What is response inhibition and how does it relate to substance use?

Inhibitory control, also known as response inhibition, has been defined as the ability to control one's attention, behavior, thoughts, and/or emotions to override a strong internal predisposition or external lure, and instead do what is more appropriate or needed (Diamond, 2013). Loss of control over one's behavior is a defining characteristic of addiction. The DSM-5 lists characteristics such as 'taking larger amounts or over a longer period than was intended' and 'unsuccessful efforts to cut down or control alcohol use' to define the loss of control over drinking (American Psychiatric Association, 2013). Moreover, inhibitory control has been proposed to play an important role at different stages of the addiction cycle, i.e., 1) initial use of substance; 2) transition from recreational use to heavier use and abuse; 3) continuation of use for those who get addicted; 4) relapse after abstinence (e.g., Garavan, Potter, Brennan, & Foxe, 2015; Koob & Volkow, 2010). Furthermore, the dual process model on addiction proposes that an imbalance between a hyper-sensitized impulsive system, which is responsible for cue-reactivity, and a compromised reflective or control system (including inhibition of impulses) are important in the development of addiction (Bechara, 2005; Gladwin, Figner, Crone, & Wiers, 2011; Volkow, Fowler, Wang, & Swanson, 2004; Volkow, Koob, Mental, Parity, & Act, 2015).

Over the past two decades, multiple studies have focused on the relationship between chronic substance use and response inhibition, but findings have been equivocal. Inhibitory impairment has been associated with chronic use of some substances (e.g., cocaine, ecstasy, methamphetamine, tobacco, and alcohol) but not for others (e.g., opioids, cannabis, see for a meta-analysis, Smith, Mattick, Jamadar, & Iredale, 2014). Results also vary in studies of single substances. For instance, heavy drinkers have been reported to make more commission errors than light drinkers on the Go/No-Go task (GNG, Kreusch, Quertemont, Vilenne, & Hansenne, 2014), while alcohol-dependent and control participants did not differ significantly on the same measure (Kamarajan et al., 2005). Two main issues might explain these conflicting findings, namely the phenomenon of polysubstance use and the use of extreme group designs (i.e., comparing control participants and problematic or disordered substance users). In addition, sample demographics and task characteristics are often not taken into consideration. In order to address these issues in this mega-analysis, we aimed to investigate the relationship between inhibition and use of multiple substances by analyzing individual-level data, while taking demographics and task characteristics into account. In doing so, we did not exclusively focus on populations diagnosed with substance use disorders (SUD, American Psychiatric Association, 2013).

Experimental paradigms: the Go/No-Go task and the Stop-signal task

Successful suppression of motor responses can involve distinct behavioral processes such as "action restraint" or "action cancellation" (Schachar et al., 2007). Action restraint refers to stopping a prepared but not yet initiated response, which is commonly measured using the GNG and its variants, such as Conners' continuous performance task (Conners &

Sitarenios, 2011; Donders, 1868/1969). These tasks focus on the ability to withhold responding if a no-go stimulus is presented. The main variables of interest are the rate of commission errors (i.e., failures to inhibit a response to no-go targets or false alarms), the rate of omission errors (i.e. failures to respond to go targets, or misses), and the response time (RT) to go stimuli. A relatively high rate of commission errors and a short go RT reflects suboptimal inhibition (Smith et al., 2014).

By contrast, action cancellation refers to stopping a response that is already underway. It is typically measured using the Stop-signal task (SST, Logan, 1994). In this paradigm, each trial starts with the presentation of a go signal that requires an overt response such as a button press. On a subset of trials (typically around 25%), the go signal is followed by a stop signal after a certain interval (stop-signal delay, SSD), upon which participants should inhibit their already initiated go response. Usually, an adaptive tracking algorithm controls the SSD, such that there is a 50% probability of inhibiting the response. A horse-race model, assuming an independent race between the 'go' and 'stop' processes, affords the estimation of the stop-signal reaction time (SSRT, Logan, 1994). Given that the response could not be withheld on *n* percent of all stop trials (usually around at 50%), SSRT is calculated by subtracting the mean SSD from the go RT that marks the *n*th percentile in the go RT distribution (Band, van der Molen, & Logan, 2003).

In contrast to the GNG, the latency of the go response and the latency of the stop process are considered to be independent (Logan & Cowan, 1984). Thus, a longer SSRT reflects an inhibitory deficit, whereas a longer go RT is interpreted as a lack of attention among other influencing factors (preparation, choice, and speed-accuracy trade-off, Lijffijt, Kenemans, Verbaten, & van Engeland, 2005).

In addition to the GNG and the SST, other experimental paradigms, such as the Stroop (Stroop, 1992) and Eriksen Flanker tasks (Eriksen & Eriksen, 1974) have been proposed to measure inhibitory capacities. However, these paradigms measure distractor inhibition rather than motor response inhibition (Nigg, 2000; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). To keep the present review focused and allow for straightforward comparisons of results, we only included studies using the GNG and SST.

Research gaps and research needs

Previous meta-analyses and reviews

To date, there are at least nine published meta-analyses or review papers examining the relationship between inhibitory control and long-term substance use or behavioral addiction. In terms of scope, these studies can be classified into three categories. First, literature overviews focusing on a single substance (e.g., alcohol: Aragues, Jurado, Quinto, & Rubio, 2011; Stavro, Pelletier, & Potvin, 2013) or non-substance related disorder (e.g., gambling disorder: Chowdhury, Livesey, Blaszczynski, & Harris, 2017; Moccia et al., 2017). These reviews associated alcohol use with prolonged inhibition impairment, up to one month after abstinence (Stavro et al., 2013) and detoxified alcohol-dependent patients showed poor inhibition compared with healthy controls (Aragues et al., 2011). Polysubstance use was not systematically described or controlled for in either of the review studies on alcohol.

Individuals with gambling disorder without comorbid SUD were reported to show large inhibition deficits (Chowdhury et al., 2017), which was attributed to impaired activity in prefrontal areas (Moccia et al., 2017). Second, other reviews focused on drawing general conclusions across multiple substances. For instance, Lipszyc and colleagues found that substance users generally did *not* differ significantly from controls in SST (Lipszyc & Schachar, 2010) and GNG performance (Wright, Lipszyc, Dupuis, Thayapararajah, & Schachar, 2014). However, such a review does not provide a clear profile for the effects of these substances in isolation or of specific interactions (i.e., greater than additive or compensation effects). A third category of literature reviews included multiple substances and the results were specified by the substance. Examples include a recent systematic review focused on neuroimaging findings (Luijten et al., 2014) and a meta-analysis focused on behavior (Smith et al., 2014). The latter meta-analysis indicated that inhibitory deficits were apparent for heavy use/disorders related to cocaine, ecstasy, methamphetamine, tobacco, alcohol, and gambling but not for opioids or cannabis, without testing the interaction effect of using multiple substances (Smith et al., 2014). In sum, the current findings and conclusions of reviews and meta-analyses are rather inconsistent. If a conclusion can be drawn, it appears to be the counterintuitive conclusion that reviews and meta-analyses that focused on a specific addictive substance or behavior are *more* likely to report a significant association with inhibitory control compared to those reporting on multiple substance use. Importantly, none of these reports have considered several key variables that might bias the results, which will be highlighted in the next section.

Important factors to consider

Polysubstance use

Polysubstance use broadly refers to the consumption of more than one drug over a defined period, either simultaneously or at different times (Connor, Gullo, White, & Kelly, 2014; Subbaraman & Kerr, 2015). This involves different sub-categories, namely using different substances, the dependence of one substance and co-use of other substances or dependence on multiple substances. For instance, tobacco smoking is strongly associated with alcohol and marijuana use (Connor et al., 2014), opioids, and benzodiazepines are often prescribed simultaneously (Jones, Mogali, & Comer, 2012), and stimulants users are more likely to be heavy drinkers (McCabe, Knight, Teter, & Wechsler, 2005). Note that there is some evidence indicating that concurrent use of substances can lead to additionally toxic effects because of a toxic metabolite, as was reported for alcohol and cocaine (Pennings, Leccese, & Wolff, 2002). It is also possible that the use of one substance decreases the negative effect of another substance, as found with alcohol and cannabis (Schweinsburg, Schweinsburg, Nagel, Eyler, & Tapert, 2011). Hence, studying interactions between drugs on neurocognitive functions is important, given the frequent occurrence and possible interaction effects. However, studies comparing substance users versus non-users or light users have typically focused on the primary substance of concern, while ignoring secondary substances. Up to now, only a few studies have investigated the relationship between polysubstance use and inhibition (Gamma, Brandeis, Brandeis, & Vollenweider, 2005; Moallem & Ray, 2012;

Verdejo-García, Perales, & Pérez-García, 2007). Heavy drinking smokers did not show poorer SST response inhibition than smokers only and heavy drinkers only (Moallem & Ray, 2012). Similarly, ecstasy polysubstance users did not show more strongly disturbed inhibitory brain mechanisms compared with controls (Gamma et al., 2005), and cocaine and heroin polysubstance users showed similar commission error rates as controls in the GNG (Verdejo-García et al., 2007). A limitation of the latter two studies is that the greater-than-additive effect could not be examined without a group of single substance users. The lack of studies calls for a synthesis of research that does take polysubstance use into account.

Substance use as a continuous variable

All the above-mentioned reviews and meta-analyses included comparisons between a control or light user group and a heavy or problematic user group. Scores retained as a result of such extreme group designs are often coded and analyzed in terms of low versus high, reducing individual differences into a binary code. This practice involves ignoring individual-differences of substance use in favor of creating quasi-arbitrary groups assumed to be homogeneous on the variable of interest (MacCallum, Zhang, Preacher, & Rucker, 2002; Preacher, K. J., Rucker, D. D., MacCallum, R. C., & Nicewander, 2005; Royston, Altman, & Sauerbrei, 2006). In the current study, we aimed to quantify substance use as a continuous variable.

Abstinence

Studies on long-lasting effects of substance use have generally been conducted by testing recently abstinent users. With respect to response inhibition, some studies have found that abstinence from cocaine, methamphetamine and heroin normalized inhibitory function (Morie et al., 2014; Schulte et al., 2014), however, one study found sustained suboptimal performance after heroin abstinence (e.g., Fu et al., 2008). In addition, the duration of abstinence appears to moderate the return to normal functioning, which may explain these conflicting findings (Schulte et al., 2014). In order to preclude this as a confounder, we did not include studies on abstinence in (formerly) dependent users. All participants indicated substance use in everyday life, but were requested to refrain from using all substances (in most cases excluding tobacco) 24 hrs to one week before testing.

Individual-level and task-level variables

Some individual-level and task-level factors are known to affect inhibitory control and are therefore included in this mega-analysis, including the demographic variables age, sex, and education years. For GNG, six task parameters were controlled for: no-go percentage, number of experimental trials, working memory load (taxed or not), substance-related stimuli (used or not), cued GNG or not, and task complexity. For the SST, five task parameters were controlled for: number of experimental trials, stop-trial percentage, SSD settings, stop-signal modality, and SSRT calculation method. Reasons for controlling these confounders are based on a large primary literature on these tasks and are summarized in Supplementary Materials **S1** (see appendix to this chapter). Except for sex, for which the interaction with substance use was considered, all other factors were only controlled for regarding their main effect.

Why a mega-analysis rather than a meta-analysis?

A meta-analysis combines the summary statistics (i.e., effect sizes of included studies), while a mega-analysis combines the raw individual data from different studies. The latter method allows studying the combined effect of individual characteristics (cf. Price et al., 2016) and examining the interaction effect of multiple substances used with enhanced statistical power (Riley, Lambert, & Abo-Zaid, 2010). Therefore, we implemented a mega-analysis with individual-level data.

The goal of the current study

Our primary goal was to examine the main and interaction effects of various kinds of long-term substance use on response inhibition. As the interaction effects of substance use on inhibition are rarely investigated and reported, we explore these interactions in the current study. We do so while controlling for demographics (e.g., age, sex, education years) and task-related factors (e.g., no-go percentage, number of trials, whether stimuli are substance-related) that likely explain performance variance between studies and individuals. Interactions between substance use and sex were also included. Based on the literature reviewed above, we tested the following hypotheses: 1) According to Smith et al (2014) and other findings (Colzato, van den Wildenberg, & Hommel, 2007; Fillmore & Rush, 2002; Quednow et al., 2007), we assumed that the inhibitory deficit would be more pronounced in users of psychostimulants (e.g., cocaine, ecstasy, methamphetamine, tobacco, and alcohol), especially for cocaine and amphetamines, given the known neuropsychopharmacology of the cortical and subcortical networks underlying impulse control (i.e., the right dorsolateral and inferior frontal cortices, Koob & Volkow, 2010; Smith, Mattick, Jamadar, & Iredale, 2014); 2) Given the literature, and as a validation of our individual-level mega-analysis, we expect some demographics (e.g., age and sex) and task characteristics (e.g., no-go percentage, whether stimuli are substance-related) to be associated with inhibition performance (see for expected directions of effects, Supplementary Materials **S1**).

Method

Study identification and selection

PsycINFO, Medline, EMBASE, Web of Science, CINAHL, and Cochrane Library were searched until 01/03/2016. Search terms and synonyms indicating substance use (alcohol, amphetamine, cocaine, cannabis, heroin, ketamine, methamphetamine, benzodiazepines, gambling, gamer, and internet addiction) were combined with terms indicative of inhibition (go/no-go, inhibitory control, inhibitory process, response inhibition, stop task, etc.). Published meta-analyses and reviews were also checked for additional studies (Horsley, Dingwall, & Sampson, 2011). Although behavioral addictions (e.g., gambling, internet addiction) were initially included, there were too few relevant studies to allow further analyses.

Eligibility criteria

The first author (YL) assessed the eligibility of all records using the following initial inclusion criteria: (a) presented in English; (b) conducted on human participants; (c) reported at least one measure from the following: no-go commission errors or go RT in the GNG; SSRT or go RT in the SST; (d) reported use of at least one kind of substance (e.g., alcohol, tobacco, cannabis, amphetamine, cocaine, ecstasy). Note that we included behavioral data from fMRI/EEG studies if available. In addition, we ran supplementary analyses to investigate whether inhibition performance varied with study type (behavioral/EEG/fMRI). It turned out that study type did not systematically influence behavioral performance (see Supplementary Materials **S2**). We excluded studies (a) that presented stop signals using a single SSD, as this is known to induce a performance strategy of delayed responding (Logan, 1994); (b) in which the percentage of no-go or stop trials was higher than 50%, as this is known to invalidate the task (Nieuwenhuis, Yeung, & Cohen, 2004; Randall & Smith, 2011); (c) that focused on the acute effects of substances on inhibition; (d) that recruited participants with a family history of substance dependence; (e) that excluded polysubstance users; (f) with participants that already received treatment for SUD or abstained from substance use; (g) with participants younger than 18. The exclusion of both intoxicated and abstinent consumers may have kept heavily affected/addicted participants from being included in the sample.

After applying the inclusion and exclusion criteria by YL, a second rater (YG) assessed the eligibility of a random subset (20%) of the records and obtained 100% agreement. Authors of eligible studies were invited via email to contribute raw data. Repeated attempts were made (i.e., four reminders were sent) if no response was received. Corresponding authors of the identified studies were asked to share their raw individual data, following our instructions on data requirements. The 'essential variables' included a set of pre-identified variables, including sociodemographic characteristics (e.g., age, sex, and education), typical alcohol and tobacco use (as alcohol and tobacco are two most commonly used substances), and task performance (**Table S1a, S1b**). 'Optional variables' (Supplementary Materials **S3**) included other demographic information recorded (e.g., race), other substance use (e.g., cocaine, cannabis) and questionnaires administered (e.g., Alcohol Use Disorder Identification Test (AUDIT), Saunders, Aasland, Babor, De la Fuente, & Grant, 1993). The 'optional variables' were defined in a more flexible format with open questions. A study was included in our mega-analysis only if information about all 'essential variables' could be provided.

Quality assessment and data extraction

As the quality of included studies can influence mega-analysis in unpredictable ways (i.e., shortcomings in original studies will be carried over to the mega-analysis and thus weaken its conclusions, Müller, Brändle, Liechti, & Borgwardt, 2019), a quality assessment of original studies was conducted. The methodological quality of studies was assessed by two authors (YL and YG) separately. We used the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, which is widely used and recommended by Cochrane for quality assessment of observational and cross-sectional studies (**Table S2**, National Heart and Blood Institute, 2014). The total

agreement (Good/ Fair/Suboptimal) between assessors was high (GNG: 20/24 = 83%, SST: 16/20 = 80%). Inter-rater reliability, measured using Spearman's rank correlation coefficient was high for GNG (r = 0.84, p < 0.001) and moderate for SST (r = 0.56, p = 0.01, Kendall, 1938).

All provided data, including predictors (i.e., substance use, demographics, task characteristics) and dependent variables were merged into four datasets separated based on the four dependent variables (i.e., the commission error rate in GNG, go RT in GNG, SSRT in SST, and go RT in SST. As speed-accuracy trade-off is a potential issue in GNG (Zhao, Qian, Fu, & Maes, 2017), a balanced integration score was calculated (Liesefeld & Janczyk, 2019). Main results applying this score as the outcome are presented in Supplementary Materials **S4**. The first author performed the data merging, which was verified by two authors (RW and WW).

Publication bias check

To examine whether significant findings in the original papers are indicative of evidential value, a *p*-curve was calculated and plotted (Simonsohn et al., 2015). In a *p*-curve, the x-axis represents *p*-values below 0.05, and the y-axis represents the percentage of studies yielding such a *p*-value. A right-skewed *p*-curve indicates evidential value, whereas a left-skewed *p*-curve, many *p*-values just below 0.05, may be indicative of flexibility in data analysis (Simonsohn et al., 2015). If the data did not indicate evidential value, a 33% power test is performed to examine whether the absence of evidential value is due to insufficient power. A *p*-curve disclosure table was created (**Table S3**) according to Simmons and Nelson (2015). *P*-curves and corresponding analyses were conducted using the *p*-curve app 4.06 (http://www.p-curve.com/app4, 2018).

Individual participant data meta-analysis

The analysis was conducted in the following steps: 1) apply additional exclusion criteria to the merged datasets; 2) standardize all continuous independent variables; 3) determine substance-related one-way variables; 4) dummy code all discrete variables; 5) determine and generate substance-related interaction variables; 6) multiple imputations of the missing values using all main and interaction variables; 7) build the linear mixed regression model with fixed effects of all predictors and a random intercept; 8) variable selection by stepwise backward elimination. These eight steps are outlined in more detail below.

Construction of the database

Individual and group exclusion criteria

The data from the included studies were stacked into a single data file for each dependent variable, with unique identifiers for each study and for each participant. We further applied some minimal exclusion criteria to the individuals. That is, we excluded a participant if (1) he/she was younger than 18 years old; (2) he/she had missing data on all indices of substance use; (3) the dependent variable of current analysis (e.g., commission error rate) was missing; (4) SSRT was negative.

A group of substance users from a certain study was excluded if the substance was not

included as a predictor in the model. This happened when there was limited data provided for that substance (see criteria in 'One-way variables'). For example, if it was concluded that opiate use was assessed insufficiently across all studies, we did not add opiate as a predictor. Consequently, opiate users were excluded from the analysis. The excluded cases and groups from each study are listed in **Table 1** and **Table 2**.

Standardization of independent variables

Continuous variables

Demographics like age and education level were transformed respectively into continuous variables years and years of education according to the education system in the country where the study was conducted. Task characteristics such as no-go percentage and number of trials in both tasks were also treated as continuous variables.

Alcohol consumption was converted into the continuous variable grams of ethanol per month. Data on alcohol consumption were provided in two different ways. Most researchers provided data based on timeline follow-back (TLFB). These data were either already in grams per month or could be transformed by making use of standard drinks adjusted for country (Cooper, 1999). Some studies only had data from more general questionnaires. For instance, three studies (de Ruiter, Oosterlaan, Veltman, van den Brink, & Goudriaan, 2012; Luijten, O'Connor, Rossiter, Franken, & Hester, 2013a; Rossiter, Thompson, & Hester, 2012) provided the raw data of the AUDIT (Saunders et al., 1993). In that case, we multiplied midpoints of item 1 (frequency), midpoints of item 2 (drinking days per month) and standard drinks in the country where the study took place. Similarly, four studies (Littel et al., 2012; Luijten et al., 2011; Luijten, Meerkerk, Franken, van de Wetering, & Schoenmakers, 2015; Luijten et al., 2013b) provided Quantity Frequency Variability (QFV) score (Lemmens, Tan, & Knibbe, 1992). Again, items of quantity, frequency, and standard drinks were multiplied together. Smoking was coded as cigarettes per day. Two studies (Moallem & Ray, 2012; Rossiter et al., 2012) only had data from the Fagerström Test for Nicotine Dependence (FTND, Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). In these cases, the midpoint of the answer to item "How many cigarettes a day do you smoke" was used for daily cigarette use. One study used a self-developed 7-point Likert scale for the past 6 months tobacco consumption, for which we estimated daily cigarette use with the midpoint scores (Ames et al., 2014). Alcohol and tobacco use were standardized across the full dataset. All the other substance use variables had to be treated as dichotomous variables, as insufficient information was provided for treating it as a continuous variable in the model (see details below).

Dichotomous variables

For interpretability, dichotomous variables were effect-coded with value +1 or -1. Except for alcohol and tobacco use, other substances were coded as 'lifetime use (yes = 1/no = -1)'.

Four dummy task-characteristics were defined to classify the GNG studies: 'working memory load (low/high)', 'substance-related (yes/no)' 'cued GNG (yes/no)', and 'task complexity (low/high)'. High working memory load, substance-related, cued GNG versions and complicated tasks were assigned the value of 1 (otherwise -1). Tasks with high working

memory load were also assigned a value of 1 for task complexity as the association between stimuli and response was more complicated in these tasks.

Similarly, for the SST, three dummy task characteristics were extracted, including 'stop-signal modality (visual/auditory)', 'SSD (fixed/staircase-tracking)' and 'SSRT calculation (integration/others)'. These variables were assigned a value of 1 if auditory stop signals were used; staircase-tracking procedure for SSD; and integration method for SSRT calculation (otherwise -1).

Identification and generation of substance-related variables

Except for alcohol use and tobacco use, other kinds of substances had missing data as not all studies provided information. Data provided varied in the level of detail, the way questions were asked, and the substances of main interest. For instance, depending on the primary substance of interest, some studies provided detailed information for cannabis use but no information on cocaine use (Bidwell et al., 2013), with an opposite pattern for others (Colzato et al., 2007). In the following section, we explain the criteria for including substance-related variables in the model.

One-way variables

Due to missing data, a criterion was needed to include a variable in the model. We decided on a minimum of 100 participants per cell for a substance (which comes down to a power of 0.94 for the effect size of 0.5). As a result, final models for the GNG (both commission error rate and go RT) included cannabis, cocaine, amphetamine, ecstasy, and hallucinogens, in addition to alcohol and tobacco. For the SST (both SSRT and go RT), the final models included cannabis, cocaine, and ecstasy in addition to alcohol and tobacco.

Two-way variables

There were two types of two-way variables; the interaction of sex × substance and substance1 × substance2. Variables of sex × substance were created by multiplying sex with substance directly. For the second type, in order to evaluate whether there was sufficient data to assess these interactions, we again applied a criterion for inclusion. For example, dummy coding cannabis and cocaine use yielded a two by two table cannabis (yes/no) × cocaine (yes/no). The corresponding interaction was only entered into the model if all four cells had more than 20 entries. For alcohol and tobacco use, we dichotomized the data by a median split for table construction only. We performed an additional analysis to test whether the number of substances used was a predictor of inhibition performance, and this was not the case (see Supplementary Materials **S5**). The list of included two-way variables can also be found in **Table S4a-S4d**. Demographics (in addition to sex) and task parameters could further moderate the relationship between substance use and inhibition. This, however, was not the focus of the current paper. In order to explore this potential issue, we analyzed interactions between alcohol on the one hand and demographics and task parameters on the other (see Supplementary Materials **S6**).

Three-way variables

Three-way variables were generated based on the substance1 × substance2 variables combined with sex. The corresponding variables were entered into the model only when all the eight cells in the three-way table sex (male/female) × substance1 (yes/no) × substance2 (yes/no) consisted of at least 10 entries. The list of three-way variables can be found in **Table S4a-4d**.

Missing data for independent variables and their interactions

In the analysis of GNG commission error rate, the percentage of missing values ranged from 0 to 68.2% (highest: alcohol × hallucinogens × sex) and in the GNG go RT analysis, it ranged from 0 to 69.6% (highest: alcohol × hallucinogens × sex). For the SST, the percentage of missing values ranged from 0 to 84% for the SSRT (highest: tobacco × ecstasy × sex) and from 0 to 83.2% for the go RT (highest: tobacco × ecstasy × sex, a full list of missing data per variable can be found in **Table S4a-s4d**).

In order to deal with these missing data, we used multiple imputations (Rubin, 2004). The default imputation option in SPSS was chosen. It first scans the data and determines the suitable method for imputation (Monotone or Fully Conditional Specification, FCS; Dong & Peng, 2013). All variables in the mixed regression model, including the main and interactive predictors and the dependent variable, were used for imputation. Apart from that, the discrete variable of 'tobacco lifetime use' was also used, as some studies assessed tobacco use dichotomously (smokers/non-smokers). It has been suggested that the number of imputations should be similar to the percentage of cases that are incomplete (I. R. White, Royston, & Wood, 2011) and the precision improves by increasing the number of imputations (Bodner, 2008). Therefore, 100 complete data sets were generated, which were combined into a pooled result using the method proposed by Rubin (Rubin, 2004) and Schafer (Schafer, 1997).

Statistical analysis

Backward elimination was used for variable selection. Initially, each imputed dataset was analyzed with a linear mixed model including all the above-mentioned main, second order, and third order effects as fixed effects and a random intercept (for which a model summary can be found in **Tables S4a-S4d**). We did not include random slopes and thus assumed that predictors had similar effects in each study. The fixed effects that were least significant (i.e., the one with the largest *p*-value) were removed and the model was refitted. Each subsequent step removed the least significant variable in the model until all remaining variables or its higher order variables had *p*-values smaller than 0.05 (Draper & Smith, 2014). For instance, if the variable alcohol × tobacco was significant, then variables of alcohol and tobacco would also be included in the model, irrespective of their independent significance.

Results

Study Selection

Summary of authors' responsiveness

Applying the inclusion and exclusion criteria resulted in a sample of 153 potentially eligible studies (**Fig. 1**). Out of these targeted papers, 4 researchers responded that they no longer had access to the datasets, 21 declined to participate, 52 did not respond to our invitation and 11 did not have all the basic information we asked for. In total, we obtained raw data from 65 studies. Out of these, 22 had to be excluded because the authors could not provide all the 'essential variables', such as data on monthly alcohol use in grams was unavailable (9 studies), missing data of tobacco use (5 studies), participants were abstaining from substance use (3 studies), participants were younger than 18 years old (2 studies), uncommon tasks were used (2 studies) and unsuitable outcome measures (1 study, provided stop latency instead of SSRT). The full list can be found in Supplementary Materials **S7**. The final dataset for the GNG comprised of 23 independent datasets from 24 papers (in some cases, more than one paper was published with the same dataset). For the SST, 19 datasets from 20 papers were included. In addition, one study administered both GNG and SST; therefore 43 unique studies were included in total.

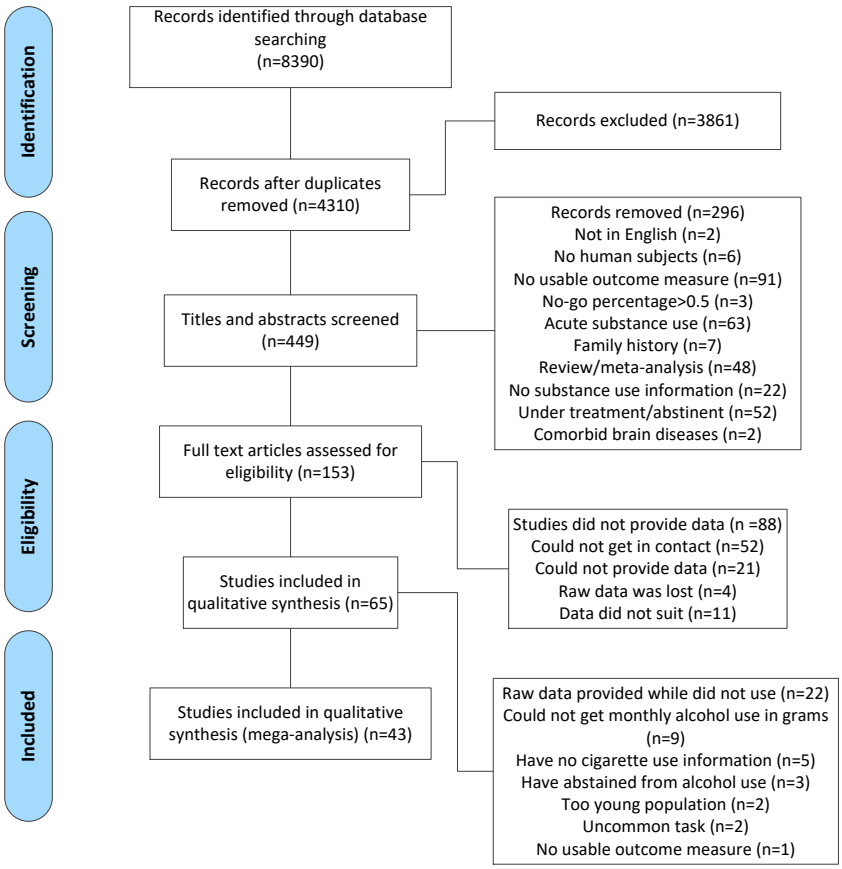


Figure 1. PRISMA for the mega-analysis detailing our search and selection decisions.

The final list of eligible studies was slightly different from the list of studies included in Smith and colleagues meta-analysis on summary statistics (Smith et al., 2014). For the GNG, there were 11 studies in common. For the SST, there were 6 studies in common. These discrepancies were related to different research questions. Since we aimed to assess the unique and combined effects of different substances, while Smith and colleagues focused on the unique effect of a single substance, some studies that were excluded by Smith and colleagues were included here and vice versa. In addition, individual data mega-analysis typically has a lower response rate compared to traditional meta-analysis, as it requires more work from the researchers (Riley et al., 2010; Riley, Simmonds, & Look, 2007).

Study description

Table 1 and **Table 2** present descriptive characteristics of the included GNG and SST studies before imputation, respectively.

Findings in original studies

For GNG, out of the 24 studies included, 9 (37.5%) reported that (heavy/problematic) substance users/excessive gamers made more commission errors than controls/light users (3 for alcohol, 2 for tobacco, 1 for ecstasy, 1 for inhalant and 2 for excessive gamers), 1 (4.2%) reported opposite findings (i.e., opiate users made fewer commission errors compared to controls), 11 (45.8%) reported no significant differences (5 for alcohol, 2 for tobacco, 1 for ecstasy, 1 for inhalant and 2 for polysubstance use), and 3 (12.5%) didn't have such an analysis (See **Table 1** footnote). For the SST, out of the 20 studies, 5 (25%) reported substance users/gamblers had longer SSRT than controls (2 alcohol, 2 cocaine and 1 pathological gambling), 1 (5%) reported the opposite direction (alcohol), 8 (40%) reported no difference (3 alcohol, 2 tobacco, 1 cannabis, 1 cocaine, and 1 pathological gambling) and 6 (30%) did not provide such an analysis (see **Table 2** footnote).

Table 1 Description of studies included in the dataset of GNG: commission error.

Study	Demographic information				Substance of use			Task characteristics						Task performance		Behavioral findings reported in the original publication.	Number of cases excluded	Groups excluded
	Sample size (reserved)	Age M(SD)	Males (%)	Education years M(SD)	Main substance	criteria for the heavy/problematic substance use group	Other substance use info provided	Trial number	No-go percentage (%)	Substance-related	Working memory load	Task complexity	Cued GNG	No-go commission error (%) M(SD)	go-RT M(SD)			
Ames et al, (2014)	41	20.46 (1.27)	41	NA	Alcohol	21 heavy drinker with AUDIT score>8, binge drink > twice/week and 15 drinks (female 8)/week	NA	200	20	Yes	No	Yes	No	10 (6.22)	439(48)	There was no difference between light and heavy drinker on commission error rate, and mean go-RT.		
Claus et al, (2013)	144	32.64 (9.65)	69	14.2 (2.25)	Alcohol	81 participants were diagnosed with alcohol dependence according to DSM-5	NA	624	6.41	No	Yes	Yes	No	59 (16.37)	335(59)	There was no correlation between alcohol use disorder severity and inhibition performance.		
Hendershot et al, (2015)[a]	83	19.86 (0.81)	48	12.99 (1.34)	Alcohol	All participants at least binged drink once in the past month.	Cannabis, cocaine	62	20	No	No	No	Yes	7 (7.8)	315(28)	Response inhibition was worsened following the rising limb of blood alcohol concentration (BAC), which pattern increased during BAC plateau. Only baseline data (without alcohol intake) were used in the current study.		
Kamarajan et al, (2005)	59	29.4 (7.14)	53	13.46 (2.89)	Alcohol	30 participants were alcoholic patients according to SDM-5	Cannabis, cocaine, amphetamine, hallucinogens	100	50	No	No	Yes	No	5 (11.02)	297(20)	There was no difference between alcoholics and controls in commission error rate and go-RT.	1	
Kreusch et al, (2014)	30	21.47 (3.01)	47	14.5 (2.37)	Alcohol	15 heavy drinkers with AUDIT >11	NA	100	25	Yes	No	No	No	4 (4.55)	335(61)	For the letter GNG task, heavy drinkers made more commission errors than light drinkers, while no difference on go-RT; For alcohol GNG, light and heavy drinkers did not differ in commission errors and go-RT.		
Littel et al, (2012)	56	21.91 (4.17)	61	NA	Game	25 excessive gamers had a VAT score>2.5	Cannabis, cocaine, amphetamine, ecstasy, hallucinogens	636	11.6	No	Yes	Yes	No	43 (19.08)	339(55)	Excessive gamers made more commission errors than controls.	26	Excessive gamers
López-Caneda et al, (2014)	57	18.74 (0.55)	46	14 (0)	Alcohol	Binge drinkers binge drink at least once a week OR binge drink once a month with at least three drinks per hour for at least two years.	Cannabis	150	50	No	No	Yes	No	4 (4.06)	529(40)	There was no difference between binge drinkers and controls in go-RT and commission error rate.	1	
Luijten et al, (2011)	39	21.46 (2.05)	72	14.44 (1.13)	Tobacco	Smokers smoked at least 10 cigarettes per day for at least two years.	Cannabis, cocaine, amphetamine, ecstasy, hallucinogens	896	25	Yes	No	No	No	30 (15.09)	261(32)	Smokers made more commission errors than controls, while there was no correlation between daily cigarette consumption and commission error rate. And there was no group difference of go-RT.		
Luijten et al, (2013a)	32	25.25 (5.21)	63	15.75 (2.2)	Tobacco	Smokers smoked at least 15 cigarettes per day for at least two years.	Cannabis, cocaine, amphetamine, hallucinogens	160	12.5	No	No	Yes	No	21 (13.94)	408(53)	Smokers did not differ from controls in commission error rate and go-RT.		
Luijten, et al, (2013b)	48	22.17 (2.42)	67	14.89 (1.45)	Tobacco	Smokers smoked at least 15 cigarettes per day for at least three years.	Cannabis, cocaine, amphetamine, ecstasy,	927	11.86	No	Yes	Yes	No	39 (14.49)	356(51)	Smokers made more commission errors and also had longer go-RT compared with non-smokers.		

							hallucinogens									
Luijten et al, (2015)	16	21.38 (3.03)	100	15.88 (1.02)	Gamer	Problem gamers scored more than 2.5 on VAT.	Cannabis, cocaine, amphetamine, ecstasy, hallucinogens	927	12	No	Yes	Yes	No	43 (14.96)	409(42)	Problem gamers made more commission errors than controls, while there was no group difference in go-RT.	18	Excessive gamers
Mahmood et al, (2013)	36	18.64 (0.34)	72	14 (0)	No specific	High frequency substance users had any drug use over 180 occasions.	Cannabis, cocaine, amphetamine, ecstasy, hallucinogens	180	32	No	No	Yes	No	14 (8.82)	NA	There was no difference in commission error rate between high and low-frequency substance users.	44	
Petit et al, (2012)	35	21.29 (1.98)	51	14 (0)	Alcohol	Heavy social drinkers had on average 20 drinks per week, and with AUDIT>11.	NA	798	30	Yes	No	No	No	19 (7.67)	288(31)	Heavy drinkers made more commission error than light drinkers when the background picture is alcohol-related.		
Paz et al, (2018)[b*]	203	21.06 (1.87)	48	15.04 (1.1)	Alcohol	Binge drink was assessed with the last three items of AUQ.	Cannabis, cocaine, ecstasy	256	12.5	No	No	No	No	14 (10.15)	393(45)	NA		
Pike et al, (2015)[c]	91	39.93 (8.28)	64	11.67 (1.91)	Cocaine	There was no control group and all participants reported cocaine use for the past month.	Cannabis, amphetamine, hallucinogens	125	20	Yes	No	Yes	Yes	10 (12.13)	356(60)	Cocaine users made more commission errors to a no-go target following a cocaine image as the go cue compared to a neutral image as a go cue; While the correlation between the severity of use and inhibition performance was not reported.		
Quednow et al, (2007)	51	24.29 (4.75)	100	12.69 (1.46)	Ecstasy & cannabis	Ecstasy group used ecstasy 50 times over a period of at least 1 year. Cannabis group was chronic users of cannabis.	Cocaine, amphetamine, hallucinogens	160	50	No	Yes	Yes	No	25 (12.35)	1168(283)	Ecstasy group made more commission errors than cannabis users who performed as well as the controls. Besides, across groups, the commission error rate correlated with cumulative cannabis dose, years of amphetamine use, cocaine use per week, years of cocaine use and the cumulative cocaine dose.	6	
Rass et al, (2014)	82	25.29 (5.36)	48	15.82 (1.91)	Tobacco	Daily smokers smoked<25 cigarettes per day, daily use for at least 1 year, and scored ≥4 on the FTND.	Cannabis, cocaine, amphetamine	500	20	No	No	No	No	25 (12.25)	239(43)	Smokers and controls did not differ in commission error rate and go-RT.		
Roberts et al, (2010)	39	22.38 (2.93)	51	16.44 (2.45)	Ecstasy	Ecstasy group were current ecstasy users and consumed at least 40 ecstasy tablets over a period of a year.	Cannabis, cocaine, amphetamine	500	10	No	Yes	Yes	No	45 (17.51)	316(42)	Ecstasy users did not differ from controls in commission error rate and go-RT.	1	

Roberts et al, (2013)	59	23.26 (2.99)	44	NA	Ecstasy & poly	Ecstasy group needs to take ecstasy for at least five occasions.	Cannabis, cocaine	240	25	No	No	Yes	No	6 (5.78)	363(61)	Ecstasy polysubstance users, non-ecstasy polysubstance users, and controls did not differ in commission error rate and go-RT.	1	
Rossiter et al, (2012)	124	26.43 (6.79)	48	15.47 (2.48)	Alcohol	The harmful alcohol use group with AUDIT ≥16.	NA	160	12.5	No	Yes	Yes	No	37 (17.25)	338(55)	The harmful alcohol use group made fewer commission errors compared with controls under the delayed reward condition; The opposite pattern was observed under the immediate punishment condition. And there was no difference with regards to go-RT.		
Takagi et al, (2011, 2014)	30	20.49 (1.48)	43	10.73 (1.51)	Inhalant & cannabis	Inhalant users had inhalants daily or almost daily use for more than 12 months.	cocaine, amphetamine, ecstasy	300	10	No	No	No	No	22 (15.8)	332(48)	Inhalant users and controls did not differ in commission error rate and go-RT (ref 2011); The inhalant group had lower d-prime score compared with controls (ref 2014).	44	Inhalant
Verdejo-García et al, (2012)	19	28.68 (7.92)	58	12.26 (1.19)	Opiate	Opiate dependents had an average score on SDS of 8.3.	Cannabis, cocaine, amphetamine, ecstasy, hallucinogens	300	23.33	No	No	No	No	17 (9.08)	315(36)	Controls made more commission errors compared with opiate dependents.	38	Opiate
Wetherill et al, (2013)	18	19.49 (0.99)	33	12.89 (1.32)	Alcohol	Heavy drinkers had at least 4 drinks per occasion, less than once per month but more than once per year.	Cannabis	180	32	No	No	Yes	No	9 (6.79)	514(62)	Heavy drinkers and controls did not differ in commission error rate.	22	

Note: go-RT: reaction time for correct go trials; M: Mean; SD: Standard Deviation; NA: Not Available; AUDIT: Alcohol Use Disorder Identification Test; VAT: Videogame Addiction Test; AUQ: Alcohol Use Questionnaire; FTND: Fagerström Test for Nicotine Dependence; SDS: Severity of Dependence Scale

*unpublished dataset at the time of literature search

Why comparisons between substance users and controls could not be obtained from the original paper

[a] interested in the difference between the increasing and decreasing limb of BAC but we only used baseline data when participants were sober

[b] the correlation between commission error rate and binge score was not reported

[c] focused on the experimental effect (different kinds of cued GNG) instead of the individual difference

Table 2 Description of studies included in the dataset of SST: SSRT.

Study	Demographic information				Substance of use			Task Characteristics					Task performance		Behavioral findings reported in the original publication.	Number of cases excluded	Groups excluded
	Sample size (reserved)	Age M(SD)	Male (%)	Education years M(SD)	Main substance	Criteria for the heavy/problematic substance use group	Other substance use info provided	Trial number	No-go percentage (%)	Stop signal modality	SSD	SSRT computation	SSRT M(SD)	go-RT M(SD)			
Bidwell et al. (2013)[a]	150	21.56 (3.16)	64	NA	Cannabis	All participants used cannabis at least once a week in the past month and at least 10 times in the past 6 months.	NA	192	25	Auditory	Staircase	Other	274(66)	576(183)	NA	1	
Bø et al. (2016)	119	21.71 (2.12)	5	14.95 (1.56)	Alcohol	All participants use alcohol on a regular basis, binge score was calculated based on the last three items of AUQ.	NA	320	25	Auditory	Staircase	Other	189(54)	357(76)	Binge score was not a significant predictor of SSRT.	2	
Bø et al. (2017)*	186	36.22 (12.8)	32	16.45(2.7)	Depression	No special requirement for substance use.	Cannabis, cocaine	320	25	Auditory	Staircase	Other	187(50)	413(123)	Weekly alcohol consumption was negatively correlated with SSRT.	120	Major depressive disorder
Colzato et al. (2007)	24	29.33	83	NA	Cocaine	Recreational cocaine users should consume cocaine 1 to 4 gram per month by snorting route for a minimum of two years.	NA	520	30	Visual	Staircase	Integration	215(27)	375(39)	SSRT was significantly longer for cocaine users than non-users.		
Courtney et al. (2012, 2013)[b]	304	37.15 (10.81)	7	13.29 (3.25)	Alcohol	All participants were problem drinkers, with a minimum of 48 standard drinks per month.	NA	64	25	Auditory	Staircase	Other	241(90)	525(96)	SSRT could not explain alcohol use and alcohol problems.	6	
de Ruiter et al. (2012)	35	34.2 (9.25)	1	11.86 (1.67)	Gambling & Tobacco	Problem gamblers were diagnosed by DSM-5. Heavy smokers smoked at least 15 cigarettes per day.	NA	360	32	Visual	Staircase	Other	270(46)	435(87)	Problem gamblers, heavy smokers, and controls did not differ in SSRT and go-RT.	17	Gambling
Filbey et al. (2013)	74	24.14 (7.2)	74	13.5(2.68)	Cannabis	All participants were cannabis users with at least 4 uses per week for at least 6 months prior. Among them, 44 were diagnosed with cannabis dependents according to SDM-5.	cocaine, ecstasy	384	25	Auditory	Staircase	Integration	190(44)	512(76)	Cannabis dependents and cannabis non-dependents did not differ in SSRT and go-RT.		
Fillmore et al. (2002)	44	40.27 (6.66)	61	12.18(1.4)	Cocaine	Participants in the cocaine use group need to score ≥4 on DAST, habitually used cocaine for a minimum of 6 months and used it in the past week.	NA	176	27	Auditory	Fixed	Integration	318(91)	NA	Cocaine users showed prolonged SSRT compared with controls, while go-RT was comparable.		

Galván et al. (2011)	59	19.49 (1.1)	61	13.75 (1.17)	Tobacco	Daily smokers should smoke cigarettes daily for at least 6 months.	NA	256	25	Auditory	Staircase	Integration	164(61)	479(90)	Smokers did not differ from controls in SSRT and go-RT.	74	
Glass et al. (2009)	495	44.1 (4.97)	47	13.9(2.27)	Alcohol & Tobacco	A self-developed variable of alcohol severity was used, with 65 participants categorized as alcohol abuse, 55 as alcohol dependence without physical dependence, 33 as alcohol dependence with physical dependence.	Cannabis, cocaine	256	25	Auditory	Staircase	Other	250(76)	839(202)	Both SSRT and go-RT had a significant negative correlation with alcoholism severity.	77	
Karoly et al. (2014)[b]	53	28.3 (6.91)	47	15.55 (1.85)	Alcohol	All participants were categorized as heavy drinkers with at least 2 drinks (3 for men) twice per week. Among them, 12 participants were with AUDIT score ≥16.	Cannabis	198	26	Auditory	Staircase	Integration	172(48)	568(108)	NA		
Kräplin et al. (2015)	75	26 (7.92)	39	11.74 (0.76)	Gambling & Tobacco	Pathological gambling (PG) and nicotine dependence (ND) were dragonized with DSM-5.	Cannabis	205	20	Visual	Staircase	Integration	298(93)	557(159)	PG led to prolonged SSRT compared with controls. There was no difference between PG and ND; ND and PG comorbid ND with regard to SSRT.	44	Gambling disorder
Moallem et al. (2012)	287	30.97 (10.61)	73	14.68 (2.59)	Alcohol & Tobacco	Smokers should smoke cigarettes no less than 10 per day and had less than 3 months' smoking abstinence in the past year. Heavy drinkers should weekly drink >14 (women > 7) or drinks per occasion ≥ 5 (≥ 4 for women) at least once per month over the past year.	NA	64	25	Auditory	Staircase	Other	223(88)	509(90)	Heavy drinkers, smokers, heavy drink smokers did not differ in SSRT and go-RT; After controlling for age, heavy drinker smokers showed slower go-RT compared with smokers.	11	

Papachristou et al. (2012a)[c]	42	25.5 (9.66)	24	NA	Alcohol	All participants were light to moderate social drinkers with an average AUDIT score of 7.7.	NA	256	25	Auditory	Staircase	Other	222(50)	344(63)	NA		
Papachristou et al. (2012b)	75	23.29 (5.2)	33	NA	Alcohol	Heavy and light social drinkers were classified by the cut-off score of 11 of AUDIT.	NA	256	25	Auditory	Staircase	Other	203(32)	NA	Light and heavy drinkers had similar SSRT.		
Paz et al. (2018)[d*]	182	21.15 (1.83)	49	15.1(1.08)	Not specific	Binge drink was assessed with the last three items of AUQ.	Cannabis, cocaine, ecstasy	256	25	Auditory	Staircase	Integration	227(47)	694(175)	NA	21	
Tsaur et al. (2015)[c]	21	34.73 (12.47)	76	13.9(1.18)	Tobacco	All participants were smokers with at least 10 cigarettes per day for the past year.	NA	192	25	Auditory	Staircase	Other	252(52)	560(112)	NA		
Vonmoos et al. (2013)	163	30.03 (8.18)	71	10.45 (1.74)	Cocaine	Cocaine dependence was diagnosed with DSM-5. All cocaine users should have primarily used cocaine as the illegal drug, cocaine use of >0.5 g per month, and abstinence duration of <6 months.	Cannabis, ecstasy, amphetamine	192	25	Auditory	Staircase	Integration	291(63)	745(192)	Two cocaine use group (recreational users and dependent users) and the control group had similar SSRT and go-RT.	3	
Zack et al. (2015)	12	33.75 (11.23)	1	15.92 (0.52)	Gambling	Pathological gambling (PG) was diagnosed with DSM-5 and a score ≥5 on the SOGS.	Cannabis	512	25	Auditory	Staircase	Other	182(27)	482(115)	There was no difference between PG and healthy controls with regard to go-RT and SSRT.	13	Gambling

Note: SSD: Stop-Signal Delay; SSRT: Stop-Signal Reaction Time; go-RT: reaction time for correct go trials; M: Mean; SD: Standard Deviation; NA: Not Available; AUQ: Alcohol Use Questionnaire; DAST: Drug and Abuse Screening Test; AUDIT: Alcohol Use Disorder Identification Test; SOGS: South Oaks Gambling Screen; BIS-11: Barratt Impulsiveness Scale

[*] unpublished dataset at the time of literature search

Why comparisons between substance users and controls could not be obtained from the original paper

[a] focused on how genes moderated impulsivity

[b] only reported MRI results

[c] focused on experimental effect rather than individual difference with a within-subject design

[d] the correlation between SSRT and binge score was not reported

[e] longitudinal study, only baseline data was used

Quality assessment

We rated the methodological quality of the studies according to the NHLBI assessment tool (see **Tables 3a and 3b**). For the GNG, most (58.3%) of the studies were of intermediate quality, 37.5% of high quality and 4.2% of suboptimal quality. For the SST, 40% of studies were of high quality and another 60% of intermediate quality. The main limitations were small sample size, especially for the studies focused on neuroimaging findings, and insufficient control of confounders such as the history of other kinds of drug use. For a few studies, the population was not fully described, lacking information of where and when the participants were recruited. To explore whether different study types differ in methodological quality, we did a chi-square test based on **Table 3**. The results indicate that the percentages of studies of *good, fair and suboptimal* quality did not differ between behavioral (10/23, 13/23, 0/23), EEG (4/8, 3/8, 1/8) and fMRI (3/12, 9/12, 0/12) studies (χ^2 (4, N = 44) = 6.51, p = 0.15).

Table 3a Quality assessment scores of included GNG studies according to the NHLBI Quality Assessment Tool.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality Rating
Ames et al, (2014)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Claus et al, (2013)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Hendershot et al, (2015)	yes	yes	NR	yes	no	yes	yes	yes	yes	yes	yes	NR	NA	yes	**fair**
Kamarajan et al, (2005)	yes	yes	NR	no	no	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Kreusch et al, (2014)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Littel et al, (2012)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
López-Caneda et al, (2014)	yes	yes	NR	yes	no	yes	yes	yes	yes	yes	yes	NR	NA	yes	**good**
Luijten et al, (2011)	yes	yes	NR	yes	no	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Luijten et al, (2013a)	yes	no	NR	CD	yes	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Luijten et al, (2013b)	yes	yes	NR	CD	no	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Luijten et al, (2015)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Mahmood et al, (2013)	yes	yes	NR	yes	no	yes	yes	yes	yes	yes	yes	NR	NA	yes	**good**
Petit et al, (2012)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Paz et al, (2018)	yes	yes	NR	yes	no	yes	yes	yes	yes	yes	yes	NR	NA	no	**fair**
Pike et al, (2015)	yes	yes	NR	yes	yes	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Quednow et al, (2007)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Rass et al, (2014)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Roberts et al, (2010)	yes	no	NR	yes	no	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Roberts et al, (2013)	yes	no	NR	yes	no	no	no	no	yes	no	yes	NR	NA	yes	**suboptimal**
Rossiter et al, (2012)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Takagi et al, (2011)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Takagi et al, (2014)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	no	**fair**
Verdejo-García et al, (2012)	yes	yes	NR	yes	yes	yes	yes	yes	yes	no	yes	NR	NA	yes	**good**
Wetherill et al, (2013)	yes	yes	NR	yes	no	yes	yes	no	yes	no	yes	NR	yes	yes	**good**

Note: CD: cannot determine; NA: not applicable; NR: not reported; Meanings of criteria Q1-Q14 can be found in Table S2.

Table 3b Quality assessment scores of included SST studies according to the NHLBI Quality Assessment Tool

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality Rating
Bidwell et al. (2013)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Bø et al. (2016)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Bø et al. (2017)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Colzato et al. (2007)	yes	yes	NR	yes	no	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Courtney et al. (2012)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Courtney et al. (2013)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
de Ruiter et al. (2012)	yes	yes	NR	no	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Filbey et al. (2013)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Fillmore et al. (2002)	yes	yes	NR	yes	no	no	no	no	yes	no	yes	yes	NA	yes	**fair**
Galván et al. (2011)	yes	yes	NR	yes	no	no	no	no	yes	no	yes	NR	NA	yes	**fair**
Glass et al. (2009)	yes	no	NR	no	no	yes	yes	yes	yes	no	yes	yes	NA	yes	**good**
Karoly et al. (2014)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	no	**fair**
Kräplin et al. (2015)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Moallem et al. (2012)	yes	yes	NR	yes	yes	no	no	yes	yes	no	yes	NR	NA	yes	**good**
Papachristou et al. (2012a)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Papachristou et al. (2012b)	yes	yes	NR	yes	no	no	no	yes	yes	no	yes	NR	NA	yes	**fair**
Paz et al, (2018)	yes	yes	NR	yes	no	yes	yes	yes	yes	yes	yes	NR	NA	no	**fair**
Tsaur et al. (2015)	yes	yes	NR	yes	yes	no	CD	yes	yes	no	yes	NR	yes	yes	**fair**
Vonmoos et al. (2013)	yes	yes	NR	yes	yes	yes	CD	yes	yes	no	yes	NR	NA	yes	**good**
Zack et al. (2015)	yes	yes	NR	yes	yes	no	no	no	yes	no	yes	NR	NA	yes	**fair**

Note: CD: cannot determine; NA: not applicable; NR: not reported; Meanings of criteria Q1-Q14 can be found in Table S2.

Publication bias check

To examine evidential value in the original studies, a *p*-curve was created (**Fig. S1**). Out of the 31 effect sizes (unavailable for some studies), 11 were statistically significant ($p < 0.05$), with 8 $p < 0.025$. The *p*-curve analysis on the association between substance use and response inhibition indicated no evidential value (full *p*-curve $z = -0.98$, $p = 0.16$; half *p*-curve $z = 0.58$, $p = 0.72$). However, this was likely due to a lack of power (33% power test, full *p*-curve z = -0.95, $p = 0.17$).

Main outcomes

GNG: no-go commission errors

None of the substance-related variables or their interactions had a significant effect on the commission error rate. Among all other variables, two demographic variables and three task characteristics significantly predicted commission error rates. Age significantly predicted commission error rate ($\beta = -0.01$, $p < 0.01$, 95% CI [-0.02, 0.00]), indicating that older participants showed decreased commission error rates. Education years also significantly predicted commission error rate ($\beta = -0.01$, $p = 0.03$, 95% CI [-0.02, 0.00]), indicating the

higher the educational level, the lower the commission error rates. The nominal variable working memory load had a significant effect on commission error rate (β = 0.10, p < 0.01, 95% CI [0.07, 0.14]), indicating that when working memory load was high, participants made more commission errors. The no-go percentage had a significant effect on commission error rate (β = -0.04, p < 0.01, 95% CI [-0.07, -0.02]), such that the higher the no-go percentage, the lower the rate of commission errors. The number of trials also had a significant effect on commission error rate (β = 0.04, p < 0.01, 95% CI [0.02, 0.07]), indicating higher commission error rates when there were more trials.

SST: SSRT

Lifetime cannabis use significantly predicted SSRT, with users showing longer SSRT than non-users (β = 5.59, p = 0.03, 95% CI [0.41, 10.77]). Tobacco use was positively, although not significantly, associated with SSRT (β = 3.21, p = 0.06, 95% CI [-0.13, 6.55]), indicating that the more tobacco was consumed, the longer SSRT. The tobacco × cannabis interaction also had a significant effect on SSRT (β = -4.19, p = 0.03, 95% CI [-8.03, -0.37], **Fig. 2**). Post-hoc analyses were performed by splitting the imputed data sets and fitting the same restricted model without the interaction term. These analyses revealed that for the cannabis non-users, higher tobacco use was associated with longer SSRT (β = 6.44, t = 2.70, p < 0.01). For cannabis users, no effect of tobacco use on SSRT was observed (β = -0.15, t = -0.05, p = 0.96). When split based on cigarette smoking (median-split of z-score), the following effects were obtained: for low tobacco users, cannabis lifetime users did not differ significantly from cannabis non-users in SSRT (β = 7.62, t = 1.90, p = 0.06). A similar finding was observed among high tobacco users (β = 4.80, t = 1.74, p = 0.08).

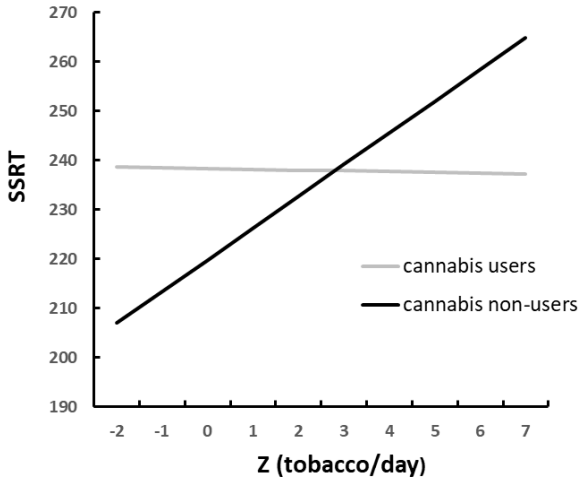


Figure 2. The interaction between cannabis and tobacco use on SSRT. Only for cannabis non-users, the more tobacco a person smoked on a daily basis, the longer his/her stopping latency. For cannabis users, a mild negative association was found between tobacco use and SSRT.

Education years also significantly predicted SSRT (β = -9.33, p < 0.01, 95% CI [-12.88, -5.80]), indicating that the higher the education level, the shorter the SSRT. Age

significantly predicted SSRT (β = 13.46, p < 0.01, 95% CI [9.29, 17.63]), with an increase in SSRT along with an increase in age. The number of trials also significantly predicted SSRT (β = -17.44, p < 0.01, 95% CI [-30.60, -4.28]), indicating a decrease in SSRT when there were more trials. In addition, stop-signal modality had an effect on SSRT (β = -28.58, p = 0.01, 95% CI [-50.61, -6.56]), indicating that auditory stop signals induced shorter SSRT compared to visual stop signals. SSD also had a significant effect on SSRT (β = -33.29, p = 0.04, 95% CI [-64.61, -1.96]), indicating that the staircase-tracking procedure resulted in shorter SSRT compared to the fixed SSD procedure.

For both SSRT and commission error rate, models including the interaction between alcohol use on the one hand and demographics and task parameters on the other resulted in largely comparable findings as presented here[1]. Only in the GNG, an interaction between alcohol use and age appeared (β = 0.01, p = 0.02, 95% CI [0.001, 0.02]). For light drinkers, older people made less commission errors (β = -0.02, t = -2.56, p = 0.01), which was in line with the main effect of age. Whereas for heavy drinkers, this relationship was absent (β = -0.01, t = -1.50, p = 0.14). All other interactions with alcohol were found to be non-significant (Supplementary Materials **S6**).

Outcomes for go RT in GNG and SST can be found in Supplementary Materials **S8**. Briefly, older people had longer go RT in both GNG and SST. Higher educated people had shorter go RT in SST. Although the interaction between cocaine and tobacco had an effect on go RT in SST, post-hoc analysis revealed no significant simple effect.

Discussion

Previous individual studies, reviews, and meta-analyses investigating inhibitory control deficits in relation to long-term substance use and SUD have provided mixed results (Luijten et al., 2014; Smith et al., 2014; Wright et al., 2014). These inconsistent findings might at least partly be due to insufficient control of frequently occurring polysubstance use. In addition, studies differed in sample demographics and task-related variables and used extreme group designs. The current mega-analysis aggregated data of 3610 individuals, from 43 studies, in which polysubstance use, demographics, and task parameters were included in the prediction of inhibition performance by means of an imputed multilevel analysis. Most of the included studies were of medium to high quality, which validates the overall conclusions drawn. Surprisingly, our overall pattern of results indicated that most types of substance use did not show an association with response inhibition. While for most substances no effects were found, lifetime cannabis use was found to be associated with impaired inhibition, as indexed by an increased SSRT in the SST. Tobacco use was also associated with impaired inhibition as indexed by the same variable. In addition, an interaction between lifetime cannabis and tobacco use was found on SSRT, which indicated a strong positive relationship between daily

[1] In the model including interactions with demographics and task-parameters, tobacco and cannabis use were both positively associated with SSRT. However, their interaction was not significant, but the three-way interaction with sex was. Post-hoc tests indicated that, only for male non-cannabis users, tobacco use was positively associated with SSRT (see in Supplementary Materials **S6**).

tobacco use and SSRT in participants who did not use cannabis (indicating poorer inhibition), and the absences of such a relationship in users smoking cannabis. In addition, demographic factors such as age and years of education and task characteristics such as no-go percentage, affected inhibition performance in the expected direction, strengthening the credibility of the other results.

Response inhibition and substance use

The main significant finding of our mega-analysis was that lifetime cannabis use was associated with prolonged response inhibition in the SST. One possible explanation is that this could (partly) involve subacute effects of cannabis use (i.e. lasting 7 hours to 4 weeks after last cannabis use, Gruber & Yurgelun-Todd, 2005; Pope & Yurgelun-Todd, 1996; Schulte et al., 2014). Acute cannabis use (i.e., 0-6 hours after last cannabis use) has been consistently reported to impair response inhibition in the SST (Metrik et al., 2012; Ramaekers et al., 2006). In contrast, findings of its long-term effect (i.e., 3 weeks or longer after last cannabis use) were mixed (Crean, Crane, & Mason, 2011), with some confirming an impairing effect (Moreno et al., 2012), while others did not (Tapert et al., 2007). To have a closer look at the effect of cannabis, we compared cannabis daily users with less frequent users. A linear mixed regression model was built with the fixed effect of 'cannabis daily users (yes/no)' and a random intercept. It indicated that cannabis daily users did not differ from less frequent users on their stopping latency (i.e., SSRT., β = -6.42, p = 0.90, 95% CI [-114.27, 127.10]), which does not support the hypothesis of subacute cannabis effects. Despite conflicting behavioral findings of the relationship between cannabis use and response inhibition, abnormalities in neural activation have often and more consistently been reported in relation to acute as well as chronic cannabis use compared with non-users (systematic review: Wrege et al., 2014). Age of onset may have a moderating effect on the neural effects of cannabis (Hester, Nestor, & Garavan, 2009), but we did not have sufficient data to test this hypothesis.

In line with previous findings, tobacco use tended to impair inhibition. Participants with a higher level of tobacco dependence demonstrated a lower level of response inhibition capacities (Billieux et al., 2010), and smokers performed worse than non-smokers in a smoking-related GNG (Luijten et al., 2011). However, it should be noted that the main effect of tobacco use was qualified by a significant interaction with cannabis use, indicating a negative effect of tobacco use only in non-cannabis users. Another study reported that co-administration of cannabis and tobacco attenuated the impairment in delayed recall memory caused by cannabis alone (Hindocha, Freeman, Xia, Shaban, & Curran, 2017), and other reports have indicated weaker impairment on some measures after polysubstance use (e.g., alcohol and cannabis, Schweinsburg et al., 2011). One possible interpretation of these findings is that cannabis has a protective effect when used together with other substances such as alcohol and tobacco (cf., Viveros, Marco, & File, 2006). Due to the high co-occurrence of cannabis and tobacco use (Badiani et al., 2015; Leatherdale, Ahmed, & Kaiserman, 2006), and the fact that concurrent tobacco use contributes to cannabis dependence symptoms (Ream, Benoit, Johnson, & Dunlap, 2008), further studies of the combined and single effects on response inhibition are warranted to elucidate these findings.

What could explain the low evidence for a relationship between (most) long-term

substance use and inhibition? On closer inspection, only 30% of studies included reported evidence for negative associations between substance use (or gambling) and response inhibition (**Tables 1 and 2**). In contrast, other studies reported evidence for positive associations between substance use and inhibition performance in GNG and SST (significant: Glass et al., 2009; nonsignificant: Galván, Poldrack, Baker, McGlennen, & London, 2011; Papachristou, Nederkoorn, Havermans, van der Horst, & Jansen, 2012; Vonmoos et al., 2013). In light of this, it is less surprising that the integrated results indicated overall largely null findings (most of the confidence intervals ranged around zero). Similarly, only one out of the five studies included in a recent review (Carbia, López-Caneda, Corral, & Cadaveira, 2018) reported impaired response inhibition—as measured by SST and GNG tasks—in binge drinkers compared with controls (Czapla et al., 2015).

One explanation is that chronic recreational substance use without a diagnosis of SUD is not associated with response inhibition impairment. In other words, a threshold effect rather than a linear effect might exist between substance use and response inhibition performance. Alternatively, there might be a linear relationship, albeit shallow and we only see the effects when comparing very extreme groups (e.g., healthy controls vs. SUD in clinical samples). As a result of our exclusion criteria, **Fig. S2a** and **S3a** indicate that only a minority of the participants reached the level of SUD (either reported in individual paper or categorized based on questionnaire score), and most others were still within the normal range of use. It is conceivable that inhibition is only impaired in SUD (Bjork, Hommer, Grant, & Danube, 2004; Fernández-Serrano, Pérez-García, & Verdejo-García, 2011; Noël et al., 2007; Petit et al., 2014). Alternatively, inhibition problems may play a role in the transition from heavy use to SUD. In the SST sample, there were more people diagnosed with tobacco dependence (about 10%, **Fig. S3a**), which might explain why a positive (although not significant) association of SSRT and tobacco use was found.

A second possibility is that substance use is actually associated with impaired inhibition, but we were unable to detect this. Possible reasons include: sample characteristics (as was discussed in the last paragraph), the type of tasks included, outcome measures (i.e., effects may only be visible in biological markers but not in behavior), and statistical power. Regarding *tasks included*, there is the possibility that (heavy) use of psychoactive substances does not lead to a general inhibition problem, but only to a specific problem in the domain of substance use (hence an interaction between an appetitive process and suboptimal control, Jones, Duckworth, Kersbergen, Clarke, & Field, 2018). A related explanation can be that self-control failures like maladaptive substance use may reflect a reduced mobilization of inhibitory control in substance-related contexts rather than generally impaired inhibitory control competencies (Krönke et al., 2018; Krönke, Wolff, Benz, & Goschke, 2015; Wolff et al., 2016). However, in a secondary analysis, we did not find that substance-related GNG moderated the relationship between alcohol and commission error rate (see details in the next section). Furthermore, the SST and GNG measure stimulus-driven (exogenous) inhibition, which may not closely match real-world 'loss of control' behavior related to substance use (e.g., an initial intention to have one drink escalating into a binge-drinking session, failed suppression of craving, etc). These examples reflect a different type of inhibition, namely endogenous or intentional rather than exogenous inhibition. Intentional inhibition paradigms

such as the Marble task (Schel et al., 2014) could be considered in future research. Regarding *outcome measures*, it is possible that biological but not behavioral markers might be more sensitive to inhibition impairments among substance users (Garrison & Potenza, 2014). Relatedly, some of the included MRI studies reported specific group-related abnormalities in brain activation but not in behavioral outcomes (e.g., Claus, Ewing, Filbey, & Hutchison, 2013; de Ruiter et al., 2012; Galván, Poldrack, Baker, McGlennen, & London, 2011; Karoly, Weiland, Sabbineni, & Hutchison, 2014; Luijten et al., 2013a; Roberts & Garavan, 2010). In addition, a recent study indicated that resting state fMRI connectivity might serve as a promising biomarker of alcohol use disorder severity (Fede, Grodin, Dean, Diazgranados, & Momenan, 2019; see further, Steele, Ding, & Ross, 2019 for additional recent approaches to identifying biormarkers for addiction). Alternatively, Kwako, Bickel, and Goldman (2018) suggested a dimensional approach to biomarkers in terms of executive functions (inhibitory control, working memory, etc.), which includes measuring neuropsychological tests and epigenetic changes in relevant genes (e.g., COMT). With respect to *statistical power,* polysubstance use was coarsely defined, such that substances other than alcohol and tobacco had to be coded in a binary lifetime use variable. It is still possible that (heavy) use of a specific combination of substances at the same time (e.g., cocaine and alcohol, Schulte et al., 2014) does have a negative impact, which did not emerge from our analysis here using binary variables. In addition, the total author response rate was low, which we discuss as a limitation. Currently, it remains an open question whether substance use is not associated with a motor inhibition impairment or if we were incapable of detecting such an impairment.

Demographics and task parameters

Our results indicate that age is a significant predictor of performance. In the GNG-task, the age-related increase in accuracy is most likely due to the strategic slowing of responses (confirmed by longer go RTs). In the SST, SSRT increased with age. Education was positively correlated with inhibition capability in both tasks. There was not a significant effect of sex on inhibition, nor any interactions between sex and substance use. In the GNG, higher working memory load, lower no-go percentages, and a higher number of experimental trials resulted in more commission errors. These effects are in line with the primary literature on these tasks and are further discussed in Supplementary Materials **S1**. Somewhat surprisingly, we did not obtain an effect of substance-related GNG on performance measures compared to classical task versions. This is in line with a recent meta-analysis, where the main effect of appetitive cues was not observed after correction for publication bias, and where drinking status (light vs. heavy drinkers) also did not moderate this effect (Jones, Duckworth, Kersbergen, Clarke, & Field, 2018). In a small exploratory analysis, we examined the alcohol × substance-related task interaction effect, which was not a significant predictor of commission error rates in GNG (Supplementary Materials **S6**). Still, since our conclusion is based on only 5 out of 23 included studies, future research should address this question. In the SST, visual (vs. auditory) stop signals, fewer number of trials and fixed SSDs (vs. staircase-tracking procedure) induced prolonged SSRT (elaboration in Supplementary Materials **S1**).

Implications

Our results showed no relationship between the use of most substances and impaired response inhibition, except for a relationship between cannabis use and impaired inhibition, and in non-cannabis users an association between cigarette use and impaired inhibition. What are the theoretical implications? First, these findings could be of relevance for the current debate on the question whether addiction should be considered a chronic brain disease or not (Heather et al., 2017; Leshner, 1997; Lewis, 2015; Volkow et al., 2015). The current findings do not support the idea that long-term recreational substance use leads to irreparable problems in inhibition, although it cannot be excluded that inhibition problems are present in (a subgroup of) people diagnosed with SUD. Second, in many dual process models of addiction, suboptimal inhibition of stimulus-driven appetitive processes (cue-reactivity) plays an important role in the escalation of use (e.g., Baler & Volkow, 2006; Wiers et al., 2007). An alternative perspective does not emphasize the competition between stimulus-driven and goal-directed processes, but rather between different goal-directed processes (Moors, Boddez, & de Houwer, 2017). Individuals learn to mobilize and allocate resources strategically according to goal saliency and importance (Köpetz, Lejuez, Wiers, & Kruglanski, 2013). In this way, the inhibition capability of substance users is expected to fluctuate moment-to-moment (i.e., state-like) based on the external and internal context. Note again that the current findings do not exclude the possibility that in severe addiction(s), chronic inhibition problems of stimulus-driven processes do play a role. It merely underscores the goal-directed nature of (heavy) substance use. Third, impaired response inhibition as an immediate consequence of substance consumption may be more important than general inhibitory impairments in the long term. Compared with long-term (non-dependent)substance use, acute use is more consistently related to impaired inhibitory control that enhances further consumption (Gan et al., 2014).

Limitations and suggestions for future study

There are several limitations of the current study worth considering. First, the response rate was rather low. Although more than 100 studies met our inclusion and exclusion criteria, authors of only 65 studies provided raw data. The reasons for this include inaccessibility of the data, data could not be shared due to regulations, and a lack of success in contacting the authors. The low response rate is an obstacle encountered commonly in mega-analyses (Riley et al., 2010, 2007). We calculated and compared the effect sizes of studies that were included, studies that provided data but that were not included, and studies did not provide data. It was found that these three kinds of studies did not differ significantly on effect size (**Fig. S4**, see statistics in Supplementary Materials **S9**). In light of this, an open science framework is recommended in order to increase the transparency and availability of data for future research. Despite these obstacles, we received raw data from 3610 participants, which should provide sufficient power to test effects on inhibition of substance use. Second, and relatedly, we noticed that the original studies did not score the use of every substance, for example, data on opiates were scarce. Although we tried to remedy this by means of multiple imputations, the analyses on the effects of these substances might have been underpowered. Third, except for alcohol and tobacco use, other substances could only be coded as a binary ‘lifetime use’

variable. It would be optimal if a standard way of assessing all substances could be used in the future when assessing the relationship between substance use and inhibition (or other neuropsychological functions). Guidelines for experimental protocols and assessment of substance use would facilitate future multicenter comparisons, which could be stimulated by funding agencies requiring a standard assessment of all commonly used substances in a uniform format. Fourth, studies did not focus on poly-substance use. Studies recruited individuals taking one substance and recorded one/several other substances. Therefore, the samples are highly selective and not representative of poly-substance users. In addition, future studies are suggested to include a standard index of trait impulsivity (e.g., Eysenck's personality inventory, Eysenck & Eysenck, 1965; BIS-11, Patton, Stanford, & Barratt, 1995) as it is possible that within-sample variability on this dimension is obscuring common effects of drug exposure, or has stand-alone effects, especially for stimulant users (Ersche et al., 2012). Last, the effects of age and education years should be considered in the analysis and explanation of results. Task characteristics like stop trial percentage that consistently influence task performance should also be considered when comparing across studies.

Conclusions

The current mega-analysis aggregated raw data from 3610 participants in 43 studies on long-term (mostly) light to moderate substance use and response inhibition. The main finding is that limited evidence was found for impaired response inhibition in substance users, with two exceptions: lifetime cannabis use, and cigarette smoking in people who do not use cannabis. The validity of these findings is underscored by expected findings for demographics (e.g., age, education level) and task characteristics (e.g., stop percentage). Broad assessment, standardized recording and reporting of substance use are highly needed in future studies.

SUPPLEMENTARY MATERIALS

Table S1a Essential variables (GNG)

Subject No.	demographic variables			substance use		GNG variables (Report at least one measure) Percentage of no-go signals:_____		
	Age (years)	Sex (F/M)	Education (highest level)	Alcohol	Tobacco	No-Go Commission Errors	Go Omission Errors	Go RT
1								
2								
3								
4								
5								
……								

Note:

1. Check the unit of demographic variables, if different from suggestion please provide additive legend or explanation
2. For the use of alcohol and tobacco, please provide the measurement you used (e.g. the unit, Does the number signifies the average amount per day during how many past weeks/months?)

Table S1b Essential variables (SST)

Subject No.	demographic variables			substance use		SST (Report at least one measure) Percentage of stop signals:_____	
	Age (years)	Sex (F/M)	Education (highest level)	Alcohol	Tobacco	SSRT	Go RT
1							
2							
3							
4							
……							

Note:

1. Check the unit of demographic variables, if different from suggestion please provide additive legend or explanation
2. For the use of alcohol and tobacco, please provide the measurement you used (e.g. the unit, the number signifies the average amount per day during the past several weeks?)

Table S2 Quality assessment tool for observational cohort and cross-sectional studies (National Heart, Lung, and Blood Institute (NHLBI), 2014)

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Note: CD, cannot determine; NA, not applicable; NR, not reported

Table S3 P-curve disclosure table: association between substance use and response inhibition

original paper	1) quoted text from original paper indicating prediction of interests to researchers	2) study design	3) key statistical result	4) quoted test from the original paper with statistical results	5) results	6) robustness results
Ames et al. (2014)	We expect that alcohol cues as No-Go signals will lead to more inhibitory errors (i.e., difficulty withholding a response). Thus, these errors should be greater among heavier drinkers relative to the lighter drinkers.	two-cell: heavy drinker vs light drinker	difference of means	Although not statistically significant, heavy drinkers made more inhibitory errors during the No-Go trials than the lighter drinkers ($p < 0.106$).	t(39)=1.26, p=0.21 (calculated from mean, SE and N in table)	
Bidwell et al. (2013)	We also examined the interactions among cannabinoid-related genetic variation and two measures of behavioral impulsivity: (a) the capacity to inhibit already initiated responses as measured by the Stop Signal Task (Logan et al., 1997) (no clear hypothesis on behavioral measures)	NA (focused on gene: CNR1 or FAAH)	NA	NA	NA	
Bø & Landrø, (2017)	We expect to find a stair-case relation between a greater level of alcohol consumption and SSRT and PES, respectively. The highest consumers are expected to have longer SSRTs, indicative of less efficient inhibition	one way ANCOVA, 5-cell: compare five drinking levels on SSRT.	linear trend/main effect	There was a significant main effect of alcohol consumption on SSRT at the $p < .05$ level for five consumption levels [$F(4, 389) = 2.867$, $p = .023$, $\mu = .029$].	F(4,389)=2.867, p=0.023	

Note: NA: not available

Filbey & Yezhuvath, (2013)	We expected greater functional connectivity between inhibitory control networks in cannabis-dependent users vs. nondependent cannabis users.	two-cell: cannabis dependent vs nondependent	difference of means	The groups also did not differ in … or SSRT (dependent: 185.1 ±30 ms, nondependent: 198.4 ±38.2 ms).	t(72)=1.67, p=0.10	
Fillmore et al. (2002)	We predicted that cocaine abusing individuals would display a specific deficit in the ability to inhibit behavioral prepotent responses as measured in the stop-signal paradigm.	two-cell: controls vs cocaine users	difference of means	Table 2 also shows that cocaine users displayed significantly longer SSRTs than did controls (t42=2.4, P=0.020). A 2 group ANCOVA also obtained a significant difference in SSRT after controlling for subjects' weekly alcohol use, (F1,41=7.4, P=0.009).	t(42)=2.4, p=0.02	
Galván et al. (2011)	Task-related activity in PFC regions, critical for response inhibition, would be negatively associated with smoking behavior.	two-cell: smokers vs nonsmokers	difference of means	There were no significant group differences in task performance	t(48)=0.7342, p=0.466 (calculated from mean and SD in table)	
Glass et al. (2009)	We examined whether chronic alcoholism and chronic smoking have effects on executive function	regression: alcohol severity & smoking in predicting executive function	correlation coefficients	read from table: alcohol severity: r(238) = -0.167; smoking: r(238) = -0.221	1) r(238)=-0.167, p= 0.009; 2) r(238)=-0.221, p < 0.001	
Kamarajan et al. (2005)	In the present study, along with ERPs, we have therefore attempted to examine the spatial distribution of current source density (CSD) which may give distinct topographic features specific to alcoholism during response inhibition. (no clear hypothesis about the direction)	two-cell: alcoholic vs. control	difference of means	Although alcoholics committed more errors during the button-press responses of Go and No-Go condition separately, this difference was not statistically significant.	t(59)= 1.605, p= 0.114	
Karoly et al. (2014)	Further explicate the nature of the relationship between cue-induced craving and response inhibition among heavy drinkers with a stop-signal paradigm that is combined with the presentation of visual	NA (focused on fMRI)	NA	NA	NA	

	alcohol cues and control (nonalcoholic beverage) cues. (no clear hypothesis is stated)					
Kräplin et al. (2015)	1)We hypothesized that the comorbid PG (pathological gambling, without ND: nicotine dependence) group would show higher response and choice impulsivity than healthy controls; 2)Therefore, our hypothesis was that PG (without ND) is related to an increased choice impulsivity compared to ND (nicotine dependence), whereas response impulsivity may be comparable to ND; 3)We hypothesized an additive effect of comorbid PG and ND on impulsivity compared with only ND.	a couple of two-cell: control vs PG, PG vs ND, PG vs PG&ND	difference of means	The PG group displayed a significant higher SSRT than the control group (ATT/average treatment effect of the treated = 75.67, 95% confidence interval, CI [1.84, 206.12]),	NA	
Kreusch et al. (2014)	We first hypothesized that heavy drinkers, by comparison to light drinkers, would exhibit inhibition deficits revealed by more FA during No-go trials involving letters; in the modified Go/No-go task, we expected reduced inhibition performances towards alcohol-related cues in heavy drinkers as compared to light drinkers.	1) two-cell (light drinker vs heavy drinker); 2) 2 (heavy vs light drinker)×2(high vs. low alcohol avoider)× (alcohol-related picture vs. neutral picture)	1) difference of means; 2) no clear hypothesis on this, no further report on this three-way interaction	The t-tests computed … and the percentage of FAs in the letter Go/No-go task revealed a significant difference on FAs ($t(28)= 2.24$, $p= 0.03$). Heavy drinkers made more FA than light drinkers (mean= 5.6%, SD=5.4 in heavy drinkers and mean= 2.1%, SD = 2.5 in light drinkers).	$t(28)=2.24$, $p=0.03$	

Note: NA: not available

Littel et al. (2012)	We hypothesize excessive gamers to show reduced NoGo N2 amplitudes in response to NoGo trials and reduced ERN and Pe amplitudes in response to errors. Because of inconsistencies in results of previous studies, no specific hypotheses are formulated with regard to behavioral indices of response inhibition.	2 (group: control vs excessive computer gamers) × (trial: go vs no-go)	simple effect (only the effect of group on no-go trials)	Furthermore, a significant Group × Error interaction was found, $F(1,50) = 11.44$, $P < 0.001$. Excessive gamers made more errors in response to No-Go trials (54%, M = 40.12, SD = 11.93) than controls (41%,M = 30.67, SD = 12.17; $P < 0.01$).	t(50)=2.82, p=0.007 (self-calculated from mean and SD)	
López-Caneda et al (2014)	We tested the hypotheses that …lower amplitudes of the NoGo-P3 component in Ex-BDs than in BDs but larger than in controls. no hypothesis about behavioral data.	3-cell (control vs. binge drinkers vs. ex-binge drinkers)	linear trend	There were no significant differences between groups (Controls, BDs, and Ex-BDs) for any of the behavioral variables analyzed (RT, percentage of correct responses, and percentage of correct inhibitions).	F(2,54)=0.42, p=0.66	
Luijten et al. (2011)	It is expected that smokers will make more mistakes when they have to inhibit their response to infrequent NoGo stimuli; we expect these effects to be more pronounced on trials which include smoking-related stimuli.	2 (group: smokers vs. non-smokers) ×2 (picture: smoking vs. non-smoking) (attenuated interaction)	two-way interaction	Trend to significance was found for the Group × Inhibition interaction, $F(1,37) = 3.27$, $p = 0.08$.	F(1,37)=3.27, p=0.08	

Luijten et al. (2013a)	We hypothesized that smokers would have significantly greater difficulty inhibiting their response to an immediate rewarding stimulus when compared to matched control participants, neutral conditions or both. With regard to punishment, we expected that non-smoking controls would adopt a more cautious responding style when failed inhibition resulted in an immediate punishment, while this was not expected to influence behavior to the same extent in smokers.	Reward: 2 (group: smokers vs. controls) ×2 (condition: neutral vs. reward) Punishment: 2 (group: smokers vs. controls) ×2 (condition: neutral vs. punishment)	Reward: two simple effects Punishment: two simple effects	For both reward & punishment: RM-ANOVAs did not show significant main or interaction effects of group and condition for either NoGo, Go and Go-Money accuracy rates.	Calculate from the table in paper: neutral condition, control vs smoker: t(34)=0.42, p=0.70; reward condition, control vs smoker: t(34)=0.10, p=0.92; punishment condition, control vs smoker: t(34)=1.40, p=0.17	
Luijten et al. (2013b)	We hypothesized that haloperidol will reduce inhibitory control and associated brain activation. Second, based on the inverted 'U' curve theory of dopamine and cognitive control, and reported baseline differences between smokers and controls in dopamine D2 receptor density in subcortical regions, we expected that haloperidol will have differential effects on brain activation associated with inhibitory control in smokers and non-smokers. (no hypothesis about behavioral data)	2 (medication: haloperidol vs placebo) ×2(group: smokers vs. controls)× 2 (trial: go vs no-go)	only one simple effect, under the placebo condition, smokers vs controls.	We performed an additional explorative Group x Condition RM-ANOVA for accuracy rates on the first test occasion in order to exclude possible learning effects on task performance. A Group x Task Condition interaction was found, $F(1,46)=4.72$, $p<0.05$. Post-hoc t-tests revealed that, for NoGo trials, smokers performed less accurately than non-smoking controls ($p<0.05$; Msmokers=53.31, SD=14.22, Mcontrols=61.90, SD=15.10), whereas there was no difference for Go accuracy between the groups, $F(1,46)=0.33$,ns.	t(46)=2.03, p=0.048 (self-calculated from mean and SD)	

Luijten et al. (2015)	Impairments in inhibitory control, error processing, and attentional control were expected for behavioral measures of the Go/No-Go and the Stroop task.	2 (go vs. no-go)×2 (problem gamers vs. controls)	simple effect	In addition, both the Group main effect, showing reduced accuracy in problem gamers, $F(1,31)=4,91$, $p<0.05$, and the Group×Inhibition interaction, $F(1,31)=4,27$, $p < 0.05$,were significant. Post-hoc tests revealed that problem gamers were less accurate for No-Go trials, $p<0.05$, compared with non-problematic gamers,	$t(32)=2.177$, $p=0.037$ (self-calculated from M and SD value)	
Moallem & Ray (2012)	This study compares across substance using groups to examine unique and additive effects of impulsivity. (no clear hypothesis other than this was reported)	3-cell: controls vs smokers vs heavy drinker smokers	linear trend	Initial omnibus tests revealed no significant main effect of group on SSRT ($F(2, 376)=1.42$, $p=.24$)	$F(2,376)=1.42$, $p=0.24$	
Papachristou et al. (2012)	It is expected that heavy drinkers will score higher on measures of trait impulsivity and STR and will display poorer response inhibition relative to light drinkers.	2 (drinking group: heavy vs. light drinkers)×2 (impulsivity: high vs. low in impulsivity)×4 (cue exposure: baseline water, water exposure, baseline alcohol, alcohol exposure)	difference between means	There was no significant difference in the SST ($F[1, 40]<1$, n.s.) and CARROT ($F[1, 40]<1$, n.s.) performances between the two drinking groups.	$t(40)=0.10$, $p=0.92$ (self-calculated from mean and SD in table)	
Papachristou et al. (2012)	It is hypothesized that social drinkers with impaired response inhibition experience higher cue-elicited craving for alcohol than social drinkers with good response inhibition	correlation between AUDIT score and SSRT (this is not the main analysis in the paper but our focus)	correlation coefficient	$r(36) = -0.17$ (from the table)	$r(36)=-0.17$, $p=0.31$	

Paz et al. (2018)	We first hypothesized that increases in binge drinking behavior throughout participation will be significantly correlated with poor inhibitory performance assessed at follow-up (T2). Second, we hypothesized those who substantially increased their binge drinking during participation, compared to those who substantially decreased their binge drinking, will show a decline in inhibitory performance from baseline assessment (T1) to T2.	1) correlation (negative between the increase in binge score and inhibition). However, this was done separately for males and females; 2) 2 (group: increase binge score vs decrease binge score) × (session: T1 vs T2) (reversing interaction)	1) correlation coefficient; 2) two simple effect	1) A significant correlation was found with a change in AUQ binge score and SSRT among females only, where an increase in binge drinking score from T1 to T2 positively correlated with poor performance in the SST at T2, $r(82) = 0.276$, $p = 0.012$. 2) Results of the repeated-measures ANOVA showed no significant main or interaction effects between binge drinking groups and inhibitory performance from T1 to T2 (see Table 5).	NA	
Quednow et al. (2007)	We expected elevated levels of impulsivity and a decision-making deficit in MDMA users in comparison with both control groups.	3-cell: (MDMA vs. cannabis vs. control)	MDMA vs control	An initial ANOVA did not reveal any significant main effect between the groups in the dependent variables	calculated through mean and SD displayed in the table, MDMA vs control: $t(31)=0.32$, $p=0.75$	cannabis vs control: $t(30)=1.00$, $p=0.32$

Note: NA: not available

Rass et al. (2014)	Although not statistically significant, heavy drinkers made more inhibitory errors during the NoGo trials than the lighter drinkers ($p < 0.106$). We expected that smokers would commit more commission errors (false positives) and exhibit faster reaction times (RTs) than ITS (intermittent smokers) and nonsmokers during inhibitory control tasks, reflecting greater behavioral disinhibition. We expected that it would fall between smokers and nonsmokers in terms of those measures.	3 (smoker vs ITS vs control) × 2 (condition: frequent vs rare)	under the rare condition, smoker vs control	For the assessment of errors, a group (3) ×condition (2) repeated measures ANOVA found more errors in the rare condition ($F[1,79] = 231.66$, $p < 0.001$). There was no main effect of group ($F[2,79] = .08$) and no group _ condition interaction ($F[2,79] = .51$).	$t(50)=0.96$, $p=0.34$ (calculated from provided data)	under the rare condition, smoker vs ITS: $t(50)=1.69$, $p=0.96$
Roberts et al. (2010)	The hypothesis was that polysubstance users who predominantly used ecstasy would report elevated measures of state and trait impulsivity and reveal dysregulated brain functioning during response inhibition and performance monitoring compared to healthy controls.	two-cell (group: ecstasy vs control)	difference of means	Independent-group t-tests revealed that the groups did not differ … on any GO/NOGO performance measures including % STOPs ($p \leq 0.5$), the error of commission reaction times ($p \leq 0.6$) …	$t(38)=1.769$, $p=0.085$ (calculated from mean, SE and N from table)	

Roberts et al. (2013)	The aim of the current study was to observe whether there are any behavioral or electrophysiological differences between ecstasy users and controls in a task measuring inhibitory control (Go/No-Go). In view of the previous literature it is predicted that any behavioral differences will be negligible, however observable differences in components of the elicited ERPs are predicted in line with compensatory mechanisms.	3-cell: (ecstasy users vs polydrug users vs control)	linear trend	Univariate ANOVA revealed that there was no significant difference between groups in performance on this task F(2,57)=1.15, p=0.33. The mean 'No-Go' errors (i.e. responding to a letter other than an X that required no response/inhibition of response) were used as the measure of performance in this case (Ecstasy users: 2.7±1.95, polydrug users: 3.4±2.80, drug naïve: 4.35±4.92).	F(2,57)=1.15, p=0.32	
Rossiter et al. (2012)	The aim of these contingencies was (1) to examine the influence of delayed reward on inhibitory control over immediate reward-related stimuli (when compared to non-reward stimuli), in the presence or absence of punishment; and (2) the influence of alcohol abuse behavior on the interaction between reward, punishment and inhibitory control. (no clear hypothesis is declared)	2 (group: harmful drinkers vs non-hazardous drinkers) ×2 (gender: male vs. female) × 3(condition: neutral vs delayed reward vs immediate punishment)	only on simple effect: under neutral condition, the group effect	A 2 group × 2 gender × 3 incentive condition (Neutral, DR, IP) ANOVA, indicated response inhibition performance was significantly influenced by incentive context, $F(2,162) = 22.6$, $p = .00$, but not group, $F(1,81) = .01$, $p = .90$, or gender, $F(1,81) = .13$, $p = .71$.	t(83)=0.63, p=0.53 (self-calculated from mean, se and N in table)	

Takagi et al. (2014)	We hypothesized the inhalant users would have lower d-prime scores relative to the other groups.	3-cell: (inhalant vs cannabis vs control)	difference between means: inhalant vs control; inhalant vs cannabis	There were significant differences between the three groups on measures of d-prime on the Go/No-Go task. Games–Howell post hoc tests revealed significant differences between the inhalant and control groups (p = .021, d = .88), with inhalant users having significantly lower d_ scores. The d-prime score between the inhalant and cannabis groups was not significant (p = .21, d = .55). but we focused on commission error rate	calculated from the data provided: inhalant users vs controls: t(47)=2.49, p= 0.17; inhalant users vs cannabis users: NA	
Tsaur et al. (2015)	We hypothesized that craving would be intensified and response inhibition deteriorated during abstinence compared with baseline.	NA (we only used baseline data, not compare baseline with abstinence periods)	NA	NA	NA	
Verdejo-García et al. (2012)	We sought to address these unresolved questions by examining the performance of opiate dependent individuals on a series of well-validated measures of attention and inhibitory control both before and after exposure to an autobiographical craving script (looks like exploratory analysis)	two-cell (opiate-dependent vs. control) (this is what we are interested)	difference of means	There were no significant differences in performance on tests of attention and inhibitory control between groups (p> 0.05), with the exception of GNG number of commission errors, which was significantly higher in controls, t=−2.81, p=0.007.	t(56)=−2.81, p=0.007	

Note: NA: not available

Vonmoosa et al. (2013)	We expected to find increased trait and behavioral impulsivity in DCU and similar, albeit less pronounced, results in RCU	3-cell (control vs recreational cocaine users vs dependent cocaine users)	linear trend	None of the SST parameters revealed a significant main group effect.	F(2,153)=1.885, p=0.16	
Zack. et al (2015)	It was predicted that AMPH would lead to increased cardiovascular and HPA response in PG vs HC subjects, as indexed by HR, blood pressure and plasma cortisol response, particularly in the later stages of the dose.	MANOVA controls vs. pathological gamblers on different outputs of SST	difference of means	A MANOVA of Go RT, SSRT, go errors and stop errors on the Stop Signal Task yielded no significant effects, ps>0.13. SSRT, 185 (31) ms for HC vs 220 (86) ms for PG;	t(21)=1.27, p=0.22	

Table S4a The full model results and percentage of missing values per variable: GNG commission error

Variables	Missing data %	*β*	*t*	*p*	95% Confidence Interval	
					Lower Bound	Upper Bound
Age	0.0%	-0.01	-2.52	0.01*	-0.03	0.00
Sex	0.0%	0.00	0.01	0.99	-0.02	0.02
Education years	11.3%	-0.01	-1.87	0.06	-0.02	0.00
Alc_Q	0.0%	0.00	-0.04	0.97	-0.04	0.04
Cig_Q	8.8%	0.00	-0.61	0.54	-0.02	0.01
Cannabis_lifetime	29.7%	0.00	-0.14	0.89	-0.01	0.01
Cocaine_lifetime	34.8%	-0.01	-0.58	0.56	-0.03	0.01
Ampetamine_lifetime	57.5%	0.00	-0.25	0.80	-0.03	0.02
XTC_lifetime	57.9%	0.00	-0.22	0.83	-0.02	0.01
Hallusinogens_lifetime	68.0%	0.00	0.43	0.67	-0.01	0.02
Working_memory	0.0%	0.11	5.31	0.00**	0.07	0.15
Substance_related	0.0%	0.01	0.71	0.48	-0.01	0.03
Task_complexity	0.0%	-0.01	-0.30	0.76	-0.04	0.03
Cue_GNG	0.0%	-0.03	-1.03	0.30	-0.08	0.02
Nogo_percentage	0.0%	-0.05	-3.14	0.00**	-0.07	-0.02
Trial_number	0.0%	0.03	2.17	0.03*	0.00	0.06
Alc*cig	9.2%	-0.01	-1.52	0.13	-0.03	0.00
Alc*can	27.2%	-0.01	-0.69	0.49	-0.03	0.01
Alc*cocaine	30.1%	0.00	0.27	0.79	-0.02	0.03
Alc*amphe	58.1%	0.00	0.03	0.97	-0.03	0.04
Alc*XTC	57.9%	0.00	0.14	0.89	-0.02	0.03
Alc*HALL	68.2%	-0.01	-0.69	0.49	-0.04	0.02
Cig*can	35.3%	0.01	1.01	0.31	-0.01	0.02
Cig*cocaine	40.4%	0.00	-0.56	0.58	-0.02	0.01
Cig*XTC	63.6%	0.00	-0.32	0.75	-0.01	0.01
Can*cocaine	34.9%	0.00	0.34	0.73	-0.01	0.02
Can*amphe	57.8%	0.00	-0.01	0.99	-0.01	0.01
Can*XTC	58.0%	-0.01	-0.64	0.52	-0.02	0.01
Coc*amphe	57.9%	0.00	-0.32	0.75	-0.02	0.01
Coc*XTC	58.1%	0.00	-0.48	0.63	-0.02	0.01
Coc*HALL	68.0%	0.00	-0.14	0.89	-0.02	0.02
Amphe*HALL	68.0%	0.00	-0.68	0.50	-0.02	0.01
Alc*sex	0.0%	-0.01	-0.77	0.44	-0.05	0.02
Cig*sex	8.8%	0.00	-0.19	0.85	-0.01	0.01
Can*sex	29.7%	0.00	-0.12	0.91	-0.01	0.01
Coc*sex	34.8%	0.01	0.86	0.39	-0.01	0.03
Amphe*sex	57.5%	0.00	0.39	0.70	-0.01	0.02
XTC*sex	57.9%	0.00	-0.39	0.69	-0.02	0.01
HALL*sex	68.0%	-0.01	-0.71	0.48	-0.02	0.01
Alc*cig*sex	9.2%	0.01	0.73	0.47	-0.01	0.02
Alc*can*sex	30.1%	0.01	1.46	0.14	0.00	0.03
Alc*cocaine*sex	35.1%	0.00	-0.07	0.94	-0.02	0.02
Alc*amphe*sex	58.1%	-0.01	-0.36	0.72	-0.04	0.03
Alc*XTC*sex	57.9%	0.01	0.82	0.41	-0.01	0.04
Alc*HALL*sex	68.2%	0.00	-0.30	0.76	-0.03	0.03
Cig*can*sex	35.3%	0.00	-0.44	0.66	-0.01	0.01
Cig*cocaine*sex	40.4%	0.01	1.31	0.19	0.00	0.02
Cig*XTC*sex	63.6%	-0.01	-1.07	0.28	-0.02	0.01
Can*cocaine*sex	34.9%	0.00	-0.52	0.60	-0.02	0.01
Can*XTC*sex	58.0%	0.00	0.54	0.59	-0.01	0.02
Co*amphe*sex	57.9%	0.00	0.00	1.00	-0.01	0.01

*Note: *p<0.05, **p<0.01*

Table S4b The full model results and percentage of missing values per variable: GNG go RT

Variables	Missing value%	*β*	*t*	*p*	95% Confidence Interval	
					Lower Bound	Upper Bound
Age	0.0%	11.21	3.48	0.00**	4.90	17.52
Sex	0.0%	-2.33	-0.47	0.64	-12.05	7.38
Education_years	10.9%	-0.74	-0.27	0.78	-6.04	4.56
Alc_Q	0.0%	-3.35	-0.35	0.73	-22.35	15.65
Cig_Q	13.6%	0.41	0.11	0.91	-6.59	7.41
Cannabis_lifetime	30.2%	3.69	0.91	0.36	-4.28	11.65
Cocaine_lifetime	35.5%	-2.73	-0.51	0.61	-13.26	7.81
Ampetamine_lifetime	59.0%	3.39	0.59	0.56	-7.91	14.70
XTC_lifetime	59.2%	-1.27	-0.31	0.76	-9.29	6.74
Hallusinogens_lifetime	69.4%	4.40	0.94	0.35	-4.84	13.63
Working_memory	0.0%	126.53	2.82	0.00**	38.55	214.51
Substance_related	0.0%	5.33	0.86	0.39	-6.77	17.42
Task_complexity	0.0%	-15.44	-0.40	0.69	-90.50	59.61
Cue_GNG	0.0%	-23.54	-0.43	0.67	-130.63	83.56
Nogo_percentage	0.0%	102.02	3.18	0.00**	39.14	164.90
Trial_number	0.0%	-60.57	-1.77	0.08†	-127.56	6.43
Alc*cig	14.0%	-2.09	-0.48	0.63	-10.70	6.51
Alc*can	30.6%	3.37	0.67	0.50	-6.51	13.25
Alc*cocaine	35.7%	5.07	0.77	0.44	-7.82	17.95
Alc*amphe	59.3%	-1.08	-0.12	0.91	-19.28	17.12
Alc*XTC	59.2%	-5.37	-0.75	0.45	-19.48	8.75
Alc*HALL	69.6%	5.27	0.69	0.49	-9.82	20.36
Cig*can	39.0%	2.24	0.69	0.49	-4.14	8.63
Cig*cocaine	44.2%	1.41	0.45	0.65	-4.68	7.50
Cig*XTC	68.1%	1.22	0.40	0.69	-4.72	7.16
Can*cocaine	35.5%	-3.78	-0.86	0.39	-12.45	4.89
Can*amphe	59.0%	7.61	1.56	0.12	-1.99	17.21
Can*XTC	59.3%	1.72	0.44	0.66	-5.91	9.36
Coc*amphe	59.2%	-4.02	-0.88	0.38	-13.01	4.97
Coc*XTC	59.4%	1.13	0.27	0.79	-7.02	9.28
Coc*HALL	69.4%	-5.31	-1.07	0.28	-15.04	4.42
Amphe*HALL	69.4%	4.70	1.11	0.27	-3.63	13.02
Alc*sex	0.0%	-5.29	-0.54	0.59	-24.48	13.90
Cig*sex	13.6%	0.26	0.08	0.94	-6.14	6.65
Can*sex	30.2%	1.18	0.32	0.75	-5.97	8.33
Coc*sex	35.5%	-7.37	-1.32	0.19	-18.34	3.61
Amphe*sex	59.0%	-2.13	-0.42	0.67	-12.06	7.80
XTC*sex	59.2%	-1.48	-0.37	0.71	-9.28	6.32
HALL*sex	69.4%	7.38	1.43	0.15	-2.78	17.53
Alc*cig*sex	14.0%	-1.85	-0.41	0.68	-10.72	7.02
Alc*can*sex	30.6%	2.19	0.44	0.66	-7.66	12.03
Alc*cocaine*sex	35.7%	2.10	0.33	0.74	-10.32	14.51
Alc*amphe*sex	59.3%	-3.41	-0.37	0.71	-21.57	14.75
Alc*XTC*sex	59.2%	-1.32	-0.18	0.85	-15.45	12.81
Alc*HALL*sex	69.6%	-2.63	-0.34	0.73	-17.70	12.44
Cig*can*sex	39.0%	1.19	0.40	0.69	-4.66	7.03
Cig*cocaine*sex	44.2%	3.12	0.99	0.32	-3.07	9.31
Cig*XTC*sex	68.1%	-0.43	-0.14	0.89	-6.30	5.45
Can*cocaine*sex	35.5%	-2.27	-0.50	0.62	-11.13	6.59
Can*XTC*sex	59.3%	3.73	1.07	0.29	-3.13	10.58
Coc*amphe*sex	59.2%	-2.77	-0.65	0.52	-11.17	5.63

*Note: †0.05<p<0.1, *p<0.05, **p<0.01*

Table S4c The full model results and percentage of missing values per variable: SST SSRT

Variables	Missing value%	β	t	p	95% Confidence Interval	
					Lower Bound	Upper Bound
Sex	3.40%	-3.81	-1.19	0.23	-10.09	2.47
Age	0.00%	12.95	5.92	0.00**	8.66	17.24
Education_years	14.20%	-9.7	-5.15	0.00**	-13.39	-6.01
Alc_Q	5.40%	-0.57	-0.18	0.86	-6.84	5.7
Cig_Q	5.40%	2.15	0.89	0.38	-2.61	6.92
Cannabis_lifetime	44.30%	6.21	1.41	0.16	-2.44	14.86
Cocaine_lifetime	51.30%	3.41	0.7	0.48	-6.13	12.95
XTC_lifetime	82.50%	-1.9	-0.81	0.42	-6.53	2.73
SST_version	0.00%	-27.16	-2.06	0.04*	-53.02	-1.3
SSD	0.00%	-39.51	-2.19	0.03*	-74.92	-4.1
SSRT_computation	0.00%	-3.82	-0.47	0.64	-19.62	11.98
Trial_number	0.00%	-17.49	-2.38	0.02*	-31.92	-3.07
Nogo_percentage	0.00%	-6.56	-1.07	0.29	-18.63	5.52
Alc*cig	8.60%	2.6	1.05	0.3	-2.28	7.48
Alc*cannabis	48.30%	-4.56	-0.85	0.39	-15.08	5.96
Alc*cocaine	53.60%	9.75	1.88	0.06†	-0.46	19.96
Alc*MDMA	82.50%	-0.3	-0.1	0.92	-6.32	5.72
Alc*sex	7.10%	-1.25	-0.43	0.67	-7.02	4.51
Cig*cannabis	49.10%	-1.91	-0.75	0.45	-6.9	3.09
Cig*cocaine	55.10%	-5.05	-1.73	0.08†	-10.8	0.69
Cig*MDMA	83.20%	0.81	0.4	0.69	-3.22	4.85
Cig*sex	7.10%	0.3	0.13	0.9	-4.26	4.85
Can*sex	47.20%	3.02	0.74	0.46	-4.96	11
Can*cocaine	56.40%	3.76	1.03	0.3	-3.4	10.91
Coc*sex	54.30%	-4.74	-1.29	0.2	-12	2.52
Cocaine*XTC	82.50%	-0.51	-0.23	0.81	-4.83	3.8
XTC*sex	83.40%	-0.64	-0.34	0.73	-4.33	3.05
Alc*cig*sex	10.30%	-0.72	-0.29	0.77	-5.65	4.22
Alc*cannabis*sex	49.60%	-0.12	-0.02	0.98	-12.22	11.97
Alc*cocaine*sex	55.00%	-1.94	-0.39	0.7	-11.84	7.96
Alc*XTC*sex	83.40%	-0.87	-0.31	0.76	-6.46	4.72
Cig*cannabis*sex	50.50%	-4.58	-1.76	0.08†	-9.72	0.55
Cig*cocaine*sex	56.50%	-0.81	-0.27	0.78	-6.63	5.01
Cig*XTC*sex	84.00%	-0.42	-0.22	0.83	-4.21	3.38
Can*cocaine*sex	59.30%	6.66	1.93	0.05*	-0.13	13.45
Cocaine*XTC*sex	83.40%	-0.69	-0.34	0.74	-4.73	3.35

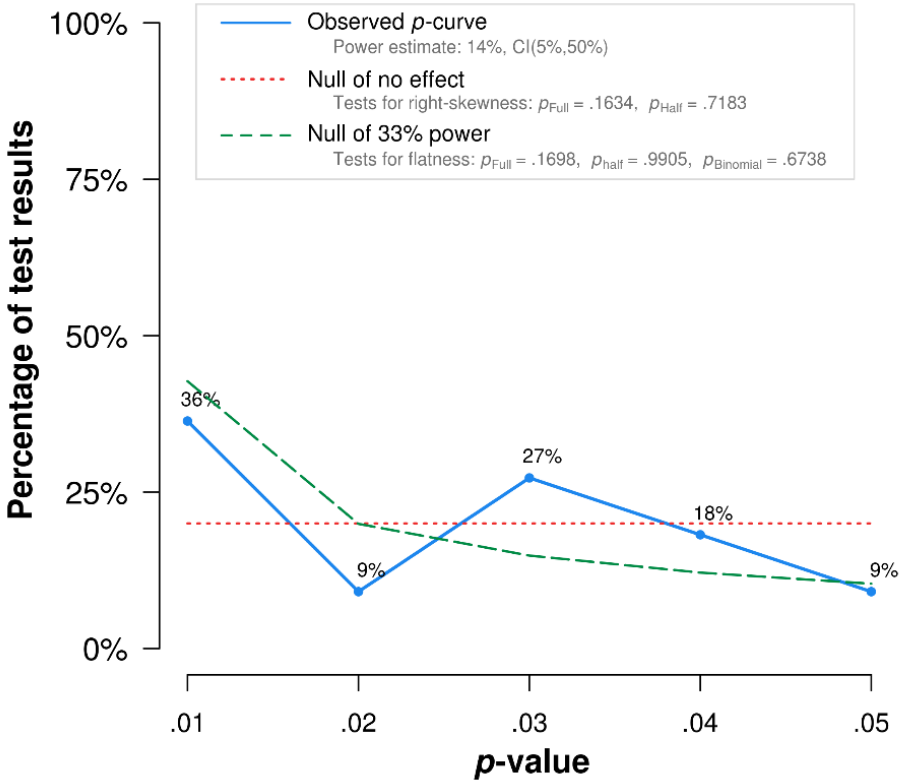
*Note: †0.05<p<0.1, *p<0.05, **p<0.01*

Table S4d The full model results and percentage of missing values per variable: SST go RT

Variables	Missing value%	β	t	p	95% Confidence Interval	
					Lower Bound	Upper Bound
Age	0.00%	32.55	6.96	0.00**	23.39	41.71
Sex	3.6%	-2.05	-0.35	0.73	-13.58	9.47
Education_years	11.5%	-14.11	-3.54	0.00**	-21.91	-6.30
Alc_Q	5.7%	-3.12	-0.30	0.76	-23.31	17.07
Cig_Q	5.7%	-2.10	-0.42	0.68	-11.99	7.79
Cannabis_lifetime	41.5%	2.14	0.29	0.77	-12.34	16.63
Cocaine_lifetime	50.6%	-0.95	-0.12	0.91	-16.96	15.07
XTC_lifetime	81.6%	0.44	0.10	0.92	-8.25	9.12
SSRT_comput	0.00%	48.25	1.47	0.14	-16.15	112.65
SST_version	0.00%	41.99	0.91	0.36	-48.47	132.45
Nogo_percentage	0.00%	-4.33	-0.21	0.84	-45.15	36.49
Trial_number	0.00%	-31.25	-1.06	0.29	-89.14	26.64
Alc*cig	9.0%	0.44	0.10	0.92	-8.68	9.57
Alc*cannabis	45.7%	1.39	0.13	0.90	-20.27	23.04
Alc*cocaine	53.0%	2.59	0.19	0.85	-24.76	29.93
Alc*sex	7.5%	1.05	0.10	0.92	-18.79	20.89
Alc*XTC	81.6%	-1.18	-0.20	0.84	-12.72	10.36
Cig*cannabis	46.6%	1.74	0.40	0.69	-6.87	10.35
Cig*cocaine	54.6%	-9.50	-1.92	0.06†	-19.22	0.21
Cig*sex	7.5%	4.20	0.87	0.38	-5.27	13.66
Cig*XTC	82.2%	0.83	0.19	0.85	-7.64	9.30
Can*cocaine	54.1%	-3.80	-0.63	0.53	-15.68	8.07
Can*sex	44.5%	-1.46	-0.21	0.83	-15.03	12.12
Coc*sex	53.8%	2.14	0.30	0.76	-11.69	15.96
Cocaine*XTC	81.6%	2.23	0.49	0.63	-6.73	11.20
MDMA*sex	82.5%	-0.60	-0.14	0.89	-8.90	7.69
Alc*cig*sex	10.9%	3.04	0.68	0.49	-5.69	11.78
Alc*cannabis*sex	47.1%	5.36	0.48	0.63	-16.46	27.19
Alc*cocaine*sex	54.5%	6.04	0.41	0.68	-22.70	34.79
Alc*XTC*sex	82.5%	0.70	0.12	0.91	-11.27	12.67
Cig*cannabis*sex	48.0%	-0.47	-0.10	0.92	-9.37	8.44
Cig*cocaine*sex	56.1%	0.87	0.17	0.87	-9.30	11.04
Cig*XTC*sex	83.2%	-1.45	-0.35	0.72	-9.52	6.62
Can*cocaine*sex	57.1%	-6.08	-1.04	0.30	-17.57	5.42
Cocaine*XTC*sex	82.5%	-2.89	-0.68	0.50	-11.31	5.52

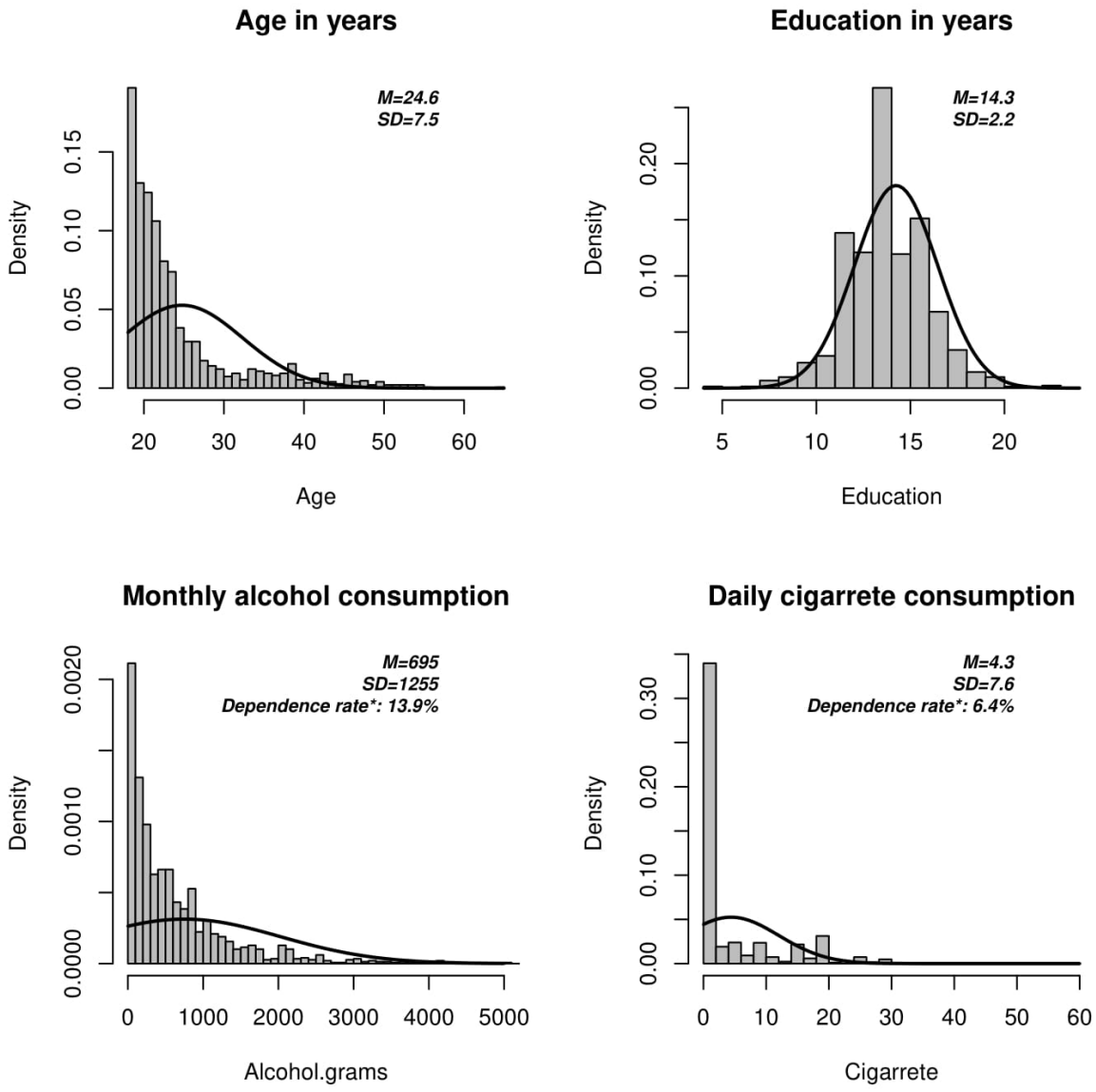
*Note: $^{\dagger}0.05<p<0.1$, *$p<0.05$*

Figure S1: P-curve on the significant association between substance use and response inhibition.



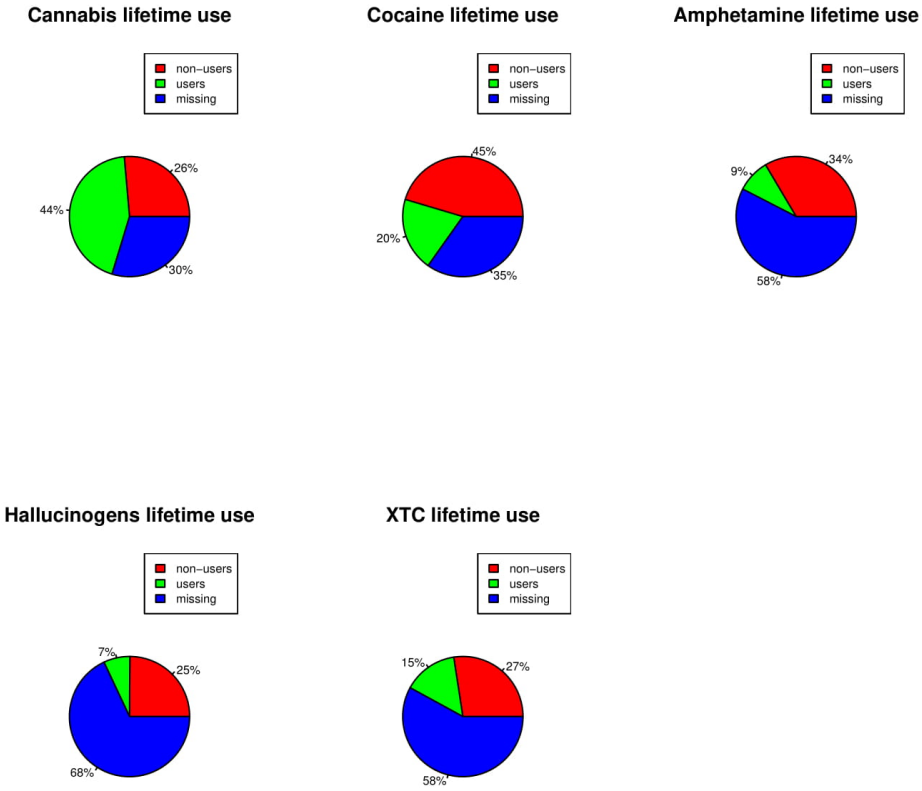
Note: The observed *p*-curve includes 11 statistically significant ($p < .05$) results, of which 8 are $p < .025$. There were 20 additional results entered but excluded from *p*-curve because they were $p > .05$.

Figure S2a: Histograms of demographics and continuous variables of substance use in GNG: commission error rate



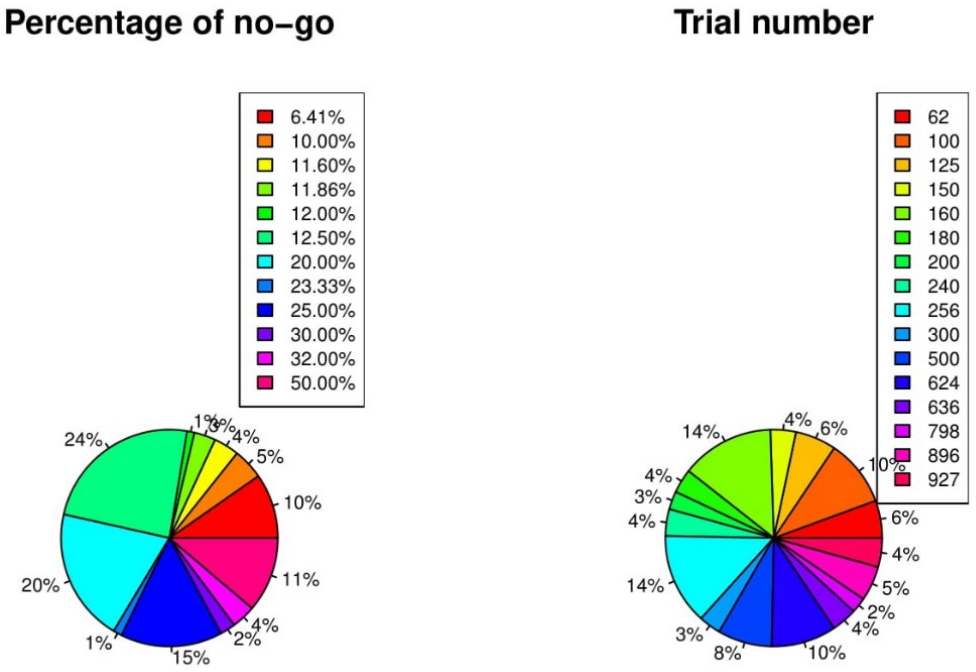
**Alcohol dependence was roughly evaluated through DSM-5, alcoholics reported in the original paper or an AUDIT (Alcohol Use Disorders Identification Test) score higher than 16; Tobacco dependence was roughly evaluated if FTND (Fagerstrom Test for Nicotine Dependence) was above 5. This plot is based on raw data provided before imputation.*

Figure S2b: Pie charts of discrete variables of substance use in GNG: commission error rate



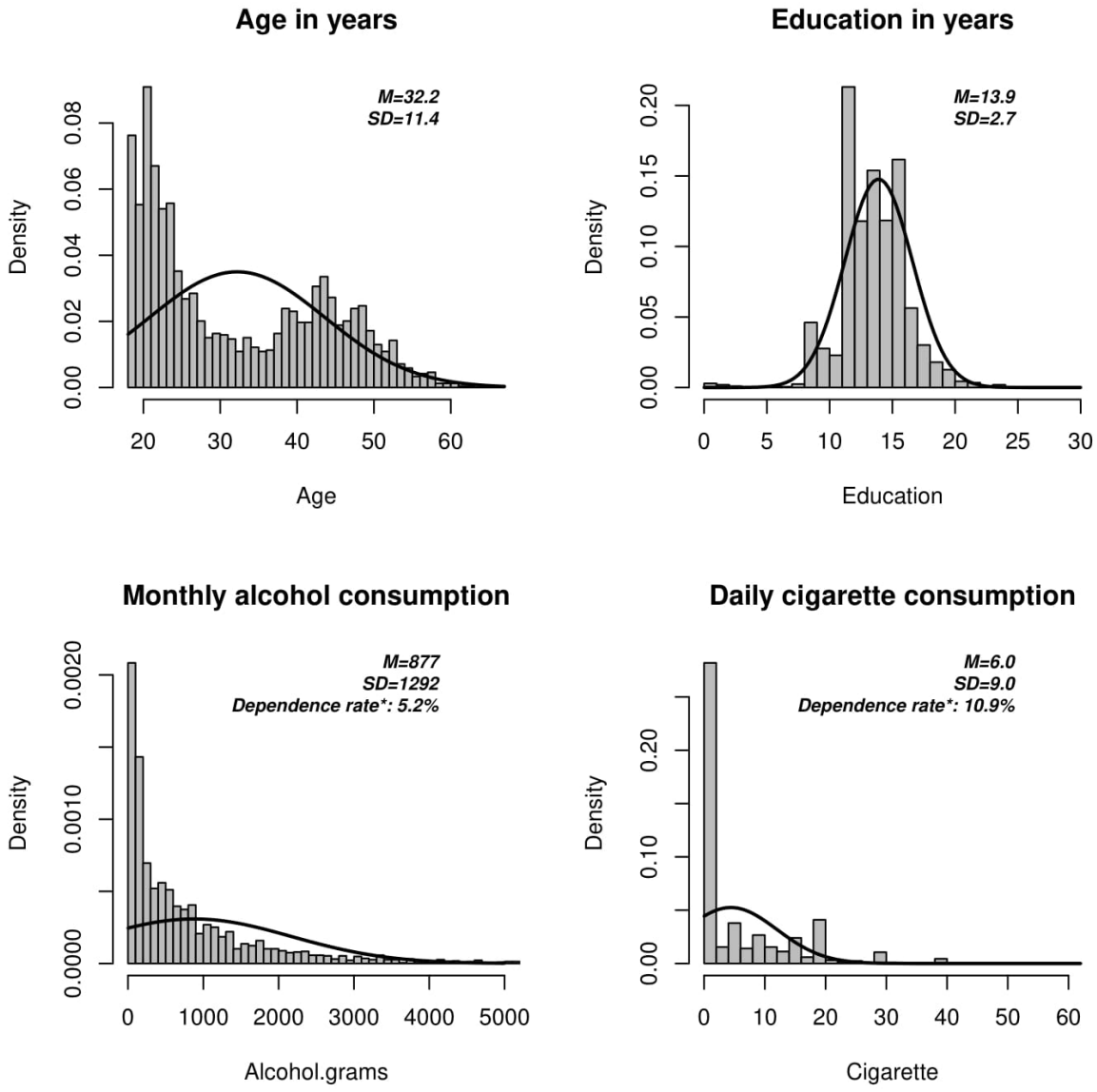
*****_This plot is based on raw data provided before imputation._

Figure S2c: Pie charts of task parameters in GNG: commission error rate



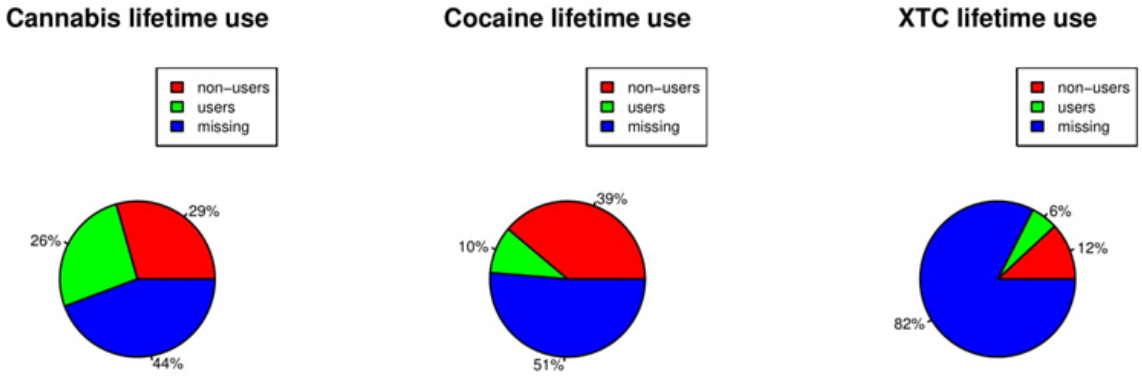
**This plot is based on raw data provided before imputation, and there was no missing data.*

Figure S3a: Histograms of demographics and continuous variables of substance use in SST: SSRT



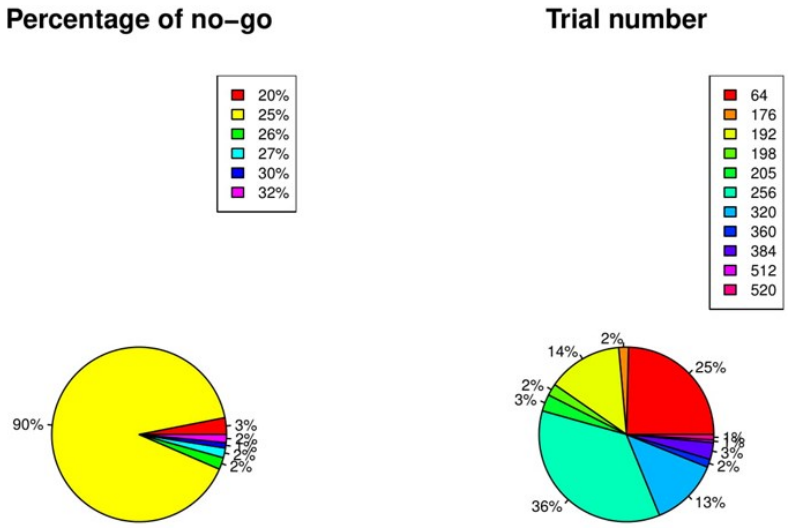
**Alcohol dependence was roughly evaluated if the AUDIT (Alcohol Use Disorders Identification Test) score was higher than 16; Tobacco dependence was roughly evaluated if FTND (Fagerstrom Test for Nicotine Dependence) was above 5. This plot is based on raw data provided before imputation.*

Figure S3b: Pie charts of discrete variables of substance use in SST: SSRT



** This plot is based on raw data provided before imputation.*

Figure S3c: Pie charts of task parameters in SST: SSRT



** This plot is based on raw data provided before imputation, and there was no missing data.*

S1: Demographics and task parameters (detailed Introduction and Discussion)

Introduction

Sex

For a single study, it is hard to investigate the effect of sex due to the often disproportionate ratio of male and female substance users. For instance, out of the 62 studies in Stavro and colleagues' meta-analysis on alcoholism and cognitive deficits, 40% sampled only males, 19% assessed both males and females at a comparable rate and 5% studied female-only samples (Stavro et al., 2013).

Sex may, however, relate to response inhibition. Research about sex differences in response inhibition produced mixed results (Weafer & de Wit, 2014). Some found females outperformed males (Sjoberg & Cole, 2018). Some other studies reported no sex difference in behavioral outcomes (i.e. SSRT) but show differential brain activation (e.g., globus pallidus, thalamus, bilateral medial frontal cortex and cingulate cortex, and parahippocampal gyrus) related to response inhibition (Li, Huang, Constable, & Sinha, 2006; T. P. White et al., 2014).

Furthermore, sex may moderate the association between substance use and inhibition (Fattore & Melis, 2016). Taking alcohol studies as an example, the effect of alcohol on inhibition was reported to be most pronounced in females (Nederkoorn, Baltus, Guerrieri, & Wiers, 2009; Smith, Iredale, & Mattick, 2016; Smith & Mattick, 2013). However, other studies reported no main effect of sex nor interactions between sex and substance use on response inhibition (Henges & Marczinski, 2012; López-Caneda et al., 2012; Rossiter, Thompson, & Hester, 2012; van der Plas, Crone, van den Wildenberg, Tranel, & Bechara, 2009). In the current study, therefore, we included main and moderating effects of sex on the relationship between substance use and response inhibition.

Age & education years

A second demographic variable that should be controlled for is age, as inhibition performance typically shows an inverted U-shaped curve across the lifespan (Williams, Ponesse, Schachar, Logan, & Tannock, 1999), with a peak during young adulthood. As the studies in our mega-analysis only include adults, we included age as a continuous linear variable. In addition, education level also has a substantial effect on inhibitory performance, with middle to highly educated participants performing better (e.g., Stroop Color and Word Test, van Hooren et al., 2007). Therefore, education level was also taken into account in the present study.

GNG task characteristics

In order to aggregate data over studies, we should account for six task characteristics that may affect inhibition and differ between studies. First, no-go percentages in the GNG task vary largely between studies. There is a debate about whether inhibition is required in equiprobable GNG tasks, where responding and non-responding is required to an equal extent (Aron, Robbins, & Poldrack, 2014; Wessel, 2018). In line with Smith and colleagues (2014), we included these studies into our analysis while controlling for no-go percentage. Second, the number of trials differed a lot between studies, ranging from 40 to 600 in Metin and

colleagues' meta-analysis on ADHD (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012). The number of trials, however, could negatively impact the reliability of the outcome if there are too few, and induce fatigue effects if there are too many. Third, tasks also vary in working memory load. Working memory is taxed when the go and no-go signals are conditional. For instance, Luijten and colleagues (2015) required participants to press a button in response to letters (go trials) but to inhibit if the same letter was repeated (no-go trials). Here, the letter shown on the last trial should be stored in memory and updated continuously. Therefore, the main effect of working memory load of the task was considered. Fourth, studies also differed in whether the task context was substance-related or not. The GNG used in addiction research sometimes contains substance-related stimuli that are response-related (e.g., issue a response to non-alcohol-related pictures and inhibit responses to alcohol-related stimuli, Ames et al., 2014) or task-irrelevant (e.g., background consisting of smoking-related pictures and non-smoking-related pictures, Luijten, Littel, & Franken, 2011). According to the incentive sensitization theory of addiction, brain reward systems are hypersensitive to drugs and drug-associated stimuli (Robinson & Berridge, 1993, 2003). Consequently, the global response inhibition deficits in substance abusers would be especially pronounced when confronted with substance-associated stimuli (Zack et al., 2011). The main effect of this task characteristic rather than its interaction with substance was taken into account as incentive sensitization has been related to addiction in general and there are too few studies included to break it up for different substances (see Method). Fifth, GNG may include a cue predicting a go or no-go stimulus. Here, the urgency of inhibition is increased if the cue incorrectly predicts a go stimulus (Hendershot et al., 2015). Therefore, we took into account whether the task was cued or not. Finally, the level of task complexity also varied among studies with variations of stimulus-response (S-R) mappings. A design with only one go stimulus and one no-go stimulus is fairly easy, but it is harder if two or more stimuli are associated with either a go or an inhibition instruction. The main effect of this task characteristic was therefore included.

SST characteristics

Similarly, five task characteristics that varied between SST studies might affect task performance. These include the number of experimental trials, stop-trial percentage, stop-signal delay settings, stop-signal modality, and SSRT calculation method. First, the number of trials used in the SST is highly inconsistent across studies, ranging from 96 to 1920 (review: Alderson, Rapport, & Kofler, 2007). This broad range obscured interpretations concerning the origin of performance differences, i.e., whether they reflected deficient response inhibition, an inability to sustain attention or both (Alderson et al., 2007). Second, stop signal probability varied between studies, which may affect go RT (Lansbergen, Böcker, Bekker, & Kenemans, 2007). Third, stop-signal modality varied. Studies traditionally use either visual go stimuli (e.g., "X" and "O") coupled with an auditory tone as the stop signal, or visual go and stop signal stimuli (Rubia, Oosterlaan, Sergeant, Brandeis, & Leeuwen, 1998). Auditory stop signals compared to visual stop signals shortened the stopping latency, as stop tones are perceived as more intense than visual stop signs (van der Schoot et al., 2005) Fourth, stop-signal delay (SSD, the interval between the onset of the go signal and the onset of the stop

signal) varied. Basically, there are two procedures for determining the SSD. The fixed method uses a variety of fixed delays whereas the staircase tracking procedure adjusts the SSD as a function of inhibition success (Levitt, 1971). With fixed SSDs, participants are likely to delay their go response in anticipation of a stop signal (Logan, Schachar, & Tannock, 1997). In addition, although these two procedures evoked similar neural activities for successful inhibition, individual differences were more pronounced for fixed SSD (Fauth-Bühler et al., 2012). Fifth, SSRT calculation varied. Several methods for estimating SSRT are described in the literature (Logan, 1994), with the integration method currently considered the most reliable procedure (Verbruggen & Logan, 2009). We, therefore, controlled for these five variables by including them as main effects in the analysis.

Discussion

In addition to the analyses of the primary (substance) predictors, the current mega-analysis also found relationships between inhibition variables and demographics. First, age showed opposite effects in the two tasks, indicating better inhibition in the GNG with age and poorer inhibition in the SST. Although this may at first be surprising, it points to the fundamentally different processes assessed with these two tasks: action restraint with the GNG and action cancellation with the SST. In the GNG, this age-related increase in accuracy is most likely due to the strategic slowing of responses, which was confirmed by longer go RTs we found. In the SST, older people need a longer time to cancel their initiated action, in line with previous findings (Keilp, Sackeim, & Mann, 2005). In addition, higher educated people demonstrated better inhibition in both tasks. An indirect reason is that high education level is related with the high intellectual ability (Deary, Penke, & Johnson, 2010), which is related to strong inhibitory control (Macapagal, Janssen, Fridberg, Finn, & Heiman, 2011). In terms of sex, no main effect nor interaction with substance use was significant. This is in line with the broader picture of rather weak sex differences in executive functions such as cognitive control (van der Plas et al., 2009), with exceptions for mental rotation (Garavan, Hester, Murphy, Fassbender, & Kelly, 2006) and fine motor tasks (Nicholson & Kimura, 1996). The absence of an interaction effect seems to contrast with the findings that females are more susceptible to the effects of substance use (Nederkoorn et al., 2009; Smith et al., 2016; Smith & Mattick, 2013). Yet, these studies mainly focused on alcohol use, studies considered multiple substances by sex interactions was rarely documented. Factors such as age (adolescents vs. young adults), the severity of use (with/without a diagnosis of SUD), abstinence that might moderate the substance by sex interaction can be considered in the future (Fattore & Melis, 2016).

In GNG, increased working memory demands resulted in more commission errors (Simmonds, Pekar, & Mostofsky, 2008), which is a likely result of a larger number of S-R associations that have to be kept in working memory. Our results also showed that the higher the no-go percentage, the lower the commission error rates: when the stop probability is low, there is strong readiness to give a response, which makes it difficult to stop (Donkers & van Boxtel, 2004). In addition, the number of experimental trials also played a role, with more trials inducing higher commission error rates, likely due to task-related fatigue. In addition, a

somewhat surprising finding was that a modified substance-related task did not differ in results from the typical tasks using neutral stimuli. This would be in line with a recent meta-analysis, which showed that when publication bias was corrected, exposure to alcohol-related cues did not significantly impair response inhibition among alcohol users (Jones, Duckworth, Kersbergen, Clarke, & Field, 2018). However, note that in the current study only 5 out of 23 studies included used a substance-related version, and therefore power was low. In the SST, visual stop signals induced longer SSRT compared to auditory stop signals (in line with Ramautar, Kok, & Ridderinkhof, 2006). One explanation is that the neural pathway for sound perception is shorter than that for visual perception (Elliott, 1968; Goldstone, 1968; Woodworth & Schlosberg, 1954). Alternatively, stop tones are perceived as more intense than visual stop signals (van der Schoot et al., 2005). In addition, in contrast to GNG findings, in the SST a larger number of trials led to shorter SSRTs. Practice effects might play a role, given that previous research has indicated that practicing SST indeed improved performance (Manuel, Bernasconi, & Spierer, 2013). Furthermore, compared to the staircase-tracking procedure, fixed SSDs resulted in longer SSRT. Based on direct comparisons, the tracking procedure is recommended (Verbruggen & Logan, 2009).

S2: Analyses of the effect of study type (behavioral/EEG/fMRI)

We performed two extra analyses to make sure study type (behavioral/EEG/fMRI) did not systematically influence behavioral performance (i.e., SSRT and commission rate).
In the first extra analysis, we added the variable 'research type' as a fixed effect in the original full model, followed by 100 imputations of missing values, then backward elimination based on *p*-values. This analysis procedure is exactly the same as what we have reported in the main analysis.

For the GNG commission error rates, in the initial full model with 52 variables, the effect of 'research type' was not significant (β = 0.01, p = 0.69, 95% CI [-0.050, 0.07]). In the stepwise elimination, it was removed from the model at the 9nd step (β = 0.01, p = 0.70, 95% CI [-0.05, 0.07]).

For SSRT, in the initial full model with 37 variables, the effect of 'research type' was not significant (β = -16.80, p = 0.11, 95% CI [-37.27, 3.58]). During stepwise elimination, it was removed from the model at the 22nd step (β = -17.87, p = 0.08, 95% CI [-37.82, 2.09]).

S3: Optional variables list

Demographic Variables:

☐ Country where study took place ☐ Race/Ethnicity

☐ Education (the highest level, if student sample please signify)

☐ Beck Depression Inventory ☐ State Trait Anxiety Inventory (trait/ state)

☐ Special populations involved? (e.g., ADHD, ODD/CD, Drug-dependent, intellectually challenged)

☐ other information collected, please explain

Alcohol:

☐ age of onset: ☐ years of use ☐ AUDIT score ☐ SADQ score

☐ Binge drinking score ☐ DSM-IV or DSM IIIR score on alcohol

☐ Craving for alcohol(Alcohol Urge Questionnaire)

☐ other information collected, please explain

Tobacco:

☐ age of onset

☐ Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)

☐ Subscales of Shiffman/JavikWithdrawal Scale

☐ Fagerström Test for Nicotine Dependence(FTND)

☐ other information collected, please explain

Cannabis

☐ Cannabis Use Disorder Identification Test - Revised (CUDIT-R)

☐ daily use of cannabis

☐ other information collected, please explain

Other drug use

☐ MDMA ☐ Opioids ☐ Methamphetamine

☐ Khat ☐ Amphetamine ☐ Hallucinogens ☐ Barbiturates

☐ Marijuana ☐ Cocaine

☐ other information collected, please explain

S4: Analyses of speed-accuracy trade-off in GNG

Speed-accuracy trade-off is a potential problem in GNG. In fact, in addition to analyzing commission error rates and go RT in GNG separately, we also analyzed their combined score. A balanced integration score (BIS) was calculated by subtracting the standardized go RT from the standardized correct response proportions according to Liesefeld and Janczyk (2019), a higher score thus indicating better performance. Similar analysis procedures as those reported in the main text were applied to BIS. Predictors in the final model included education years (β = 0.05, p = 0.04, 95% CI [0.003, 0.09]), no-go percentage (β = -0.40, p = 0.02, 95% CI [-0.56, -0.23]), and working memory load (β = -1.1, p < 0.01, 95% CI [-1.32, -0.88]). This indicated that higher educated people had better performance, lower no-go percentage induced better performance, and without working memory load produced better performance. All directions are as expected.

S5: Analyses of the effect of 'number of substances used' in the model

According to Kaag and colleagues (2017), a sum score of the number of substances used was calculated based on the imputed data. Then a multilevel regression analysis was conducted with predictors of demographics, task parameters, this sum score and its interaction with sex. In GNG, similarly, number of substance of use was not a predictor of commission error rates (β = -0.002, p = 0.68, 95% CI [-0.01, 0.01]), nor was its interaction with sex (β = -0.001, p = 0.83, 95% CI [-0.01, 0.01]). In the SST, this variable did not significantly predict SSRT (β = 3.63, p = 0.08, 95% CI [-0.48, 7.74]) nor did its interaction with sex (β = -0.91, p = 0.60, 95% CI [-4.32, 2.50]).

S6: Effect of interactions 'alcohol×demographics' & 'alcohol×task parameters'

We performed an extra analysis to explore the possible moderation effect of demographics and task parameters in the relationship between substance use and inhibition. As alcohol use was the most complete substance-related variable, as a first step, we tested its interactions with demographics (e.g., alcohol×age) and task parameters (e.g., alcohol×no-go percentage) for both tasks. The analysis procedure was similar to that of the main analysis.

We found that none of these interaction variables survived the stepwise elimination.

In the GNG commission error rate, predictors remained in the final model included working memory (β = 0.10, p < 0.01, 95% CI [0.07, 0.13]), age (β = -0.02, p < 0.01, 95% CI [-0.03, -0.01]), no-go percentage (β = -0.04, p < 0.01, 95% CI [-0.07, -0.02]), trial number (β = 0.04, p = 0.002, 95% CI [0.02, 0.07]), alcohol×age (β = 0.01, p = 0.02, 95% CI [0.001, 0.02]) and alcohol (β = -0.005, p = 0.30, 95% CI [-0.01, 0.004]). Post-hoc test revealed that for light drinkers, older people made less commission errors (β = -0.02, t = -2.56, p = 0.01). This relationship was absent among heavy drinkers (β = -0.01, t = -1.50, p = 0.14). In addition, the effect of alcohol use was not significant either within the younger subsample (β = 0.003, t = 0.64, p = 0.52) nor within the older subsample (β = -0.002, t = -0.20, p = 0.84).

In the SST/SSRT, predictors reserved in the final model were age (β = 13.61, p < 0.01, 95% CI [9.45, 17.77]), education years (β = -9.64, p < 0.01, 95% CI [-13.24, -6.04]), cannabis (β = 6.52, p = 0.01, 95% CI [1.31, 11.74]), tobacco×cannabis×sex (β = -4.16, p = 0.03, 95% CI [-

7.97, -0.36]), number of trials (β = -16.35, p = 0.04, 95% CI [-31.76, -0.94]), tobacco (β = 3.74, p = 0.04, 95% CI [0.19, 7.28]), tobacco×cannabis (β = -3.22, p = 0.11, 95% CI [-7.16, 0.73]), cannabis×sex (β = -1.48, p = 0.52, 95% CI [-6.00, 3.04]), sex (β = -0.86, p = 0.59, 95% CI [-4.00, 2.28]), tobacco×sex (β = 0.56, p = 0.73, 95% CI [-2.66, 3.78]). Post-hoc analysis of this three-way interaction tobacco×cannabis×sex revealed that only for males, the interaction between tobacco and cannabis was significant (β = -5.41, p = 0.03, 95% CI [-10.38, -0.45]). Furthermore, it was found that, only for male non-cannabis users, tobacco use was positively associated with SSRT (β = 8.76, t = 2.78, p = 0.005).

S7: List of studies provided raw data but were not included (plus reasons)

Baldacchino, A., Balfour, D. J. K., & Matthews, K. (2015). Impulsivity and opioid drugs: differential effects of heroin, methadone and prescribed analgesic medication. *Psychological medicine*, *45*(6), 1167-1179. *(Affective GNG was used.)*

Behan, B., Connolly, C. G., Datwani, S., Doucet, M., Ivanovic, J., Morioka, R., ... & Garavan, H. (2014). Response inhibition and elevated parietal-cerebellar correlations in chronic adolescent cannabis users. *Neuropharmacology*, *84*, 131-137. *(Monthly alcohol use in grams unavailable.)*

Berkman, E. T., Falk, E. B., & Lieberman, M. D. (2011). In the trenches of real-world self-control: neural correlates of breaking the link between craving and smoking. *Psychological science*, *22*(4), 498-506. *(Monthly alcohol use in grams unavailable.)*

Choi, J. S., Park, S. M., Roh, M. S., Lee, J. Y., Park, C. B., Hwang, J. Y., ... & Jung, H. Y. (2014). Dysfunctional inhibitory control and impulsivity in Internet addiction. *Psychiatry research*, *215*(2), 424-428. *(No alcohol and tobacco use information.)*

Christiansen, P., Cole, J. C., Goudie, A. J., & Field, M. (2012). Components of behavioural impulsivity and automatic cue approach predict unique variance in hazardous drinking. *Psychopharmacology*, *219*(2), 501-510. *(No tobacco use information)*

Colder, C. R., & O'connor, R. (2002). Attention bias and disinhibited behavior as predictors of alcohol use and enhancement reasons for drinking. *Psychology of Addictive Behaviors*, *16*(4), 325. *(Participants were too young (13-14 years old).)*

Colzato, L. S., Ruiz, M., van den Wildenberg, W. P. M., Bajo, M. T., & Hommel, B. (2011). Long-term effects of chronic khat use: impaired inhibitory control. *Frontiers in psychology*, *1*, 219. *(No tobacco use information)*

Czapla, M., Simon, J. J., Friederich, H. C., Herpertz, S. C., Zimmermann, P., & Loeber, S. (2015). Is binge drinking in young adults associated with an alcohol-specific impairment of response inhibition? *European addiction research*, *21*(2), 105-113. *(No tobacco use information)*

Fink, B. C., Steele, V. R., Maurer, M. J., Fede, S. J., Calhoun, V. D., & Kiehl, K. A. (2016). Brain potentials predict substance abuse treatment completion in a prison sample. *Brain and behavior*, *6*(8), e00501. (*Participants refrained from alcohol.*)

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S8: Results on go RT in GNG task and SST

GNG

None of the substance-related variables had a significant effect on go RT. Age had a significant effect on go RT (β = 10.01, p < 0.01 , 95% CI [4.45, 15.58]), indicating a longer go RT when age increased. Working memory load had a significant effect on go RT (β = 91.71, p < 0.01, 95% CI [26.03, 157.39]), indicating a longer RT when there is working memory load. Percentage of no-go trials also had a significant effect on go RT (β = 115.94, p < 0.01 , 95% CI [57.15, 174.73]). This indicated that, when the stopping probability is low, there is strong readiness to give a response.

SST

The interaction of cocaine and tobacco smoking significantly predicted go RT (β = -8.19, p = 0.04, 95% CI [-16.05, -0.32]). Neither tobacco (β = -1.77, p = 0.68, 95% CI [-10.11, 6.58]) nor cocaine (β = -1.27, p = 0.82, 95% CI [-12.44, 9.90]) use alone significantly predicted go RT. Post-hoc analyses by splitting the imputed data sets and fitted the same restricted model without the interaction term revealed that for cocaine users, go RT non-significantly decreased as a function of tobacco consumed per day (β = -3.10, t = -0.38, p = 0.71), with an opposite non-significant pattern observed for cocaine non-users (β =4.30 , t = 1.03, p = 0.30). Age (β = 31.44, p < 0.01, 95% CI [22.82, 40.06]) and education years (β = -13.47, p < 0.01, 95% CI [-21.06, -5.88]) had a significant effect on go RT. This indicated that go RT was longer as age increased, and was shorter as education years increased.

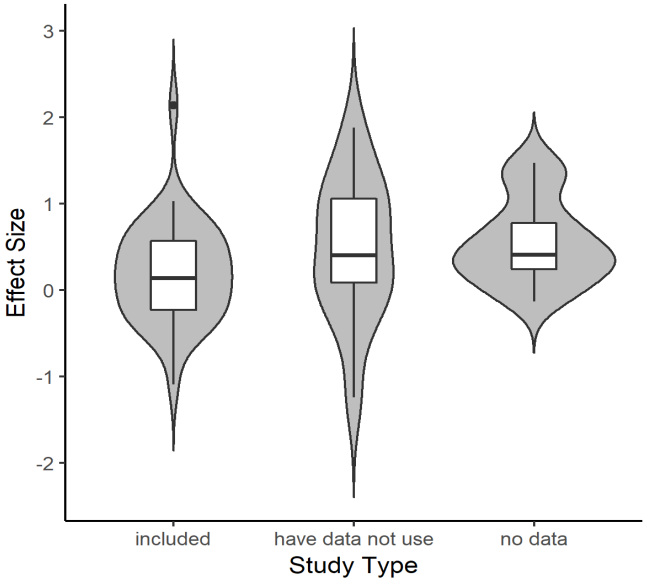
S9: Effect size comparison between studies included and those not included (plus **Fig. S4**)

We calculated and compared the effect sizes of studies included, studies provided data but were not included, and studies that did not provide raw data.
Three online calculators were used:

1) http://www.polyu.edu.hk/mm/effectsizefaqs/calculator/calculator.html (mainly);
2) http://www.campbellcollaboration.org/escalc/html/EffectSizeCalculator-SMD28.php (only use for more than two groups F test, with each groups mean and N);
3) https://www.psychometrica.de/effect_size.html#fvalue (use point 6: ANOVA if only F value and sample size for each group are known; point 13: transformation into Cohen's d)

The one-way ANOVA indicated that there was no significant difference of effect sizes between the three kinds of studies (F (2,69) = 2.60, p = 0.08, **Fig. S4**).

Figure S4 Violin plot: effect size distribution compared between three study types



Chapter 3

“Free won't” after a beer or two: Chronic and acute effects of alcohol on neural and behavioral indices of intentional inhibition

This chapter has been submitted for publication as:

Liu, Y., van den Wildenberg, W. P. M., González, G. F., Rigoni, D., Brass, M., Wiers, R. W., & Ridderinkhof, K. R. “Free won't” after a beer or two: Chronic and acute effects of alcohol on neural and behavioral indices of intentional inhibition.

ABSTRACT

Background

Response inhibition can be classified into stimulus-driven inhibition and intentional inhibition based on the degree of endogenous volition involved. In the past decades, abundant research efforts to study the effects of alcohol on inhibition have focused exclusively on stimulus-driven inhibition. The novel Chasing Memo task measures stimulus-driven and intentional inhibition within the same paradigm. Combined with the stop-signal task, we investigated how alcohol use affects behavioral and psychophysiological correlates of intentional inhibition, as well as stimulus-driven inhibition.

Methods

Experiment I focused on intentional inhibition and stimulus-driven inhibition in relation to lifetime alcohol use. The Chasing Memo task, the stop-signal task, and questionnaires related to substance use and impulsivity were administered to 60 undergraduate students (18-25 years old). Experiment II focused on behavioral and neural correlates acute alcohol use on performance on the Chasing Memo task by means of electroencephalography (EEG). Sixteen young male adults (21-28 years old) performed the Chasing Memo task once under placebo and once under the influence of alcohol (blood alcohol concentration around 0.05%), while EEG was recorded.

Results

In Experiment I, AUDIT (Alcohol Use Disorder Identification Test) total score did not significantly predict stimulus-driven inhibition or intentional inhibition performance. In Experiment II, the placebo condition and the alcohol condition were comparable in terms of behavioral indices of stimulus-driven inhibition and intentional inhibition as well as task-related EEG patterns. Interestingly, a slow negative *readiness potential* (RP) was observed with an onset of about 1.2 s, exclusively before participants stopped intentionally.

Conclusions

These findings suggest that (both lifetime and acute) alcohol use has limited effects on stimulus-driven inhibition and intentional inhibition. The RP might reflect processes involved in the formation of an intention in general.

Background

Imagine having cocktails with friends at a bar during happy hour time, and experiencing a strong urge to order one more. But then you realize that you need to prepare for an important meeting the next morning and you decide to refrain from having another drink. In examples like this, there is no external cue signaling a brake, yet you voluntarily suppress your urge for the sake of other priorities. Here, we refer to this type of cognitive control as intentional inhibition. In the current study, we will investigate how intentional inhibition 1) is associated with typical alcohol use and 2) affected by acute alcohol consumption.

Alcohol Use and Inhibition

Inhibitory control is defined as the ability to control one's attention, behavior, thoughts, and/or emotions and instead do what is more appropriate or needed (Diamond, 2013). This ability enables us to override strong internal predispositions or external lures, and do what is more appropriate or needed. Long-term alcohol use has been associated with structural as well as functional neural deficits that are related to inhibition (Li, Luo, Yan, Bergquist, & Sinha, 2009). For instance, alcohol-dependent patients show selective deficits in prefrontal gray and white matter volume (Pfefferbaum, Sullivan, Mathalon, & Lim, 1997); compared to light drinkers, heavy drinkers were slower to stop inappropriate responses and showed deviant amplitudes of the P3 (a brain potential that correlates with the efficiency of response inhibition, Smith & Mattick, 2013). Despite relatively robust neurological evidence for inhibition deficits, alcohol use severity is not consistently associated with impaired behavioral performance of response inhibition (Bø & Landrø, 2017; Courtney et al., 2012; Papachristou, Nederkoorn, Havermans, van der Horst, & Jansen, 2012). Acute alcohol use (moderate to high dosage), by contrast, was more consistently related with inhibition deficits (Gan et al., 2014; Loeber & Duka, 2009) and reduced amplitudes of inhibition-related brain potentials (Easdon, Izenberg, Armilio, Yu, & Alain, 2005).

Intentional Inhibition

Theoretically, motor inhibition can be classified into stimulus-driven inhibition and intentional inhibition based on the degree of endogenous volition involved (Ridderinkhof, van den Wildenberg, & Brass, 2014). A daily-life example of stimulus-driven inhibition is stopping to a traffic-light that suddenly turns to red. The past decades have seen abundant research efforts exclusively into the effects of alcohol on stimulus-driven inhibition (see reviews: Aragues, Jurado, Quinto, & Rubio, 2011; Smith, Mattick, Jamadar, & Iredale, 2014; Stavro, Pelletier, & Potvin, 2013). However, rather than relying on external cues, deciding independently when and/or whether to abort an action plays an even more important role in daily life (Aron, 2011). Intentional inhibition refers to the capacity to voluntarily suspend or inhibit an about-to-be-executed action at the last moment (Filevich, Kühn, & Haggard, 2012). In terms of drinking, the priming dose effect of alcohol, i.e., loss of control over further

consumption after a priming dosage, reflects the insufficiency of intentional inhibition rather than stimulus-driven inhibition (Field, Wiers, Christiansen, Fillmore, & Verster, 2010).

There have been several attempts to study intentional inhibition using varieties of the Libet task (Brass & Haggard, 2007), the Marble Task (Kühn, Haggard, & Brass, 2009), and the modified go/no-go task (Parkinson, Garfinkel, Critchley, Dienes, & Seth, 2017; Xu, Fan, Li, Qi, & Yang, 2019). To investigate intentional inhibition, these tasks usually included a free-choice condition, where participants were encouraged to act/inhibit voluntarily and roughly equally across all the trials. Such "free choice" design is suboptimal in at least three ways regarding the concept of intentional inhibition. First, the choice between acting and withholding is relatively arbitrary; little (if anything) really hinges on whether the participant decides to act or not on any particular trial. Accordingly, participants might behave in the way that they believe will satisfy the experimenters' definition of volition. Second, participants are subject to substantial time pressure, which may prevent the time-consuming development of spontaneous intentions. Third, participants may pre-decide on whether and when to inhibit ahead of time (even before the start of the trial) rather than on the fly (Schel et al., 2014), even when emphasizing that this is to be avoided. Thus, the study of intentional inhibition may be augmented by using more ecologically valid tasks.

The Present Study

To address these points, a novel task was developed, in which stimulus-driven and intentional inhibition can be measured under comparable conditions that are ecologically more representative (Rigoni, Brass, van den Wildenberg, & Ridderinkhof, *unpublished manuscript*). In the current study, we will investigate if and how alcohol use affects intentional inhibition in two complementary ways. Experiment I focuses on prolonged alcohol use in relation to intentional versus stimulus-driven inhibition with a relatively large sample. The Chasing Memo task, as well as the classic stop-signal task (SST), were administered. Experiment II investigates the behavioral and neural effects of acute alcohol use on the Chasing Memo task performance. Electroencephalographic (EEG) activity was recorded in a smaller sample, with a double-blind, placebo-controlled, within-subject design.

Experiment I

Introduction

The aim of the Experiment I was to test whether typical alcohol use influenced stimulus-driven as well as intentional inhibition. Extensive research into the effects of long-term alcohol use on stimulus-driven inhibition has been documented, but the conclusions are inconsistent. Some researchers found that compared to controls, heavy drinkers showed impaired stopping performance, signified by either longer stop-signal reaction time (SSRT) on the SST (Bø & Landrø, 2017) or higher commission error rates in the go/no-go task (GNG, Kreusch, Quertemont, Vilenne, & Hansenne, 2014; Petit, Kornreich, Noël, Verbanck, &

Campanella, 2012). These findings, however, conflict with a series of other studies. For instance, a meta-analysis of differences between heavy drinkers and controls reported null-effects with respect to inhibitory impairments in 9 out of 12 GNG studies and in 7 out of 9 studies using the SST (Smith et al., 2014). Similarly, in a recent retrospective epidemiological study among 2230 adolescents, longitudinal analyses showed that four years of weekly heavy drinking did not result in impairments in basic executive function, including inhibitory control (Boelema et al., 2015).

In the literature, two types of impulsivity have been discerned that may trigger failures of inhibitory control: 'stopping impulsivity' and 'waiting impulsivity', which rest on largely distinct neural circuits (Dalley & Robbins, 2017; Robbins, Gillan, Smith, de Wit, & Ersche, 2012). 'Stopping impulsivity' refers to impairments in the ability to interrupt an already initiated action, whereas 'waiting impulsivity' refers to impairments in the ability to refrain from responding until sufficient information has been gathered or a waiting interval has elapsed. Stopping and waiting impulsivity have typically been tested in the SST and in the delay discounting task, respectively (Reynolds & Schiffbauer, 2004). In the Chasing Memo task (Rigoni et al., *unpublished manuscript*), participants were asked to use the computer mouse to move the cursor and chase a small fish, called Memo, as it moves across the screen ("swimming" against a nautical background picture). Participants disengaged from visuomotor tracking in response to either an external stop cue (i.e., stimulus-driven inhibition) or at will (i.e., intentional inhibition).

Meanwhile, to supplement and validate the stimulus-driven inhibition component of the new task, the conventional SST was also administered (van den Wildenberg et al., 2006). In addition to laboratory-based tasks, two sets of questionnaires were also administered. The Barratt Impulsiveness Scale (BIS-11, Patton & Stanford, 1995) and Dickman's Impulsivity Inventory (DII, Dickman, 1990) were used to test impulsivity. Substance use was tested by the AUDIT (Alcohol Use Disorder Identification Test, Saunders, Aasland, Babor, de La Fuente, & Grant, 1993), the mFTQ (modified version of the Fagerström tolerance questionnaire, Fagerström, 1978), the CUDIT-R (cannabis use disorder identification test revised, Adamson et al., 2010), and the CORE (the core alcohol and drug survey, Presley, 1993).

The current study focuses on college students, for whom alcohol is one of the most frequently used substances, and it gives rise to unsafe drinking-&-driving behavior and the consumption of other substances (Karam, Kypri, & Salamoun, 2007). Although prior work (as reviewed above) has not yielded consistent results, we tested the hypothesis that higher AUDIT scores were associated with prolonged SSRT (analogous to longer disengage latencies in the cued version of the Chasing Memo task). For intentional inhibition in the Chasing Memo task, we conceived of two opposing scenarios: analogous to stimulus-driven inhibition, long-term alcohol use induces 'stopping impulsivity' and delays intentional disengagement; alternatively, it induces 'waiting impulsivity' and results in faster disengagement times (Dalley & Robbins, 2017). Although the lack of existing studies on alcohol and intentional inhibition prevents us from inferring strong theory-based hypotheses, the present task set-up will allow us to empirically distinguish between them.

Methods

Participants

Eighty-six undergraduate students (10 males) were recruited (age: *Mean* = 20.77, *SD* = 1.86). Inclusion criteria included: 1) between 18-25 years old; 2) no report of head injuries, colorblindness or seizures; 3) no depression; 4) proper mastery of Dutch, as all task instructions and questionnaires were shown in Dutch. Due to incorrect settings of refresh rates on some test computers, we cannot use the Chasing Memo data from a subset of 26 participants. Thus, the analyses of the Chasing Memo task were based on the remaining 60 subjects (6 males, 20.75 ± 2.01 years old).

Questionnaires

The BIS-11 is a 30-item questionnaire designed to assess the personality/behavioral construct of impulsiveness (Patton & Stanford, 1995). The DII included two subscales: functional impulsivity (11 items) and dysfunctional impulsivity (12 items). The AUDIT is a 10-item survey used as a screening instrument for excessive or hazardous alcohol use (Saunders et al., 1993). It covers the domains of recent alcohol consumption (items 1-3), alcohol dependence symptoms (items 4-7), and alcohol-related problems (items 8-10). The mFTQ assesses the level of nicotine dependence among adolescents (Fagerström, 1978). The CUDIT-R was used to identify individuals who have used cannabis in problematic or harmful ways during the preceding 6 months (Adamson et al., 2010). The CORE was originally designed to examine the use, scope, and consequences of alcohol and other drugs in the college settings (Presley, 1993). In the current research, participants were asked to indicate how often within the last year and month they had used each of the 11 types of drugs. Reliability of these questionnaires can be found in Supplementary Materials (see appendix to this chapter).

Behavioral tasks

Chasing Memo task

In this task, an animated fish called Memo is moving ('swimming') at 360 pixels/sec against the background of the bottom of an ocean, changing directions at random angles between 0 and 115 degrees, at intervals between 556 and 1250 ms. The participants' main task was to track the fish by keeping a yellow dot (operated through the computer mouse) within close proximity of Memo (i.e., within a green zone of 2 cm radius surrounding it). Points were earned per second during successful tracking and accumulated points were displayed in the bottom right corner of the screen (tracking points). These points accumulated faster as a linear function of time spent within the green proximity zone. Accumulation rate was indicated to the subject by a red/green bar, which turned from red to green as a function of accurate tracking (see **Fig. 1**). Upon failures to chase Memo (i.e., failing to keep the yellow dot within the green zone), accumulation rates were reset, and accumulation of points would again start slowly as soon as the participant resumed successful tracking and then rise as a function of accurate tracking time. Participants were told that tracking points were

converted to real money, which can yield up to 5 euro extra at the end of the experiment. Thus, participants had a strong immediate incentive motivation to continue accurate tracking.

A circle at the top left corner of the green zone served as the external signal to start and stop tracking. At the beginning of the trial, the circle was colored orange; after a variable delay (between 3 and 6 seconds) it turned blue (*go signal*), indicating that participants can start tracking the target. The specific instructions differed depending on the experimental condition.

In the *cued condition,* participants were instructed to start tracking as fast as possible when the *go signal* appeared (cued engagement) and stop as soon as possible if the circle turned orange again, i.e., the *stop signal* (cued disengagement). Participants were asked to disengage by leaving the mouse completely still in its end position. The trial ended 2 s after tracking disengagement. Within the colored circle, there was a counter with a serial display of digits constituting a number (between 100 and 999). Every 100 ms, that number incremented by 1 until the value of 999 was reached, after which the counter was reset to 100. Participants had to remember the number when the *stop cue* appeared and type in the number by the end of a trial and how confident they were about their answers (from 1 to 7). This is used as the timing accuracy index.

In the *free condition,* participants can freely decide when to start tracking after the *go signal* appeared. After uninterrupted successful tracking for 2 s, a *bonus signal*, signified by a yellow star, was displayed next to the red/green meter (**Fig. 1**). Its appearance signaled the beginning of a 20 s (participants did not know the length) temporal window within which participants were to continue tracking until they felt the urge to stop. Disengagement meant foregoing the immediate reward (increase in normal points) in favor of the future reward (bonus points). The number of bonus points varied between 2 and 50 and was determined by the disengagement moment. Participants were instructed that some variability in their tracking latency (within the margins of not stopping too soon nor too late) would benefit an optimal amount of bonus points. Unbeknownst to the participants, the time at which the star was lost was determined stochastically by drawing randomly from a normal distribution, such that the optimum waiting time was 10 s on average; prolonged tracking would be highly beneficial on some trials but highly detrimental on others. Within each block of the *free condition*, bonus points were accumulated across trials and converted into extra time (one second per earned bonus point) for tracking in a later *bonus trial*. In a *bonus trial*, participants can earn tracking-points 4 times as fast as that in a regular trial. Thus, more bonus points result in a higher total of tracking-points (and hence in greater earnings). In order to prevent undesirable response tendencies, participants were instructed and trained to follow their urge rather than preplan their time of disengagement or use external cues (such as spatial position or counter value) to determine the time of disengagement. As in the *cued condition*, participants now had to register and report the number of this counter at the time they first felt the urge (or conscious intention) to disengage, i.e., the W-moment (Libet, Gleason, Wright, & Pearl, 1983).

Detailed instructions were provided at the beginning of the experiment, and participants performed a guided practice session to familiarize them with the task. The entire

experimental session consisted of 6 cued and 6 free blocks of 10 trials each. Cued and free blocks were presented in alternating order and every free block was followed by a bonus trial.

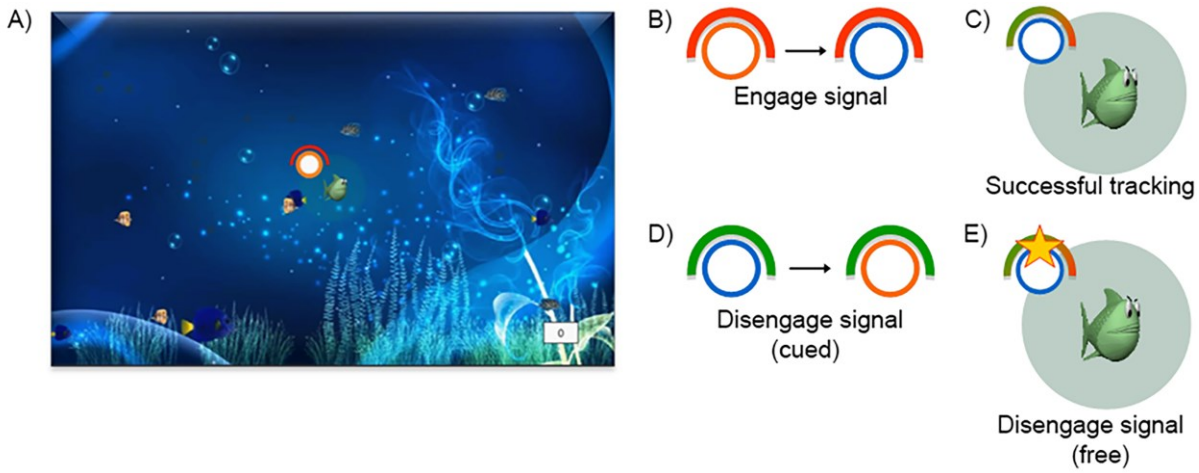


Fig. 1 The Chasing Memo Task

(A) Background display for the motor tracking task. Participants were instructed to track fish Memo around the screen by keeping the mouse within the green zone surrounding the target. On each trial, a counter was displayed on the bottom right of the screen which displayed the points earned during successful tracking; (B) When the circle turned from orange to blue, participants started tracking either at will (intentional condition) or as quickly as possible (cued condition); (C) During successful tracking, the half-circle red bar gradually turned green, signaling that the participant started to earn points; (D) In the cued condition, the circle switched back to orange to signal that the participant has to stop tracking as quickly as possible; (E) In the intentional condition, the appearance of a star indicated the beginning of a time window in which the participant can earn additional bonus points. In these trials, participants can decide voluntarily when to disengage from motor tracking in order to collect the bonus points.

SST

Similar to the task used by van den Wildenberg et al., (2006), participants were required to respond quickly and accurately with the corresponding index finger to the direction of a right- or a left-pointing green arrow (*go trials*). Arrow presentation was response-terminated. The green arrow changed to red on 25% of the trials (*stop trials*), upon which the go response had to be aborted. Intervals between subsequent go signals varied randomly but equiprobably, from 1750 to 2250 ms in steps of 50 ms, where a black fixation point (10 x 10 pixels) was presented. A staircase-tracking procedure dynamically adjusted the delay between the onset of the go signal and the onset of the stop signal (SSD) for each hand separately to control inhibition probability (Levitt, 1971). SSD started at 100 ms and increased by 50 ms after a successful inhibition, and decreased by 50 ms after a failed inhibition. The SST consisted of five blocks of 60 trials, the first of which served as a practice block to obtain stable performance (van den Wildenberg et al., 2006). The SST measures both the efficiency of response execution (mean reaction time to correct go-signals,

go RT) and the latency of stimulus-driven inhibitory control (SSRT), where longer SSRT reflects a general slowing of inhibitory processes (Schachar, Tannock, Marriott, & Logan, 1995). The integration method was used for SSRT calculation (Logan, 1994; Logan & Cowan, 1984).

Procedure

All participants signed informed consent prior to participation. They performed two computer tasks in a counterbalanced sequence, with a series of questionnaires in between, and the behavioral tasks were administered using Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA). The procedures were approved by the local ethics committee and complied with institutional guidelines and the declaration of Helsinki. Participants were rewarded either €15 or 1.5 credit points upon accomplishment.

Data preparation and statistical analysis

Chasing Memo task

Although Disengage RT was our measurement of primary interest, Engage RT was also analyzed to verify whether chronic alcohol use affected basic response speed. Engage RT (the time from the engage color change until the start of tracking) was calculated for both cued and free conditions. Engage RTs less than 100 ms were discarded from the analysis, resulting in 3360 (93.3%) out of 3600 trials for the cued condition and 3381 (93.9%) for the free condition. Disengage RT in the cued condition was calculated by subtracting the time of the disengage color change from the time at which tracking was completely halted. For the free condition, Disengage RT is the time from the appearance of the bonus star until the time of arrested tracking. Before analysis, 376 (10.4%) trials in the free condition were removed as intentional inhibition failures, i.e., participants did not stop tracking within the provided time window (20 s).

The W-interval in the free condition was computed as the interval between the reported W-moment until the time of the actual stopping. In the cued condition, timing accuracy was the difference between the reported and the actual appearance moment of the stop signal.

For all RT-related dependent variables, the median rather than mean value was used for further analysis as RT distributions were not normally distributed for all of the participants (skewed to the left for some participants and to the right for others). Engage RT and Disengage RT were analyzed using multiple linear regressions with AUDIT sum[1] score (AUDIT sum was nearly normally distributed with Skewness of 0.06 and Kurtosis of -0.68) and Inhibition Category (free vs. cued) as predictors, controlling for gender[2]. W-interval was analyzed with AUDIT score as a predictor and controlled for timing accuracy. These analyses were performed using SPSS 24.0 (IBM Corp., 2016).

[1]Participants were not dichotomized into light and heavy drinkers during recruitment and data analysis stage as there was individual variance of alcohol consumption in these broad groups and artificial dichotomization reduces the power to detect subtle individual differences (Royston, Altman, & Sauerbrei, 2006).

[2]Other substances use were not added as a covariate as they were highly correlated with the AUDIT score (see **Table 2a**).

SST

The successful inhibition percentages on inhibition trials ranged from 28.3% to 63.3% (*M* = 49.6%, *SD* = 4.67%), which meets the requirements of the integration method for SSRT calculation (Logan, 1994). To compute go RT, only correct responses were taken into account. Afterward, similar regression analyses as the Chasing Memo task was performed for SSRT and go RT separately without the factor of Inhibition Category. We analyzed data once with all the participants (N = 86) and once with those also had Chasing Memo task performance (N = 60).

In addition, two correlation matrices were built: 1) correlations between different substances use; 2) correlations between different measures of impulsivity (Disengage RT in the free condition, SSRT, BIS-11 score, and DII score).

Combination of conventional and Bayesian-based analysis

To quantify the strength of our findings beyond standard significance testing and to remedy the relatively small sample size caused by the technical failure, the main hypotheses were also examined by calculating a Bayes Factor using Bayesian Information Criteria (Jarosz & Wiley, 2014; Rouder, Morey, Speckman, & Province, 2012; Wagenmakers, 2007; Wetzels, Grasman, & Wagenmakers, 2012). The Bayes factor provides the odds ratio (BF_{01}) for the null versus the alternative hypotheses given a particular data set (BF_{10} is simply the inverse of BF_{01}). A value of 1 means that the null and alternative hypotheses are equally likely; values larger than 1 suggest that the data are in favor of the null hypothesis, and values smaller than 1 indicate that the data are in favor of the alternative hypothesis. To arrive at a decision in practice, recommended cut-offs are that a BF_{01} greater than 3 (or less than one third) represents 'substantial evidence' (Dienes, 2014; Kolmogorov & Natarajan, 1998). The BFs were calculated with JASP 0.9.2.0., an open-source statistical package (JASP Team, 2018).

Results

Sample characteristics

Descriptive statistics (i.e., mean, standard deviation, minimum and maximum values) of the tested variables (demographics, substance use, task performance, and trait impulsivity) can be found in **Table 1**.

Table 1 Descriptive statistics for substance use, task performance and trait impulsivity.

		Substance Use					SST			Chasing Memo task[2]						Trait Impulsivity					
	Age	AUDIT	CUDIT	Fagerstroim	CORE[1]/Last Year	CORE/Last Month	go RT	SSRT	stop rate	Disengage RT		Engage RT		W interval	Timing Accuracy	BIS attention	BIS motor	BIS non-planning	BIS total	DII dysfunctional	DII functional
										cued	free	cued	free								
Min.	18	0	0	0	0	0	327.7	90	28.33	353	1017	304.5	205	-526	16.67	9	13	13	40	1	2
Max.	25	23	24	6	320	140	1014	272.3	63.33	3793	15157	756	722.5	7749	5168	30	33	33	81	10	9
Mean	20.75	10.07	2.5	1.53	90.25	25.25	441.3	197.8	49.67	748.7	8662	410.7	407.6	528.7	852.4	17.25	20.3	23.25	60.8	5.42	5.87
SD	2.01	5.6	4.33	1.39	84.79	39.46	135.9	33.87	4.65	583.6	3619	86.34	76	1233	932.5	3.86	4.07	4.1	9.25	2.16	1.49

Note: [1]Sum score of CORE excluding alcohol use; SST: stop-signal task; [2]Mean and SD for RT-related variables in the Chasing Memo task were calculated based on median values.

Chasing Memo task

Variables used in the regression analyses were checked for multicollinearity using variance inflation factors (VIF) before being entered into the multivariate analyses; VIF for all variables were below 2 for the following regression models. The linear regression model for Engage RT was not significant (F (3, 116) = 0.99, p = 0.39), with a R^2 of 0.025. None of the explanatory variables significantly predicted Engage RT (AUDIT: β =0.10, p = 0.29; Inhibition Category: β = -0.02, p = 0.84; gender: β = 0.12, p = 0.19). Bayes factor analysis with default mixture of variance priors, and with reference to the full model with three covariates, indicated evidence for a lack of effects of AUDIT (BF_{01} = 2.19), gender (BF_{01} = 1.62), or Inhibition Category (BF_{01} = 3.57).

The linear regression model for Disengage RT was significant (F (3, 116) = 94.48, p < 0.01), with a R^2 of 0.71. Inhibition Category significantly predicted Disengage RT (β = 0.84, p < 0.01). Disengage RT was much longer in the free condition than in the stimulus-driven inhibition (8662 ms vs. 749 ms). Neither AUDIT (β = -0.06, p = 0.27) nor gender (β = 0.06, p = 0.27) predicted Disengage RT. Bayes factor analysis confirmed this by indicating evidence for the effect of Inhibition Category (BF_{10} = 7.0×10^{28}), and a lack of evidence for effects of AUDIT (BF_{01} = 7.6) and gender (BF_{01} = 7.5).

The linear regression model for W-interval was not significant (F (2, 57) = 0.14, p = 0.87), with a R^2 of 0.005. None of the explanatory variables significantly predicted W-interval (AUDIT: β = -0.007, p = 0.96; timing accuracy: β = -0.071, p = 0.60). Bayes factor analysis confirmed this by indicated evidence for a lack of effects of either AUDIT (BF_{01} = 4.56) or timing accuracy (BF_{01} = 3.45).

SST

There were no qualitative differences between the outcomes with different sample size (86 vs. 60). We report the results for the smaller sample size (same as the Chasing Memo task) below, and the larger sample size in Supplementary Materials. The linear regression model for SSRT was not significant (F (2, 57) = 0.47, p = 0.63), with a R^2 of 0.13. None of the explanatory variables significantly predicted SSRT (AUDIT: β = 0.11, p = 0.43; gender: β = 0.07, p = 0.58). Bayes factor analysis confirmed this by indicated evidence for a lack of effects of either AUDIT (BF_{01} = 2.58) or gender (BF_{01} = 3.04). The linear regression model for go RT was not significant either (F (2, 57) = 2.40, p = 0.10), with a R^2 of 0.078. AUDIT was a significant predictor of go RT (β = -2.68, p = 0.04), indicating the higher the AUDIT score the shorter the go RT. Gender was not a strong predictor of go RT (β = -0.08, p = 0.52). Bayes factor analysis, however, only indicated anecdotal evidence for the effect of AUDIT (BF_{01} = 0.46), and a lack of evidence for the effect of gender (BF_{01} = 4.56).

Correlation matrix

As was shown in **Table 2a**, alcohol use and other substances use (e.g., cigarette and cannabis use) were highly correlated, which can be expected. In **Table 2b**, the correlation matrix revealed three significant correlations between different impulsivity measures. SSRT correlated negatively with the attentional subscale of BIS-11 (r = -0.20, p = 0.03, BF_{10} =

1275 and correlated positively with the motor subscale of BIS-11 (r = 0.22, p = 0.01, BF_{10} =2122).

In addition, the motor subscale of BIS-11 and the dysfunctional subscale of DII were negatively correlated (r = -0.21, p = 0.02, BF_{10} = 1395). Subscales of impulsivity, either measure by BIS-11 or DII were not correlated with Chasing Memo task performance.

Table 2a Correlation matrix between substance use

			1	2	3	4
1	**AUDIT**	r				
		BF_{10}				
2	**CUDIT**	r	0.27**			
		BF_{10}	8296.00			
3	**Fagerström**	r	0.32**	0.41**		
		BF_{10}	30554.00	1593.00		
4	**CORE/last month**	r	0.30**	0.41**	0.70**	
		BF_{10}	24639.00	5988.00	6.436e +14	
5	**CORE/last year**	r	0.61**	0.48**	0.64**	0.73**
		BF_{10}	7.271e +10	368020.00	1.679e +11	3.534e +18

Note: * $p < 0.05$, ** $p < 0.01$

Table 2b Correlation matrix between impulsivity measures

			1	2	3	4	5	6	7
1	**Disengage RT (free)**	r							
		BF_{10}							
2	**Disengage RT (cued)**	r	-0.17						
		BF_{10}	0.38						
3	**SSRT**	r	0.02	0					
		BF_{10}	0.16	0.16					
4	**BIS attentional**	r	0.06	-0.05	-0.20*				
		BF_{10}	0.18	0.17	1275				
5	**BIS motor**	r	0.17	0.12	0.22*	0.27**			
		BF_{10}	0.37	0.25	2122	9251			
6	**BIS non-planning**	r	0.06	0.15	0.09	0.30**	0.58*		
		BF_{10}	0.18	0.31	0.18	26303	1.863×10^{9}		
7	**DII dysfunctional**	r	-0.09	-0.16	0.17	0.04	-0.21*	-0.11	
		BF_{10}	0.2	0.33	0.68	0.12	1395	0.22	
8	**DII functional**	r	0.09	-0.03	-0.1	-0.15	-0.04	-0.14	-0.41**
		BF_{10}	0.206	0.165	0.206	0.43	0.126	0.353	4859

Note: * $p < 0.05$, ** $p < 0.01$

Discussion

In the first experiment, long-term alcohol use showed no relationship with any of the inhibition-related tasks and questionnaires. In the SST, alcohol use slightly speeded response latency, but had no influence on the inhibition process. In the Chasing Memo task, typical alcohol use hardly had any effect on Engage RT and Disengage RT, nor did it influence the W-interval. The correlation analysis confirmed the existence of polysubstance use and the multidimensional feature of impulsivity (i.e., impulsivity measures are not largely correlated).

Stimulus-driven inhibition

Our findings on stimulus-driven inhibition were comparable between the Chasing Memo task and the standard SST. For stimulus-driven inhibition as tested by the SST, the present null findings of long-term alcohol use are replications of some recent studies (Boelema et al., 2015; Franken, Luijten, van der Veen, & van Strien, 2017), but conflicted with some others (Smith et al., 2014). Against the backdrop of the fairly inconsistent literature, it's time to ask whether the stimulus-driven inhibition deficit is a real finding among drinkers. In the current study, alcohol use was regarded as a continuous variable, which allowed drawing conclusions from a relatively complete population. A recent individual-level mega-analysis based on 3610 participants also did not confirm the negative relationship between alcohol use and response inhibition performance (Liu et al., 2019). By contrast, the so-called *extreme group design*s were frequently used in this field, e.g., comparing light/non-drinkers versus people with alcohol use disorder (AUD, American Psychiatric Association, 2013). Studies with such designs yielded more positive findings (Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2006; Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009). Seemingly, people located at the very right end of the continuum, i.e., those diagnosed with alcohol use disorder indeed have difficulties in inhibition. But it does not necessarily mean these findings can be generalized readily to the majorities who drink alcohol on a regular/non-hazardous basis, at least on the behavioral level (Bednarski et al., 2012).

Intentional inhibition

Given that this was the first attempt, we did not have firm *a priori* predictions on the presence and direction of effects of alcohol use on intentional inhibition. At least in the current context, there was no clear effect of alcohol use on intentional inhibition. The latency of intentional inhibition was expressed by the Disengage RT in the free condition. Its histogram for each individual either showed a rectangle or approximately normal (with mean of near 10 s) distribution, which confirms the validity of the manipulation, in the sense that strategies other than 'following one's urge' (such as counting or waiting strategies) would have resulted in heavily peaked and/or skewed distributions. Though in the free condition participants appeared to start tracking as soon as possible, this did not invalidate the operationalization. As Engagement is less of our focus, we did not emphasize the 'free will' as much as for the Disengagement. Also, no consequences were associated with the engage response pattern.

For the W-interval, participants reported to consciously feel the urge to stop about half a second before the actual disengagement. The W-interval was similar for both groups. In the Libet task, the W-moment was reported 200 ms before intentional action (Libet et al., 1983). This difference in timing might be due to the dissimilarity between voluntary action and voluntary inhibition, as well as specific task features, which will require further investigation.

Although some limitations may apply, the consistency of effects and the robustness of the evidence in favor of the null hypotheses (as confirmed by Bayesian analyses) appears to justify the conclusion that a limited period of heavy drinking does not affect intentional or stimulus-driven inhibition (at least not in university students). However, before accepting such a conclusion, we seek further evidence through adopting a manipulation that in past research has proven more potent in inducing alcohol-related effects on stimulus-driven inhibition. Alcohol use may increase maladaptive behaviors either because of lasting sequelae of chronic use or through its direct, acute effects (Jentsch & Taylor, 1999). Acutely, alcohol may impair cue-based inhibition and result in an increased likelihood of engaging in risky behaviors, such as driving while intoxicated. In addition, alcohol-induced impairments may also affect the likelihood of further unplanned consumption of alcohol (de Wit, 2009). Several laboratory studies showed that a moderate acute dosage of alcohol use leads to impaired inhibition on GNG and SST (de Wit et al., 2000; Mulvihill, Skilling, & Vogel-Sprott, 1997). Therefore, as a next step, we explored if alcohol intoxication affects stimulus-driven and intentional inhibition. In addition to behavioral measures, we also used EEG to record neural activity. This may reveal the acute effects of alcohol on information processing that remain hidden when focusing on behavioral outcomes. For example, EEG highlighted the nature of the effects of alcohol consumption (vs. placebo) on performance monitoring and error correction (Ridderinkhof et al., 2002). Likewise, EEG signals have reflected differences between alcohol effects in light versus heavy drinkers in the absence of differences in behavior (Ames et al., 2014; Easdon et al., 2005; Maurage, Pesenti, Philippot, Joassin, & Campanella, 2009).

EXPERIMENT II

Introduction

The aim of Experiment II was to test whether and how acute alcohol use influence intentional inhibition. Compared to chronic alcohol use, acute alcohol administration was more consistently related to impaired stimulus-driven inhibition (Easdon & Vogel-Sprott, 2000; Fillmore & Vogel-Sprott, 1999; Loeber & Duka, 2009; Marczinski & Fillmore, 2003; Rose & Duka, 2007; Rose & Duka, 2008). By analogy, acute alcohol administration might also be more likely to influence intentional inhibition than chronic alcohol use. Loss-of-control over drinking depicts the phenomenon that small to moderate amount of alcohol use induces physical demand/craving for further drink and promotes alcohol-seeking behavior (Hodgson, Rankin, & Stockwell, 1979; Jellinek, 1952; Field et al., 2010). In this way, people

are likely to fail in intentional inhibition and drink more than planned on a typical drinking occasion.

If alcohol affects intentional inhibition, it may affect not only the time of overt disengagement but also the temporal unfolding of that intention. With its unique temporal resolution, EEG may provide a useful candidate study tool for this purpose. The EEG component we are interested in is the readiness potential (RP) or Bereitschaftspotential. It was first recorded by Kornhuber and Deecke (1964) and attracted broad attention after Libet and colleagues' striking work in 1983. In their experiment, participants were instructed to press a response button whenever they became aware of the intention to do so and report the time of this urge (the W-moment, Libet et al., 1983). They found that the W-moment occurred some 200 ms prior to actual action and about 500 ms after the RP onset (Libet et al., 1983). This finding was explained as the brain decides to initiate certain actions prior to any reportable subjective awareness (Libet et al., 1983), which raised perhaps unprecedented discussion in the literature. It was recently claimed that the RP might neither give rise to the W-moment (conscious intention) nor to the voluntary movement, as the RP occurs 1) before a motor act even without consciousness of commanding it; 2) in situations that do not involve movement, such as decision-making in mental arithmetic (Alexander et al., 2014), and 3) in externally triggered action (Bianco et al., 2017). Our concern here is not so much with the interpretation but with the development and time course of the processes associated with intentional inhibition.

Only a few studies have investigated the neural mechanisms of intentional inhibition using EEG (Bianco et al., 2017a, 2017b; Parkinson et al., 2017; Parkinson & Haggard, 2015; Walsh, Kühn, Brass, Wenke, & Haggard, 2010; Xu et al., 2019). Tasks in those studies were suboptimal in terms of 1) the choice between acting and withholding is relatively arbitrary; 2) pre-decision on whether and when to inhibit cannot be excluded; 3) perhaps tapping into selective choice rather than inhibition, especially when equiprobable go and no-go trials are used (Bianco et al., 2017a, 2017b). Thus, the underlying mechanism might entail not only intentional inhibition but be confounded by other components. The Chasing Memo task remedies these limitations, at least to some extent. A further departure from some previous studies was that components that are closely related to stimulus-driven inhibition, such as N2/P3 (Gajewski & Falkenstein, 2013) were not analyzed, as we focused on the neural activities preceding intentional inhibition.

In Experiment II, we adopted a double-blind, within-subject cross-over design with participants tested once under alcohol and once under placebo. Brain activities were recorded with EEG when they were performing the Chasing Memo task. We hypothesized that the RP appears only in the intentional inhibition condition but not in the stimulus-driven inhibition condition. Second, in line with Experiment I, acute alcohol use may incur either stopping impulsivity or waiting impulsivity in disengaging from the action. The finding reported by Libet and colleagues (1983) suggests that the RP is positively associated with cognitive engagement and effort with respect to the impending movement. The more the participant thinks about the action, the earlier and larger is the RP (Haggard, 2019). Thus, in the case of stopping impulsivity, the activation required to implement and set off the disengagement

from action may take longer to build up, and may require higher criterion levels of such activation; hence, acute alcohol should result in an earlier onset of the RP and a larger area between onset and peak (area under the curve, AUC). Likewise, in the case of alcohol-induced waiting impulsivity, a RP onset that occurs at a relatively brief interval relative to the time of disengagement and a smaller AUC of the RP should be expected. As exploratory measures of secondary interest, we also compute peak amplitudes, and RP interval (from onset latency to peak latency).

Methods

Participants

Twenty right-handed male adults participated in this study, with an age range of 21 to 28 years old (M = 24.6, SD = 2.3). Participants were psychology students recruited from the local campus. According to self-report, they had a normal or corrected-to-normal vision, were subjectively in good health, and had no history of head injuries or neurological or psychiatric disorders, including obesity and anorexia. Although all participants were light to moderate drinkers in daily life, they did not engage in excessive consumption of alcohol or drugs and were not addicted to alcohol or other drugs. The study was approved by the local ethics committee and complied with the declaration of Helsinki, relevant laws, and institutional guidelines.

Alcohol administration

Drinks were orange juice mixed with either 40% alcoholic vodka or water. The amount of vodka was calculated depending on the participants' body weight to obtain blood alcohol levels (BAC) of 0.05%. The mixture was divided into three equal portions. Two of the drinks were served with 5 min apart, prior to commencing the task. Up to 3 min was allowed for drinking each unit, followed by 2 min of mouth-wash to remove the residual alcohol in the mouth. About forty minutes after the second drink, the third booster drink was served to reduce noise due to measuring during the ascending versus descending limbs of the blood alcohol curve (Korucuoglu, Gladwin, & Wiers, 2015). To enhance the alcohol taste, all the drinks had a lemon soaked in vodka, and the glass in which drinks were served was sprayed with vodka beforehand. To mask the alcohol taste all drinks contained three drops of Tabasco sauce (McIlhenny Co., USA; Korucuoglu, Gladwin, & Wiers, 2016). Thus in either condition, participants were unable to distinguish alcohol from placebo on the basis of smell or taste.

Procedure

Each participant performed the experiment twice with 2 to 7 days in between. In one test session, they received alcoholic drinks; in the other session, they were given placebo drinks. Sessions took place between 12:00 and 6:00 p.m. at fixed times across conditions per individual. The order of experimental conditions was randomized in a double-blind cross-over design. Breath alcohol concentration (BrAC) was measured using the Lion alcolmeter® SD-400 (Lion Laboratories Limited, South Glamorgan, Wales) and registered at four times during each session (i.e., baseline, after the first two drinks, pre and post the third drink, and

by the end of the computer task). BrAC was measured by a second experimenter, who also prepared the beverages, with the primary experimenter always remaining blind to alcohol conditions and BrAC. Participants provided informed consent prior to participation and were compensated with 20 euro for participation, plus a maximum of 5 euro extra depending on their performance. They were allowed to leave the lab only when their BrAC value was below 0.02% in the drink session.

Chasing Memo task

Task details were identical to those reported in Experiment I, except for a color adjustment (the circle that turned from orange to blue and v.v. in Experiment I turned from red to green and v.v. in Experiment II), to better mimic traffic light-related associations with stopping and going. A practice stage and a test stage containing three free blocks and three cued blocks were included.

EEG data recording and preprocessing

Continuous EEG data were recorded using the BioSemi ActiveTwo system (BioSemi, Amsterdam, The Netherlands) and sampled at 2048 Hz. Recordings were taken from 64 scalp electrodes placed on the basis of the 10/20 system, and two additional electrodes were placed on the left and right mastoids. In addition, four electrodes were used to measure horizontal and vertical eye movements. In the BioSemi system, the ground electrode is formed by the Common Mode Sense active electrode and the Driven Right Leg passive electrode.

All EEG data were preprocessed and analyzed with EEGLAB v.13.5.4b, an open source toolbox for Matlab (MATLAB 2015a, The MathWorks, Natick, MA) and Brain Vision Analyzer 2.0 software (Brain Products, Gilching, Germany). Four participants were excluded from the analysis. One participant always disengaged when the star was presented on the screen (contrary to instructions). Three other participants had to be discarded due to technical malfunctions. Therefore data analyses were based on the remaining 16 participants. Data were imported to EEGLAB with average mastoids as the reference. Then, downsampled to 512 Hz and digitally filtered using a FIR filter (high pass 0.016 Hz and low pass 70 Hz, with an additional 50 Hz notch-filter). The EEG traces were then segmented into epochs ranging from −3000 to 1000 ms (-3000 to -2500 was used for baseline correction), time-locked to the last disengagement moment before the completion of a trial.

Before artifact removal, trials in the free condition without a valid voluntary disengagement (i.e., disengagement occurring within 2 s following the bonus star, after which the trial ended automatically) were discarded, as intentional inhibition cannot be verified in these cases. Subsequently, artifact removal was accomplished in two steps. The first step consisted of visual inspection of the epochs to remove those containing non-stereotyped artifacts such as head or muscle movements, on the basis of manual and semi-automatic artifact detection (50 μV/ms maximal allowed voltage step; 150 μV maximal allowed difference of values in the epoch). This resulted in averages (SD) of 45.06 (7.30), 44.56 (9.37), 53.0 (7.47), and 52.94 (7.45) trials for alcohol/free, placebo/free, alcohol/cued, and placebo/cued conditions, respectively. The number of epochs removed never exceeded 25%. Secondly, an independent component analysis (ICA) was performed using the ‘runica’

algorithm available in EEGLAB (Makeig, Jung, Bell, Ghahremani, & Sejnowski, 1997). The extended option was used that implements a version of the infomax ICA algorithm (Lee, Girolami, & Sejnowski, 1999) resulting in better detection of sources with sub-Gaussian distribution, such as line current artifacts and slow activity. Then we applied the algorithm ADJUST that automatically identifies artefactual independent components by combing stereotyped artifact-specific spatial and temporal features (Mognon, Jovicich, Bruzzone, & Buiatti, 2011). ADJUST is optimized to capture blinks, eye movements, and generic discontinuities and has been validated on real data (Mognon et al., 2011). After exclusion of artefactual components the data were reconstructed based on an average (SD) of 55.57 (3.72), 57.69 (2.91), 56.75 (3.15), and 58.75 (3.21) ICA components in the alcohol/free, placebo/free, alcohol/cued, and placebo/cued conditions, respectively. The number of independent components removed did not exceed 14% of the total in any of the conditions.

Afterward, data were re-referenced using the current source density (CSD) transformation (Perrin, Pernier, Bertrand, & Echallier, 1989) as implemented in Brain Vision Analyzer (with the parameters degree of spline = 4; maximum degrees the Legendre polynomial = 15). The CSD transformation uses surface Laplacian computation to provide a reference-free estimate of the local radial current density rather than distant/deep (neural) sources (Hjorth, 1975; Nunez & Pilgreen, 1991). A major advantage is that CSD leads to the enhanced spatial precision of the recorded EEG activity (Babiloni et al., 1996; Babiloni, Carducci, Babiloni, & Urbano, 1998) and thus acts as a spatial filter. Finally, epochs were averaged for each participant and experimental condition for further statistical analysis. Previous literature indicates that the supplementary motor areas contribute considerably to the generation of the RP. Although some studies have analyzed the RP based on a pool of electrodes surrounding FCz, several studies suggest that the activity of these regions is best captured by electrode FCz (Shibasaki & Hallett, 2006; Steinmetz, Fürst, & Meyer, 1989), especially after CSD transformation. This was confirmed by visual inspection for each participant. Statistical analyses were therefore conducted only on this electrode.

Data preparation and statistical analysis

Task performance

The calculations for median Engage RT, Disengage RT and W-interval were the same as in Experiment I. Engage RTs of less than 100 ms were removed, resulting in 916 (95%), 885 (92%), 892 (93%), and 931 (97%) trials for alcohol/free, placebo/free, alcohol/cued, and placebo/cued conditions, respectively. For Disengage RT in the free condition, if the participant did not voluntarily disengage within the provided time, that trial was removed. This resulted in 788 (82%) trials for the alcohol condition and 836 (87%) trials for the placebo condition. Independent t-tests were performed to compare performance under placebo and alcohol conditions for each of these dependent variables.

EEG

Four indices extracted from the ERP topographic plots were analyzed, including RP onset latency, RP peak amplitude, AUC, and RP build-up interval (from onset latency to peak latency). For RP onset latency, since automated algorithms failed to yield consistent and

robust latencies for most participants, three authors (YL, GFG, & RR) independently judged the EEG time courses for each individual trial, while they remained blind to Inhibition Category. The raters hand-picked (through computer-aided scrolling procedures) the RP onset as the moment in time (in ms) when the signal began to deviate and showed a steady switch towards the negative direction. The inter-rater reliability calculated by intraclass correlation was 0.96, which indicated high consistency among raters. AUC was quantified as the total surface in the time window between onset latency and peak latency, using the R package 'stats' (version 3.3.0). A two-way within-subject repeated-measures ANOVA was implemented with Alcohol (alcohol/placebo) and Inhibition Category (free/cued) as factors.

Conventional and Bayesian-based analysis

As in Experiment I, we did both conventional and Bayesian-based paired *t*-test and repeated-measures ANOVA analysis for the main dependent variables. Bayesian repeated-measures ANOVA compares all the models against the null model. BF was provided every time a main factor or interaction was added to the model, allowing us to establish how each main factor and the interaction contributed to the model.

Results

BrAC

The descriptive values at each reading can be found in Supplementary Materials. In brief, BrAC peaked after the third drink, with a mean value of 0.06 % and a standard deviation of 0.10.

Task performance

In brief, acute alcohol use did not exert meaningful effects on Engage RT/Disengage RT in either the cued or free condition. Similarly, alcohol did not influence timing accuracy and W-interval. More detailed information can be found in Supplementary Materials.

EEG

RP onset latency

Repeated-measures ANOVA confirmed that the main effect of Inhibition Category was significant (F (1, 15) = 46.89, $p < 0.001$, $\eta^2 = 0.70$), with much earlier onsets in the free condition (M = -1,229 ms, SD = 710) than in the cued condition (M = -205 ms, SD = 464, see **Fig. 2** and **Fig. 3**). The main effect of Alcohol was not significant (Alcohol: M = -693 ms, SD = 839; Placebo: M = -742 ms, SD = 745; F (1, 15) = 0.14, p = 0.72). The interaction between Alcohol and Inhibition Category was also not significant (F (1, 15) = 0.20, p = 0.66). Bayesian repeated-measures ANOVA showed that a model that contained only Inhibition Category provided a fit that was 3.6 times better than a model that added the factor Alcohol, and 10.3 times better than a model that further added the interaction effect. These results together confirmed the significant main effect of Inhibition Category in the absence of main and interaction effects of Alcohol.

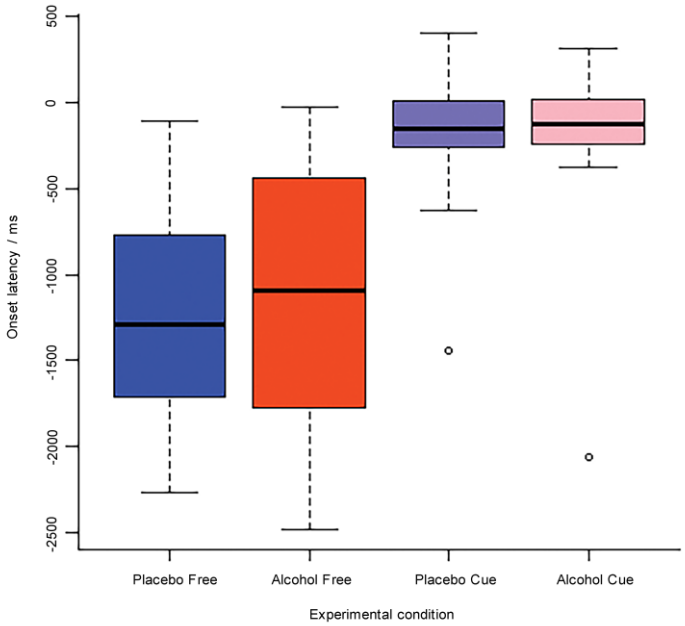


Fig. 2 Boxplot of the onset latency (in ms) of the Readiness Potential per group: Alcohol (alcohol vs. placebo) × Inhibition Category (cued vs. free). Only a main effect of Inhibition Category is observed.

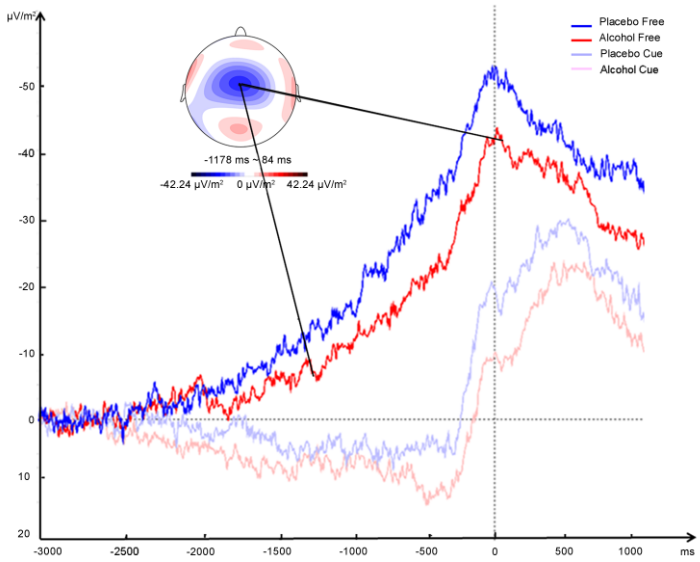


Fig. 3 Surface Laplacians over electrode FCz for the free and cued inhibition under alcohol or placebo conditions. Traces are time-locked to disengagement time (time 0). The scalp map shows mean activity in the time window of the RP, as defined by RP onset and peak amplitude for the free inhibition condition under alcohol. Electrode FCz is marked in the scalp maps (black dot).

AUC

Repeated-measures ANOVA confirmed a significant main effect of Inhibition Category ($F(1, 15) = 21.04$, $p < 0.001$, $\eta^2 = 0.58$), with a much greater AUC in the free condition (M = -40,563 ($\mu V/m^2$)*ms, SD = 37,332) than in the cued condition (M = -13,348 ($\mu V/m^2$)*ms, SD = 13,815, **Fig. 4**). Although the AUC appeared reduced under alcohol compared to placebo, the main effect of Alcohol failed to obtain significance (Alcohol: M = -23,323 ($\mu V/m^2$)*ms, SD = 25,692; Placebo: M = -30,588 ($\mu V/m^2$)*ms, SD = 35,771; $F(1, 15) = 1.22$, $p = 0.29$). The interaction between Alcohol and Inhibition Category was not significant ($F(1, 15) = 0.29$, $p = 0.60$). Bayesian repeated measures ANOVA showed that a model that contained only Inhibition Category in the model provided a fit that was 2.3 times better than model that added the factor Alcohol and 5.8 times better than a model that further added the interaction effect. These results together confirmed the significant main effect of Inhibition Category in the absence of main and interaction effects of Alcohol.

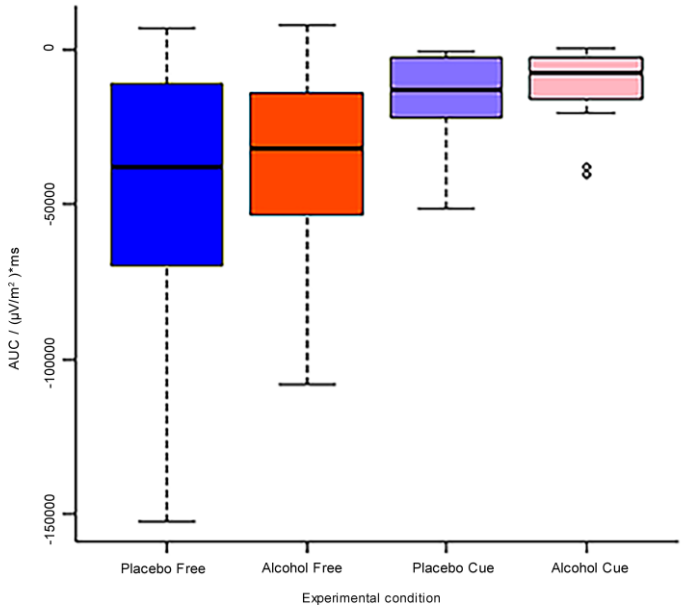


Fig. 4 Boxplot of the area under the curve (AUC) (in ($\mu V/m^2$)*ms) of the Readiness Potential per group: Alcohol (alcohol vs. placebo) × Inhibition Category (cued vs. free). Only a main effect of Inhibition Category is observed.

Summary of EEG results

Since the results of the analyses on RP peak amplitude and build-up interval were highly redundant to those of AUC, these results can be found in Supplementary Materials. In general, the four ERP indices provided a consistent pattern of the RP that was influenced considerably by the factor Inhibition Category but was not influenced by the factor Alcohol. Under free inhibition, the RP began to develop almost 1000 ms earlier than under cued inhibition. Also, under free inhibition, the RP reached higher peak amplitudes than under

cued inhibition. Accordingly, the AUC is larger for free than for cued inhibition. Generally speaking, only under free inhibition condition, there was a clear RP before disengagement. But these effects were not impacted by the acute effects of alcohol.

Discussion

In this experiment, we tested how acute alcohol use influences intentional inhibition and stimulus-driven inhibition, at behavioral as well as neural levels. RP developed over the frontocentral cortex about 1200 ms before intentional inhibition was effectuated but not before stimulus-driven inhibition. It turned out that alcohol administration had hardly any effect, either behaviorally or on neural correlates of intentional inhibition and stimulus-driven inhibition. These null-findings were corroborated by Bayesian analyses that confirmed there was stronger evidence for the null hypothesis than for the alternative hypothesis.

Stimulus-driven inhibition

In contrast to previous findings on impaired stimulus-driven inhibition after alcohol intake (Fillmore et al., 2009; Fillmore & Vogel-Sprott, 1999; Fillmore & Vogel-Sprott, 2000; Loeber & Duka, 2009; Marczinski & Fillmore, 2003; Rose & Duka, 2007; Rose & Duka, 2008), no alcohol effects were observed on stimulus-driven inhibition as measured in the Chasing Memo task. Since the present study did not include a SST or a GNG task, we cannot tell whether the lack of effects is specific to the Chasing Memo task or pertains to our alcohol manipulation in the present sample.

A number of potential reasons may explain the discrepancy between the present and previous findings in the literature. First, the doses of alcohol administered in the present study may have been too low to produce manifest alcohol effects. Previous studies have demonstrated effects on ERP components under comparable alcohol doses and sample size (Ridderinkhof et al., 2002). But compared with the flanker task they used, disengaging from visuomotor tracking in the Chasing Memo task was relatively easy. And it has been pointed out that the easier the task, the more alcohol is needed to cause performance impairments (Field et al., 2010). Second, alcohol effects may be confounded with individual differences in alcohol expectancy effects (Brown, Christiansen, & Goldman, 1987). For instance, it has been observed that those who expect less alcohol-induced impairment indeed displayed less impairment, irrespective of actual consumption (Fillmore, Carscadden, & Vogel-Sprott, 1998; Fillmore & Vogel-Sprott, 1994; Fillmore & Vogel-Sprott, 1995). Without an additional control group (participants who do not get any alcohol, and who know so) in the current study, it is difficult to distinguish between expectancy and pharmacological effects of alcohol (Testa, Vanzile-Tamsen, Livingston, & Buddie, 2006). Third, although alcohol intake resulted in similar BACs across participants, there might still exist non-trivial individual differences in the actual impairment instilled by alcohol (Testa, et al., 2006).

Intentional inhibition

Previous studies did not examine the EEG effects of alcohol on intentional inhibition. We observed no effects, neither from the perspective of stopping impulsivity nor waiting impulsivity. The factors that were discussed that potentially play a role in the absence of

alcohol effects on stimulus-driven inhibition may also pertain to intentional inhibition. In particular, individual differences in the actual impairment caused by alcohol (Testa et al., 2006). Indeed, individual data in our study showed that roughly half of the participants had earlier RP onsets under alcohol, while the opposite pattern was observed among the other half. In this way, the overall effect of alcohol was eliminated. Future studies may explore such individual differences more systematically. Second, the requirement to report the W-moment might interfere with the main task at hand (continue/disengage tracking). This process required attention shifting (i.e., have a glance of the counter) and working memory storage (i.e., keep this number in memory). Meanwhile, the reliability of reported W-moment has been questioned (Mele, 2007). Therefore, future studies not focused on consciousness may consider discarding this element.

General Discussion

Many studies have investigated the relationship between alcohol use and inhibition, but all previous studies focused on stimulus-driven inhibition, typically tested with varieties of the GNG and SST. Here, we expanded this focus by testing alcohol effects on intentional inhibition in two studies: focused on long-term and short-term alcohol use respectively. Both intentional inhibition and stimulus-driven inhibition were tested. We found no relationship between long-term alcohol use with both types of inhibition and no differences related to acute alcohol administration. The main finding was that the RP showed an earlier onset and higher peak values for intentional compared to stimulus-driven inhibition, independent of alcohol administration.

Regarding stimulus-driven inhibition, its null association with long-term alcohol use is to some extent in correspondence with the literature. Presumably, a threshold effect rather than a linear relationship exists between typical alcohol use and response inhibition. That is, only when the accumulated alcohol consumption surpassed a certain threshold or a diagnosis of alcohol use disorder is confirmed, long-term alcohol use is accompanied by impaired inhibition (Bjork, Hommer, Grant, & Danube, 2004; Fernández-Serrano, Pérez-García, & Verdejo-García, 2011; Noël et al., 2007; Petit et al., 2014). On the other hand, our lack of effects of acute alcohol use on stimulus-driven inhibition is more at odds with previous research. A study by Marczinski et al. (2005) using a cued GNG showed impaired inhibition of a button press (i.e., a discrete motor response) under the influence of alcohol. However, alcohol did not influence inhibition performance if participants had to *release* instead of *press* a button (i.e., a continuous movement). This latter response type seems to resemble the ongoing tracking movements in the Chasing Memo task. The employment of discrete go responses can explain why the acute effects of alcohol are frequently reported on GNG and SST (Fillmore & Vogel-Sprott, 1999; Marczinski & Fillmore, 2003) but not in our task.

Regarding intentional inhibition, our studies represent the first exploration of a potential link with alcohol use and misuse. Neither effects of trait drinking patterns (social/problematic) nor acute alcohol effects were observed. This negative finding coincides with a recent finding in Parkinson patients. Three groups of participants (healthy control, Parkinson with and without impulsive-compulsive behaviors) did not differ on intentional

inhibition performance measured by the Marble Task (Ricciardi et al., 2017). This suggests that populations that typically show comorbid impaired reactive inhibition, such as Parkinson disease, ADHD, and substance use disorder, can still keep intentional inhibition capability intact.

At the neural level, a slow negative potential appeared 1200 ms exclusively before intentional inhibition, which provides evidence that the RP also reflects the preparation of stopping a motor action. Together with the evidence that the RP develops prior to the process irrelevant to action (Alexander et al., 2016; Trevena & Miller, 2010; Vinding, Jensen, & Overgaard, 2014) and its amplitude is influenced by the degree of intentionality (Davide, Simone, Giuseppe, & Marcel, 2011; Jo, Wittmann, Hinterberger, & Schmidt, 2014; Rigoni, Brass, Roger, Vidal, & Sartori, 2013), it is concluded that RP reflects neural processes related to intention formation rather than motor preparation (Alexander et al., 2016; Eagleman, 2004; Rigoni, Wilquin, Brass, & Burle, 2013). This can also be interesting in relation to the current discussion on the brain disease model of addiction (Heather, 2017) and with respect to the question if long-term alcohol-dependent patients show problems in intention formation and/or execution.

We acknowledge a number of limitations of our study. First, in the Chasing Memo task, participants were obliged to disengage on all free trials. The moment of disengagement was 'at will', but disengagement at any point during a free trial was mandatory rather than voluntary. If we had added the 'whether' option and let participants determine more freely if and when to disengage, alcohol might still influence decisional aspects of intentional inhibition (Marcel & Patrick, 2008). Just like the priming effect of alcohol, preload drinking promoted loss of control over further drinking behavior (Field et al., 2010). In that way, acute alcohol use should increase the *probability* of accepting another beer rather than *when* you accept it. We are currently exploring intentional inhibition and effects of alcohol in a modified version of the Chasing Memo task with a 'whether' option added. Second, gender was disproportionally distributed in both experiments. In Experiment I, there were more females than males. We, therefore, added gender as a covariate in the main analyses and confirmed its null effect. Experiment II included only male participants given sex differences in metabolic alcohol processing. We cannot be sure if the current findings generalize to females. Future studies might aim at more gender-balanced samples. Third, our sample size in Experiment II is relatively small, but studies with a similar topic and study design confirmed its power (Bianco et al., 2017a).

We end by providing a few suggestions for future research into this field. First, the target population may include heavier binge drinkers and/or alcohol-dependent patients. It has been shown that impairments in inhibitory control after a moderate dose of alcohol are more pronounced in binge drinkers than in non-binge drinker subjects (Marczinski, Combs, & Fillmore, 2007). This might help explain that when these individuals become intoxicated, they are less able to refrain from the impulse or desire to consume more alcohol, leading to further binge drinking. Further, one might employ intravenous alcohol administration to keep the BAC at a steady level for a prolonged time (Ramchandani, Plawecki, Li, & O'Connor, 2009). This can help control the acute tolerance effect of alcohol (reduced impairment at a given BAC on the descending limb, Fillmore, Marczinski, & Bowman, 2005). In addition,

alcohol-related cues may be embedded in the task as they are more salient for heavy drinkers (compared to light drinkers) and can impact on inhibitory processes (Herrmann, Weijers, Wiesbeck, Böning, & Fallgatter, 2001; Sinha, Sinha, Li, Sinha, & Li, 2007). Also, it is interesting to explore whether only a subgroup of the drinkers with specific drinking patterns and personalities show intentional inhibition deficits.

Conclusion

This is the first empirical study on the role of intentional inhibition in relation to alcohol use. In two experiments, we found that both chronic and acute alcohol did not affect intentional inhibition, suggesting that alcohol does not moderate the ability to stop at will in the present study. Factors that might explain these null findings, such as the lifetime amount of alcohol used, alcohol administration dosage, and research paradigms were discussed. In addition, we found an event-related brain potential, the readiness potential (RP), that appeared 1.2 s before the intentional inhibition of action. No RP was visible before stimulus-driven inhibition. This indicates that the RP might reflect the formation of an intention in general rather than only signifying motor preparation.

SUPPLEMENTARY MATERIALS

Experiment I

Reliability of questionnaires:

AUDIT: The Dutch version was approved to be a reliable instrument (Hildebrand & Noteborn, 2015). Cronbach's alpha in the current study was 0.85.

The modified version of the fagerström tolerance questionnaire (mFTQ): Diagnostic score as follows: 0-2 indicates no dependence, 3-5 indicates moderate dependence and 6-9 indicates substantial dependence. The Dutch version had test-retest reliability ranging from 0.70 to 0.91 for different sex (Hildebrand & Noteborn, 2015).

The cannabis use disorder identification test revised (CUDIT-R): The CUDIT-R was shown to be a reliable and valid screening test (Adamson et al., 2010). A cut-off score of 8 or higher is used to indicate a reasonable suspicion of problematic cannabis use.

Core alcohol and drug survey (CORE): the eleven substances include alcohol, tobacco, marijuana, cocaine, amphetamines, sedatives, hallucinogens, opiates, inhalants, designer drugs, and steroids.

Barratt Impulsiveness Scale -11: Cronbach's alpha for the Dutch version is 0.81 (A E Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2008).

Dickman's Impulsivity Inventory: Cronbach's alpha coefficient of the Dutch version was 0.84 for the dysfunctional dimension and 0.76 for the functional dimension (Claes, Vertommen, & Braspenning, 2000).

Results for the stop-signal task for the 86 participants sample

The linear regression model for SSRT was not significant (F (2, 83) = 0.57, p = 0.57), with an R^2 of 0.014. None of the explanatory variables significantly predicted SSRT (AUDIT: β = 0.07, p =0.52; gender: β = 0.09, p =0.41). Bayes factor analysis confirmed this by indicated evidence for a lack of effect of AUDIT (BF_{01} = 3.28) and gender (BF_{01} = 2.89).

The linear regression model for go RT was not significant (F (2, 83) = 0.17, p = 0.17), with an R^2 of 0.04. Neither AUDIT (β = -0.21, p =0.06) nor gender (β = 0.025, p =0.82) was a significant predictor of go RT. Bayes factor analysis indicated anecdotal evidence for the effect of AUDIT (BF_{10} = 1.36) and a lack of evidence for the effect of gender (BF_{01} = 4564).

Experiment II

BrAC values at each reading

The BAC measured 5 minutes after finishing the second drink ($BrAC_1$) ranged from 0.014% to 0.087% BAC (M = 0.05%, SD = 0.09). $BrAC_2$, measured before the third drink

ranged from 0.018% to 0.064% (M = 0.039%, SD = 0.05). $BrAC_3$, measured after completion of the third drink, ranged from 0.025% to 0.094% (M = 0.062%, SD = 0.10). $BrAC_4$, measured by the end of the task, ranged from 0.009% to 0.073% (M = 0.046%, SD = 0.06).

Behavioral findings

Engage RT

Basic response speed (i.e. Engage RT in the cued condition) was similar across alcohol (M = 431 ms, SD = 75.6) and placebo conditions (M = 411 ms, SD = 78). This 20 ms difference was statistically reliable ($t(15) = 2.18$, $p = 0.05$, $d = 0.55$). However the Bayesian paired t-test provided only anecdotal support in favor of for the alternative hypothesis ($BF_{10} = 1.62$).

In the free condition, participants started tracking a bit slower than in the cued condition. Engage RT did not differ between conditions (alcohol: M = 524 ms, SD = 263.3; placebo: M = 551 ms, SD = 299; $t(15) = 0.89$, $p = 0.39$). A Bayesian t-test provided anecdotal to moderate evidence for the null hypothesis ($BF_{01} = 2.78$).

To sum up, compared to placebo, acute alcohol use did not exert meaningful effects on Engage RT in either the cued or free condition.

Disengage RT

In the cued condition, participants stopped tracking within one second following the external stop signal. Participants appeared to be slower to disengage under alcohol than under placebo condition (M = 554 ms, SD = 162, vs. M = 517 ms, SD = 151 respectively), but this effect did not reach statistical significance ($t(15) = 0.89$, $p = 0.39$). This was confirmed by a Bayesian t-test ($BF_{01} = 2.78$), indicating marginal evidence in favor of the null hypothesis.

In the free condition, participants fully exploited the available time window to disengage from tracking, with Disengage RTs ranging between 4 and 20 s, averaging to 11-12 s. Participants appeared to be slightly slower to disengage under alcohol than under placebo (M = 11,738 ms, SD = 2,354, vs. M = 11,684 ms, SD = 2,223), but this effect did not approach statistical significance ($t(15) = 0.09$, $p = 0.93$), as confirmed by a Bayesian t-test ($BF_{01} = 3.9$), indicating moderate support in favor of the null hypothesis.

Thus, compared to placebo, alcohol failed to exert meaningful effects on Disengage RT in either the cued or free conditions.

Time reporting

Timing accuracy was inferred by subtracting the reported time of stop-signal presentation from the actual presentation time in the cued condition. Alcohol (M = 380 ms, SD = 231) and placebo conditions (M = 436 ms, SD = 367) were associated with comparable of time estimations ($t(15) = -0.99$, $p = 0.34$, $d = -0.25$, $BF_{10} = 2.57$), indicating that alcohol did not affect time estimation.

In the free condition, the W-interval amounted less than half a second. Though participants were faster to disengage once they felt the urge under alcohol (M = 195 ms, SD = 1,413) than under placebo (M = 470 ms, SD = 2,141), but this difference was not significant ($t(15) = 0.43$, $p = 0.65$), as confirmed by Bayesian analysis ($BF_{01} = 3.61$).

EEG results

RP peak amplitude

Repeated-measures ANOVA confirmed a significant main effect of Inhibition category ($F(1, 15) = 15.06$, $p < 0.001$, $\eta^2 = 0.50$), with an increased peak amplitude in the free condition (M = -55.43 μV/m^2, SD = 30.53) than for cued condition (M = -35.83 μV/m^2, SD = 19.41). Although the peak amplitude appeared reduced under alcohol compared to placebo, the main effect of Alcohol failed to reach significance (Alcohol: M = -41.77 μV/m^2, SD = 25.01; Placebo: M = -49.49 μV/m^2, SD = 29.18; $F(1, 15) = 1.84$, $p = 0.20$). The interaction between Alcohol and Inhibition category was not significant ($F(1, 15) = 0.12$, $p = 0.74$). Bayesian repeated measures ANOVA showed that a model that contained only inhibition category in the model provided a fit that was 1.5 times better than model that added the factor Alcohol condition and 4.3 times better than a model that further added the interaction effect.

RP build-up interval

Repeated-measures ANOVA confirmed that the main effect of Inhibition category was significant ($F(1, 15) = 42.66$, $p < 0.001$, $\eta^2 = 0.74$), with a much slower build-up interval in the free condition (M = 1,353 ms, SD = 692) than in the cued condition (M = 594 ms, SD = 427). The main effect of Alcohol was not significant (Alcohol: M = 945 ms, SD = 702; Placebo: M = 1,002 ms, SD = 682; $F(1, 15) = 0.24$, $p = 0.63$). The interaction between Alcohol and Inhibition category was not significant ($F(1, 15) = 0.60$, $p = 0.45$). Bayesian repeated measures ANOVA showed that a model that contained only Inhibition category provided a fit that was 3.5 times better than a model that added the factor Alcohol condition, and 7.3 times better than a model that further added the interaction effect.

Chapter 4

Moderate acute alcohol use impairs intentional inhibition intentional inhibition rather than stimulus-driven inhibition

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ABSTRACT

Moderate alcohol intake may impair stimulus-driven inhibition (SI) in go/no-go and stop-signal tasks. Exposure to alcohol-related cues has been found to exacerbate this impairment. By contrast, the effect of alcohol use on intentional inhibition (II), or the capacity to voluntarily suspend an action, has rarely been investigated. We investigated whether and how moderate alcohol intake affects SI (stop-signal task) and II (Chasing Bottles task), during exposure to alcohol-related stimuli. One hundred and eleven participants were randomly assigned to an alcohol (male: 0.55g/kg, female: 0.45g/kg), placebo or control group. For the stop-signal task, ANOVAs were performed on stop-signal reaction time (SSRT) and go-RT with Pharmacological and Expectancy Effect of Alcohol, Stimulus Category (alcohol-related or neutral), and Sex as factors. For the Chasing Bottles task, multilevel survival analysis was performed to predict *whether* and *when* II was initiated, with the same factors. In the stop-signal task, sex moderated the Pharmacological Effect of Alcohol on SSRT: only for females, alcohol consumption shortened SSRT; and for those did not drink alcohol, males had shorter SSRT than females. Regarding II, the alcohol group initiated II less often, especially when stimuli were non-alcohol related. These findings indicate that 1) SI and II reflect different aspects of response inhibition; 2) moderate alcohol intake affects II (but not SI) negatively. Speculatively, the observed impairment in II might underlie the lack of control over alcohol drinking behavior after a priming dose. This study highlights the potential role of II in the development of addiction.

Introduction

Loss of control over alcohol consumption is one of the main defining criteria of alcohol use disorder and dependence according to the DSM-5 (American Psychological Association, 2013). This is characterized by a larger amount of drinking over a longer period of time than intended, and/or failure to reduce consumption. One of the most common behavioral measures of this *loss of control* is a reduction of response inhibition. Studies on the relation between alcohol use (either long-term chronic effects or acute intoxication) and response inhibition have focused exclusively on exogenously driven inhibition. This refers to situations in which the stop process is triggered by an external no-go or stop signal (presented in the context of a go/no-go task or stop-signal task, respectively). Endogenously driven inhibition, on the other hand, has rarely been investigated. Here, inhibition is instigated intentionally, without external stimulus. The current study reports a double-blind, placebo-controlled investigation of the acute effects of alcohol intake on these two qualitatively different types of inhibitory control over behavior, namely stimulus-driven inhibition versus intentional inhibition.

Acute alcohol use and stimulus-driven inhibition

There is abundant research on the acute effects of alcohol on response inhibition using the go/no-go task (Donders, 1969) and the stop-signal task (Logan, 1994). Compared with the go/no-go task, which primarily measures inhibition errors, the stop-signal task provides an estimate of the time needed to stop an initiated action after the presentation of an external stop signal (stop-signal reaction time, SSRT). It was found that moderate to high doses of alcohol (ranging from 0.4g/kg to 0.8g/kg) lengthened SSRT compared to placebo and control conditions (see **Table S1a** for an overview of relevant studies), although findings are mixed (e.g., Loeber & Duka, 2009). A rather recent line of research further showed that including alcohol-related stimuli in the task impaired inhibitory control in heavy/dependent alcohol users even when they were sober (for a meta-analysis, see Jones, Duckworth, Kersbergen, Clarke, & Field, 2018). Given these findings, it is likely that inhibitory control deficits caused by acute alcohol use are exacerbated during exposure to alcohol-related stimuli (Field, Kiernan, Eastwood, & Child, 2008). A directly relevant study examined the acute effect of alcohol intake on stopping in male problem drinkers using a lexical stop-signal task (Zack et al., 2011). Participants classified words and non-words presented on a computer screen with a left- vs. right-hand button press. The results show that SSRT prolonged gradually from the control group to the placebo and alcohol groups (0.7g/kg), irrespective of word category (alcohol-related vs. neutral words). Additionally, a stress manipulation moderated the effect of words category. That is, only under stress, alcohol-related words induced longer stopping. However, the conclusions could not be generalized to females, as acute alcohol may have different effects in males than in females (Fillmore & Weafer, 2004; Quinn & Fromme, 2016; Weafer & Fillmore, 2012). To examine the generalization of these findings to females, we administered a similar lexical stop-signal task to a larger sample with a similar number of females and males, without the stress manipulation.

Intentional inhibition

In the go/no-go task and the stop-signal task, external cues trigger the inhibition process. The capacity to decide *internally* to inhibit an action without any external instruction comprises another important aspect of self-control. Intentional inhibition has been defined as the capacity to voluntarily suspend or inhibit an about-to-be-executed action at the last moment (Filevich, Kühn, & Haggard, 2012). It recruits cortical mechanisms partially distinguishable from those characterizing stimulus-driven inhibition (Kühn, Haggard, & Brass, 2009). The impairment of intentional inhibition occurs in several clinical disorders such as attention deficit hyperactivity disorder (ADHD), addiction, and certain personality disorders (Kühn et al., 2009). Regarding acute alcohol consumption, a widely quoted description of the 'loss of control' phenomenon was that "any drinking of alcohol starts a chain reaction which is felt by the drinker as physical demand for alcohol. It lasts until the drinker is too intoxicated or too sick to ingest more alcohol" (Jellinek, 1952). This indicates that a priming dose triggers the craving for alcohol, promoting further consumption, which likely happens in a typical drinking occasion.

Over the years, there have been several attempts to study intentional inhibition with paradigms such as the marble task (Kühn et al., 2009), and modified go/no-go tasks (Parkinson & Haggard, 2014). These tasks adopted a "free choice" design, where participants could freely decide on which trials to inhibit/go, with an average inhibition rate close to 50%. However, the methodology of these studies is acknowledged to be suboptimal. First, the possibility of pre-decision cannot be ruled out. Hence, the decision to trigger inhibition is not necessarily made on the spot. Second, participants' choices are somewhat arbitrary. Typically, their decision to inhibit or not does not entail any consequences. To mitigate these limitations, we developed the Chasing Memo task, in which participants are instructed to use a computer mouse to track a moving fish (Liu et al., submitted). They can freely decide when to disengage from visuomotor tracking (i.e. intentionally inhibit). Our previous study has indicated that light and heavy drinkers did not differ in their intentional stop-tracking times; comparable behavioral patterns were found after alcohol administration. Three main modifications were made for the present study. First, inspired by the *www-model* of intentional action (Brass & Haggard, 2008), we designed our task such that it separates the *whether* and *when* components of intentional inhibition. According to the *www-model*, intentional inhibition should include three components of *what*, *when* and *whether*. These components are partially independent at the cognitive as well as the neural implementation level (Zapparoli et al., 2018; Zapparoli, Seghezzi, & Paulesu, 2017). We, therefore, distinguished '*whether* to inhibit' from '*when* to inhibit' to examine potential differential effects of alcohol on these distinct components. Second, the little fish was replaced by beverage bottles to increase ecological validity. In this way, the task was renamed as the Chasing Bottles task. Third, the decision either to continue or to stop tracking yielded different rewards. To continue tracking led to immediate reward (cf. the instant pleasure from drinking), whereas to stop tracking was associated with higher future reward.

The present study

The current experiment conforms largely to previous experimental designs. As shown in **Table S1a**, studies of acute alcohol use and response inhibition usually included an alcohol group and a placebo group. This allowed examining the pharmacological effect of alcohol as both groups expected alcohol delivery. To also explore the expectancy effect of alcohol on inhibitory control, we added a control group. The fully balanced placebo design was not adopted as the anti-placebo group (i.e., drink alcohol but expect non-alcoholic beverage) is difficult to realize (Martin & Sayette, 1993). We also administered questionnaires about impulsivity and reward sensitivity. Impulsivity was measured by Dickman's Impulsivity Inventory (DII, Dickman, 1990). Previous studies have found a positive correlation between SSRT and the dysfunctional impulsivity subscale (van den Wildenberg & Christoffels, 2010). The sensitivity to punishment and reward questionnaire (SPSRQ) was administered to explore whether performance on the Chasing Bottles task can be explained by variance in reward sensitivity (Torrubia, Ávila, Moltó, & Caseras, 2001). In addition, two questionnaires measuring the response to alcohol were also administered. The Self-Rating of the Effects of Alcohol (SRE) was used to test general sensitivity to alcohol (Piasecki et al., 2012; Schuckit, Smith, & Tipp, 1997), and the Brief Biphasic Alcohol Effects Scale (B-BAES) was used to test sedative and stimulant responses at different time points after alcohol administration (Rueger, McNamara, & King, 2009).

The main aim of the present study was to examine the effect of a moderate dose of alcohol on both stimulus-driven and intentional inhibition through a lexical stop-signal task and the Chasing Bottles task, respectively. The two computer tasks included a condition with alcohol-related stimuli to examine the effect of appetitive cues and their interaction with alcohol intoxication on inhibition performance. Equal numbers of males and females were recruited for a moderation effect test. We hypothesized that: 1) alcohol intake impairs both stimulus-driven and intentional inhibition; 2) these alcohol-related effects are stronger in a context with alcohol-related stimuli compared to non-alcohol related stimuli; 3) sex moderates the relationship between the group and task performance, with males being more influenced by alcohol; 4) stop-signal task performance, Chasing Bottles task performance, and DII should be weakly associated, as they represent different aspects of impulsivity.

Methods

Participants

A total of 111 participants were recruited, mostly university students. Inclusion criteria were: 1) aged between 18-25; 2) weight between 50-100 kg; 3) no alcohol-naïve and no alcohol dependency, identified by an AUDIT (Alcohol Use Disorder Identification Test, Saunders, Aasland, Babor, De la Fuente, & Grant, 1993) score between 5 and 16; 4) daily cigarettes < 4; 5) fluent in Dutch; 6) not on any medication; 7) normal or corrected to normal eyesight; 8) no diagnosis of neurological problems including epilepsy, head trauma; 9) Beck Depression Inventory for Primary Care score < 5 (Beck, Guth, Steer, & Ball, 1997). Prior to the experiment, written informed consent was obtained from all participants.

Questionnaires

Alcohol use disorder identification test (AUDIT)

The AUDIT (Saunders et al., 1993) is a 10-item survey used as a screening instrument for excessive or hazardous alcohol use. A total score of 8 is a reasonable cut-off for a variety of adverse outcomes (Conigrave, Hall, & Saunders, 1995). It has good reliability with median Cronbach's alpha of 0.80 in a review (Reinert & Allen, 2002).

Self-Rating of the Effects of Alcohol (SRE)

The individual level of response to alcohol can be determined with the 12-item SRE (Schuckit et al., 1997). Subjects are asked to indicate how many alcoholic beverages they would need to elicit one of four possible effects on three different moments in time (i.e. the first five times they ever drank: SRE-5; 3 months of drinking once a month: SRE-3; the period of heaviest drinking: SRE-H, Schuckit et al., 1997). The higher the SRE score, the lower the sensitivity to alcohol (Piasecki et al., 2012). SRE has good reliabilities in both self-reported and interview administrations (Ray, Hart, & Chin, 2011).

Brief Biphasic Alcohol Effects Scale (B-BAES)

The 6-item B-BAES is a measure of alcohol's acute stimulant and sedative effects (Rueger, McNamara, & King, 2009). The stimulation subscale consists of the adjectives energized, excited and up, while the sedative subscales make use of the words sedated, slow thoughts and sluggish. Both subscales use an 11-point Likert scale ranging from 0 ("not at all") to 10 ("extremely"). Subjects in the alcohol and placebo condition filled it out each time a breath sample was taken except for the baseline.

Dickman's impulsivity inventory (DII)

The DII (Dickman, 1990) includes two subscales to measure dysfunctional and functional impulsivity. The 23 items are in a yes/no format. Eleven items focus on functional impulsivity (e.g., "People have admired me because I can choose quickly"). Twelve other items tap dysfunctional impulsivity (e.g., "I often say and do things without considering the consequences"). Cronbach's alpha coefficient for the Dutch version was 0.84 for the dysfunctional dimension and 0.76 for the functional dimension (Claes, Vertommen, & Braspenning, 2000).

Sensitivity to punishment and sensitivity to reward questionnaire (SPSRQ)

The SPSRQ (Torrubia et al., 2001) is a 48-item yes/no response questionnaire developed to assess the Behavioral Inhibition System (BIS) and the Behavioral Activation System (BAS). The Sensitivity to Punishment scale (SP) measures behavioral inhibition under specific conditions of threat or punishment; and the Sensitivity to Reward scale (SR) reflects approach behavior to specific conditioned and unconditioned rewards, notably money, social status and sexual partners (Dawe & Loxton, 2004). Reliability of the SR and SP subscales in this study was good (i.e. Cronbach's alpha of 0.70, and 0.83, respectively).

Other questionnaires, including typical alcohol use (frequency of alcohol use, drinks per occasion, frequency of binge drinking, Korucuoglu, Gladwin, & Wiers, 2015), other

substance use (e.g., Core alcohol and drug survey, CORE, Presley, 1993), Desire for Alcohol Questionnaire (DAQ, Love, James, & Willner, 1998), Positive and Negative Affect Scale (PANAS, Watson, Clark, & Tellegen, 1988), and Rutgers Alcohol Problem Index (RAPI, White & Labouvie, 1989) are described in Supplementary Materials **S1** (see appendix to this chapter).

Modified stop-signal task

A lexical stop-signal task based on the study by Zack and colleagues (2011) was used to test stimulus-driven inhibition. Participants were instructed to press corresponding buttons ('Z' and '/') to actual words and non-words that were presented on a computer screen. A change in font color from grey to red indicated the external stop signal, which occurred on 25% of the trials. The actual words were selected by a separate group of participants, with length and frequency matched to the alcohol-related words. Forty alcohol-related words (in Dutch), 40 neutral words, and 80 non-words were selected and used in the testing stage (**Table S2**). Each trial started with a fixation screen for 500 ms, followed by a letter string that disappeared upon response or until 1500 ms had elapsed. Then a jittered inter-trial interval (ITI) followed, ranging from 1250 to 1750 ms in steps of 50 ms. The initial stop-signal delay (SSD) was 200 ms, and increased/decreased by 50 ms, respectively, after a successful/failed inhibition. This dynamic tracking procedure was adopted across blocks and for each word category separately. The testing stage consisted of a practice block and five equivalent experimental blocks. Each block consisted of 160 trials with all the selected stimuli in a random sequence without repetition. To practice the lexical decision task, a familiarization block (96 trails) with different stimuli was administered before drinking. The stop task took about 40 minutes to complete.

Chasing Bottles task

In this intentional inhibition task, a bottle moved ('floated') at 360 pixels/sec against the background of the bottom of an ocean, changing directions at random angles between 0 and 115 degrees and at intervals between 556 and 1250 ms. The participants' main task was to track the bottle by moving the computer mouse and to keep a yellow dot within a green zone of 2 cm radius (**Fig. 1a-1b**). A smaller bottle preceded the target bottle to indicate its course and to facilitate the ease and accuracy of tracking. A circle at the top left corner of the green zone served as the *go signal* (from red to green). After uninterrupted successful tracking for 2 s, a yellow star was displayed, which signaled the onset of a 20 s window. During this period, participants can stop tracking if they felt the urge to do so, or continue tracking to the end of a trial. Two counters presented reward feedback. For a stopped trial, participants earned points and a lottery ticket (**Fig. 1c**). The number of points was a random number between 2 and 50. Stopping too early and too late was associated with only 2 points and was discouraged. For a non-stopped trial, participants always earned 60 points (**Fig. 1d**). The points accumulated were converted into payment with the ratio of 1500:1 on the spot. The accumulated lottery tickets were associated with the chance of winning a €10 voucher upon project completion. Participants were instructed and trained to follow their urge to stop rather than preplan or use external cues (e.g., the spatial position of the bottle). They were also

instructed that some variability of tracking latency and decision to disengage/engage was monetary beneficial. A plastic bottle without brand was used in the familiarization stage. Two categories of bottles (alcoholic vs. non-alcoholic beverages, see **Fig. S1**) were used in the testing stage with valence, arousal, and urge values matched (Pronk, Deursen, Beraha, Larsen, & Wiers, 2015). The testing stage included 6 blocks, with 10 trials each. There was no repetition of bottles within one block. And stimuli were presented in a randomized order. At the end of this task, bottles were evaluated in terms of valence, arousal, and dominance with a 9-Likert scale. This task took about 35 minutes to finish.

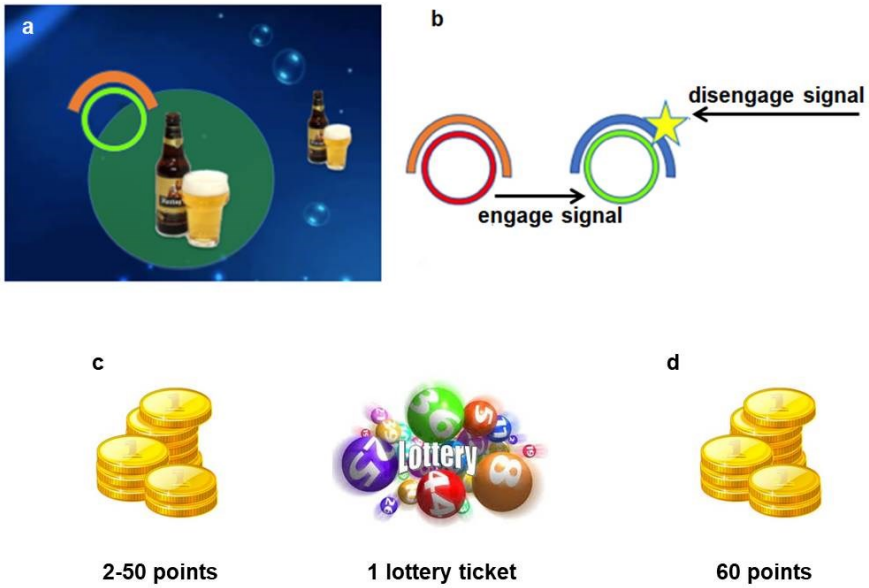

Fig. 1a The screen background and layout of the Chasing Bottle task. Participants move the mouse and keep the cursor within the green zone in order to track the floating bottle. **b** The engage and disengage signal of the task. When the circle turned from red to green, participants should start tracking. The appearance of the star signaled the beginning of a 20 s time window, within which participants can stop tracking if they felt the urge to do so. Otherwise, they can continue tracking until 20 s has elapsed and the trial reached its end automatically. **c** If the participant stopped tracking within the 20 s, the feedback for that trial included a lottery ticket (related to the possibility of winning a voucher in the future) and a random number of points (between 2 and 50, related to the extra payment). **d** If the participant did not stop tracking within the 20 seconds, they always got 60 points

Alcohol administration

Blood alcohol concentrations (BAC) of males and females were matched by administering 0.55g/kg and 0.45 g/kg of alcohol, respectively. The volume of vodka (40% alcohol by volume) was calculated through the following formula (Korucuoglu et al., 2015).

$$Males: volume = weight \times 0.55 \frac{g}{kg} \div 0.789 \frac{g}{ml} \div 40\%$$

$$Females: volume = weight \times 0.45 \frac{g}{kg} \div 0.789 \frac{g}{ml} \div 40\%$$

(Where 0.789 g/ml represents the density of ethyl alcohol)

A maximum of 4 standard drinks were administered to females and 5 for males, which was associated with the maximized weight. Alcoholic drinks were prepared with one portion of vodka and three portions of orange juice and divided into three drinks. The placebo drink was prepared with tonic water instead of vodka. To make it smell and taste like alcohol, drinks for the alcohol and placebo groups were prepared with a slice of lemon soaked in vodka, vodka sprayed on the rim of the glass and three drops of Tabasco sauce (McIlhenny Co., USA) on the top (Korucuoglu, Gladwin, & Wiers, 2016). The control group drank tap water.

Procedure

Participants were instructed to refrain from alcohol (24 h), other substances (1 week), smoking (4h), caffeine-containing drinks (4 h) and big meals (4 h) prior to the experiment. The tests took place between noon and 19 p.m.

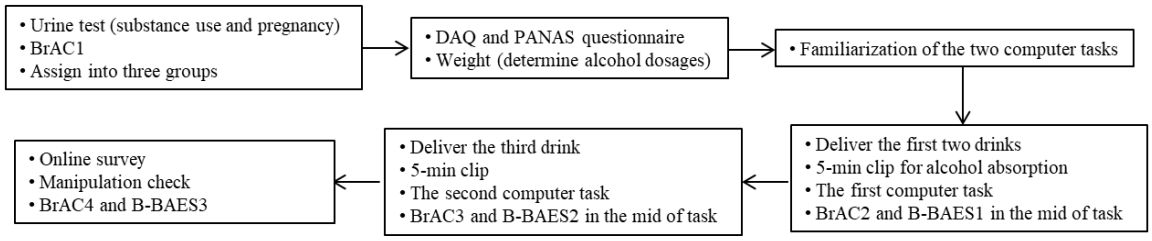

Fig. 2 The procedure of the experiment. BrAC: Breath Alcohol Concentration, DAQ: Desire for Alcohol Questionnaire, PANAS: Positive and Negative Affect Scale, B-BAES: Brief Biphasic Alcohol Effects Scale, the online survey included SRE (Self-Rating of the Effects of Alcohol), RAPI (Rutgers Alcohol Problem Index), DII-short (Dickman's impulsivity inventory short-version), SPSRQ (Sensitivity to punishment and sensitivity to reward questionnaire) and frequency of alcohol and binge drinking

As summarized in **Fig. 2**, the experiment consists of six mini parts. First, upon arrival in the lab, a urine test and a baseline breath alcohol concentration test (BrAC, by Alcoscan ALC-1) were performed to exclude past week substance use, pregnancy (females) and alcohol use in advance. Participants were then randomly assigned to one of three groups (i.e., Alcohol, Placebo or Control). Second, participant weight was measured to determine alcohol dosage to be administered. The DAQ and the PANAS were tested prior to alcohol administration as craving and mood were likely to be influenced by intoxication. Third, participants got familiar with the computer tasks by explanation and practice with different task stimuli. Fourth, the first two drinks were served continuously. Each had 3 minutes to finish and 2 minutes for mouth-wash. Next, a 5-minute short clip was played before performing the first computer task to allow alcohol absorption (Korucuoglu et al., 2015). Fifth, the third *top-up* drink was delivered, followed by another short clip and the second computer task. The order of the two computer tasks was counterbalanced across participants. Sixth, an online survey was administered, including the SRE, the RAPI, the DII, the SPSRQ, typical alcohol use questions, and the manipulation check question "How much alcohol do you think you have had?". BrAC

and the B-BAES were measured sequentially three times across the session (i.e., mid of the two computer tasks and end of the experiment). The procedure for the control group was almost the same, except that BrAC was only tested at baseline, B-BAES and the manipulation check question were untested. The whole experiment took about two hrs and 15 min to finish.

Participants received 20 euro or 2 course-credits, and up to €2.50 extra payment based on their performance in the Chasing Bottles task. The study was approved by the local ethics committee and complied with the 1989 Helsinki Declaration.

Statistical analysis

Questionnaires

For questionnaires AUDIT, CORE, DAQ, PANAS, SRE, PAPI, DII, and SPSRQ, a series of one-way ANOVAs were performed to compare the three groups. Breath Alcohol Concentration (BrAC) was analyzed within the alcohol group. One independent t-test was performed to compare males and females when they were performing the tasks; two paired t-tests were performed to compare values during different tasks, and the second and the third reading ($BrAC_2$ vs. $BrAC_3$)[1]. With regard to B-BAES stimulant and sedative subscales, two repeated-measures ANOVAs were performed with Group (alcohol/placebo) and Time Points as factors. To evaluate the 10 bottle pictures used in the Chasing Bottles task, three parallel one-way MANOVAs were performed for three different dimensions (i.e., valence, arousal, and dominance, see details in Supplementary Materials **S1**).

Stop-signal task

Four main dependent variables were calculated: the mean RT for correct go trials (go-RT), stop rates, SSRT, and SSD. The integration method was used to estimate SSRT, with longer SSRT indicating prolonged inhibition (Logan, 1994; Logan & Cowan, 1984). Repeated-measures ANOVAs were performed with Word Category (alcohol-vs. non-alcohol related) as within-subject factor, Sex, Consume Alcohol (yes/no), and Expectancy of Alcohol (yes/no) as between-subject factors. In that way, the three groups (alcohol, placebo, and control) were attributed with value (1,1), (0, 1), and (0,0) for the last two factors. For the non-words, similar ANOVAs were conducted without the factor of Word Category. In a secondary analysis, the correlation coefficients between SSRT and DII two subscales were calculated by averaging Fisher's Z of correlation coefficient of each group and transforming back to correlation coefficient (Silver & Dunlap, 1987).

Chasing Bottles task

There were two outcomes for each trial, namely whether the participants stopped tracking or not, and if stopped, the stopping latency. Survival analysis was performed on the time-to-event data (Ferreira & Patino, 2016; Sloan et al., 2019). Here the event is disengagement from tracking, which will be censored if the participant did not stop tracking

[1] $BrAC_2$ & $BrAC_3$: Breath alcohol concentration reading in the middle of the first and the second task, respectively.

within the 20 s time window as the survival time is incomplete. Multilevel survival analysis with *trial* as the first level and *participant* as the second level was adopted. Cox proportional hazards models were built by using the coxme package (Therneau & Lumley, 2015) in R 3.4.4 (Team, 2013). We found that Expectancy of Alcohol did not meet the proportional hazard assumption (Ng'andu, 1997) of the Cox model (χ^2 (1, N = 102) = 195, $p < 0.001$). Thus, the Cox model was fitted by stratifying the data set on that variable (Kleinbaum & Klein, 2012). The model included the main effect of Bottle Category, Consume Alcohol, Sex, their interactions, and the stratification variable Expectancy of Alcohol. A random subject ('frailty') term was included to account for inter-individual differences. In a secondary analysis, SSRT (alcohol-related, neutral), DII subscale scores, and reward sensitivity score was used to predict stopping probability in the Chasing Bottles task, one at a time.

Results

Randomization check

Table 1. Group comparison: Demographics, substance use and relevant questionnaires

Variables	Alcohol (n = 33)	Placebo (n = 40)	Control (n = 38)	*F*	*P*
Age	21.12(1.91)	21.10(1.96)	21.29(1.96)	0.11	0.90
Sex (M/F)	17/16	20/20	19/19	χ^2=0.02	0.99
AUDIT	8.91(2.74)	9.13(2.88)	9.29(3.09)	0.15	0.86
Smoker/ non-smoker	5/28	6/34	6/32	χ^2=0.01	0.99
Daily cigarette	2.2(0.84)	2.0(0.89)	2.0(0.89)	0.17	0.85
SRE					
SRE-5	4.27(1.58)	4.42(1.28)	4.26(1.59)	0.15	0.86
SRE-3	6.16(2.01)	6.71(1.94)	6.56(2.55)	0.61	0.54
SRE-H	8.11(2.72)	7.95(2.76)	7.90(3.30)	0.05	0.95
DII					
Functional	7.64(2.06)	7.45(2.54)	7.68(2.56)	0.1	0.90
Dysfunctional	2.85(2.70)	2.45(2.00)	3.26(2.52)	1.11	0.33
SPSRQ					
Punishment	9.31(5.44)	7.8(4.49)	9.16(4.49)	1.14	0.32
Reward	12.78(4.20)	13.13(3.50)	14.37(3.50)	1.83	0.17

Note. Mean (Standard Deviation), SRE-5: First 5 time, SRE-3: Last 3 months, SRE-H: Drunk the most, DII: Dickman's impulsivity inventory, SPSRQ: Sensitivity to punishment and sensitivity to reward questionnaire

Table 1 and **Table S3** together indicated that the three experimental groups did not differ in demographics (age, sex ratios), alcohol use severity (AUDIT, RAPI), tobacco use, other substance use (CORE), sensitivity to alcohol (SRE), impulsivity (DII), sensitivity to

reward and punishment (SPSRQ), pre-drinking craving (DAQ), and pre-drinking mood (PANAS), *ps* ≥ 0.15.

BrAC

Males and females showed comparable BrACs when they were performing the tasks (Males: *M* = 0.40 ‰, *SD* = 0.10, Females: *M* = 0.38 ‰, *SD* = 0.11, *t*(64) = 0.63, *p* = 0.53), indicating that the incoordinate amount of alcohol administered induced similar BrAC values among males and females. BrACs were similar during two tasks (stop-signal task: *M* = 0.39 ‰, *SD* = 0.10, Chasing Bottles task: *M* = 0.39 ‰, *SD* = 0.11, *t*(32) = 0.06, *p* = 0.96). However, $BrAC_2$ was lower than $BrAC_3$ (*M* = 0.34, *SD* = 0.09 vs. *M* = 0.44, *SD* = 0.09, *t*(32) = -8.69, *p* < 0.01, **Fig. S2**). This was controlled by adding *Task Sequence* as a covariate in the main analyses of both tasks.

Manipulation Check

There are two measures related to the manipulation check. These are; perceived alcohol consumed and B-BAES. First, participants in the alcohol group thought they drank more alcohol (*M* = 3.88, *SD* = 1.55, Rang: 1-10) than those in the placebo group (*M* = 2.04, *SD* = 1.50, Range = 0-5, *t*(71) = 5.20, *p* < 0.01), which was expected (Testa et al., 2006). Importantly, perceived alcohol contents in both groups were significantly above 0 (*ps* < 0.01), validating the placebo manipulation. Second, the stimulation subscale of B-BAES revealed a main effect of Time Point (*F* (2, 142) = 20.16, *p* < 0.01, η^2 = 0.22, **Fig. S3a)**. It reduced on average of 0.80 from the mid of the first task to the mid of the second task (*p* < 0.01), followed by an averaged decline of 0.10 at the end of the experiment (*p* = 0.73), indicating subjects felt less stimulated as the session proceeded. The main effect of Group (alcohol vs. placebo) was not significant (*F* (1, 71) = 2.96, *p* = 0.09), nor was its interaction with Time Point (*F* (2, 142) = 1.10, *p* = 0.35). This indicated a consistent effect of Time Points across Groups on B-BAES stimulant. The sedative subscale also revealed a main effect of Time Points (*F* (2, 142) = 3.95, *p* = 0.02, η^2 = 0.05, **Fig. S3b**). It increased by an average of 0.06 from the mid of the first task to the mid of the second task (*p* = 0.70), followed by a reduction of 0.43 at the end of the experiment (*p* < 0.01). The main effect of Group was also significant (Alcohol: *M* = 5.17, *SD* = 1.86, Placebo: *M* = 4.20, *SD* = 1.92, *F* (1, 71) = 5.87, *p* = 0.02, η^2 = 0.08), indicating subjects felt more sedated after alcohol than after placebo. The interaction between Time Point and Group was non-significant (*F* (2, 142) = 0.02, *p* = 0.98).

Stop-signal task

Data from five participants were excluded from the analysis, including three in the placebo group disbelieved drinking alcohol, one participant with a baseline BrAC level above zero, and one participant tested positive for Tetrahydrocannabinol. **Table 2** displays task performance (go-RT, stop rates, SSRT, and SSD) per drink condition of the analyzed sample (N = 106). The repeated-measures ANOVA of SSRT revealed a significant interaction between Consume Alcohol and Sex (*F* (1, 99) = 5.02, *p* = 0.03, η^2 = 0.05, see **Fig. S4a**). Post-hoc test revealed two simple effects. Females who drank alcohol had significantly shorter SSRT than females who did not drink alcohol (216 (70) vs. 239 (60), *F* (1, 51) = 4.35, *p* =

0.04, $\eta^2 = 0.08$); For those who did not have alcohol (placebo and control), males had shorter SSRT than females (210 (60) vs. 238 (60), F (1, 73) = 10.03, p = < 0.01, $\eta^2 = 0.09$). No main or interaction effects were significant with regard to go-RT, stopping rates and SSD. As to the non-words, no main effect of Consume Alcohol, Expectancy of Alcohol, Sex, task sequence, nor their interactions were significant concerning go-RT, stop rates, SSRT and SSD.

Table 2. Stop-signal task performance: Descriptive values

Gender	Male						Female					
Drink Condition	Alcohol (N = 17)		Placebo (N = 18)		Control (N = 18)		Alcohol (N = 16)		Placebo (N = 18)		Control (N = 19)	
Word Category	Alcohol	Neutral	Alcohol	Neutral	Alcohol	Neutral	Alcohol	Neutral	Alcohol	Neutral	Alcohol	Neutral
go-RT	705 (137)	712 (124)	640 (110)	637 (112)	640 (126)	663 (148)	699 (123)	717 (135)	702 (139)	712 (126)	703 (98)	712 (91)
Stop Rates	46.65 (9.51)	48.23 (8.36)	48.23 (7.31)	49.75 (7.55)	46.43 (10.61)	50.04 (9.52)	47.60 (6.57)	47.96 (7.86)	46.23 (13.92)	45.98 (9.04)	46.49 (11.01)	48.62 (10.88)
SSRT	219 (79)	221 (79)	214 (59)	199 (82)	206 (52)	212 (51)	207 (61)	226 (79)	261 (71)	250 (49)	231 (51)	225 (63)
SSD	463 (120)	472 (130)	397 (89)	408 (76)	418 (139)	416 (142)	454 (145)	471 (136)	443 (167)	461 (156)	459 (140)	452 (117)

Note. Mean (Standard Deviation)

Chasing Bottles task

Data from nine participants were excluded from the analysis, including the first five participants that received different reward instructions (the ratio of immediate and delayed reward differed from the remaining participants), two disbelieved drinking alcohol (one less than in the stop-signal task as one participant expressed disbelief after finishing the stop task), one baseline BrAC violated zero and one tested positive for Tetrahydrocannabinol. The main effect of Consume Alcohol on stopping probability was significant. Alcohol consumption decreased the rate of disengagement by approximately 53% compared with placebo and control over the course of a trial (likelihood ratio test: χ^2 *(1)* = 1333.16, $p < 0.01$, Hazard Ratio (*HR)* = 0.47, 95% CI [0.29, 0.78]). The interaction between Consume Alcohol and Bottle Category was also significant (χ^2 *(1)* = 5.51, $p = 0.02$, *HR* = 1.10, 95% CI [0.91, 1.34], **Fig. 3**). Post-hoc analysis revealed that, 1) participants in the alcohol group stopped more often when tracking alcohol-related bottles compared to soft drink bottles (χ^2 *(1)* = 418.59, $p = 0.03$, *HR* = 1.14, 95% CI [1.01, 1.28]); 2) compared with those who did not drink alcohol, participants in the alcohol group had lower stopping probability tracking soft drink bottles (χ^2 *(1)* = 570.81, $p < 0.01$, *HR* = 0.60, 95% CI [0.41, 0.88]) and marginally also for alcohol-related bottles (χ^2 *(1)* = 587.33, $p = 0.09$, *HR* = 0.71, 95% CI [0.48, 1.04]). The effect of Expectancy effect of Alcohol on stopping probability was depicted in **Fig. 4**. For the first 7 s, participants who expected alcohol were more likely to stop tracking, which was the opposite for the remaining 13 s.

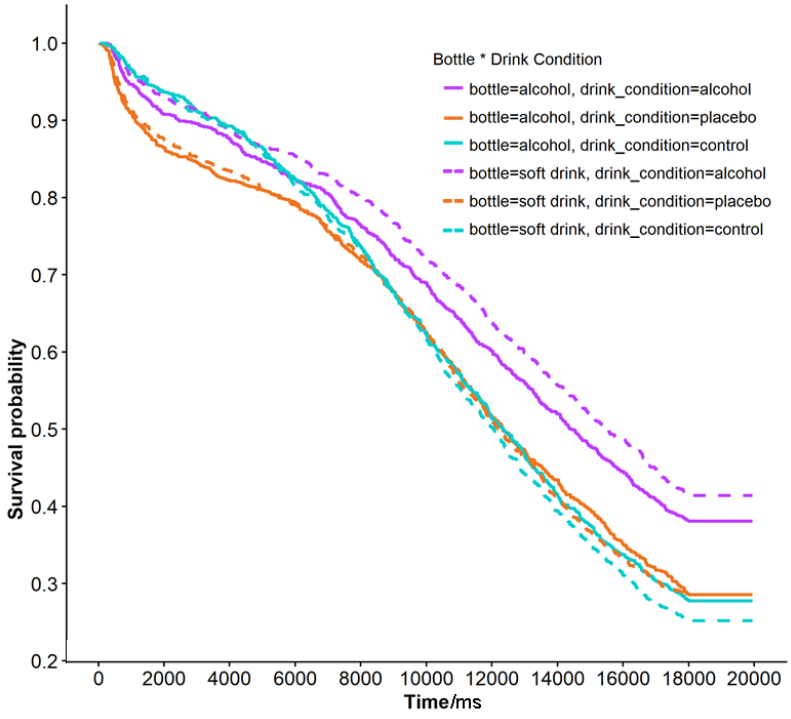

Fig. 3 Survival curve for each drink condition per bottle category. People who drank alcohol generally stopped less frequently compared with the placebo group and the control group. The placebo and the control group showed similar stopping probability as the survival lines almost overlap, especially from 8 s on. For the alcohol group, people were less willing to stop tracking soft drink bottles than alcohol bottles

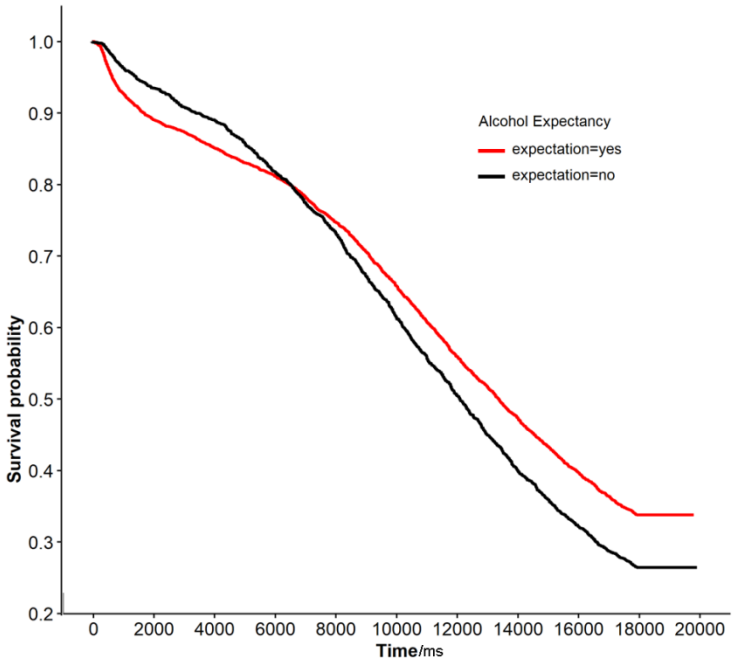

Fig. 4 The effect of Alcohol Expectancy on stopping probability as a function of time. For the first 7 s, participants who thought they had alcohol (i.e., the alcohol group and the placebo group), were more likely to stop tracking compared with the control group. While for the remaining 13 s, the opposite pattern was observed, i.e., participants who expected alcohol were more likely to continue tracking compared with controls at any time point

Correlation Analyses

Detailed results for this section can be found in Supplementary Materials **S2**. In brief, SSRT to alcohol-related words and neutral words were both negatively correlated with functional impulsivity (r = -0.26, $p < 0.01$; r = -0.24, p = 0.02, respectively), but unrelated with stopping probability in the Chasing Bottles task. This indicated that a lower functional impulsivity score was associated with prolonged stimulus-driven stopping latency. Neither DII subscales nor reward sensitivity was a significant predictor of stopping probability in the Chasing Bottles task.

Discussion

The current study explored the effect of a moderate dose of alcohol on stimulus-driven inhibition as well as intentional inhibition. For stimulus-driven inhibition, alcohol consumption shortened SSRT in females; and for those who did not drink, males had shorter SSRT than females. Regarding intentional inhibition, participants who drank alcohol were less likely to disengage from tracking compared with participants in the placebo and control conditions, especially when viewing soft-drink bottles. In addition, the expectancy effect of alcohol showed a time-dependent pattern on intentional disengagement rate, namely decreasing the stopping probability after an initial increase. What's more, SSRT was

negatively associated with functional impulsivity, but unrelated with stopping probability in the Chasing Bottles task.

Acute alcohol use and stimulus-driven inhibition

Opposite to Zack and colleagues, who reported alcohol consumption prolonged SSRT in a group of male problem drinkers, we failed to find such a main effect in a sample with males and a similar number of females without a problematic drinking history. Specific factors of the present study might explain this difference. To clarify those potential factors, we did a brief literature review (see **Table S1a**) and followed up with some preliminary analyses (see results in **Table S1b**). We compared studies that *did* find the impairing effect of alcohol on the stop-signal task performance with studies that *did not* in terms of sample characteristics, task parameters, the dosage of alcohol administered, and the study design. Regarding *sample characteristics*, gender ratio and typical alcohol use are possible moderators. It is suggested that males are more vulnerable to the acute effect of alcohol than females (Fillmore & Weafer, 2004), and heavy drinkers are hypersensitive to the short-term effect of alcohol compared to light drinkers (Field, Wiers, Christiansen, Fillmore, & Verster, 2010). However, both assumptions have very limited empirical and theoretical support. As to *task parameters*, the most relevant one is the modality of the stop signal. It was stated that studies using *auditory* stop signals report statistically significant differences in SSRT compared to studies using *visual* stop signals (Guillot, Fanning, Bullock, McCloskey, & Berman, 2010). The underlying reasons remain unclear, except that auditory stop stones are perceived as more intense (van der Schoot, Licht, Horsley, & Sergeant, 2005). Regarding the *dosage of alcohol administered*, in principle, a high dose of alcohol was more likely to cause impaired inhibition than a smaller amount (0.8g/kg vs. 0.4g/kg, Caswell, Morgan, & Duka, 2013). However, exceptions exist such that even a high dose failed to impair response inhibition (BAC: 0.10%: Guillot, Fanning, Bullock, McCloskey, & Berman, 2010; 0.8g/kg: Dougherty, Marsh-Richard, Hatzis, Nouvion, & Mathias, 2008), and a low dose was sufficient to cause stopping impairment (0.4g/kg, de Wit, Crean, & Richards, 2000; Nikolaou, Critchley, & Duka, 2013; Reynolds, Richards, & de Wit, 2006). The *study design* mainly refers to whether alcohol and placebo manipulation is a between-subject or within-subject factor and whether there is a baseline/pre-drink measure. These design options are relevant as individuals differ in their response to alcohol and there is a day-to-day variance of inhibition performance (Campbell, Chambers, Allen, Hedge, & Sumner, 2017). The fact that our groups were matched in terms of demographics, typical alcohol use, and *especially* sensitivity to alcohol, made these concerns less vital in our study. Overall, **Table S1b** revealed that none of these potential factors had a significant effect on research findings (i.e., positive/negative). Therefore, the current absence of an alcohol effect on SSRT might not readily be attributed to participants' *low* typical alcohol use, the use of *visual* rather than *auditory* stop signals, the *low* amount of alcohol administered, and/or *between* rather than *within-subject* design without a baseline measure. Note that, **Table S1b** might have not included all relevant studies due to a non-exhaustive literature search, and statistical analyses that simultaneously take multiple factors in consideration might be more appropriate than t-test for study comparison.

In sum, the effect of alcohol consumption on stimulus-driven inhibition was less robust as one might have imagined. In fact, nearly half of the studies that used the stop-signal task failed to identify a significant main effect of alcohol (see **Table S1a** here, and Table 5 in Bartholow et al., 2018). By contrast, studies used the cued go/no-go task (Marczinski, Abroms, van Selst, & Fillmore, 2005) *all* confirmed the acute alcohol effect (Bartholow et al., 2018). A potential reason is that the prepotency/urgency of stopping is increased by invalid go cues in the cued go/no-go (Bartholow et al., 2018). Furthermore, alcohol may influence inhibitory control only during the decreasing limb of BAC (Bartholow et al., 2018), which helps explain the less apparent effect when the whole BAC curve was considered. As a next step, researchers can consider adding (in)valid cues into the stop-signal task, and investigate why alcohol influences inhibition as a function of the BAC curve.

In addition, we found an interaction between sex and the pharmacological effect of alcohol use on SSRT. That is, females who drank alcohol had significantly shorter SSRT than females in the other two groups, and males who did not drink alcohol (placebo and control) had shorter SSRT than females. However, both effects were likely due to the prolonged SSRT of females in the placebo group (**Fig. S4b)**, which was not due to strategical slowing-down of go RT (see comparable mean go RT with females in the other two groups in **Table 1**).

Acute alcohol use and intentional inhibition

Our most important finding is a pharmacological effect of alcohol on intentional inhibition. Participants who received alcohol stopped less often compared with participants in the placebo and control groups. This is in line with the assumption that alcohol primes an intentional inhibition impairment, which contributes to increased drinking or loss of control over alcohol-seeking behavior (Field, Wiers, Christiansen, Fillmore, & Verster, 2010). This finding might pertain to attention narrowing and/or delay aversion. First of all, alcohol is hypothesized to induce a narrowing of the attentional focus, such that dominant cues become the center of attention and peripheral cues are ignored (Steele & Josephs, 1990). In the current context, tracking bottles is the primary assignment; thinking about disengagement and the corresponding reward is of secondary concern. Accordingly, after alcohol intake, participants might be more focused on the things at hand and prefer to continue tracking. Alternatively, delay aversion might be augmented after alcohol intake. In the Chasing Bottles task, to continue tracking yielded greater immediate reward, whereas disengagement was associated with future reward. Thus, choosing not to stop to some extent reflects myopia for the future, which is associated with alcohol intake (Reynolds et al., 2006). In our previous work (Liu et al., submitted), that focused merely on the *when* component of intentional inhibition, an alcohol effect was absent. This coincides with the fact that results from the survival analysis got fully replicated in a traditional ANOVA of the *whether* component with the same factors. In contrast, the *when* component-related ANOVA indicated no effect of alcohol use. This dissociation is supported by separable neuromechanisms underlying the *three W* components (see Zapparoli et al., 2018), and emphasized alcohol's unique effect on the *whether* component. In terms of the expectancy effect of alcohol, it let participants adopt

compensatory strategies to counteract its disruptive effects such as not stopping during the first 7 s (Marczinski & Fillmore, 2005). The remaining 13 s showed an opposite, pharmacologically driven reduction in intentional inhibition.

The salience of alcohol-related stimuli

An important neuroadaptation in addiction is that the brain's *wanting* system becomes hypersensitive ("sensitized") to drugs and drug-associated stimuli (Robinson & Berridge, 1993). Stimulus type (alcoholic vs. non-alcoholic words) did not affect stimulus-driven inhibition in our sample of non-dependents, similar to what Zack and colleagues found (Zack et al., 2011). Confrontation with alcohol-associated stimuli might induce response inhibition deficits in substance abusers, and more so when dependence progresses (Robinson & Berridge, 2001). In the Chasing Bottles task, opposite to our hypothesis, those who drank alcohol had a higher stopping probability when tracking alcohol-related than soft-drink bottles. This counterintuitive finding matched some others (Adams, Ataya, Attwood, & Munafò, 2013; Monk, Qureshi, Pennington, & Hamlin, 2017). A possible explanation is that a general difficulty in inhibiting appetitive stimuli (e.g., alcohol, water vs. washing liquid) is likely to be formed once a motivational state was activated (Wadhwa, Shiv, & Nowlis, 2008). Alternatively, some participants may successfully teach themselves to treat alcohol-related stimuli as a stop-signal after drinking (cf. Fishbach & Shah, 2006). In a broader picture, the incentive-sensitization theory was only partially confirmed by Jones and colleagues' recent meta-analysis (2018). They found that the exacerbated impairment caused by appetitive cues disappeared after correcting for publication. Future studies might consider inducing a stronger effect by creating a multi-sensory substance-related context (visual, olfactory and locomotor, Field & Jones, 2017).

Stimulus-driven inhibition versus intentional inhibition

There are two possible explanations why results diverged between the two inhibition tasks. One interpretation is that intentional inhibition and stimulus-driven inhibition are considered to be fundamentally distinct (Ridderinkhof, van den Wildenberg, & Brass, 2014). This raises the importance of introducing intentional inhibition to the addiction-related field as its deficits might underlie the entrenched pattern of drinking. Alternatively, the discrepant findings might be due to different cue forms used (lexical cues in the stop-signal task vs. graphical cues in the Chasing Bottles task). However, cue modality was proved to have limited influence on stimulus-driven inhibition (Jones et al., 2018). Therefore, the first explanation appears more convincing. Contemplating on these findings gives rise to an interesting speculation, such that stimulus-driven inhibition and intentional inhibition displayed vulnerability to alcohol at different stages of a drinking episode. Intentional inhibition is likely to be influenced by a small to moderate amount of alcohol, which promotes further consumption. Afterward, when the accumulated consumption reaches a threshold, stimulus-driven inhibition is likely to be impaired, reflected by impulsive behavior. This hypothesis needs further testing.

Limitations and future directions

Some limitations should be mentioned. First, the BrAC levels varied between the tasks and were relatively lower than expected. Using an alcohol clamping method that minimizes the variability might be considered for future research (Ramchandani et al., 2006). Second, in the Chasing Bottles task, a longer tracking period was not always associated with more immediate reward. This may be criticized as it did not mimic the ever-increasing pleasure acquired from continued drinking in reality. However, if the immediate reward kept increasing during that 20s, the premium response (i.e. to disengage tracking just before the 20 s window elapsed to maximize their total reward) would be very likely to be executed, which discouraged intentional inhibition. Such criticism does not apply to non-stopped trials as it indeed produced immediate reward and thus was closer to reality. This also helps explain the effect of alcohol particularly on the *whether* component. A better balance between free will and ecological validity was required for the task. Third, incorporating incentive feedback in the Chasing Bottles task might have tapped into other cognitive processes such as strategy learning. This rewarding system was designed on purpose, as one feature of volition is reason-responsive (i.e. all (non-)actions have a reason, Haggard, 2018). Unfortunately, it introduced some adverse influence in addition to the benefits. Fourth, the 20s time-window for participants to decide to stop tracking was rather arbitrary. In other words, if a longer decision period was allowed, such as 60s, the intentional stopping probabilities might have been different. This can be argued against as alcohol consumption consistently decreased the stopping rate at any time point within that 20s (i.e., survival curves representing the alcohol condition were consistently above the other two conditions), and in reality one hardly hesitated/struggled for 1 min before a decision to accept/reject the next beer can be made.

Conclusion

In the current study, we investigated the acute effect of alcohol on two forms of response inhibition: stimulus-driven inhibition and intentional inhibition. Alcohol intake did not systematically affect stimulus-driven inhibition. It shortened females' SSRT compared to placebo and control, and males in the placebo and control groups had shorter SSRT than females. Intentional inhibition, as tested with the Chasing Bottles task, was negatively influenced by alcohol intake. Participants who drank alcohol were less likely to stop their bottle-tracking behavior. In sum, stimulus-driven inhibition and intentional inhibition represented two types of response inhibition; the importance of intentional inhibition in the development and maintenance of addiction should be considered.

SUPPLEMENTARY MATERIALS

S1. Questionnaires

Description

The Core alcohol and drug survey (CORE, Presley, 1993) examines the use, scope, and consequences of alcohol and other drugs in college settings (Presley, 1993). Respondents were asked to indicate how often within the last month they had used each of the 11 specific types of drugs (alcohol, tobacco, marijuana, cocaine, amphetamines, sedatives, hallucinogens, opiates, inhalants, designer drugs, and steroids).

Desire for Alcohol Questionnaire (DAQ, Love, James, & Willner, 1998). The DAQ is developed to measure three aspects of craving: (a) strong desires/intentions to drink (DAQ-crave), (b) negative reinforcement (DAQ-negative), and (c) positive reinforcement and ability to control drinking (DAQ-positive) (Kramer et al., 2010). The 14-item questionnaire uses a 7-point Likert scale, ranging from "strongly disagree" to "strongly agree". Reliability of the DAQ-total score and subscale scores were found to be adequate with Cronbach's α of 0.70, 0.70, 0.76 and 0.86 respectively (Courtney et al., 2013).

Positive and Negative Affect Scale (PANAS, Watson, Clark, & Tellegen, 1988). The PANAS is used to provide measures of positive and negative affect. The 20 items describe either a positive (e.g., interested) or a negative (e.g., distressed) feeling or mood state. Subjects are asked to indicate to what extent these words describe how they feel at the present moment or have felt over the past week. The PANAS uses a 5-point Likert scale ranging from "very slightly" to "very much". The Cronbach's alpha reliabilities for both scales are high, generally ranging from .83 to .90 for Positive Affect, and from .85 to .90 for Negative Affect (Watson & Clark, 1999).

Rutgers Alcohol Problem Index (RAPI, White & Labouvie, 1989). The RAPI is a 23-item screening tool used to assess alcohol-related problems. It uses a 4-point Likert scale: never, 1-2 times, 3-5 times, and more than 5 times. Subjects are asked to indicate how many times they experienced each statement, e.g., "Not able to do your homework or study for a test". The coded numbers (0-3) were added together across items to form a scale ranging from 0 to 69. This scale has a reliability of .92 and a 3-year stability coefficient of .40 for the total sample (Helene R White & Labouvie, 1989).

Questions on the frequency of alcohol use and binges (Korucuoglu et al., 2015). Alcohol use frequency, quantity and binge drinking were assessed separately for weekdays and weekends. Different from Korucuoglu et al., (2015), the timeframe we used was last month instead of the past three months. An extra question about maximum drinks in a 24 hour period was also asked.

Analyses

For all these questionnaires (i.e. CORE, DAQ, PANAS, PAPI), a one-way ANOVA was carried out with Drink Condition (Alcohol/Placebo/Control) as the independent variable.

For the evaluation of bottles (i.e. those used in the Chasing Bottle task), three parallel one-way MANOVAs were carried out for Pleasant, Arousal and Dominance separately. For each MANOVA, evaluations of 10 different bottles were the dependent variables and Drink Condition was the independent variable.

Results

Among the 111 participants, there were 33 (17 males) participants in the alcohol group, 40 (20 males) in the placebo group and 38 (19 males) in the control group. **Table S3** listed the descriptive and statistical data for comparison between the three groups. There were no significant differences for all these questionnaires and their subscales between the three groups (all $p \geq 0.15$).

The MANOVA revealed non-significant associations between the pleasantness of bottles and Drink Condition (F (4, 214) = 0.70, *Wilk's* Λ = 0.97, p = 0.59). Similarly, there were non-significant associations between the arousal of bottles and Drink Condition (F (4, 214) = 1.61, *Wilk's* Λ = 0.96, p = 0.33) and dominance values of bottles and Drink Condition (F (4, 214) = 1.76, *Wilk's* Λ = 0.94, P = 0.14). These findings together indicated that the three groups have similar evaluations of alcohol bottles and soft drink bottles in terms of pleasantness, arousal, and dominance.

S2. Chasing Bottles task: SSRT and personalities in predicting stopping probability

SSRT to alcohol-related words did not predict stopping probability for alcoholic bottles (*HR* = 1.00, p = 0.43, 95% CI [0.999, 1.002]). Similarly, SSRT to neutral words did not predict stopping probability for soft drink bottles (*HR* = 1.00, p = 0.46, 95% CI [0.998, 1.001]). This indicated that stimulus-driven inhibition, as assessed by SST, and intentional inhibition, assessed by the Chasing Bottle task, represented different aspects of response inhibition. In addition, none of the following personality aspects predicted stopping probability; functional impulsivity (*HR* = 1.04, p = 0.08, 95% CI [1.00, 1.08]), dysfunctional impulsivity (*HR* = 1.02, p = 0.35, 95% CI [0.98, 1.07]), and reward sensitivity (*HR* = 0.98, p = 0.06, 95% CI [0.96, 1.00]). This indicated that inhibition measured by the Chasing Bottles task was unrelated to trait impulsivity measured by the questionnaires; variances of stopping probability cannot be explained by the variance of reward sensitivity.

Table S1a Overview of studies on acute alcohol use and stop-signal task

Study	Stop signal modality	Male %	Drinks per week	Alcohol to placebo comparison	Pre-drink/ baseline condition	N	Number of trials	Ratio of stop	Alcohol dose	SSRT calculation	Main findings	Effect size	Positive finding?§
Bartholow et al. (2018)	Visual	50%	7.5	Between (alcohol/placebo/control)	Yes	216	160	25%	0.80 g/kg (men), 0.72 g/kg (women)	Median	The stop-signal performance was impaired by alcohol relative to placebo and control only on the decreasing limb of BrAC.	$\eta_p^2 = 0.07$	Partially
Campbell et al. (2017)	Visual	37.50%	Audit < 16, at least 6 binge occasions for the past year.	Within (alcohol/placebo)	Yes	40	288	25%	0.8 g/kg	Integration	Time (pre-post drink)× condition (alcohol/placebo) was significant. post-hoc test was not reported.	$\eta_p^2 = 0.13$	Yes
Caswell et al. (2013)	Visual	50%	19.8	Between (placebo/low dose/high dose)	No	48	120	25%	0.4g/kg or 0.8 g/kg	Integration	Only high dose induced longer SSRT than placebo.	$\eta_p^2 = 0.16$	Partially
de Wit et al. (2000)	Auditory	70%	5	Within	Yes	17	64	25%	0.2 g/kg, 0.4 g/kg, 0.8 g/kg	NA, SSRT was calculated from the last block, 64 trials.	The 0.4 g/kg and 0.8 g/kg dose prolonged SSRT compared to placebo.	$\eta_p^2 = 0.26$	Yes
Dougherty et al. (2008)	Visual	50%	10(male), 6(female)	Within (placebo and four different doses of alcohol)	Yes (tested -0.5h, 0.25h, 1h, 2h after drinking)	30	NA	25%	0.2, 0.4, 0.6, 0.8 g/kg	NA, stop rate is the main dependent variable.	Only a main effect of time was found (impulsive response kept increasing), regardless of alcohol dose.	NA	No
Dougherty et al. (2015)	Visual	60%	19(male), 22(female)	Between (placebo/alcohol)	Yes	179	NA	25%	0.3 k/kg × three times separated by one hour each.	NA, stop rate is the main dependent variable.	Compared with placebo, alcohol intake increased the rate of failed inhibition.	NA	Yes

Easdon & Vogel-Sprott, (2000)	Auditory	100%	10	Between (alcohol/placebo)	Yes	16	176	28.4%	0.62 g/kg	NA	Compared to baseline, alcohol caused more failed inhibition, which was not the case for placebo.	$\eta_p^2 = 0.46$	Yes
Fillmore & Blackburn, (2002)	Auditory	81.25%	7	Between (control/alcohol/placebo)	Yes	48	176	28.4%	0.65 g/kg	NA	People who drank alcohol failed more inhibition compared with placebo and control.	$\eta_p^2 = 0.19$	Yes
Fillmore & Vogel-Sprott, (1999, 2000)	Auditory	100%	7	Between (alcohol/placebo)	Yes	14	176	27%	0.62 g/kg	NA	Compared to baseline, alcohol caused more failed inhibition, which was not the case for placebo.	NA	Yes
Gan et al. (2014)	Visual	74%	10	Within (alcohol/placebo)	No	42	320	20%	0.6 g/kg	Integration	Alcohol significantly prolonged SSRT.	Cohen's d = 0.63	Yes
Guillot et al. (2010)	Visual	44%	About 10.5	Between (placebo/alcohol)	No	141	100	80%	Target BAC: 0.00%, 0.05%, 0.075% and 0.10%	NA, stop rate is the main dependent variable.	No main effect of alcohol, nor its interaction with gender was significant.	NA	No
Kareken et al. (2013)*	Visual	61%	13.9	Within (placebo/alcohol)	No	18	360	66.7%	BrAC of 0.06%	Integration	Alcohol infusion produced longer SSRT than placebo saline infusion.	NA	Yes
Loeber and Duka (2009)[a]	Auditory	53%	24	Between (placebo/alcohol)	Yes	36	320	25%	0.8 g/kg	Median	Time × group interaction was found. Post-hoc test found alcohol group had lengthened SSRT compared to baseline. No clear difference between alcohol and placebo at T2 was reported.	Time x Group Interaction $\eta_p^2 = 0.13$;	Partially

Loeber and Duka (2009)[b]	Auditory	50%	23.2	Between (placebo/alcohol)	Yes	32	320	25%	0.8 g/kg	Median	Only marginal interaction between time and group was found. The post-hoc test revealed that the alcohol group had longer SSRT at T2 compared to baseline. And no clear difference between alcohol and placebo group at T2 was reported.	Time x Group Interaction $\eta_p^2 = 0.11$	No
Loeber and Duka (2009)[c]	Auditory	50%	24.5	Between (placebo/alcohol)	Yes	32	320	25%	0.8 g/kg	Median	Alcohol group had longer SSRT compared with placebo after drink, but no difference at baseline.	Time x Group Interaction $\eta_p^2 = 0.52$; Post-hoc alcohol vs. placebo post drinking: Cohen's d = 1.40	Yes
McCarthy et al. (2012)	Visual	55%	NA	Within alcohol (increasing & decreasing limb) vs control	No	29	NA	NA	0.72 g/kg for men, 0.65 g/kg for women	NA	Alcohol session produced marginally longer SSRT (p=0.052).	$\eta_p^2 = 0.12$	No
Mulvihill et al. (1997)	Auditory	50%	5.5	Between (alcohol/placebo/control)	Yes	48	176	27%	0.62 g/kg for men, 0.54 g/kg for women		Compared to baseline, alcohol caused more failed inhibition, which was not observed for the placebo and control group.	$\eta_p^2 = 0.22$	Yes
Nikolaou et al. (2013)	Visual	50%	26	Between (placebo, low dose, high dose)	Yes	42	120	25%	0.4 g/kg or 0.8 g/kg	Mean	No difference at baseline, however, both alcohol groups had longer SSRT compared with placebo.	Time x Group Interaction: $\eta_p^2 = 0.156$, High dose vs placebo: Cohen's d = 0.93	Yes

Peacock et al. (2015)	Visual	100%	7.4	Within (placebo/alcohol/alcohol mixed with 500ml energy drink/alcohol mixed with 750ml energy drink)	No	19	48 per session, three sessions (0.05% ascending BrAC, ~0.08% peak BrAC, and ~0.05% descending BrAC)	25%	Target BAC: 0.05% and 0.08% after first and second administration, respectively.	Mean	No main effect of condition, time and their interaction. Only when BrAC was 0.08%, the alcohol mixed with 750ml energy drinks condition had longer SSRT than the alcohol condition.	Cohen's d = 0.37	No
Plawecki et al. (2018)	Visual	50%	14.5	Within (alcohol/placebo)	Yes	49	180	33%	BrAC 60 mg/dL	NA	Alcohol significantly reduced P3 amplitude in the slow SSD compared to the fast SSD group, but significantly increased P3 latency in the fast SSD compared to the slow SSD group.	NA	NA
Reynolds et al. (2006)	Auditory	46%	6.6	Within (placebo/ low dose/high dose)	No	24	NA	25%	0.4g/kg or 0.8 g/kg	Median	Both low and high dose alcohol consumption lengthened SSRT compared to placebo.	$\eta_p^2 = 0.30$	Yes
Spinola et al. (2017)	Auditory	48%	NA (moderate to heavy drinkers)	Within (control/placebo/alcohol)	Yes	75	192	25%	0.65g/kg	NA	No beverage condition or beverage condition × time interaction effects on inhibition were found.	beverage group × time: $\eta_p^2 = 0.04$, beverage group: $\eta_p^2 = 0.02$	No

Note. BrAC: Breath Alcohol Concentration, NA: not available, *descriptive data shown in this table were from the family history negative group only, §In total, 7 studies found the null effect of alcohol, 11 studies found impairing effect of alcohol on stop signal performance, 3 studies partially confirmed the impairing effec

Table S1b Comparison of studies with positive findings vs. negative findings

Variables	Positive findings (n = 16[1])	Negative findings (n = 12[1])	*t*	*p*
Male percentage	62.23 (18.92)	55.08 (15.64)	-1.06	0.30
Units of alcohol/week	15.71 (13.28)	10.85 (5.88)	-1.08	0.29
Sample size	40.69 (39.06)	51.83 (44.28)	0.71	0.49
Number of trials	190.77 (99.81)	134.86 (93.77)	-1.22	0.24
Stop signal probability	27.97 (10.50)	35.00 (22.25)	0.98	0.35
Stop signal (auditory/visual)	9/7	3/9	χ^2= 2.73	0.10
Study design (between/within-subject)	9/7	4/8	χ^2= 1.45	0.23
Baseline measure (yes/no)	11/5	7/5	χ^2= 0.32	0.57
Alcohol dose administered (high/medium/low/super low)[2]	0/2/7/7	2/2/3/4	χ^2= 3.62	0.31

Note. Mean (Standard Deviation), [1]For studies administered different amount of alcohol, we treated them as multiple cases, [2]high: more than 0.65g/kg, medium: 0.65g/kg to no more than 0.4g/kg, low: 0.4g/kg to more than 0.2g/kg, super low: no more than 0.2g/kg

Table S2 Stimuli used in the stop-signal task (in Dutch)

Neutral words (n = 40)	**Alcohol-related words (n = 40)**	**Corresponding non-words (n = 80)**	
prothesen	alcoholisch	priseson	alhevadich
huig	fust	syoi	fult
promo	baco	prami	bazo
verhuiswagen	kroegentocht	verleukwaben	krielenbosch
eiffeltoren	bacardi	eiffilbaken	banarvo
oplezen	bavaria	opkezen	bamalia
wegvaren	brandewijn	weglarpen	bravolijf
zeebaars	jenever	zeemijrs	jegevol
vlaktes	brouwen	vlintis	breizen
voltage	likeur	vokleume	libeut
zuidwest	heineken	zijdpast	hoevekel
taille	pils	tauti	pirs
zakmes	merlot	zakfos	murlos
kleven	tappen	klabon	tappin
decennia	slijterij	deseunijke	sleutekij
vuilnisbakken	aangeschoten	veuperlaazen	aanbeschalen
berechten	dronkenschap	bewochten	droewenschip
kous	port	koum	pijrt
reizigers	brouwerij	reimigors	breikerij
musical	cocktail	mivicol	cochlirt
pijlen	zuipen	pijwen	zuimen
wolk	rum	wolg	rom
fraai	shot	froei	shab
puin	gin	peum	gon
lampen	tequila	lanven	teqoleu
staken	kater	stirgen	kijter
gelijke	cognac	gezeupe	cownam
heuvels	kroeg	hoekems	kroew
zonen	wodka	zoben	voplo
weglopen	uitgaan	wetlagen	uitgook
ogenblik	alcohol	ogelblot	alcijlijs
fabriek	borrel	faltreik	bozzim
eisen	proost	eiben	preuks
bomen	whisky	boben	whekijs
adres	drank	adlis	drand
been	bier	beol	biem
rol	wijn	rov	weun
namen	dronken	nonen	dromkin
koud	feest	kolp	fijst
slang	brak	sleung	braf

Table S3 Comparison of three groups on questionnaires

Variables	Alcohol (N = 33)	Placebo (N = 40)	Control (N = 38)	*F*	*P*
	M (SD)	*M (SD)*	*M (SD)*		
Alcohol use past month					
drinking days (weekend)	4.00(2.10)	4.39(2.46)	3.99(2.13)	3.40	0.67
drinking days (weekdays)	4.80(3.37)	5.58(3.21)	4.61(3.33)	0.94	0.40
drinks per occasion (weekend)	4.94(2.47)	4.68(2.12)	4.82(2.49)	0.12	0.89
drinks per occasion (weekdays)	3.47(2.53)	3.48(2.39)	3.76(2.66)	0.21	0.81
binge drinking days (weekend)	10.58(7.95)	13.38(7.89)	14.88(7.61)	2.73	0.07
binge drinking days (weekday)	7.62(7.22)	9.14(7.31)	10.84(8.11)	1.61	0.21
Max within 24 hrs. (weekend)	12.21(5.08)	12.05(5.52)	12.89(4.78)	0.29	0.75
Max within 24 hrs. (weekday)	9.56(6.24)	9.80(5.11)	9.99(6.20)	0.05	0.95
CORE					
Alcohol	10.45(9.30)	11.15(10.91)	13.95(11.81)	1.07	0.35
Marijuana	1.36(2.26)	0.38(1.35)	1.45(3.66)	1.95	0.15
Cocaine	0.15 (0.87)	0	0	1.17	0.31
Cigarette	4.24(10.47)	3.72(9.58)	5.14(10.83)	0.18	0.83
Ecstasy	0.3(1.21)	0.13(0.8)	0	1.22	0.30
Hallucinogens	0	0	0	--	--
Stimulants	0	0.13(0.8)	0	0.91	0.41
Calming agents	0	0.13(0.8)	0.26(1.13)	0.92	0.40
Opiates	0	0	0	--	--
Volatile substances	0.15(0.87)	0	0	1.17	0.31
Club drugs	0.15(0.87)	0.26(1.12)	0.13(0.81)	0.19	0.83
DAQ					
Crave	13.45(4.02)	13.75(4.22)	12.92(4.99)	0.34	0.71
Negative	9.73(3.88)	10.03(3.45)	9.05(4.62)	0.59	0.56
Positive	20.21(2.58)	19.80(2.68)	19.92(3.03)	0.21	0.81
PANAS					
Positive	32.79(5.95)	33.00(6.13)	32.97(5.77)	0.01	0.99
Negative	16.94(4.74)	16.55(5.19)	16.00(5.01)	0.31	0.73
RAPI	9.24(6.56）	7.20(4.09）	8.29(5.77)	1.26	0.29

Note. CORE: Core alcohol and drug survey (how many times were these drugs used in the past month), DAQ: Desire for Alcohol Questionnaire, PANAS: Positive and Negative Affect Scale, RAPI: Rutgers Alcohol Problem Index

Fig. S1. Bottles used in the Chasing Bottles task

Source: Amsterdam Beverage Picture Set (Pronk, van Deursen, Beraha, Larsen, & Wiers, 2015)

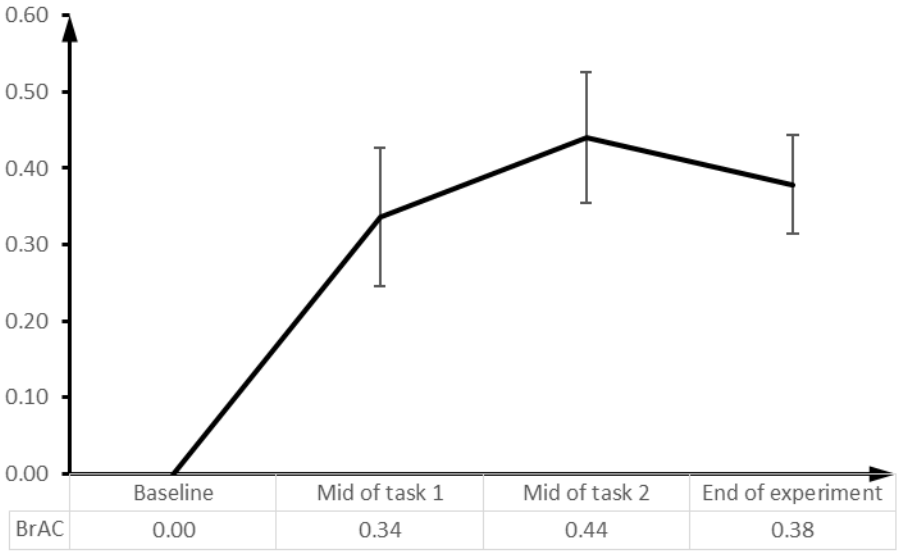

Fig. S2. Breath alcohol concentration at each reading

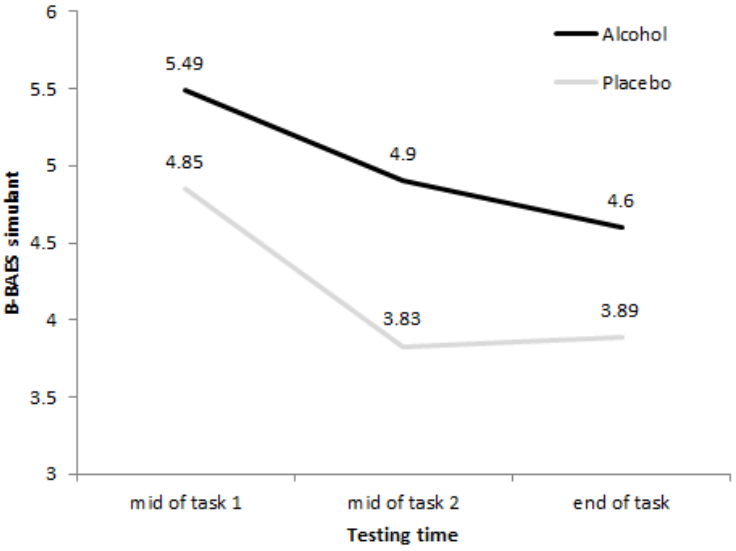

Fig. S3a. Simulant subscale of B-BAES for alcohol and placebo groups at different time points. For both groups, the simulant ratings declined significantly from the mid of task 1 to the mid of task 2. Though at each testing points the alcohol group felt more stimulant than the placebo group, this difference did not reach statistical significance

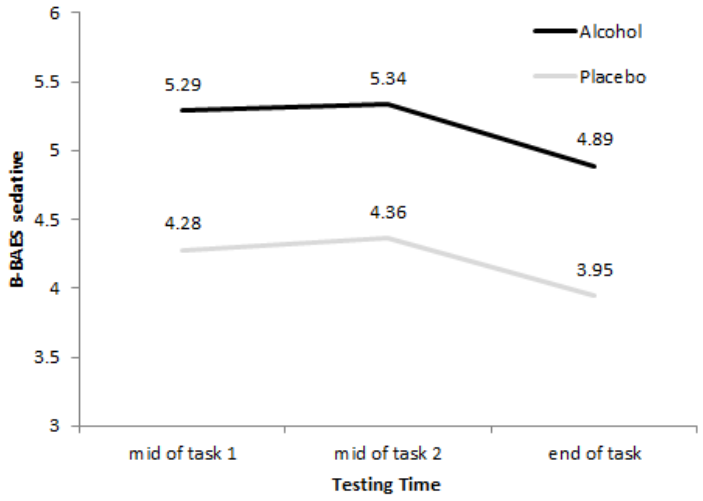

Fig. S3b. Sedative subscale of B-BAES for alcohol and placebo groups at different testing points. The alcohol group felt more sedative than the placebo group throughout the whole study. Also, there was a significant decline of sedative rating from the mid of task 2 to the end of task for both groups

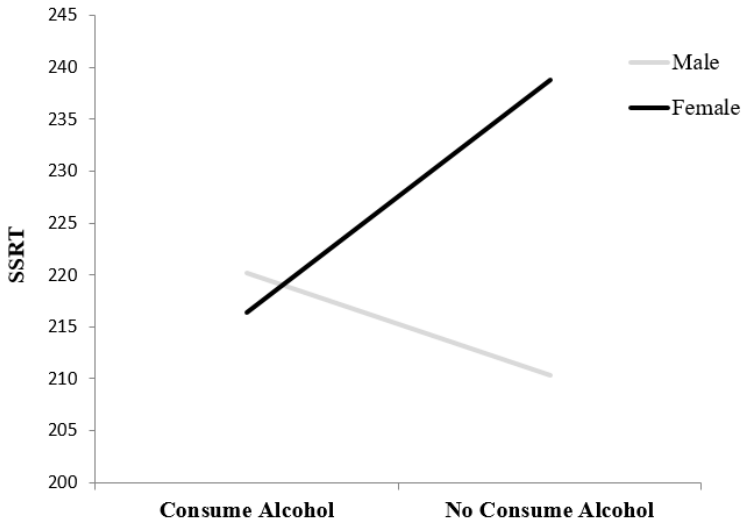

Fig. S4a. The interaction between Sex and the pharmacological effect of alcohol in SSRT. Only for females, drinking alcohol shortened SSRT significantly, and for those who did not drink alcohol, males had shorter SSRT than females

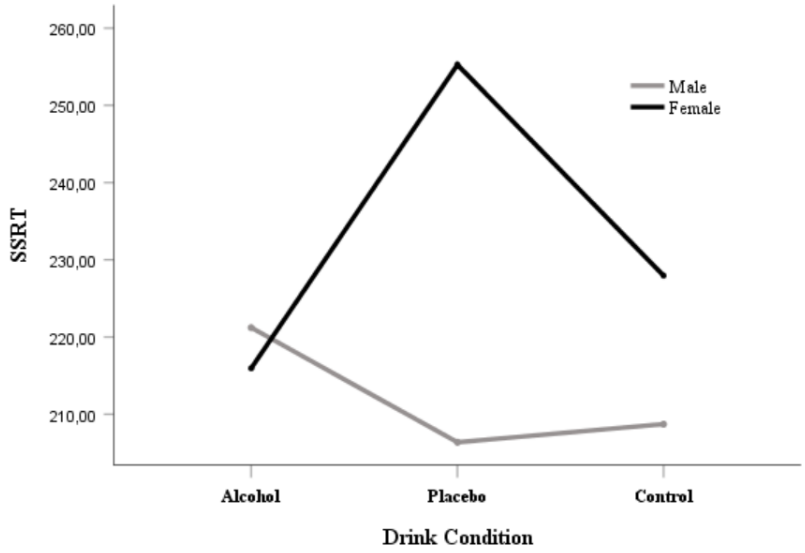

Fig. S4b. Sex and Drink group interaction on SSRT. As can be seen, interaction in **Fig. S4a.** was mainly driven by the lengthened SSRT of females in the placebo group

Short Clips:

Neistat, C. Make it Count. (2012). Retrieved from

https://www.youtube.com/watch?v=WxfZkMm3wcg March 20, 2017.

DreamWorksTV. Penguins of Madagascar. (2014). Retrieved from

https://www.youtube.com/watch?v=AWxy9C5svFU March 20, 201

Chapter 5

Keep it cool: Combining implementation intentions and monetary incentives to moderate alcohol consumption in a bar

This chapter has been submitted for publication as:

Liu, Y., van den Wildenberg, W. P. M., Ridderinkhof, K. R., Wiers, R. W. Keep it cool: Combining implementation intentions and monetary incentives to moderate alcohol consumption in a bar.

ABSTRACT

We tested the effectiveness of implementation intentions in reducing alcohol consumption in a natural context: a bar. Participants (n=121) visiting a local pub were randomized into three conditions: control, motivational trigger, and motivational trigger plus implementation intentions. There was no effect of condition on the amount of alcohol consumption. However, the combined condition was associated with an increase in *feeling influenced to drink less*, which in turn was predictive of drinking less directly after the brief intervention. Although the two brief interventions failed at the group level, the combined interventions did show promise in reducing drinking in a bar-context.

Introduction

Alcohol-related morbidity and mortality are severe global problems that come with huge social, health, and economic costs (Rehm et al., 2009). Effective interventions targeted at reducing alcohol use and/or relapse rate, therefore, are needed. One main characteristic of people with alcohol-use problems is self-control deficits, which has been reported based on both self-reported measures (Coskunpinar et al., 2013; Stautz & Cooper, 2013) and behavioral measures (i.e., Go/No-Go task, stop task, Smith et al., 2014). An effective self-regulation strategy geared towards facilitating the control of specific critical goal-directed behaviors concerns forming specific if-then plans, called implementation intentions, in the general form: "if I am in situation X, then I will do Y" (Gollwitzer, 1999). The thus-formed association may cause the automatic activation of goal-directed behavior Y in situation X (Gollwitzer & Sheeran, 2006). Implementation intentions have positive effects on behavioral outcomes, especially in populations with action control deficits (e.g., ADHD and substance use disorders, Gollwitzer 1999; see meta-analysis by Toli et al., 2016). The main aim of this study was to test the effectiveness of implementation intentions and monetary motivation to reduce alcohol use in a public bar.

Investigating the effectiveness of implementation intentions in a bar (i.e., a *hot* context, with abundant alcohol-related stimuli, and associated with good mood and positive social interactions) is relevant for several reasons. First, many people wish to restrain their alcohol use without totally stopping drinking and avoiding high-risk situations such as a bar. For instance, all heavy drinkers participated in an online intervention wished to restrain but not totally stop drinking (Wiers et al., 2015). The failure to withdraw from a drinking situation might be caused either by the overwhelming social goal (e.g., drink on Friday after work) over the alcohol restraint goal (Köpetz et al., 2013; see goal conflict model: Stroebe et al., 2013) and/or by over-confidence in one's capacity to resist temptations (Restraint Bias Theory, Nordgren et al., 2009).

Second, retrospective accounts of alcohol consumption were widely used in studies investigating implementation intentions in reducing alcohol use (e.g., Timeline Followback, Sobell & Sobell, 1992, Alcohol Outcome Record, Norman et al., 2019, see **Table S1** for an overview). However, retrospective approaches may be suboptimal in terms of its underestimation of the actual, real-time alcohol consumed (Dulin, Alvarado, Fitterling, & Gonzalez, 2017; Monk, Heim, Qureshi, & Price, 2015), and its limitation in unpicking the independent contribution of drinking on a single occasion and the number of drinking episodes to an overall drinking decrease during a certain period (at least in the way that results were reported in many studies, e.g., Armitage, 2009, 2015; Armitage & Arden, 2016; Caudwell et al., 2018). The latter drawback is critical because self-control strategies which have to be employed when drinking are already initiated (cf. reduce alcohol use on a single occasion) differ from the ones that can be employed when avoiding high-risk situations (e.g., not visiting bars, not buying alcohol to reduce drinking episodes).

Although it was reported that implementation intentions can reduce binge drinking frequency, this cannot be equalized as a reduction of drinking per occasion, as binge drinking

was not optimally defined in those studies (i.e., heavy drinking on a daily basis rather than per occasion or within two hours, Norman & Wrona-Clarke 2016; Norman et al., 2018; Norman et al., 2019). Until now, only Moody and colleagues (2018) clearly stated that implementation intentions reduced alcohol consumption by limiting quantities per episode, in addition to a small effect on drinking frequency. In sum, evidence on the effect of implementation intentions in reducing alcohol use on a certain episode is scarce.

Third, research findings with *typical alcohol use* information (e.g., monthly alcohol consumption) cannot always be replicated by using *drinking in a specific situation*. For instance, implicit attitude towards alcohol was related with binge drinking frequency, but unrelated with alcohol intake in a (semi)naturalistic setting (i.e., a laboratory bar, Larsen et al., 2012). Possible reasons include peer influence and context priming effects (Larsen et al., 2012).

Before formulating if-then plans, it is necessary to promote the participant's motivation to limit alcohol use (Heckhausen & Gollwitzer, 1987). Many motivational interventions used persuasive communications by mentioning outcomes of the unwanted behavior, such as 'reducing alcohol use will help you avoid negative consequences'(Caudwell et al., 2018) and 'drink within the government-suggested margins' (Armitage, 2009). In order to activate a more self-involved restraint goal, we followed the strategy used by Muraven et al., (2002). As a motivational trigger to restrain drinking, they informed participants that their driving skills were tested with a driving simulator after drinking and that they received a prize if they performed well. We made two changes here. First, instead of using a driving simulator, we administered a computer driving game, which is more feasible in a bar. Second, the driving game was actually performed twice rather than only mentioned as an upcoming challenge. That is, the motivational trigger was to encourage participants to drink less and perform better an hour later in order to receive an additional payment. This rewarding technique operates in a similar way as the contingency management (CM) intervention, which reduces substance use by providing alternative non-drug reinforces; for instance, participants received a voucher with various monetary values for submitting a substance-free urine sample (Higgins et al., 1994). CM has been shown effective in reducing the relapse rates of various substances (alcohol use: Barnett et al., 2011; Barnett et al., 2017; meta-analysis: Prendergast et al., 2006). More importantly, such monetary incentive does not facilitate substance use after contingency payment (Corby, Roll, Ledgerwood, & Schuster, 2000) nor does it undermine the internal motivation of substance restraint (Petry, Alessi, Olmstead, Rash, & Zajac, 2017).

As a secondary concern, factors that might influence alcohol use in a naturalistic environment were also examined. These include personality characteristics and sex composition of a drinking group. First, personality characteristics such as impulsivity (Coskunpinar et al., 2012; Stautz & Cooper, 2013) and sensation seeking (Hittner & Swickert, 2006) have been found to positively correlate with alcohol use and alcohol-related problems. Furthermore, impulsivity has also been associated with drinking speed and ineffectiveness of restraint measures in a *hot* context (Wiers, Ames, Hofmann, Krank, & Stacy, 2010). To assess

relevant personality characteristics, the short Substance Use Risk Profile Scale (SURPS, Woicik et al., 2009) was administered.

Second, drinking-group sex composition may influence the drinking speed of males and females differently. More specifically, a study found that males drink faster in all-male groups than in mixed-gender groups, whereas females drink faster in a mixed-sex group (van de Goor et al., 1990). However, another study found that for both sexes, drinking speed was faster with mixed-sex groups than with same-sex groups (Thrul, Labhart, & Kuntsche, 2017). Inconsistent research methods (data collection through observation vs. repeated measures by Ecological Momentary Assessment), sample characteristics (general population with the majority of visitors under 25 vs. all high-education institute students) and locations of testing (the Netherlands vs. Switzerland), among other things, likely caused the discrepant research findings. Along with Thrul and colleagues (2017), we categorized sex composition as all-males, all-females, majority-males, majority-females, and mixed-equally.

To summarize, we tested the effect of a brief motivational intervention in isolation and in combination with implementation intentions on reducing alcohol use in a natural bar-context. We adopted an additive design, such that three experimental conditions were included: 1) a control group, 2) a condition with monetary motivation only, and 3) a condition with monetary motivation plus the formation of an implementation intention. Meanwhile, we also examined the effect of personality characteristics and drinking-group sex composition on drinking behavior. We hypothesized that 1) alcohol consumption is the lowest in the combined brief intervention group, followed by the motivational trigger only group, and further by the control group; 2) the higher the impulsivity and sensation seeking scores, the more alcohol is consumed. Regarding the effect of drinking-group sex composition, due to the inconsistency of previous findings, we did not formulate a specific hypothesis.

Methods

Participants

One hundred and twenty-one participants were recruited while they were drinking alcohol in a pub on campus. The majority of them were students or university employees. Participants met the following criteria: 1) aged between 18-35; 2) have not drunk more than 4 standard drinks before participation; 3) planned to drink alcohol in the next hour; 4) no tourists; 5) planned to stay in the pub for at least eighty minutes (i.e., time needed for testing). Eligible participants were asked whether they were interested in participating in a study about drinking and healthy eating behavior. Note that multiple participants from the same drinking group were allowed to participate.

Materials

Questionnaires

We used two questionnaires to assess typical alcohol use. The Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) reliably identifies individuals who are hazardous

drinkers and are likely to have an alcohol use disorder (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998; Frank et al., 2008; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993). For assessment of drinking pattern, a binge drinking score was calculated from the Alcohol Use Questionnaire (AUQ, Mehrabian & Russell, 1978) with the equation of (Item 10) × 4 + Item 11 + (Item 12) × 0.2 (Townshend & Duka, 2005). Craving for alcohol was tested with 5-items visual analogue scales (Adams et al., 2017). A mean score was calculated by dividing the sum score by the count of entries. The SURPS consists of 23 items that assess four personality traits: hopelessness, anxiety sensitivity, impulsivity, and sensation seeking. Cronbach's alphas for these subscales were 0.73, 0.85, 0.71, and 0.78 for the English version (Long et al., 2018), and 0.85, 0.69, 0.67, and 0.68 for the Dutch version (Malmberg et al., 2010).

Monetary motivation

The driving game called Road Lane Splitter was selected and downloaded from the Microsoft store. On the screen, a motorcycle is running with high speed through ever-changing traffic. Participants should use keyboard buttons A/D or Left/Right to control the motorcycle. Action control is called for to avoid colliding with other vehicles. Meanwhile, hitting coins on the way helps to collect points. Given that this game was served to enhance motivation to reduce alcohol consumption, its performance was only used to reward participants, rather than as an outcome measure. Participants in the two active motivation conditions were told that (unknown to the control group): "*You will play this driving game again one hour from now. If your performance improves (i.e., collect more coins), your reward gets doubled for the post-drinking stage (i.e., €5 instead of €2.5). However, after playing the game for the first time, you will realize that it is a challenging game. Like real driving, your performance is likely to be negatively influenced by the consumption of alcohol*".

Implementation intentions: The formation of 'If-Then' associations

Implementation intentions were formed by asking participants to write down an if-then sentence. Alcohol-related if-then sentences were adopted from Arden and Armitage (2012) and rephrased to match the bar settings. Participants in the control condition and those in the motivation condition were instructed to formulate a fast-food related if-then sentence. This was designed to dissociate the possible effects of alcohol-related implementation intentions from general demands associated with asking people to plan to change their behavior. For both alcohol and fast-food related implementation intentions, three examples of if-situations and three examples of goal-directed then-actions were provided on a form (see Supplementary Materials **S2-3**, appendix to this chapter). Participants can freely choose their if-then sentence by combining one pair of provided examples or by formulating their own if-then sentence. Either way, they were asked to write down the sentence and process the contents.

Before making the food-related if-then plans, participants in the control condition and the motivation condition were told that: "*Drinking and healthy eating behavior are closely related to each other. For example, if you feel hungry when leaving the bar, you might want*

to go to a snack bar and buy something that is not healthy. To help you develop a healthier eating habit, we will ask you to formulate a snack-related if-then sentence".

By contrast, participants in the motivation plus alcohol-related implementation intention condition were told that: "*people are more likely to stick to their plans when they formulate an 'if-then' sentence*"

Procedure

The experiment consisted of three stages, as depicted in **Fig 1**. In stage one, participants in all three groups: 1) were given half a glass of water for mouth-wash; 2) filled out an online survey through Qualtrics including demographics, AUDIT-C, the last three items of AUQ, and SURPS; 3) were asked how much alcohol they already had on the day of testing; 4) played the driving game for the first time; 5) were breathalyzed by Alcoscan ALC-1 (Breath Alcohol Concentration, $BrAC_1$). The second half of stage 1 involved the intervention, where participants received different experimental instructions and implementation intention forms according to the experimental conditions (see above). The weight and height questions were intentionally inserted into the motivation induction and implementation intentions formation to make the food-related implementation intentions more credible.

In stage two, participants continued their bar visit, drinking *ad libitum* for one hour. In the meantime, the experimenter filled out the experimenter form (Supplementary Materials **S4**). To prevent foreknowledge about the experimental conditions, participants were asked not to talk with their friends about the experiment during drinking.

In stage three, upon participants' returning, they did the mouth-wash and played the driving game for the second time. Then a short interview was conducted (Supplementary Materials **S5**), which contained two important questions relevant to our analysis. The first one was 'How much alcohol did you consume during the past hour?'. Participants were encouraged to report in as detailed as possible, including the brands and corresponding consumptions (e.g., a ¼ glass of normal beer, 2/3 of red wine). This quantity was the dependent variable in the main analysis. The second question was 'Do you think your alcohol intake was influenced by the experiment?'. Possible replies were 'Yes, I drank more', 'Yes, I drank less', and 'No influence'. Answers to this question were coded into the variable *feeling influenced to drink less* that was used in the main analysis. The experiment ended with the assessment of $BrAC_2$. Participants received €5 (€2.5 each for stage one and stage three) or €7.5 (for those not in the control group and improved driving performance) as payment. The procedure was approved by the Institutional Review Board of the University of Amsterdam (project number: 2018-COP-8774) and complied with institutional guidelines and the declaration of Helsinki. Written informed consent was obtained from all subjects.

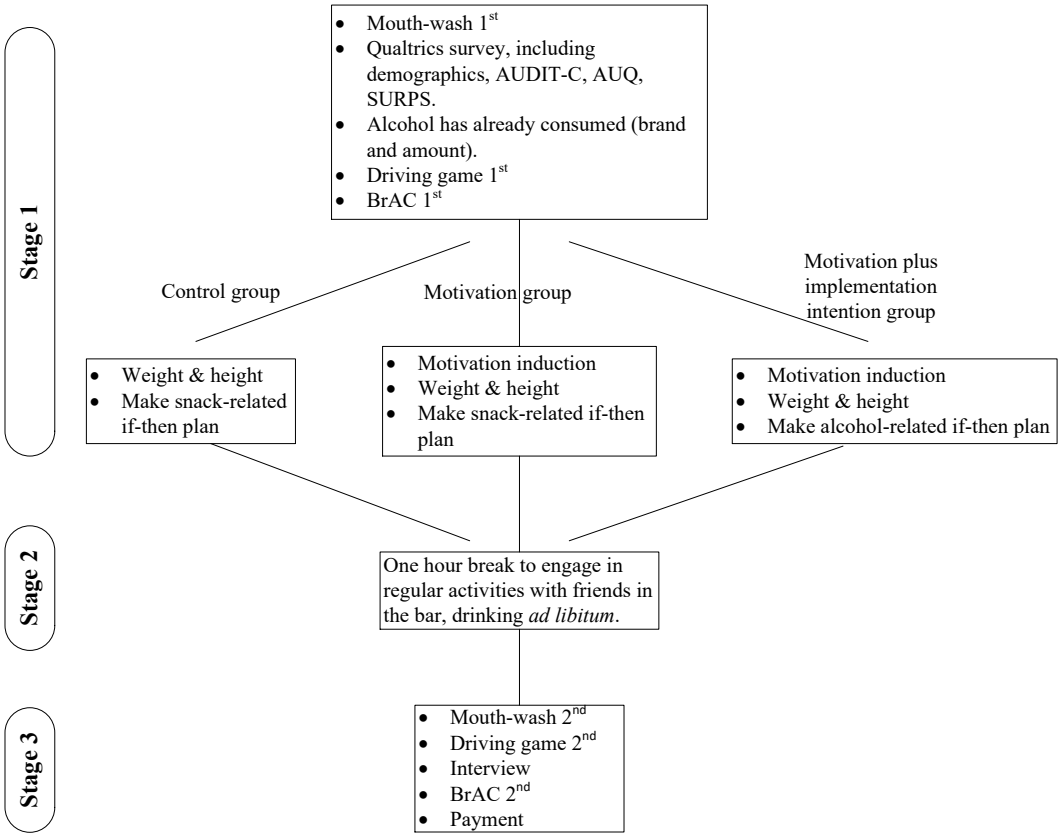

Fig 1. The procedure of the experiment. The experiment contained can be divided into three stages by the one-hour drinking period. AUDIT-C: alcohol use disorder identification test-consumption, AUQ: alcohol use questionnaire, SURPS: substance use risk profile scale, BrAC: breath alcohol concentration

Data Preparation and Analysis

Our main analysis concerns alcohol consumption during stage two. The amount of alcohol consumed was transformed into grams of ethanol according to **Table S2**. A three-step hierarchical regression was performed with predictors entered in the following sequence: (step 1) Age, Sex, Typical alcohol use (an integrated score of AUDIT-C and the Binge score, since these were highly correlated, see below), Craving, Impulsivity and Sensation seeking; (step 2) Motivational trigger (whether being promoted to drink less or not), and Implementation intentions (whether alcohol-related if-then plan was made or not); (step 3) *Feeling influenced to drink less* (yes or no).

We also performed a number of secondary analyses: 1) a Chi-square test and a series of one-way ANOVAs on Demographics, Typical alcohol use, and Personality traits, for the purpose of randomization checks; 2) a correlation analysis to test the association between Typical alcohol use and Personality traits; 3) a Chi-square test to compare the distribution/relative proportions of *Feeling influenced to drink less* across groups; 4) a validation test of self-reported alcohol consumption by its correlation with ΔBrAC (ΔBrAC = $BrAC_2$ - $BrAC_1$ + 0.15, where 0.15 is the hourly metabolism rate of alcohol for moderate drinkers; Jones 2010); 5) a linear regression analysis to examine the effect of Drinking-group

sex composition on Alcohol consumption, for males and females separately; 6) a one-way ANOVA to compare compliers to non-compliers (i.e., those who made valid versus invalid if-then plans), regarding Typical alcohol use, Personality traits, Drinking in the situation, and Drinking-group sex composition.

Results

Sample

Those who did not participate in the last stage (n=6) were excluded and the analyses were conducted with the remaining 115 participants. Of the 115 participants, 26 did not make valid if-then plans (control: 11, motivation: 7, and motivation plus implementation intention: 8; total compliance rate: 77%). We ran parallel analyses with and without those 26 participants (i.e., per protocol analysis, Norman et al., 2019). Results for the 115 sample are presented below, and the 89 subsamples in **Table S3-S6**.

Randomization check

The Chi-square test and one-way ANOVAs indicated that the three groups were comparable in terms of demographics (i.e., Sex, Age, Education level, Body mass index), Typical alcohol use (i.e., AUDIT-C, Binge score), and Personality traits (i.e., Impulsivity and Sensation seeking), all *p*-values > 0.30, see **Table 1.**

Table 1 Comparisons of demographics, alcohol use and personality traits between three groups

	Control	Motivational trigger	Motivational trigger + Implementation intentions	*F*	*P*
	N = 39	N = 39	N = 37		
Male (%)	15 (38.5)	17 (43.6)	20 (54.1)	$\chi^2 = 1.93$	0.38
Age	24.08 (4.41)	23.41 (3.52)	23.14 (3.23)	0.63	0.53
BMI	21.81 (2.47)	21.83 (2.25)	22.98 (2.92)	2.57	0.08
Education Level	5.00 (1.32)	4.67 (1.46)	4.86 (1.42)	0.55	0.58
AUDIT-C	5.69 (2.08)	6.46 (2.20)	6.08 (1.89)	1.36	0.26
Binge score	28.88 (14.90)	31.04 (19.45)	29.89 (17.49)	0.15	0.86
BrAC-1	0.23 (0.26)	0.14 (0.16)	0.18 (0.26)	1.21	0.30
BrAC-2	0.37 (0.39)	0.35 (0.27)	0.33 (0.22)	0.16	0.86
Craving	59.41 (17.77)	59.42 (16.15)	54.87 (20.56)	0.78	0.46
SURPS					
Impulsivity	10.08 (2.74)	10.90 (2.17)	10.51 (1.98)	1.22	0.30
Sensation seeking	16.51 (3.27)	17.41 (3.19)	16.73 (2.87)	0.88	0.42
Hopelessness	11.97 (2.99)	12.72 (2.93)	12.30 (3.11)	0.60	0.55
Anxiety Sensitivity	12.46 (2.42)	11.85 (2.28)	12.16 (2.04)	0.73	0.49

Note. Mean (Standard Deviation)

Main Analysis: Hierarchical regression in predicting post-intervention-hour drinking

Variables entered into the regression model were first checked for multicollinearity. Variance inflation factors (VIF) for all variables were below 1.5, which indicated no serious

multicollinearities among the predictors (Hair, Black, Babin, & Anderson, 2010). **Table 2** displays the β values of the predictors at each step. The final model was significant ($R^2 = 0.23$, F (9, 114) =3.42, $p < 0.01$). Three important predictors were confirmed during the hierarchical regression: Sex, with males drinking more than females (final model: $\beta = 0.19$, $p = 0.03$); Impulsivity , which was positively associated with alcohol consumption (final model:

Table 2 Hierarchical regression predicting post-intervention-hour alcohol intake

Variable	*B*	SE *B*	*β*
Step 1			
Sex	4.23	2.07	0.19*
Age	-0.40	0.28	-0.14
Typical alcohol	1.81	1.26	0.15
Craving	0.09	0.06	0.15
SURPS-IMP	0.92	0.43	0.20*
SURPS-SS	-0.02	0.33	0.00
Change in R^2		0.175	
F for change in R^2	$F_{(6, 108)} = 3.83$, $p = 0.002$		
Step 2			
Sex	4.42	2.11	0.20*
Age	-0.41	0.28	-0.14
Typical alcohol	1.77	1.27	0.14
Craving	0.09	0.06	0.14
SURPS-IMP	0.90	0.44	0.19*
SURPS-SS	-0.04	0.33	-0.01
Motivational trigger	0.79	2.37	0.03
Implementation intentions	-1.79	2.40	-0.08
Change in R^2		0.004	
F for change in R^2	$F_{(2, 106)} = 0.28$, $p = 0.757$		
Step 3			
Sex	4.14	2.06	0.19*
Age	-0.34	0.28	-0.12
Typical alcohol	2.10	1.25	0.17†
Craving	0.05	0.06	0.09
SURPS-IMP	0.94	0.43	0.20*
SURPS-SS	0.03	0.33	0.01
Motivational trigger	1.59	2.33	0.07
Implementation intentions	-0.78	2.38	-0.03
Feeling influenced to drink less	-7.07	2.80	-0.24*
Change in R^2		0.047	
F for change in R^2	$F_{(1, 105)} = 6.36$, $p = 0.013$		

Note. B: unstandardized beta coefficient, *SE B:* standard error for the unstandardized beta, *β:* standardized beta coefficient, $p < .05$, † $.05 < p < .1$, SURPS-IMP: impulsivity subscale, SURPS-SS: sensation seeking subscale, Motivational trigger: whether motivated to drink less or not, Implementation Intentions: whether alcohol-related if-then plans were made

$\beta = 0.20$, $p = 0.03$); and, importantly, *Feeling influenced to drink less*, which was negatively associated with alcohol consumption (the stronger the experienced impetus, the less alcohol was actually consumed; final model: $\beta = -0.24$, $p = 0.01$). However, our manipulations did

not help reduce alcohol use (final model, Motivational trigger: β = 0.07, p = 0.50; Implementation intentions: β = -0.03, p = 0.74). The finding of *Feeling influenced to drink less* was replicated in the subsample of 89 participants (**Table S4**).

Secondary Analyses

Table 3 presents the correlation matrix between Typical alcohol use and Personality traits. As was expected, AUDIT-C and binge score were strongly correlated (r = 0.59, p < 0.01), indicating the two questionnaires measured similar components. SURPS Impulsivity was positively correlated with Binge score (r = 0.26, p = 0.01), and Sensation seeking (r = 0.28, p < 0.01). SURPS Sensation seeking was positively correlated with AUDIT-C (r = 0.31, p < 0.01). The relative proportion of *feeling influenced to drink less* differed significantly between groups (Control: 2.6% vs. Motivation: 15.4% vs. Motivation plus implementation intentions: 29.7%, χ^2 (2, N = 115) = 10.62, p < 0.01). Specifically, participants who received both interventions reported a stronger tendency of *feeling influenced to drink less* than the other two groups (*Adjusted Residual* = 2.9, p < 0.01). The self-reported alcohol consumption was highly correlated with ΔBrAC (r = 0.61, p < 0.01), validating this measure.

Table 3 Correlations between alcohol use and personality traits

	1	2	3	4	5	6
Mean	6.08	29.94	12.16	12.33	10.5	16.89
SD	2.07	17.25	2.25	3	2.33	3.12
Median	6	24	12	12	10	17
Minimum	2	8	5	7	5	9
Maximum	11	96	18	22	16	24
1. AUDIT-C						
2. Binge Score	.59**					
3. SURPS-AS	-0.15	-0.09				
4. SURPS-H	-0.01	0.08	-0.03			
5. SURPS-IMP	0.12	.26**	0.07	0.16		
6. SURPS-SS	.31**	0.18	-0.12	-0.06	.28**	

Note. *p < .05, **p < .01, SD: standard deviation, SURPS-AS: anxiety sensitivity subscale, SURPS-H: Hopelessness subscale, SURPS-IMP: impulsivity subscale, SURPS-SS: sensation seeking subscale.

Table 4 Linear regression models post-intervention-hour alcohol intake separately for women and men

	Women			*Men*		
	B	S.E. *B*	*β*	*B*	S.E. *B*	*β*
Group sex composition						
Women only	Reference			-15.18	6.35	-0.38*
Women > men	-2.83	3.24	-0.11	-13.16	6.06	-0.35*
Women = men	5.77	3.66	0.20	1.43	9.53	0.02
Women < men	2.01	3.24	0.08	Reference[a]		
Men only	5.55	6.05	0.12	-10.28	4.55	-0.40*

Note. *p < .05, [a] Unlike Thrul et al. (2017), *'women < men'* rather than *'men only'* level was treated as the reference, which was a better way to show all between-level differences

Table 4 showed that males drank more in majority-males groups than in all-male groups, all-female groups, and majority-females groups, but did not differ from mixed-equally groups. For females, drinking-group sex composition generally did not influence drinking speed systematically. In addition, compared to the 89 compliers, the 26 non-compliers scored higher on AUDIT-C, were more impulsive, and drank with more males that night (**Table S7**).

Discussion

Heavy or problematic alcohol use has been associated with self-control deficits, such as failures to suppress undesirable or inappropriate behavior (Baumeister & Heatherton, 1996; Wilcox, Dekonenko, Mayer, Bogenschutz, & Turner, 2014). The current study examined the effectiveness of two brief interventions to restrain alcohol use among people in a public bar. Interventions included a motivational trigger in the form of a monetary incentive and the formation of implementation intentions. At the group level, the interventions did not effectively reduce alcohol used in the *hot* bar context compared to a control group. However, participants in the *dual* intervention group reported feeling more strongly influenced to restrain their drinking. Importantly, this *feeling influenced to drink less* predicted an actual reduction in alcohol use. In addition, we also found that impulsive individuals drank more alcohol during the hour following the intervention, and males drank more than females especially in mixed-sex groups that were dominated by males. What's more, people in compliance with making *valid* if-then plans drank less alcohol in their daily life, were less compulsive, and drank with fewer males that night. In the following paragraphs, we discuss in sequence 1) why our interventions did not work; 2) what the effect of *feeling influenced to drink less* means; 3) secondary findings; 4) limitations and suggestions for future studies.

In the present study, motivation was induced by the prospect of monetary gain (i.e., driving performance-related gain of € 2.5). This manipulation did not reduce alcohol use in this context. There are several possible reasons. First, we did not explicitly instruct participants to drink less for better performance but more generally linked drinking and driving behavior to real-life experiences. Some participants might have failed to link this to their own situation. Second, according to the self-determination theory, autonomous motivations (i.e., serving personally relevant goals) yield better health-related intentions than externally controlled motivations (e.g., monetary incentives, Deci & Ryan, 2008, 1987). Increasing the chance of winning a small monetary reward is not a strong incentive to be internalized and act as a personal goal to limit drinking. A recent online study also questioned the effectiveness of autonomous motivation in reducing alcohol use (Caudwell et al., 2018). Third, the selected driving game might have been suboptimal in inducing drinking restraint goals. Specifically, expected driving performance in the second run may have been influenced by other factors such as practice.

Regarding implementation intentions, although previous studies showed that it effectively reduced alcohol consumption (Arden & Armitage, 2012; Armitage & Arden, 2016; Norman & Wrona-Clarke, 2016), we did not observe this. It was proposed that for implementation intentions to have an effect, components of the plan need to be *precise* (i.e.,

deliberation about appropriate opportunities and responses is not required), *viable* (i.e., the specified situation will be encountered, and the specified response can be performed), and *instrumental* (i.e., the specified response facilitates goal achievement, Gollwitzer & Sheeran, 2006). With regard to *precision*, the form used to generate if-then plans was straightforward and easy to understand. *Viability* may have been slightly more problematic at first sight, as the specific cues outlined in the if-sentence may not have occurred during the drinking hour (e.g., the situation 'if I am being offered a drink'), which left the linked goal-directed response inactive (Gollwitzer & Sheeran, 2006). However, a previous study reported a spill-over effect of implementation intentions (Bieleke, Legrand, Mignon, & Gollwitzer, 2018), such that the associated behaviors can also be activated by cues similar to the formulated one (Gollwitzer & Sheeran 2006). *Instrumentality* was possibly not optimally fulfilled for a few participants. In principle, performance on the driving game should get worse as a function of alcohol intake during the ensuing hour (this was confirmed within the control group). However, some participants held strong beliefs about their driving competence under intoxication (they told the experimenter afterward). In these cases, the specified response (i.e., limiting alcohol use) should not have facilitated goal achievement (i.e., winning the additional € 2.5). One more obstacle for our intervention to work is that we tested late during a day (from 16:30 to 22:00 pm) when one's self-control has been largely depleted and hard to be executed (Baumeister & Heatherton, 1996). In a similar vein, a recent study found that vegetable if-then plans were more effective in the morning than in the afternoon (Domke, Keller, Fleig, Knoll, & Schwarzer, 2019). However, it makes no sense to delivery interventions in the morning in a bar.

Despite these negative findings, participants in the motivational trigger plus implementation intentions condition were more likely *to feel influenced to drink less* than the other two groups. Furthermore, those who felt influenced to drink less indeed drank less (about 7 grams of ethanol) during the hour after the intervention. It is likely that the participants' resolve and their implementation intentions, i.e., the formed association between the cue (e.g., being asked whether they wanted another beer) and the alternative response (e.g., order a soda) guided the drinking behavior. This meant that people who activated a suppression goal with implementation intentions were more likely to limit their drinking. Therefore, despite the absence of group-effects, we would argue that this first attempt to use a motivational trigger and implementation intentions in a natural *hot* drinking context showed promise. Although for the majority of participants, stronger interventions are called for, which can include the activation of stronger internal motivations to limit drinking (cf. Marlatt et al., 1998).

However, there might be an alternative explanation of these results, such that participants *said* they drank less and indeed *actually* did drink less (according to self-report) because of *social desirability bias* (i.e., respondents answer questions in a way that will be viewed positively by others, Nederhof, 1985). Such a social desirability bias can be argued against, as out of the 18 participants who reported to have restrained their drinking, only one realized the aim of the experiment (i.e., help them drink less). In addition, it is possible that participants understated alcohol consumed without a real change of drinking. However, this

can be ruled out as self-reported data was validated by BrAC. Finally, from an intervention perspective, feeling some pressure to change might not be bad, as social desirability might promote self-control, which in turn may facilitate reduced drinking (Yoshino & Kato, 1995).

Regarding secondary hypotheses, we found that the relationship between impulsivity and typical alcohol use (Stautz & Cooper, 2013) can be generalized to alcohol consumption on a casual occasion within one hour. Interestingly, in the model with compliers only, this relationship disappeared (**Table S4**). Moreover, non-compliers were more impulsive and typically drank more alcohol than compliers. Together, these findings suggest that impulsive people were less willing and less likely to change their behavior through this preventive effort. Effective interventions specifically targeted at this population are required. In addition, males drank faster than females, especially when drinking in mixed-sex groups with males as the majority. This finding is partially in line with findings from both Thrul et al., (2017) and van de Goor et al., (1990), which emphasized the dominance of males in the drinking group in facilitating males' drinking.

Some limitations of this study should be mentioned. First, alcohol consumption was assessed with self-reported data. Initially, we planned to measure this by self-report, breathalyzer and experimenters' observation (see experimenter form in Supplementary Materials). It turned out that BrAC readings were less reliable as alcohol metabolic rate was influenced by sex, food intake, illness, which varied a lot from individual to individual (Pikaar et al., 1988); and it was impractical for the experimenters to record alcohol consumption accurately as they might need to test multiple participants at the same time, and participants moved location, etc. In any event, such self-report instruments were found to be as accurate as biomarkers (97.1%, Armitage et al. 2014; Babor et al. 2000; del Boca and Noll 2000). Second, data on regular drinking speed during an hour was unavailable. We mention this since some studies found that both the intervention group and the control group decreased undesirable behavior compared with the baseline, though no group difference was detected (Caudwell et al., 2018). We cannot test this possibility as it is impossible to recreate an identical drinking episode where no intervention was involved. Third, the suboptimal compliance rate (77%) constrained the extent to which the lack of intervention effect at the group-level can be attributed to the technique itself or failures in formulating valid if-then plans. Though not ideal, the current compliance rate was not bad when compared with intervention studies targeted at the general population (e.g., 25% compliance rate, Armitage et al., 2011). Strategies to increase commitment to plans, such as making one's commitment public, may be an important alternative in the future. Fourth, we (deliberately) omitted the manipulation check questions after the motivation induction to prevent reactivity. As a consequence, we do not know how successful our motivation manipulation was in forming good intentions, apart from the drinking difference between the control group and the motivation group.

Conclusions

The current study tested an unobtrusive motivation induction in combination with forming implementation intentions in order to reduce alcohol use in a *hot* bar-context. These brief interventions did not lead to reduced drinking at the group level. However, participants

who received the combined interventions reported more often that they felt influenced to drink less, which in turn was related to reduced alcohol consumption. More effective interventions targeted at changing excessive drinking behavior when it is unfolding in a *hot* context are needed.

Supplementary Materials

Table S1 Summary of studies examining implementation intentions in reducing alcohol use (since 2000)

Study	Modality of II	Number of Interventions/Reminders	Outcome Measures post-intervention	Follow-Up	II Effective?
Arden and Armitage (2012)	VHS	once	TLFB: last week alcohol intake and last 2 weeks binge drinking frequency	2 weeks	yes
Armitage and Arden (2016)	experimenter provided	once	TLFB: alcohol consumption	1 month	yes
Armitage (2015)	VHS	once	TLFB: units consumed per week	1 month	yes
Armitage, et al., (2014)	self-generated	once	TLFB: alcohol use in a typical week	2 months	yes
Armitage (2009)	experimenter provided or self-generated II	once	TLFB: units consumed per week	1 month	yes
Caudwell et al., (2018)	experimenter provided or self-generated II	SMS message weekly	TLFB: weekly pre-drinking alcohol consumption	4 weeks	no
Cameron et al., (2015)[a]	self-generated	once	retrospective (past)7-day recall drinking diary	1 month, 6 month	no
Chatzisarantis and Hagger (2010)	provided IF, self-generated THEN	once	the decision to accept a free beer	2 weeks	yes
Epton et al., (2014)[a]	self-generated	once (a reminder will be sent if the participant need)	retrospective (past)7-day recall drinking diary	1 month, 6 month	no
Hagger et al., (2012)	self-generated	once	total alcohol consumption & number of binge drinking occasions	4 weeks	maybe, II reduced total alcohol consumption for UK and Estonian sample, not Finnish sample; II reduced binge drinking occasions only with UK sample.
Moody et al., (2018)	VHS	daily for two weeks	momentary assessments	1 month	maybe, effective during the intervention but not at follow-up
Norman et al., (2019)	self-generated	once	frequency of binge drinking	1 month	maybe, only effective for those made if-then plans to avoid binge drinking
Norman et al., (2018)	self-generated	once	TLFB: units consumed and number of binge drink sessions, per week	1 week, 1 month, and 6 months	no
Norman and Wrona-Clarke (2016)	self-generated	once	TLFB: units consumed and number of binge drink sessions during 1 week	1 week	yes
Ehret et al., (2018)	self-generated	once	alcohol abstinence	1 week, 2 weeks	maybe, effective 1 week later but not 2 weeks

Note. II: implementation intentions, VHS: volitional help sheet, TLFB: Timeline Followback,
[a]An online intervention targeted at four health behaviors at the same time (fruit and vegetable intake, physical activity, alcohol, smoking)

Table S2 Beverages provided in the bar

Types of drink	Volume/milliliter	ALC %	Alcohol/grams
Light beer, Radler	330	2	5.21
Regular beer/Small	220	5	8.68
Regular beer/Regular size	250	5	9.86
Regular beer/Pint	500	5	19.73
Special beer-Grolsch weizen	250	5.1	10.06
Special beer-Brouwerij 't IJwit	330	6.5	16.92
Special beer-La Chouffe	330	8	20.83
Special beer-Oedipus	330	8	20.83
Special beer-caramel Beer	330	8	20.83
Special beer-Brouwerij 't IJ Zatte	330	8	20.83
Special beer-Thai Thai	330	8	20.83
Wine, e.g. rosé	125	13.5	13.31
Liquor, Jenever	35	35	9.67

Note. Alcohol in grams $= \left(\frac{\text{volume}}{1000}\right) \times \text{Alc \%} \times 0.789$, 0.789 is the density of ethyl alcohol

Table S3 Comparisons of demographics, alcohol use and personality traits between three groups (N=89)

	Control	Motivational trigger	Motivational trigger + Implementation Intentions	*F*	*P*
	N = 28	N = 32	N = 29		
Male (%)	10 (35.7)	13 (40.6)	14 (48.3)	$\chi^2 = 0.94$	0.62
Age	23.96 (4.43)	23.69 (3.72)	22.90 (3.28)	0.60	0.55
BMI	21.77 (2.14)	21.90 (2.32)	22.58 (2.60)	0.98	0.38
Education Level	4.89 (1.40)	4.75 (1.44)	4.66 (1.45)	0.20	0.82
AUDIT-C	5.43 (2.13)	6.09 (2.10)	6.03 (1.88)	0.94	0.39
Binge score	24.95 (10.17)	28.64 (17.11)	31.38 (18.58)	1.18	0.31
BrAC-1	0.22 (0.27)	0.15 (0.17)	0.18 (0.36)	0.53	0.59
BrAC-2	0.32 (0.39)	0.35 (0.27)	0.31 (0.24)	0.15	0.86
Craving	60.75 (16.34)	59.07 (16.99)	54.72 (21.41)	0.82	0.44
SURPS					
Impulsivity	9.82 (2.74)	10.56 (2.12)	10.34 (1.93)	0.82	0.44
Sensation seeking	16.54 (3.17)	17.25 (3.12)	16.97 (2.73)	0.42	0.66
Hopelessness	11.89 (2.97)	12.84 (3.17)	11.79 (2.85)	1.14	0.32
Anxiety Sensitivity	12.50 (2.52)	11.69 (2.15)	12.28 (2.03)	1.07	0.35

Note. Mean (Standard Deviation)

Table S4 Hierarchical regression predicting post-intervention-hour alcohol intake (N=89)

Variable	*B*	S.E.*B*	*β*
Step 1			
Sex	4.23	2.30	0.21†
Age	-0.48	0.29	-0.18
Typical alcohol	1.06	1.37	0.09
Craving	0.11	0.06	0.20†
SURPS-IMP	0.67	0.48	0.15
SURPS-SS	0.08	0.36	0.02
Change in R^2		0.175	
F for change in R^2		$F_{(6, 82)} = 2.55$, $p = 0.026$	
Step 2			
Sex	4.39	2.32	0.21†
Age	-0.50	0.29	-0.19†
Typical alcohol	1.18	1.39	0.10
Craving	0.10	0.06	0.19†
SURPS-IMP	0.66	0.48	0.15
SURPS-SS	0.07	0.36	0.02
Motivational trigger	0.16	2.57	0.01
Implementation Intentions	-2.26	2.53	-0.10
Change in R^2		0.01	
F for change in R^2		$F_{(2, 80)} = 0.47$, $p = 0.625$	
Step 3			
Sex	3.59	2.28	0.17
Age	-0.37	0.29	-0.14
Typical alcohol	1.67	1.37	0.14
Craving	0.07	0.06	0.13
SURPS-IMP	0.66	0.47	0.15
SURPS-SS	0.14	0.36	0.04
Motivational trigger	0.43	2.50	0.02
Implementation Intentions	-0.62	2.56	-0.03
Feeling influenced to drink less	-7.51	3.14	-0.26*
Change in R^2		0.056	
F for change in R^2		$F_{(1, 79)} = 5.74$, $p = 0.019$	

Note. *$p < .05$, † $.05 < p < .1$, SURPS-IMP: impulsivity subscale, SURPS-SS: sensation seeking subscale, Motivational trigger: whether motivated to drink less or not, Implementation Intentions: whether alcohol-related if-then plans were made

Table S5 Correlations between alcohol use and personality traits (N=89)

	1	2	3	4	5	6
M	5.87	28.37	12.13	12.20	10.26	16.93
SD	2.04	15.85	2.24	3.01	2.27	3.00
Median	6.00	22.00	12.00	12.00	10.00	16.00
Minimum	2	8	5	7	5	11
Maximum	11	88	18	22	16	24
1. AUDIT-C						
2. Binge Score	.55**					
3. SURPS-AS	-0.21	-0.15				
4. SURPS-H	-0.01	0.10	-0.09			
5. SURPS-IMP	0.09	0.20	0.05	0.16		
6. SURPS-SS	.24*	-0.01	-0.17	-0.10	.26*	

Note. *$p < .05$, **$p < .01$, *SD*: standard deviation, SURPS-AS: anxiety sensitivity subscale, SURPS-H: Hopelessness subscale, SURPS-IMP: impulsivity subscale, SURPS-SS: sensation seeking subscale

Table S6 Linear regression models post-intervention-hour alcohol intake separately for women and men (N=89)

	Women			*Men*		
	B	S.E.*B*	*β*	*B*	S.E.*B*	*β*
Group sex composition						
Women only	Reference			-9.23	7.19	-0.25
Women > men	-2.31	3.65	-0.09	-8.18	6.39	-0.27
Women = men	5.85	4.65	0.18	5.41	9.20	0.11
Women < men	1.51	3.90	0.06	Reference[a]		
Men only	6.00	8.93	0.10	-6.94	5.11	-0.30

Note. *$p < .05$, [a]Unlike Thrul et al. (2017), *'women < men'* rather than *'men only'* level was treated as the reference, which was a better way to show all between-level differences.

Table S7 Comparison between compliers and non-compliers on typical alcohol use, personality traits, drinking speed, and number of friends around

	Compliance	*N*	*M*	*SD*	*SEM*	*t*	*df*	*p*
AUDIT-C	no	26	6.81	2.04	0.4	2.07	113	0.04*
	yes	89	5.87	2.04	0.22			
Binge score	no	26	35.31	20.81	4.08	1.82	113	0.07
	yes	89	28.37	15.85	1.68			
SURPS-IMP	no	26	11.31	2.38	0.47	2.05	113	0.04*
	yes	89	10.26	2.27	0.24			
SURPS-SS	no	26	16.73	3.56	0.7	-2.9	113	0.77
	yes	89	16.93	3	0.32			
Craving	no	26	57.18	17.97	3.52	-0.25	113	0.81
	yes	89	58.18	18.33	1.94			
Alcohol intake/hour	no	26	19.26	13.34	2.62	0.85	113	0.4
	yes	89	17.19	10.18	1.08			
Number of other females	no	26	1.31	1.39	0.26	-0.09	113	0.93
	yes	89	1.34	1.46	0.16			
Number of other males	no	26	1.31	1.19	0.23	2.18	113	0.03*
	yes	89	0.81	0.98	0.1			

Note: *$p \leq .05$, AUDIT-C: Alcohol Use Disorder Identification Test-Consumption, Binge score: calculated from items 10 to 12 of Alcohol Use Questionnaire, SURPS-IMP: impulsivity subscale of SURPS, SURPS-SS: sensation seeking subscale of SURPS

S1: Chi-square test: Comparison of replies to 'How your drinking was influenced by the experiment?' between three groups (N = 89)

The 3 (group) by 2 (Drink Less/Not Drink Less) Chi-square test was significant (Control: 3.6% vs. Motivational trigger: 9.4% vs. Motivational trigger plus implementation intentions: 31%, χ^2 (2, N = 89) = 9.71, $p < 0.01$). Post-hoc analysis revealed that people in the dual intervention group reported more *drink less* than the other two groups (*Adjusted Residual* = 3.1, $p = 0.002$).

S2a: Snack-related volitional help sheet (English)

Experimenter: _____ Participants ID: _____

Research has shown that people are more likely to stick to their plans when they formulate an 'If-then' sentence.

Here are some examples,

IF	THEN
If later tonight my friends are going to have some fast food	Then I will go home and eat something healthy
If I am hungry later tonight	Then I will buy myself something healthy
If I pass by a fast food restaurant later tonight	Then I will remind myself that fast food is bad for me

You could

Either connect the two boxes that would work best for you and copy the if-then sentence here,

If _____

Then _____

Or formulate your own if-then plan in as much detail as possible and write it down here,

If _____

Then _____

S2b: Snack-related volitional help sheet (Dutch)

Onderzoeker: _____ Deelnemer ID: _____

Onderzoek heeft aangetoond dat het waarschijnlijker is dat mensen zich aan hun plannen houden wanneer ze een ‘als-dan’ zin formuleren.

Hier zijn enkele voorbeelden,

ALS	DAN
Als mijn vrienden later vanavond fast food gaan eten	Dan zal ik naar huis gaan en iets gezonds eten
Als ik later vanavond honger heb	Dan zal ik voor mezelf iets gezonds kopen
Als ik later vanavond langs een fastfoodrestaurant loop	Dan zal ik mezelf eraan herinneren dat fast food slecht voor me is

U kunt

Of twee vakjes kiezen die voor U het meest geschikt zijn en de ‘Als-dan’ zin hier kopiëren,

Als _____

Dan _____

Of Uw eigen ‘’Als-dan’’ zin zo gedetailleerd mogelijk formuleren en hier opschrijven,

Als _____

Dan _____

S3a: Alcohol-related volitional help sheet (English)

Experimenter: _____ Participants ID: _____

Research has shown that people are more likely to stick to their plans when they formulate an 'If-then' sentence.

Here are some examples,

IF	THEN
If my friend asks me to have another drink	Then I will order a soft drink like soda instead of alcohol
If I am being offered a drink	Then I will tell myself that if I try hard enough I can keep myself from drinking
If I would like to keep up with my friends drinking	Then I will remember that if I drink I will perform worse in the game

You could

Either connect the two boxes that would work best for you and copy the if-then sentence here,

If _____

Then _____

Or formulate your own if-then plan in as much detail as possible and write it down here,

If _____

Then _____

S3b: Alcohol-related volitional help sheet (Dutch)

Onderzoeker: _____ Deelnemer ID: _____

Onderzoek heeft aangetoond dat het waarschijnlijker is dat mensen zich aan hun plannen houden wanneer ze een ‘als-dan’ zin formuleren.

Hier zijn enkele voorbeelden,

ALS	DAN
Als mijn vriend me vraagt om nog iets te drinken	Dan zal ik frisdrank in de plaats van alcohol bestellen
Als een drankje mij aangeboden wordt	Dan zal ik tegen mezelf zeggen dat als ik hard genoeg mijn best doe, ik mezelf ervan kan weerhouden om te drinken
Als ik net zoveel wil drinken als mijn vrienden	Dan zal ik mezelf eraan herinneren dat als ik drink, ik slechter zal presteren op het spel

U kunt

Of twee vakjes kiezen die voor U het meest geschikt zijn en de ‘Als-dan’ zin hier kopiëren,

Als _____

Dan _____

Of Uw eigen ‘’Als-dan’’ zin zo gedetailleerd mogelijk formuleren en hier opschrijven,

Als _____

Dan _____

S4: Experimenter form

Participant ID: ____ Experimenter: _____Date (dd/mm/yy): _____ Language: _____

- Stage one

Start test:	☐☐:☐☐
Group	☐ 1 ☐ 2 ☐ 3
How much he/she already drunk	
Game-1	Points: Meters: Duration:
BrAC-1 (‰)	

- Stage two

Start time of drinking	☐☐:☐☐
Filling out the following questions through observation	
Age	
Sex	☐ Male ☐ Female
Race	☐Asian ☐white ☐American Indian or Alaska Native ☐black or African American ☐Native Hawaiian or Other Pacific Islander
Weight/kg	
Height/cm	
Alcohol intake during one hour (in detail)	
Number of males & females drinking together (incl. pp)	Male: Female:

- Stage three

Time returned back	☐☐:☐☐
Game-2	Points: Meters: Duration:

Note for especial cases:

_____

S5: Post-drink interview

1. How many drinks did you during that one hour? (kind of drinks and how much, details)

   Regular beer☐, special beer☐, wine☐, liquor☐

   Note: _____

2. How much do you think you would have drunk during the last hour if you did not participated in the experiment? _____
3. Do you think your alcohol intake was influenced by the experiment?

   ☐ Yes (☐ dink more ☐ dink less) ☐ no
4. How long have you stayed in the bar/started drinking? _____
5. What do you think this experiment is about?

   _____
6. Did you use any strategy when you played this game? (e.g. quite familiar)

   _____
7. Did you talk with your friend(s) about the details of the experiment?

   _____

   If so, what did you discuss?

   _____

   If so, do you think this influenced your alcohol intake

   _____
8. Would you like to leave your email address in order to be informed of what this experiment was about and the results?

   _____
9. Would you like to leave your email address in order to be contacted about future research?

   _____

BrAC-2(‰)		End testing time	☐☐ : ☐☐

Chapter 6

General discussion

The general research question of this thesis was to study the relationship between substance use and two types of inhibition: stimulus-driven and intentional inhibition. To investigate these relationships, we performed four experiments and one mega-analysis, presented in the previous four chapters. As the first step, we investigated the relationship between poly-substance use and stimulus-driven inhibition by aggregating raw data from 43 qualified studies. Then we narrowed down the scope to alcohol to study effects associated with chronic and acute use. The stop-signal task and the Chasing Memo/Bottles task were used as paradigms for stimulus-driven inhibition and intentional inhibition, respectively. In addition to behavioral measures, EEG recording was utilized to reveal the temporal dynamics of intentional inhibition. Finally, a mini intervention (i.e., implementation intentions combined with motivation trigger) was employed to reduce alcohol use in a naturalistic environment of a bar. In this general discussion, I will first recap the main findings per domain, and discuss these in relation to the developing literature on the topic. Then I will reflect on the implications of these research findings and suggested possible directions for future studies.

Chronic substance use and stimulus-driven inhibition (Chapters 2 & 3)

One main contribution of our mega-analysis is that it emphasizes the importance of studying polysubstance use. Polysubstance use is highly prevalent among adolescents and young adults, and most commonly includes combinations of alcohol, tobacco, and cannabis use (Connor, Gullo, White, & Kelly, 2014). However, the combined effects on cognitive functions were rather under-investigated. Although greater-than-additive effects (i.e., concurrent use of different substances potentiate the long-term adverse effect of each drug) seem plausible, there is also speculation that use of some substances may protect against the neurocognitive impact of other substances (Yücel, Lubman, Solowij, & Brewer, 2007).

In **Chapter 2** we report that only lifetime cannabis use was associated with impaired response inhibition in the stop-signal task (SST). An interaction effect was also observed: the relationship between tobacco use and response inhibition (in the SST) differed between cannabis users and non-users. We observed a negative association between tobacco use and inhibition in the cannabis non-users. In other words, within the group that does not use cannabis, frequent tobacco users (mostly heavy cigarette smokers) show impaired stopping compared to those who smoke less. By contrast, for cannabis users, tobacco use was not significantly correlated with inhibition, suggesting cannabis may somehow alleviate the neuropsychological deficits associated with tobacco (which have recently been documented for a range of cognitive domains in a large study, Vermeulen et al., 2018). Except for tobacco and cannabis, the negative relationship between other kinds of substance use (cf. combined use) and response inhibition on the go/no-go task (GNG) and SST were not confirmed. In line with this general pattern of the mega-analysis of **Chapter 2**, the study reported in **Chapter 3**, also did not find differences between light and heavy drinkers (mostly university students) on SST performance.

What does this general absence of a relationship between long-term *recreational* substance use and stimulus-driven inhibition mean? There are two alternative explanations

that are worth mentioning. One possible explanation is that substance use without a diagnose of substance use disorder (SUD, American Psychiatric Association, 2013) is not associated with impaired response inhibition. In other words, the linear relationship is very shallow and we only see the effect when comparing very extreme groups (e.g., healthy controls vs. SUD in clinical samples). The mega-analysis in **Chapter 2** did not specifically focus on people diagnosed with SUD. Due to the inclusion criteria applied (e.g., a study was included only if data on monthly alcohol use and daily cigarette use was provided), only a small portion of the sample reached the level of SUD. And in **Chapter 3**, the substance use amount (mainly alcohol) was even lower. It is possible that substance use must exceed a certain threshold for an observable increase in the risks of inhibition deficits. This standard can refer to a diagnosis of SUD, years of substance use, accumulative consumption and patterns of use. For instance, it is conceivable that people diagnosed with SUD have response inhibition deficits compared with people without SUD (Bjork, Hommer, Grant, & Danube, 2004; Fernández-Serrano, Pérez-García, & Verdejo-García, 2011; Noël et al., 2007; Petit et al., 2014; but see conflicting findings for cocaine and amphetamine dependence: van der Plas, Crone, van den Wildenberg, Tranel, & Bechara, 2009). However, this in itself would not prove that this difference is caused by substance use, in contrast, it could be a risk factor for the development of SUD (Schulte et al., 2014; Verdejo-García, Lawrence, & Clark, 2008), then it should at least be related to duration and patterns of use (Fernández-Serrano et al., 2011).

Alternatively, it is possible that long-term substance use *is* negatively associated with response inhibition, but we were incapable of detecting it. For example, there are some indications that long-term use not only of tobacco (Vermeulen et al., 2018, in line with findings here), but also of alcohol (Eckardt et al., 1998; Parsons & Nixon, 1998) and cannabis (Bolla, Brown, Eldreth, Tate, & Cadet, 2002) are associated with general cognitive deficits. This would raise the question of why we did not find it. This could be due to sample characteristics (as discussed above), type of tasks included (GNG & SST), lack of power, or insensitive outcome measures. We will elaborate on these points in the following.

Regarding the *type of tasks* included, first, the GNG and SST provide adequate performance measures of global response inhibition, but they might be less sensitive in capturing representative subcomponents of inhibitory control that are dysfunctional amongst substance users. For instance, substance users rarely engage in the whole process of response inhibition (e.g., reaching for a beer but then stop their motor action, i.e. reactive inhibition). Instead, proactive inhibitory control processes might be more relevant (i.e., deciding not to order another beer in advance) (Baines, Field, Christiansen, & Jones, 2019). It was pointed out that inhibitory control in the SST, at the minimum, involves signal detection, response selection, and execution of the inhibition (Verbruggen, McLaren, & Chambers, 2014). Thus, effective stopping in the SST relies on detection of the stop signal, the selection of an appropriate response, and finally carrying out the planned behavior (the act of stopping). The mixed findings in this field might be due to the simplification of this concept. Similarly, SSRT, as calculated using the hierarchical Bayesian model that controls for trigger failures (failures to react to the stop signal), was about 100 ms shorter than that using the integration method (Matzke, Hughes, Badcock, Michie, & Heathcote, 2017; Skippen et al., 2019).

Therefore, future studies might consider reconceptualizing the traditional measures of SSRT and look into the subcomponents of response inhibition when investigating its association with substance use. Second, maladaptive substance use may reflect a reduced mobilization of inhibitory control in substance-related contexts rather than generally impaired inhibitory control (Krönke, Wolff, Benz, & Goschke, 2015; Krönke et al., 2018; Wolff et al., 2016). Such reduced mobilization of cognitive control may result from insufficient performance monitoring (Krönke et al., 2018). Third, the stimulus-driven inhibition measured by GNG and SST may not map well onto the loss-of-control over drinking that occurs in daily life, where the drinker's own decision making guides continued drinking, which reflects insufficient endogenous inhibition rather than exogenous inhibition. For this reason, we further explored the association between alcohol use and intentional inhibition in **Chapter 3** and **Chapter 4**.

Regarding a possible *lack of statistical power*, in the mega-analysis, except for alcohol and tobacco, other substance information that was included could only be coarsely dummy-coded according to lifetime use in terms of "yes or no". It cannot be excluded that heavy use of specific combinations of substances (for example, cocaine and alcohol: Fillmore & Rush, 2006; Schulte et al., 2014) leads to impaired response inhibition, a relationship that could not be detected in our analysis with relatively few people using both which forced us to use dummy coded variables for all substances except alcohol and tobacco.

Regarding *outcome measures*, although behavioral measures might not show substance-related inhibition deficits, psychophysiological correlates have been reported to be sensitive in this respect. Several EEG and fMRI studies included in our mega-analysis reported differential brain activity but not performance in substance users compared to controls (alcohol: Claus, Ewing, Filbey, & Hutchison, 2013; Karoly, Weiland, Sabbineni, & Hutchison, 2014; tobacco: de Ruiter et al., 2012; Galván, Poldrack, Baker, McGlennen, & London, 2011; Luijten et al., 2013a; ecstasy & cannabis: Roberts & Garavan, 2010). In addition, it was consistently reported that substance users had lower N2 amplitude (an index for early cognitive processes necessary to implement inhibitory control, Falkenstein, 2006), and dysfunctional stopping networks underlying inhibitory control (including ACC, IFG, and DLPFC) compared with controls as measured by GNG and SST (Luijten et al., 2014).

Given the above, future studies may address the following questions. First, which aspects of inhibitory control (pro- vs. reactive; different subcomponents such as signal detection, response selection, and execution of the inhibition; antecedents such as performance monitoring efficiency) are more vulnerable to the effect of (single or multiple) substance use, and does this differ between different substances? Second, which or what combinations of substances use, once exceeding a critical point (e.g., a diagnosis of SUD), is associated with impaired response inhibition. Third, given that only a small proportion of people that experimented with substance use finally develop SUD (Mclellan, 2017), driving factors should also be considered. That is, both biological (e.g., gender) and environmental factors (e.g., peer influence, parental use of substances) may influence the relationship between substance use and response inhibition. Fourth, if a standardized screening package to identify suboptimal response inhibition is proposed, what should be included? Potentially,

behavioral outcomes (GNG and SST with separable subcomponents), biomarkers (gene test; functional, structural, and resting-state fMRI), and family history of substance use can be considered.

Acute alcohol use and stimulus-driven inhibition (Chapter 4)

Compared with chronic alcohol use, acute alcohol use is more consistently associated with impaired response inhibition (acute effect, see Table 1 in Campbell et al. 2017; Day et al. 2015; chronic effect, see studies included in our mega-analysis). In **Chapter 4**, we found that the group receiving alcohol did not differ from placebo and control groups in stopping performance on a lexical SST. In order to identify reasons that possibly gave rise to this unexpected finding, we summarized relevant studies that used the stop-signal task. Information, including sample characteristics (e.g., typical alcohol use), alcohol administration (e.g., dosage), task characteristics (e.g., modality of the stop signal, stop signal rate), study design (alcohol/placebo condition is within- or between-subject design), and type of result (positive/negative finding), was extracted and listed in Table S1a of **Chapter 4**. Surprisingly, there is also a large percentage of studies that failed in identifying the impairing effects of alcohol, even for high dosages (0.8g/kg: Dougherty, Marsh-Richard, Hatzis, Nouvion, & Mathias, 2008; Loeber & Duka, 2009b). Note that not all of these studies presented results with respect to SSRT, focusing on stop rate (e.g., percentage of successful inhibition). There are two different explanations of the conflicting findings. First of all, acute alcohol use does not certainly cause impaired performance in the stop-signal task due to task insensitivity (Bartholow et al., 2018). The cued GNG task, by contrast, showed consistent sensitivity to the short-term effect of alcohol (Bartholow et al., 2018), partially owing to the strengthened urgency/prepotency of stopping through invalid go cues (Marczinski & Fillmore, 2005). Alternatively, the current null finding was attributable to sample characteristics, the dose of alcohol administered, and the experimental design that diverged from others.

With regard to *sample characteristics*, our participants consumed on average 9.4 units of drinks per week, which was rather low compared with a similar study (Zack et al. 2011 included problem drinkers consuming 30.5 drinks per week). On a related note, the alcohol-use-related inclusion criteria we used (AUDIT score between 5 and 16, Saunders, Aasland, Babor, De la Fuente, & Grant, 1993) excluded anyone with high-risks of Alcohol Use Disorder, which was just the opposite to Zack and colleagues (2011) used (score ≥ 13 on the Alcohol Dependence Scale, Skinner & Allen, 1982). Given that impairments in inhibitory control under intoxication are more pronounced among binge drinkers (vs. non-binge drinkers, Marczinski, Combs, & Fillmore, 2007), and binge drinking is highly correlated with daily-life alcohol use (see Table 3 in **Chapter 5**), heavy drinkers should also be hypersensitive to the acute alcohol effects on response inhibition.

With regard to *the dose of alcohol administered*, the volume we provided was a bit low compared with parallel studies. Nevertheless, we followed others who did find an effect with this dosage (0.04g/kg: de Wit et al. 2000; Reynolds et al. 2006; Nikolaou et al. 2013, but see Caswell et al. 2013). In addition, the low-dose alcohol effects on inhibitory control seem largely task-dependent (Weafer & Fillmore, 2016). And for tasks that emphasize the

prepotency of a quickly executed go response (either by making the go response more dominant (SST) or cueing the go response (cued GNG)), alcohol impairs inhibitory control at doses ranging from 0.2 to 0.6 g/kg and BACs ranging from 35 to 71 mg/100 ml (Weafer & Fillmore, 2016).

With regard to the *experimental design*, we used a between-subjects design without pre-drink baseline measurements. In this way, two factors might not have been well controlled for. These are the day-to-day variance of inhibition capability and individual differences in response to alcohol intoxication (Campbell et al., 2017). First, a pre-drink test has been suggested to control for day-to-day fluctuations of behavior (Caswell, Morgan, & Duka, 2013; Guillot, Fanning, Bullock, McCloskey, & Berman, 2010). This is particularly important in view of the relatively low test-retest reliability of the SST (Hedge, Powell, & Sumner, 2018; Wöstmann et al., 2013). However, this was not realistic in the current context, as participants were asked to abstain from having a big meal 4 hours in advance. Adding a pre-drink session would easily prolong the experiment to more than 3 hours in total. In addition, we included a relatively large sample size and participants were randomized according to their comparable demographics and substance use (see Table 1 in **Chapter 4**). Second, a between-subject rather than a within-subject design was used as we are not sure about practice effects on the Chasing Bottles task. We consider this is not too great a concern, as our participants were rather comparable in terms of alcohol sensitivity as measured by the SRE (self-rating of the effects of alcohol, Schuckit et al. 1997, see Table S1 in **Chapter 4**).

We compared studies with positive and negative findings. It turned out that they did not differ significantly in any of these aspects (Table S1b in **Chapter 4**). However, these are very preliminary analyses (i.e., we might have missed some studies due to a non-exhaustive literature search; or other statistical methods rather than t-test should be used). Our present knowledge does not permit an instant choice between the two possibilities. To examine the first assumption, a stop-signal task including (in)valid cues can be considered. For the second hypothesis, a comprehensive review or meta-analysis is warranted in which all confounders can be studied systematically.

Intentional inhibition (Chapters 3 & 4)

In the past decades, a large number of studies investigated substance use and stimulus-driven inhibition (see **Chapter 2**). In the commonly used GNG and SST, participants are asked to withhold their response to infrequent stop signals (Donders, 1868/1969; Logan & Cowan, 1984). In these tasks, the need to stop is triggered by an external stimulus. However, in real life, we often make stop decisions by ourselves (Aron, 2011). What's more, it was recently found that, alcohol cue exposure and alcohol intoxication promote alcohol-seeking behavior without impaired subcomponents of inhibitory controlled (measured by modified stop-signal task, Baines et al., 2019). These evidence brought up the concept of intentional action (Libet, Gleason, Wright, & Pearl, 1983) and intentional inhibition (Kühn, Haggard, &

Brass, 2009; Ridderinkhof, van den Wildenberg, & Brass, 2014). Intentional inhibition is more about distancing oneself from an intention to act rather than simply stopping the motor action (Ridderinkhof et al., 2014). As *intentional inhibition* is more difficult to measure (e.g., there is no behavioral outcome if a response is inhibited), we may resort to insights from the related field of *intentional action* (Brass, Furstenberg, & Mele, 2019; Brass & Haggard, 2008; Haggard, 2018; Libet et al., 1983). It was only recently, with the development of research paradigms such as variants of the Libet task (Brass & Haggard, 2007), the Marble task (Kühn et al., 2009), and the modified GNG task (Parkinson, Garfinkel, Critchley, Dienes, & Seth, 2017), some first attempts were made to assess intentional inhibition.

We tested the association between long-term as well as short-term alcohol use and intentional inhibition in **Chapter 3** and **Chapter 4**, respectively. For long-term alcohol use, including a sample of 60 graduate students, we did not find any associations between the AUDIT score and intentional inhibition performance in the Chasing Memo task (**Chapter 3**). This was confirmed by Bayesian analysis. Short-term alcohol effects were investigated with two experiments. The first one involved a small sample (N=16), accompanied by EEG recordings (**Chapter 3**). There, participants performed the Chasing Memo task once under alcohol (blood alcohol concentration around 0.05%), and once under placebo. We found that the alcohol condition did not differ from the placebo condition in terms of intentional inhibition latency and neural activities preceding inhibition (i.e., the Readiness Potential). The main finding was that the RP appeared 1200 ms before intentional inhibition but not before stimulus-driven inhibition. In another study (**Chapter 4**), we refined the experiment by modifying the following elements: 1) the little fish, Memo, was replaced by different kinds of bottles (alcoholic vs. soft drink bottles) to increase ecological validity; 2) the *whether* component was introduced into the task in addition to the *when* component, such that participants could also decide *whether* they stop (Brass & Haggard, 2008; Zapparoli, Seghezzi, & Paulesu, 2017); 3) a control group was recruited in addition to the alcohol group and the placebo group in order to examine the pharmacological and expectancy effects of alcohol separately (Rohsenow & Marlatt, 1981); 4) a larger group of participants was recruited (N=111). Here, to address the *whether* and *when* questions combined, a survival analysis was performed to operate time-to-event data. We found that alcohol intoxication (pharmacological effect) consistently reduced the stopping rate during the 20 s sampling window. Unexpectedly, this effect was more robust for tracking alcohol-*unrelated* bottles compared to alcohol-related bottles. The expectancy effect of alcohol influenced intentional inhibition inconsistently along time: decreasing the stopping rate after an initial increase. By contrast, neither pharmacological nor expectancy effect of alcohol had any effect on stopping latency (the *when* component).

In the next section, we discuss possible reasons underlying these findings. Factors such as sample characteristics (e.g., moderate drinkers without SUD) and study designs (between-subject vs. within-subject), that might influence the findings of stimulus-driven inhibition (summarized above) also apply to intentional inhibition and are not reiterated here.

Research Paradigms

The novel Chasing Memo/Bottles task might face the following criticisms. First, to what extent do participants have the freedom to decide for themselves? The documented intentional inhibition related paradigms, such as variants of the Libet task (Brass & Haggard, 2007; Walsh, Kühn, Brass, Wenke, & Haggard, 2010), the Marble task (Kühn et al., 2009), and the modified GNG (Parkinson et al., 2017; Xu, Fan, Li, Qi, & Yang, 2019), all adopt a free choice design. That is, participants are asked to voluntarily inhibit/disinhibit themselves for half of the trials, selected 'at random'. Although one can freely decide for which trial he/she would like to inhibit, the required 50% inhibition rate is implemented externally (i.e. by instruction) and has to be kept in mind. This instruction makes the match with intentional inhibition, in reality, less strong. One aim of such design can be that it made the comparison between *go* and *no-go* conditions easier, with roughly similar trial numbers (i.e., the ceiling and floor effects of stopping rate was prevented). This, however, goes at the expense of the participants' decision freedom. For this consideration, along with some others, it is worth the effort to develop a new task. The Chasing Memo task used in **Chapter 2** only allowed one to freely decide *when* to stop, in which both the acute and long-term alcohol use effect on stopping latency were absent. In **Chapter 3**, after adding the *whether* component into the task, the pharmacological effect of alcohol on intentional stopping rate appeared. This indicated that a priming dose of alcohol influenced *whether* rather than *when* inhibition was executed. In other words, once drinking is initiated, it is difficult to voluntarily stop (e.g., a declined stop rate). However, alcohol did not prolong the time it took to stop, such that the three groups struggled/hesitated for a similar period of time before a decision to reject the next drink (i.e., to stop tracking) was made.

Another aspect of the Chasing Memo task is the sampling window of 20 s during which participants should decide whether to stop or not. That is, if the tracking duration for each trial was, say, 60 s, the stopping rate of the alcohol group might well be just as high as that of the other two groups. It is notable that, at each time point of this 20 s, the survival curve of the alcohol group was consistently above the other two groups. To prevent possible boredom caused by long tracking time and other accompanying effects, the current trial length of 20 s appears to be safe.

Third, what is a proper feedback in an intentional inhibition task? The Chasing Bottles task we used in **Chapter 4** borrowed some ideas from the delay discounting task (Reynolds & Schiffbauer, 2004), such that continuing tracking brought more immediate reward, whereas stopping tracking produced larger future reward. This mimics the trade-off between instant pleasure from continuing drinking versus future benefits such as better physical health. However, this could incur the criticism that it was other factors, such as strategy learning (e.g., how to maximize extra reward), perhaps relying on general intelligence, rather than intentional inhibition that was being tested. It should be emphasized that one key feature of volition is that it is reasons-responsive, which involves strong connections from valence and reward circuits (Haggard, 2018). To this end, we intentionally added rewarding feedback, which is rarely seen in other paradigms. Though we would not want to call the Chasing Bottle

task a perfect task, we would argue that we made a good trade-off between the most important and secondary important factors that need to be considered/controlled.

Fourth, an operational definition of intentional inhibition might help to design a corresponding task. For instance, one study asked the participants to either make a rapid keypress or transiently inhibit the keypress before the execution. In this way, intentional inhibition was operationalized as a transient process, characterized by delayed responding (Filevich, Kühn, & Haggard, 2013). Defining intentional inhibition in alcohol-related studies involves clarifying reasons that might underlie the loss-of-control over drinking, which will be discussed in the next section.

Fifth, do we really need a computer task to measure intentional inhibition? Put differently, drinking less than planned reflects successful inhibition, whereas drinking more than planned signifies failed inhibition. Then an easy solution is to record the participant's planned and actual drinking amount every day and do the comparison. Jones et al. (2018) implemented the ecological momentary assessment method to measure inhibitory control (twice per day by SST), planned and actual alcohol consumption every day for two weeks. They found that day-to-day fluctuations (deterioration) of inhibitory control, rather than the absolute inhibitory control capacity that day, was a significant predictor of increased alcohol use. In another study from the same group, SST was administered both before and after cue exposure (i.e., alcohol-related stimuli), followed by ad libitum alcohol consumption (Field & Jones, 2017). It was found that increased ad libitum alcohol consumption following alcohol cue exposure was partially moderated by both elevated craving and impaired inhibitory control (Field & Jones, 2017). Future studies can consider how these processes might shed light on intentional inhibition.

What is the loss-of-control (over drinking)?

One key concept of this thesis is *intentional inhibition*, which is used to map onto the loss-of-control over drinking. A question that remains unanswered is whether failed inhibition of drinking could be due to diverse reasons. First, is the loss-of-control driven by impulsivity and/or compulsivity? Impulsivity and compulsivity have been argued to yield a composite addiction circle (binge/intoxication, withdraw/negative affect, pre-occupation/anticipation), in which impulsivity dominates the early stage and compulsivity together with impulsivity dominate the latter stage (Koob & Volkow, 2010). The shift from impulsivity to compulsivity is accompanied by a shift from positive reinforcement (e.g., use drugs to increase pleasant emotional experience) to negative reinforcement (e.g., use drug to reduce negative emotions, Heilig et al., 2010; Koob & Volkow, 2010). In this way, when the driving force of continued drinking is impulsivity, the actor still has the initiative to execute stopping control. Once the motivator shifts to compulsivity, one appears to be the slave of alcohol and be compelled to overuse it (Yücel et al., 2018). All participants recruited in **Chapter 3** and **Chapter 4** should not fall into the latter stage of addiction, which means they should still have the authority to hold the brake if they would like to. Future research could investigate whether intentional inhibition fluctuates during different stages of addiction. Second, according to the incentive-sensitization theory, even though a person knows cognitively that the substance will not bring

much pleasure, sensitized implicit *wanting* can surpass the low expectation of *liking* (Robinson & Berridge, 2003). In this manner, goal-directed drug-seeking behavior occurs *without conscious awareness* that pursuit is underway (Robinson & Berridge, 2003). This, to some extent, represents a momentary loss of control (Elster & Skog, 1999). Third, substance users' self-defeating behavior (i.e., lasting substance use albeit outweighing negative consequences over the benefits) should have served certain functions (e.g., goal pursuit, Kopetz & Orehek, 2015). That is, it represents failures in meeting normative standards (i.e., keep physical fitness); but on the other hand illustrates successful inhibition of alternative goals in achieving the present aim (e.g., socialization, the feeling of high) (Kopetz & Orehek, 2015). This theory, however, provides all behaviors lacking in control a good excuse.

Did we look at the most-relevant EEG component of intentional inhibition?

The RP was first recorded by Kornhuber and Deecke (1964) and attracted broad attention since Libet and colleagues' striking work in 1983. They found that the W-moment (self-reported urge to move) occurs some 200 ms prior to the actual action and about 500 ms after the RP onset (Libet et al., 1983). This finding was explained as "the brain decides to initiate certain actions at a time before there is any reportable subjective awareness", which raised perhaps unprecedented discussion in the literature (see criticism: Mele, 2014). It was recently claimed that the RP might neither give rise to the W-moment (conscious intention) nor to the voluntary movement (Alexander et al., 2014). Alternatively, the RP may represent some random-walk neural activity that can conditionally lead to movement once it crosses a threshold (Schurger, Sitt, & Dehaene, 2012).

In **Chapter 3**, we found that the RP solely appeared in the intentional inhibition condition but not in the cued inhibition condition. This, together with some other findings (mental arithmetic: Alexander et al., 2014; externally triggered action: Bianco, Di Russo, Perri, & Berchicci, 2017) suggest that the RP does not necessarily reflect motor preparation but rather represents a process that is related to intention formation in general. In addition, a *point of no return* was found, such that once the RP is detected for a movement, the person still has the chance to cancel it no later than 200 ms before the onset of the movement (Schultze-Kraft et al., 2016). More studies are called for to clarify the functional meaning of the RP.

On a related note, there are some other EEG components that might be related to intentional inhibition. These include the lateralized readiness potential (LRP, divergent neural activities between channel C3 and C4) that reflects the preparation of motor activity (Vaughan Jr, Costa, & Ritter, 1968). It was not an ideal candidate for the current purpose, as our participants continuously move their right hand for tracking. Therefore, no neural activation difference between the right and left side of the brain (i.e., C3-C4) was expected. In addition, the contingent negative variation (CNV) and the slow rising prefrontal negative component (pN) are also supposed to be associated with voluntary motor movements/inhibition (Bianco, Berchicci, Perri, Spinelli, & Di Russo, 2017; Walter et al., 1967). We did not test these components as they should be less closely associated with intentional inhibition than RP (e.g., pN was found in GNG: Berchicci, Lucci, Pesce, Spinelli, & Di Russo, 2012). It is suggested

to expand our knowledge of intentional inhibition by applying time-frequency analysis to EEG data, which provides more information in addition to temporal variations of signals (Xu, Fan, Li, Qi, & Yang, 2019).

Implementation intentions to reduce alcohol consumption in a bar (Chapter 5)

Implementation intentions are interventions that support goal attainment by assigning the control of goal-directed responses to foreseen situational cues that elicit these responses spontaneously (Gollwitzer, 1990). As a result, behavioral control is delegated from the self to the specified situation, and limited attentional and self-control sources are no longer obstacles to acting upon ones' intentions (Adriaanse, Vinkers, de Ridder, Hox, & de Wit, 2011; Gollwitzer, 1999; Parks–Stamm, Gollwitzer, & Oettingen, 2007). In **Chapter 5**, we examined whether implementation intentions acting as self-regulation strategies would reduce alcohol use in a *hot* state (i.e., drinking in a bar). Such research is needed as 1) drinking more than planned is quite prevalent and a lot of heavy drinkers want to restrain alcohol use without totally stopping drinking and/or visiting high-risk situations (Wiers, van de Luitgaarden, van den Wildenberg, & Smulders, 2005). Possible reasons for exposure to high-risk situations (e.g., a bar) include over-confidence in resisting temptations (Restraint Bias Theory, Nordgren, Harreveld, & Pligt, 2009) and social interactions (e.g., drinks on Friday after work); 2) it helps clarify the effect of implementation intentions in reducing alcohol use on a single occasion. In previous studies, the treatment effect was always determined by total alcohol consumption recorded by Timeline Followback (Sobell & Sobell, 1992) over a certain period (Armitage, 2009, 2015; Armitage & Arden, 2016; Caudwell, Mullan, & Hagger, 2018). Such retrospective techniques (e.g., recall past-week alcohol consumption on a daily basis) tend to underestimate the actual amount consumed (Dulin, Alvarado, Fitterling, & Gonzalez, 2017; Monk, Heim, Qureshi, & Price, 2015), and are limited in isolating the stand-alone contribution of drinks per occasion as opposed to the number of occasions in reducing the gross alcohol consumed during a given period. Only in a few cases, the effect on binge drinking frequency was reported and confirmed (Norman et al., 2018; Norman, Webb, & Millings, 2019; Norman & Wrona-Clarke, 2016). To our knowledge, only one study reported a small non-significant effect of implementation intentions on drinks per occasion (Moody, Tegge, Poe, Koffarnus, & Bickel, 2018). This evidence, all together, suggested that a reduction of total alcohol consumption was mainly attributable to a reduction of drinking episodes (e.g., not going to a bar, not buying alcohol). By contrast, there is very limited knowledge of whether implementation intentions are also effective in reducing alcohol use when the drinking behavior is unfolding.

In our bar study, we implemented intentions by asking the participant to make alcohol-related if-then sentences, either self-made or provided by us. To facilitate intention formation in the first place, we associated drinking with driving performance in a game, for which limited drinking guaranteed better performance and consequently extra monetary reward. It turned out that the combination of motivation and implementation intentions did not reduce alcohol use. However, this *dual* intervention increased the probability of *feeling influenced to drink less*, which was negatively associated with alcohol consumption one-hour post-

intervention. This suggests that a minimal intervention of this type could help people to drink less, preferably with a *push* to intensify its effect. This could be done by either strengthening the motivation manipulation or the implementation intentions part.

Regarding *motivation manipulation*, first, the amount of monetary incentive was very small (€ 2.5). Second, it is unknown whether this monetary reward was internalized as the participants' own goal to reduce alcohol use. The manipulation check question (i.e., immediately after manipulation we should ask participants to what extent they have formed the intention to reduce alcohol use) was deliberately omitted to prevent reactivity. Although it was reported that autonomous motivation (e.g., engaging in a behavior for intrinsic or personally relevant reasons) is more readily internalized than controlled motivation (i.e., engaging in a behavior for external reasons, Sheldon & Elliot, 1998), this is not consistently the case (see a lack of evidence of autonomy support: Caudwell, Mullan, & Hagger, 2018). Furthermore, formerly proved effective motivational messages such as 'drink within the government-suggested range' (Armitage, 2009) and 'reducing alcohol use will help you avoid negative consequences' (Caudwell et al., 2018) might come across as paternalizing and induce aversive emotions and counterproductive effect, as people in the bar just seek to have a good time. Third, we suggest that a more personalized driving game may be more effective. We may presume non-trivial individual differences in gaming performance. For those who played very well at baseline, the belief of intact performance under intoxication seems plausible, which would demotivate them from cutting down drinking. However, for those who played very poorly prior to the intervention, there was also no need to limit drinking as their performance was almost at chance level. As a result, probably only for those with medium game performance, it is worth the effort to reduce alcohol use in order to keep up performance levels. Therefore, a tailored driving game for the post-intervention session can be considered.

Regarding *implementation intentions*, more rigorous studies are called for that consider a couple of important mediators. Due to the lack of meta-analyses in the alcohol field (except for a conference poster: Cooke & Lowe, 2016), we referred to a recent meta-analysis on eating behavior (Carrero, Vilà, & Redondo, 2019). There, eleven moderators were examined: sample characteristics (e.g., age, sex, student or not) and intervention parameters (e.g., web-based/paper-based, length of intervention, with/without initial training, with/without monitoring, experimenter checked the quality of plan or not, personalized plan or not, action plan/if-then plan, negation/ignorance/ replacement implementation intentions; Carrero et al., 2019). A general conclusion was that implementation intentions are more effective in *promoting healthy* behavior than *reducing unhealthy* behavior (Carrero et al., 2019), as breaking a habit is more difficult than initiating a new behavior (Adriaanse, Gollwitzer, De Ridder, de Wit, & Kroese, 2011). This, however, cannot be easily translated to alcohol-related research as there is less of a variety of healthy beverages (e.g., fruit juice is sugary). Secondary findings suggested that the intervention is more effective in *promoting healthy* eating when it is administered to a young, nonstudent population; with initial training; without an experimenter reviewing the plan; if it is not web-based; and if it uses a specific format (action plan or if-then plan) rather than a complex combination of both (Carrero et al., 2019). In contrast, to reduce unhealthy eating behavior, only the type of implementation intentions influences its effect, such that negation/ignorance implementation intentions (e.g.,

if…, then I *will not* buy a beer) are less effective than replacement plans (e.g., if…, then I *will* buy soda instead) as participants do not know which path they should follow in the former case (Adriaanse, van Oosten, de Ridder, de Wit, & Evers, 2011; Carrero et al., 2019). This reminds us that if experimenter-provided (vs. self-generated) implementation intentions are to be used, it is better to discard the negation and ignorance plans.

Concluding marks

Why do the negative consequences produced by drinking alcohol fail to act as a warning to reduce its use? Why do we, once a drinking episode started, drink one after another and end up with drinking too much? In the addition cycle, loss-of-control is a typical characteristic of the binge/intoxication stage and acts as a risk factor of SUD development (Koob & Volkow, 2010). Investigating such loss-of-control behavior is not a new topic in the addiction field. However, the way in which it was measured is a bit problematic. That is, failures in inhibiting the response to *external* rather than *internal* stop signals were regarded as an indicator of impaired inhibitory control. Therefore, this thesis mainly explored the relationship between alcohol use and *intentional inhibition* by using the recently developed Chasing Memo task. We found that chronic and acute alcohol use were weakly associated with the *when* component of intentional inhibition. However, acute alcohol use influenced the *whether* component by promoting alcohol-seeking behavior after a priming dose. Coupled with the evidence that *acute* (vs. *chronic*) alcohol use resulted more consistently in *cued* inhibition impairments, a bold assumption is that *short-term* but not *long-term* alcohol use was truly associated with general inhibition deficits. In other words, chronic moderate alcohol users can self-control as well as the individuals who rarely drink. However, once drinking is initiated by exposure to alcohol-related stimuli (watching a beer advertisement, meeting a friend with whom one frequently enjoy drinks together, passing by a pub, etc.), it is just too late to stop (Tiffany, 1990). This hypothesis does not apply to extreme cases such as diagnosis of SUD.

Studies in the future can consider developing a more convincing way of measuring intentional inhibition. One out of the many difficulties lies in balancing free will and implementing experimental manipulations. That is, knowledge of being tested can already interfere with one's free will (i.e., I can no longer drink as naturally as usual); on the other hand, there is very little that can be done in complete observational research (e.g., experimenters observing and recording alcohol consumption). There is a long way to go.

Second, we focused on phenomenal descriptions, such as whether groups behave differently regarding intentional inhibition. But given the reasons-responsive characteristic of volition (Haggard, 2018), any (non-)action should be goal-directed, no matter whether the agent can realize it or not. For some individuals, alcohol is naturally associated with positive attributes; whereas others are easily protected from AUD by hating the taste (like me). Environmental factors (the availability of other incentives in life), as well as the drinking behavior itself (instant pleasures gained, or negative affect reduced), should be considered

(Cox, Klinger, & Fadardi, 2017). Clarifying the underlying reasons can also promote the development of more effective interventions.

Third, craving for alcohol is closely related to loss-of-control behavior, though not necessarily being the determinant (Marlatt, 1978). As a next step, possible dynamic associations between craving, loss-of-control (e.g., intentional inhibition) and drinking amount in progress with drinking can be explored.

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Summary

A main characteristic associated with problematic substance use is impulsivity, or more specifically, a tendency to take impulsive action and show problems with inhibition. This has been highlighted in many addiction-related models (e.g., dual-process models) and criteria in diagnosing substance use disorders (SUDs). Loss-of-control is thought to play an important role in different stages of addiction: initial use of a substance, transition from recreational use to heavier use and abuse, continuation of use despite experiencing increasing use-related problems and relapse after abstinence. Although the causal relationship between substance use and inhibition deficits is as-yet-unknown, most researchers support the idea of bidirectional associations, with impulsivity predicting problematic substance use and vice versa. A body of empirical studies and reviews/meta-analyses were conducted in the past two decades on the relationship between *long-term* substance use and response inhibition. For instance, a recent meta-analysis by Smith et al. (2014) found that inhibitory impairment was associated with chronic use of some substances (e.g., cocaine, ecstasy, methamphetamine, tobacco, and alcohol) but not with chronic use of other substances (e.g., opioids, cannabis). This study and many others are informative in revealing the relationship between response inhibition and *long-term* usage of a specific kind of substance. However, some important factors that may non-trivially bias research findings were not systematically examined or controlled for in this meta-analysis or other previous literature. First, poly-substance use is the rule rather than the exception, and substances may interact with each other in their relationship with response inhibition, which could entail both greater-than-additive effects and compensating effects. Second, findings on this topic are largely inconsistent, which is closely related to the variance of between-study factors. These include demographics (e.g., sex, age) and task parameters (e.g., whether substance-related stimuli are used in the task). Third, response inhibition was typically assessed by Go/No-Go and stop-signal tasks, in which inhibition was signaled by external cues. Such *cued inhibition* differs from the type of inhibition that is required to voluntarily terminate substance use (in a use-situation), referred to as *intentional inhibition*. From this perspective, performance in cued inhibition tasks may have been incorrectly used to interpret loss-of-control over substances. Compared with long-term substance use, *acute* substance use was found to be more consistently associated with inhibition impairment. However, the third point (i.e., intentional inhibition) is also relevant here as it helps explain the priming effect: further substance seeking after a priming dose.

To fill these research gaps, we first did a mega-analysis to assess the relationship between poly-substance use and response inhibition. Then we narrowed down to alcohol use. In three experiments, we examined *long-term* and *acute* alcohol use and their relationships with *stimulus-driven* and *intentional* inhibition. By the end, we steered toward a field study to reduce alcohol use in a naturalistic environment.

In **Chapter 2**, we focused on a broad range of substance use and possible relations with response inhibition. The novelty of this work can be summarized as 1) poly-substance use was systematically examined for the first time; 2) substance use was assessed in a continuous rather than discrete manner, at least for the most commonly used substances (alcohol and tobacco). In contrast to comparing two extreme groups (controls vs. problematic

users), this method is advantageous in examining a *linear* relationship and preserving within-group variances; 3) we have enough power to test the variables that can hardly be examined in a single study. With 3610 individuals' data from 39 studies, we found that 1) long-term recreational substance use without SUD was generally *not* associated with impaired inhibition. Only lifetime cannabis use was associated with suboptimal inhibition (but only in the stop-signal task); 2) lifetime cannabis use moderated tobacco's negative effect on response inhibition: in cannabis non-users only, tobacco use was associated with suboptimal inhibition; 3) the effect of demographics and task parameters were all in the predicted directions; 4) stop-signal task was more sensitive than the go/no-go task in detecting substance use related suboptimal inhibition.

Chapter 3 was composed of two studies. Study 1 compared associations between cue-induced and intentional inhibition with long-term alcohol use. Study 2 focused on acute alcohol use and intentional inhibition, while neural activity was recorded with EEG. We found that the AUDIT (Alcohol Use Disorder Identification Test) score did not predict stimulus-driven or intentional inhibition; the acute alcohol use condition did not differ from the placebo condition in its relationship with either form of inhibition and related EEG patterns. Interestingly, we found that a slow negative readiness potential (RP) was observed with an onset of about 1.2 s, exclusively before participants stopped intentionally. Given the occurrence of RP in other cognitive processes, we suspect it represents intention formation in general.

Chapter 4 was based on Chapter 2 with the following modifications: 1) a no expectancy control condition was added in addition to the alcohol and placebo condition. This helps to differentiate pharmacological effects of alcohol from expectancy effects; 2) alcohol-related stimuli (vs. neutral stimuli) were used in both paradigms to examine whether inhibition problems would be stronger in the context of alcohol-stimuli (in line with the incentive-sensitization theory of addiction); 3) a larger sample was recruited to increase statistical power; 4) in the intentional inhibition task, participants could freely decide both *when* and *whether* they would like to disengage. Survival analysis was used to treat time-to-event data. We found that moderate acute alcohol use (0.55g/kg for males, 0.45g/kg for females) impaired intentional inhibition but not stimulus-driven inhibition. In particular, the stop-signal reaction time was not influenced by alcohol use. However, in the alcohol condition, intentional inhibition was initiated less often (especially when non-alcohol related stimuli were used).

Chapter 5 is an intervention study aimed to manipulate self-control. Participants were visitors of a student bar. They were motivated to reduce their alcohol use in the next hour by an increased chance of a monetary incentive and then formed implementation intentions (making if-then sentences to bridge the gap between good intentions and goal attainment). Alcohol intake during the next hour was the main outcome. It was found that neither motivation alone nor in combination with implementation intentions resulted in a decreased drinking. However, participants in the combined condition did feel more influenced to drink less and that was negatively associated with actual alcohol consumption.

Taken together, the thesis has given rise to some take-home messages: 1) long-term recreational substance use without SUD is generally not associated with response inhibition deficits, except for cigarette smoking without also using cannabis; 2) the EEG-derived readiness potential represents intention formation in general; 3) the priming effect of alcohol appears in the context of intentional rather than stimulus-driven inhibition; 4) implementation intentions may help to reduce alcohol use in a naturalistic environment. Some challenging but valuable directions for the future are 1) progress in developing new intentional inhibition assessments. This can refer to more ecologically valid laboratory tasks or field studies with methods such as Ecological Momentary Assessment; 2) revealing mechanisms underlying the loss-of-control over substance use behavior, which might be stage-specific (intoxication/withdrawing/craving); 3) development of interventions that are user-friendly in daily life, for which some cellphone applications already show promise.

Samenvatting

Een belangrijk aspect van het problematische gebruik van middelen is impulsiviteit, en meer specifieker, de neiging om impulsief te reageren en problemen met inhibitie. Dit wordt benadrukt door verschillende modellen van verslaving (zoals *dual-process* modellen) en criteria voor het vaststellen van een stoornis op het gebied van middelengebruik. Zo wordt verondersteld dat controleverlies een belangrijke rol speelt tijdens verschillende stadia van verslaving; tijdens het initiële gebruik van een middel, de overgang van recreatief naar veelvuldig gebruik en misbruik, het blijven gebruiken ondanks een toename van gebruikgerelateerde problemen, en terugval na abstinentie. Een mogelijk causaal verband tussen middelengebruik en inhibitieproblemen is onderwerp van onderzoek, maar er wordt algemeen aangenomen dat er sprake is van een wederzijdse beïnvloeding waarbij verhoogde impulsiviteit problematisch middelengebruik voorspelt en omgekeerd. In de afgelopen twintig jaar is veel onderzoek gedaan naar de relatie tussen het verband tussen langdurig middelengebruik en responsinhibitie. Een meta-analyse van Smith et al. (2014) relateerde inhibitieproblemen aan het langdurig gebruik van bepaalde middelen (zoals cocaïne, ecstasy, methamfetamine, tabak en alcohol), maar niet van andere middelen (zoals opiaten en cannabis). Deze en andere studies geven inzicht in de relatie tussen responsinhibitie en het langdurig gebruik van specifieke middelen. Echter, een aantal belangrijke factoren blijft onderbelicht omdat ze niet zijn onderzocht of omdat er niet voor is gecontroleerd. Ten eerste is polygebruik (het nemen van verschillende middelen door en naast elkaar) eerder regel dan uitzondering. Verschillende middelen kunnen met elkaar interacteren en zo een gecombineerd effect hebben op responsinhibitie, van een compenserende tot een elkaar versterkende invloed. Ten tweede zijn de onderzoeksresultaten op dit gebied veelal inconsistent, door de grote verschillen tussen studies. Hieronder vallen demografische aspecten (zoals sekse en leeftijd) en taak-gerelateerde factoren (maakt de taak gebruik van afbeeldingen van middelen of niet). Ten derde is responsinhibitie vaak onderzocht met de go/no-go taak en de stop taak waarbij een extern signaal aanleiding geeft tot inhibitie. Een dergelijke vorm van "*cued*-inhibitie" verschilt mogelijk van de inhibitievariant die nodig is voor het vrijwillig afbreken van middelengebruik (tijdens het gebruik) die wordt aangeduid met de term "*intentionele inhibitie*". In dit licht bezien zijn de uitkomsten van *cued*-inhibitie taken mogelijk onterecht gebruikt om het controleverlies bij middelengebruik te interpreteren. Anders dan bij langdurig gebruik wordt het directe gebruik van middelen wel geassocieerd met verstoorde inhibitie. Let wel dat het derde punt (intentionele inhibitie) ook hier relevant is, aangezien het mogelijk een verklaring biedt voor het *priming* effect (doorgaan met gebruik na een *priming* dosering).

Rekening houdend met bovenstaande punten hebben we een mega-analyse uitgevoerd om de relatie tussen polygebruik en responsinhibitie te onderzoeken. Vervolgens wordt er specifieker ingegaan op de gevolgen van alcoholgebruik. In drie studies wordt de relatie onderzocht tussen de gevolgen van langdurig alcoholgebruik en de acute effecten op *cued*-inhibitie en intentionele inhibitie. Het laatste onderzoek is een veldstudie waarbij gepoogd werd alcoholgebruik te verminderen in een natuurlijke setting.

Hoofdstuk 2 gaat in op de relatie tussen verschillende vormen van middelengebruik en responsinhibitie. Het vernieuwende van dit werk heeft betrekking op 1) het gerichte onderzoek naar polygebruik; 2) het beschouwen van middelengebruik als continue in plaats

van discrete variabele, ten minste voor de veelgebruikte middelen alcohol en tabak. Anders dan het vergelijken van twee extreme groepen (een controlegroep versus probleemgebruikers) kan met deze methode een mogelijk lineaire relatie worden onderzocht, rekening houdend met de variantie tussen de groepen. Analyse van de data van 3610 individuen van 39 studies leidde tot de volgende inzichten 1) algemeen bezien is het langdurig recreatieve gebruik van middelen zonder een gebruikgerelateerde diagnose niet geassocieerd met verstoorde inhibitie. Enkel langdurig gebruik van cannabis is gerelateerd aan suboptimale inhibitie (zoals gemeten met de stoptaak). 2) Langdurig gebruik van cannabis modereert het negatieve effect van tabak op responsinhibitie; zij die naast tabak geen cannabis gebruiken vertoonden een neiging tot suboptimale inhibitie; 3) de effecten van demografische en taakgerelateerde factoren waren zoals verwacht; 4) de stoptaak is sensitiever dan de go/no-go taak als het gaat om detecteren van gebruikgerelateerde suboptimale inhibitie.

Hoofdstuk 3 bestaat uit twee studies. Studie 1 gaat in op de relatie tussen langdurig gebruik van alcohol en *cued*- en intentionele inhibitie. Studie 2 gaat over de directe gevolgen van alcoholgebruik op intentionele inhibitie, waarbij EEG werd gemeten. Het blijkt dat *cued*-inhibitie en intentionele inhibitie niet worden voorspeld door de score op de AUDIT (Alcohol Use Disorder Identification Test). Zowel de gedragsmaten als de EEG-patronen van beide inhibitievormen verschilden niet tussen de placeboconditie en de alcoholconditie. Interessant genoeg vonden we een langzame negatieve potentiaal; de *readiness* potentiaal (RP) die ongeveer 1.2 s startte voordat een proefpersoon intentioneel stopt. Omdat de RP ook voorkomt bij andere cognitieve processen, vermoeden we dat het de vorming representeert van een intentie in het algemeen.

Hoofdstuk 4 is gebaseerd op hoofdstuk 2 met de volgende aanpassingen; 1) naast de alcohol- en placebocondities werd een “geen-verwachting” conditie opgenomen. Op die manier kunnen de farmacologische effecten van alcohol worden vastgesteld, naast door de proefpersoon verwachte effecten; 2) er werden alcohol-gerelateerde stimuli (versus neutrale stimuli) gebruikt in beide paradigma’s om te onderzoeken of inhibitieproblemen worden versterkt in een context met alcohol-stimuli (zoals verondersteld door de *incentive-sensitization* theorie van verslaving); 3) de steekproef was groter ten gunste van het statistisch onderscheidingsvermogen; 4) proefpersonen waren vrij om te beslissen *of* en *wanneer* en ze stopten. De specifieke tijdseries werden geanalyseerd met *survival* analyse. Een gematigde dosis alcohol (0.55g/kg voor mannen, 0.45g/kg voor vrouwen) bleek *cued*-inhibitie (stop-signaal reactietijd) niet te beïnvloeden. Intentionele inhibitie daarentegen werd minder vaak geïnitieerd na alcoholinname (vooral bij niet-alcohol gerelateerde stimuli).

Hoofdstuk 5 is een interventiestudie gericht op het beïnvloeden van zelfcontrole van bezoekers van een studentencafé. Proefpersonen werden aangespoord om minder alcohol te drinken gedurende een uur door ze een geldbedrag in het vooruitzicht te stellen (de motivatieconditie) en door ze een implementering-intentie te laten formuleren (een *als-dan* zin opstellen om goede voornemens te koppelen aan het daadwerkelijk bereiken van een voorgenomen doel). Alcoholgebruik gedurende het uur was de belangrijkste uitkomstmaat. De motivatieconditie (noch separaat noch in combinatie met de implementering

intentieconditie) resulteerde in een afname van het drankgebruik. Echter, proefpersonen die zowel de motivatieconditie als de implementering intentieconditie doorliepen gaven na het onderzoek aan dat ze menen te zijn beïnvloed om minder te drinken, hetgeen samenhing met een verminderde alcoholconsumptie.

Samenvattend heeft dit proefschrift geleid tot de volgende inzichten 1) langdurig recreatief middelengebruik (zonder gebruikgerelateerde diagnose) wordt over het algemeen genomen niet geassocieerd met een verminderde responsinhibitie, afgezien van het roken van sigaretten zonder daarnaast cannabis te gebruiken; 2) de *readiness* potentiaal in het EEG representeert de vorming van een intentie in het algemeen; 3) het *priming* effect van alcohol treedt op bij intentionele inhibitie, niet bij *cued*-inhibitie; 4) Implementering intenties kunnen helpen om alcoholgebruik te reduceren in een natuurlijke setting. De volgende uitdagingen liggen voor ons: 1) het ontwikkelen van nieuwe methoden om intentionele inhibitie te meten. Dit heeft zowel betrekking op meer ecologisch valide laboratoriumtaken als veldstudies met methodes zoals *ecological momentary assessment*; 2) het blootleggen van mechanismen van controleverlies over middelengebruik, hetgeen mogelijk gerelateerd is aan de verschillende stadia van verslaving (onder invloed zijn/afkicken/verlangen); 3) het ontwikkelen van gebruiksvriendelijke interventies die kunnen worden toegepast in het dagelijks leven, zoals sommige veelbelovende smartphone applicaties.

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