

On the automaticity of response inhibition in individuals with alcoholism

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Abstract

Background and Objectives. Response inhibition is usually considered a hallmark of executive control. However, recent work indicates that stop performance can become associatively mediated ('automatic') over practice. This study investigated automatic response inhibition in sober and recently detoxified individuals with alcoholism.

Methods. We administered to forty recently detoxified alcoholics and forty healthy participants a modified stop-signal task that consisted of a training phase in which a subset of the stimuli was consistently associated with stopping or going, and a test phase in which this mapping was reversed.

Results. In the training phase, stop performance improved for the consistent stop stimuli, compared with control stimuli that were not associated with going or stopping. In the test phase, go performance tended to be impaired for old stop stimuli. Combined, these findings support the automatic inhibition hypothesis. Importantly, performance was similar in both groups, which indicates that automatic inhibitory control develops normally in individuals with alcoholism.

Limitations. This finding is specific to individuals with alcoholism without other psychiatric disorders, which is rather atypical and prevents generalization. Personalized stimuli with a stronger affective content should be used in future studies.

Conclusions. These results advance our understanding of behavioral inhibition in individuals with alcoholism. Furthermore, intact automatic inhibitory control may be an important element of successful cognitive remediation of addictive behaviors.

Keywords: alcoholism, automatic response inhibition, stop-signal task, cognitive remediation

1. Introduction

Response inhibition is a key component of executive control (Aron, Robbins, & Poldrack, 2004; Logan, Cowan, & Davis, 1984; Miyake et al., 2000; Nigg, 2000; Verbruggen & Logan, 2008a,b). It supports flexible and goal-directed behavior by allowing people to withhold inappropriate, no-longer relevant, or risky actions. Work in psychiatry and clinical psychology suggests that deficits in 'executive' response inhibition are associated with various clinical disorders, including alcoholism and other substance use disorders (Dalley, Everitt, & Robbins, 2011; de Wit, 2009; Smith, Mattick, Jamadar, & Iredale, 2014). However, recent work suggests that response inhibition can become 'automatic', triggered by the retrieval of previously acquired associations between stimuli and stopping (Spierer, Chavan, & Manuel, 2013; Verbruggen, Best, Bowditch, Stevens, & McLaren, 2014; Verbruggen & Logan, 2008a). In the present study, we examined whether automatic response inhibition is also impaired in individuals with alcoholism.

Loss of control of no-longer relevant or harmful behavior is central to alcoholism, and is partly due to subjects' inability to deliberately inhibit prepotent responses (Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2005; Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009; Nigg et al., 2006; Noël et al., 2001; Rubio et al., 2008; Smith & Mattick, 2013; Smith, Mattick, Jamadar, & Iredale, 2014; van der Plas, Crone, van den Wildenberg, Tranel, & Bechara, 2009). This 'disinhibition' hypothesis is supported by studies that found impaired performance (Noël et al., 2001), abnormal brain electrophysiology (Kamarajan et al., 2006) and abnormal brain metabolism (Li, Luo, Yan, Bergquist, & Sinha, 2009; Schweinsburg et al., 2004) while alcohol-dependent individuals performed various response inhibition tasks. So far, most studies have focused on deliberate and executive acts of inhibitory control in patients with alcoholism. However, response inhibition depends on an interplay between 'bottom-up' and 'top-down' processes (Verbruggen & Logan, 2008a). Several studies suggest that a stimulus can become associated with stopping; when such stimulus-stop associations are retrieved from memory, the stop response or stopping network can be activated via associative retrieval, suppressing ongoing go processes

(Spierer et al., 2013; Verbruggen, et al., 2014). This may support the development of ‘automatic’ response inhibition¹. A series of studies examined the idea that inhibitory control in go/no-go and stop-signal tasks can be triggered automatically via the retrieval of stimulus-stop associations from memory. For example, the experiments of Verbruggen and Logan (2008a) consisted of a training phase, in which a subset of the stimuli was consistently associated with stopping or going, and a test phase in which the stimulus-stop/go mapping was reversed. In this test phase, participants responded slower to stimuli previously associated with stopping compared with stimuli that they had not seen before or stimuli that were inconsistently associated with going and stopping. Furthermore, response inhibition on no-go or stop-signal trials benefited from consistent stimulus–stop associations (Lenartowicz, Verbruggen, Logan, & Poldrack, 2011; Verbruggen et al., 2014). Based on these findings, Verbruggen and Logan (2008a) proposed the ‘automatic inhibition hypothesis’: inhibitory control in go/no-go and stop-signal tasks can be triggered automatically via the retrieval of stimulus–stop associations from memory.

Preserved automatic (associatively mediated) response inhibition may be crucial in the context of cognitive training of inhibition (for meta-analyses, see Allom, Mullan, & Hagger, 2015; Jones et al., 2016), which has the potential to help reduce excessive or impulsive eating (e.g. Houben & Jansen, 2011; Lawrence, O’Sullivan, et al., 2015; Veling, Aarts, & Papies, 2011), hazardous drinking behavior (Bowley et al., 2013; Houben, Havermans, Nederkoorn, & Jansen, 2012; Houben, Nederkoorn, Wiers, & Jansen, 2011; Andrew Jones et al., 2011; Andrew Jones, Christiansen, Nederkoorn, Houben, & Field, 2013), and ultimately, encourage more healthy behaviors. However, some studies have shown associative learning impairments in patients with alcoholism in a variety of learning paradigms (e.g. Pitel et al., 2007). Therefore, the present study investigated whether recently detoxified patients with alcoholism also show impairments in learning stimulus-stop associations, which would prevent the development of automatic

¹ Instance Theory (Logan, 1988) construes automaticity as a memory phenomenon: ‘Automaticity is memory retrieval: Performance is automatic when it is based on single- step direct-access retrieval of past solutions from memory. The [Instance Theory] assumes that novices begin with a general algorithm that is sufficient to perform the task. As they gain experience, they learn specific solutions to specific problems, which they retrieve when they encounter the same problems again. Then, they can respond with the solution retrieved from memory or the one computed by the algorithm. At some point, they may gain enough experience to respond with a solution from memory on every trial and abandon the algorithm entirely. At that point, their performance is [completely] automatic.’ (Logan, 1988, p.493)

response inhibition and reduce the effectiveness of cognitive training consisting of associating response inhibition with alcohol-related stimuli. A recent study provides indirect support for the idea that subjects with alcoholism have spared ‘automatic inhibition’ (Noël et al., 2013): We found that alcohol-dependent subjects performed worse than healthy participants on three cognitive tasks assessing the inhibition of irrelevant prepotent responses, whereas group performance was similar in the tasks assessing control of proactive interference in memory (i.e. overcoming interference caused by irrelevant long-term memory representations). Some researchers have proposed that control of proactive interference in memory is more automatic and less intentional than deliberate response inhibition (e.g., Nigg, 2000). However, preserved proactive interference control could also be due to non-inhibitory factors. Therefore, more direct evidence of possible preserved automatic response inhibition is necessary, which is the purpose of the present study.

We used a modified version of a stop-signal paradigm to study automatic inhibition (see Fig. 1, Verbruggen et al., 2014). Recently detoxified individuals with alcoholism and healthy controls made speeded semantic categorizations (alcohol-related or neutral words) on a series of words. We used alcohol-related stimuli because response inhibition deficits in individuals with alcoholism are typically enhanced when alcohol-related words are used in the task (e.g. Noël *et al.* 2007). Furthermore, applied studies are likely to use alcohol-related stimuli as well. On some trials (stop trials), a visual signal was presented beneath the words, instructing participants to withhold their planned go response. Each word was presented five times within the block; the first four presentations were ‘training’ trials, the fifth and final presentation was the ‘test’ trial. There were three stimulus types within each block. ‘Stop-then-go’ stimuli (25% of all stimuli) always occurred on stop trials during training, but occurred on a go trial in the test phase (stop-stop-stop-stop-go). The ‘go-then-stop’ (go-go-go-go-stop) stimuli (25% of all stimuli) always occurred on go trials during training, but occurred on a stop trial in the test phase. Finally, control stimuli (50% of all stimuli) occurred with equal probability on stop and go trials during training but the order was otherwise random; half of them occurred on a go trial in the test phase (e.g. go-stop-go-stop-go), whereas the others occurred on a stop trial (e.g. stop-stop-go-go-stop). The overall probability of a

stop trial was 0.5. Participants were not informed about the stimulus types or the training/test structure of the blocks. New words were used in each block to prevent re-learning. Automatic inhibition in both groups was assessed by comparing stop performance in the training phase and go performance in the test phase for stop-then-go and control stimuli (Verbruggen et al., 2014). In the control group (i.e. the healthy adults), stop performance should be better in the training phase but go performance should be worse in the test phase for ‘stop-then-go’ stimuli than for control stimuli due to the retrieval of stimulus-stop associations from memory (Verbruggen & Logan, 2008a; Verbruggen *et al.* 2014). If automatic inhibition is preserved in the recently detoxified individuals with alcoholism (see above), a similar pattern should be observed in the recently detoxified individuals with alcoholism. By contrast, if associative learning is impaired in the recently detoxified individuals (as suggested by some studies), a reliable interaction between Group and Stimulus Type should be observed

2. Material and methods

2.1. Participants

Forty recently detoxified individuals with alcoholism and 40 healthy controls participated in the study. All participants were adults (>18 years old) and provided informed consent that was approved by the Ethics Committee of the Brugmann University Hospital.

Alcohol-dependent participants were recruited from the Alcohol Detoxification Program of the Psychiatric Institute, Brugmann Hospital, Université Libre de Bruxelles (ULB), Belgium. Participants had to meet Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association., American Psychiatric Association., 2013) criteria for alcohol dependence (made by CHU-Brugmann board-certified psychiatrists). Reasons for exclusion were other current DSM-IV Axis I diagnoses, a history of significant medical illness, head injury resulting in a loss of consciousness for longer than 30 minutes that might have affected the central nervous system, use of other psychotropic drugs or substances that influence cognition, and overt cognitive dysfunction. In addition, a minimum Mini-Mental State Examination (MMSE) score of 25 was required in order to exclude alcohol-dependent patients with severe cognitive impairment, such as alcohol-related dementia (Folstein, Folstein, & McHugh, 1975).

Participants were examined after they had abstained from alcohol for a minimum of 18 days and at least 5 days after a standard detoxification period. The detoxification regimen consisted of B vitamins and decreasing doses of sedative medication (diazepam). All received complete medical, neurological, and psychiatric evaluations prior to enrolment in the study.

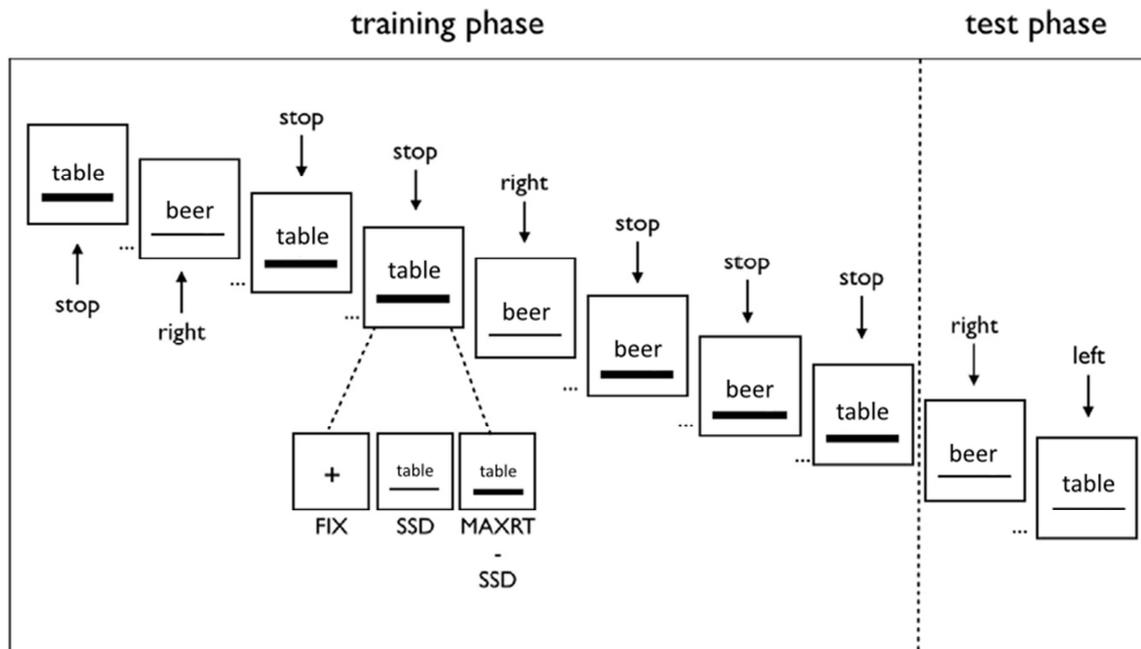
Participants from the control group were recruited by word of mouth from the community. Before being enrolled in the study, controls were first asked to complete a brief pre-screening tool estimating drug and alcohol use. Control participants were excluded if they reported to have consumed drugs within the past 12 months, or if they had consumed more than 54 grams per day of alcohol for longer than 1 month (see also Noël et al., 2013).

2.2 *Affective status, attentional control and working memory*

Affective status was rated with the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and the Positive and Negative Affect Schedule (Watson, Clark, & Tellegen, 1988). The D2 Test of Attention (Brickenkamp & Zillmer, 1998) and the Attentional Control Scale (ASC; (Derryberry & Reed, 2002) were administered to assess attentional control. Working memory was assessed using the operation span task (Ospan; Turner & Engle, 1989), in which participants were requested to solve mathematical operations while simultaneously remembering a set of unrelated words. The Ospan score was calculated according to the partial credit unit (PCU) scoring procedure (Conway et al., 2005).

2.3 *The stop-signal task (see Fig. 1)*

Fig. 1. Example of a ‘stop-then-go’ (‘table’) stimulus and a ‘control’ (‘beer’) stimulus; the first four presentations are the training phase, and the fifth presentation is the test phase. The distinction between the training and test phase is for illustration only, as subjects were not informed about this distinction. FIX = duration of the fixation interval; SSD = stop-signal delay; MAXRT = maximum reaction time.



On go trials, participants made alcohol/neutral judgments about the referents of words by pressing the ‘F’ (‘neutral’) or the ‘J’ (‘alcohol’) key on an AZERTY keyboard with the left and right index fingers, respectively. A list of 112 words (56 neutral, 56 alcohol-related) was used. The words were presented on a 21-in monitor. They appeared in a white lower case Courier font against a black background, and ranged from 12 to 52 mm in width (approximately 1.1° to 5.0°) and 4 to 7 mm (approximately 0.4° to 0.7°) in height. All words appeared above a white fixation line. On stop-signal trials, the white line got thicker, instructing participants to stop their response.

Each block consisted of a training phase (32 trials) and a test phase (8 trials). We used a new list of 8 words in every block (four alcohol-related and four neutral words), and each word was presented five times per block (four times in the training phase and one time in the test phase). In the training phase of each block, a subset of the stimuli was consistently associated with stopping or going. The remaining stimuli (control stimuli) were inconsistently associated with stopping and going. In the test phase, we reversed the stimulus-stop/go mappings for the consistent stimuli. We distinguished between three stimulus types:

1. Stop-then-go stimuli always occurred on a stop-signal trial during training (i.e. they were

consistently associated with stopping), but they always occurred on a go trial in the test phase.

2. Go-then-stop stimuli always occurred on a go trial during training (i.e. they were consistently associated with going), but they always occurred on a stop-signal trial in the test phase.

3. Control stimuli occurred on both go and stop-signal trials in the training phase (i.e. they were inconsistently associated with going and stopping). In the test phase, half of these stimuli occurred on a go trial, whereas the others occurred on a signal trial.

Alcohol and neutral words were distributed equally across the various stimulus types, and stimulus presentation was pseudo-randomized. In each block, all stimuli were presented four times in the training phase before the test phase started. Participants were not informed about the training and test phases or the stimulus types. Previous work (Verbruggen *et al.* 2014) indicates that participants are generally unaware of the training/test and stimulus manipulations in this design.

In both phases, the trials started with the presentation of the white fixation line. After 1,000 ms the go stimulus (i.e. the alcohol-related or neutral word) appeared above the line. It was removed after 2,000 ms (regardless of RT), after which the next trial started. On stop-signal trials, the white fixation line got thicker, instructing participants to stop their response. Participants are less likely to learn stimulus–stop associations when stopping is unsuccessful (Verbruggen & Logan, 2008a). Therefore, the interval between stimulus onset and the presentation of the stop-signal was continuously adjusted according to a two-up/one-down tracking procedure based on the participant's performance for control stimuli to ensure that they were able to stop their responses to those stimuli approximately 70% of the time (Verbruggen *et al.*, 2014).

The experiment consisted of 14 blocks of 40 trials. To familiarize participants with the new words, the whole list was presented at the beginning of the block for 10 seconds. There was a 30 seconds break between each block. Instructions for the stop-signal paradigm emphasized both accuracy and speed, and participants were told not to wait for the stop signal.

2.4 Procedure

Participants were tested individually across two sessions, which took place within a quiet room, located at the Medical Psychology Laboratory of the Brugmann Hospital. The two sessions took place on a different day (\geq one-day interval). During session one, participants provided informed consent, and completed the BDI, and Positive and Negative Affect Schedule. After this, participants performed the stop-signal task. During session two, participants completed the demographics and alcohol use items, the BDI, ASC, the D2 Test of Attention and the OSPAN task.

2.5 Statistical analyses

We excluded participants when the probability of a correctly executed go response on a go trial was below 60% ($n = 12$; this criterion ensures that included participants were responding above chance and were paying attention to the words) or when the probability of an incorrectly executed go response on a stop-signal trials was above 60% ($n = 2$; due to the tracking procedure, percentage of incorrectly executed go responses should be close to 30%, regardless of the latencies of the go and stop processes. Thus, error rates much higher than 30% indicate that the participant was not following the instructions.). Thirty-one alcohol-dependent subjects and 35 control subjects were considered for analyses. Sensitivity analyses (using G*Power; Faul *et al.*, 2007) indicated that the study was sufficiently powered to detect a Group x Stimulus Type interaction with a small to medium effect size.

To test the automatic inhibition hypothesis, we focused on go RTs and the probability of responding on a stop-signal in the training and test phases. The probability of a missed response was higher than in our previous research (e.g. Verbruggen *et al.*, 2014), so we analyzed this as well. For completeness, we report the probability of a correct go response in Table 1, but we did not analyze it further because this measure does not allow a straightforward test of the automatic inhibition hypothesis. To test associative learning in the training phase, we ran ANOVAs or Friedman rank-sum tests with stimulus type (go-then-stop, stop-then-go, or control) and stimulus presentation (one and two versus three and four) as within-subject factors and group (alcohol vs. control) as between-subjects factor. We

collapsed the first two training presentations (first half of training) and last two training presentations (second half of training) to increase the number of observations for the post-hoc comparisons (and reduce the number of tests). For reasons discussed in the limitation section, we could not examine the interaction between stimulus type (go-then-stop, stop-then-go, or control) and word type (alcohol-related vs. neutral word).

Descriptive statistics for the stop task appear in Table 3. The low probability of responding on stop-signal trials (due to the two-up/one-down tracking procedure) and high signal probability ensured that this design was optimal to examine stimulus-stop learning but suboptimal for the estimation of stop latencies (Verbruggen *et al.*, 2014); therefore, SSRTs were not estimated or analyzed.

3. Results

Participant characteristics appear in Table 1. BDI scores and scores on the Negative Affect Schedule were higher in alcohol dependents than in controls, $t(64) = 6.61, p < .001$ and $t(64) = 4.79, p < 0.001$, respectively. Importantly, we observed no significant correlation between scores on the BDI, Negative Affect Schedule and performance in the stop-signal task. No other significant differences were found.

Table 1. Alcohol dependent and control groups characteristics.

	Alcohol Dependent	Control
<i>n</i>	31	35
Age (years)	44.06 (9.74)	44.54 (12.17)
Gender (M/F)	25/8	19/16
Duration of alcohol abuse (years)	15.03 (11.66)	/
Mean alcohol use (<u>grams</u> per day)	213.09 (134.32)	9.05 (10.12) ***
Number of prior hospitalizations for alcohol detoxification	3.71 (3.57)	/
AUDIT	32.32 (4.79)	5.11 (3.64) ***
BDI	11.61 (8.30)	1.11 (1.45) ***
Negative Affect Schedule	24.83 (8.09)	15.77 (5.49) ***
Positive Affect Schedule	31.90 (7.49)	32.17 (5.80)
MMSE	28.41 (1.68)	29.25 (0.95)
ACS	48.29 (12.18)	52.88 (9.69)
D2	112.83 (69.41)	143.91 (75.95)
OSPAN	0.74 (0.15)	0.76 (0.17)

Note. Values shown are the mean and standard deviation (between brackets) on each measure. AUDIT = Alcohol Use Disorders Identification Test, BDI = Beck Depression Inventory, MMSE = Mini Mental State Examination., ACS = Attentional Control Scale. D2 = D2 Test of Attention, OSPAN = Operation Span Task. *** = *t*-test $p < 0.001$.

3.1 Stop-signal task - Training phase

3.1.1 Go RT according to stimulus type

We ran an ANOVA with stimulus type (go-then-stop vs. control), and stimulus presentation (one and two vs. three and four) as within-subject factors and group (alcohol dependent vs. control) as between-subjects factor. An interaction between stimulus type and presentation was found, $F(1,64) = 9.67, p = .003, \eta^2 = .131$. Post-hoc pairwise comparisons revealed that participants were slower to categorize control than go-then-stop stimuli after some training (that is, during stimulus presentation three and four), $t(65) = -2.59, p = .012$. Further analyses revealed that, throughout the training phase, participants became progressively slower to categorize control stimuli, $t(65) = -2.56, p = .013$, but not go-then-stop stimuli, $t(65) = 0.30, p = .77$ (see Fig. 2, panel A and Table 2). A similar (albeit smaller) RT increase for control stimuli was observed in Verbruggen et al. (2014), and is presumably due to slowing in anticipation of a stop signal. For go-then-stop stimuli, this slowing is counteracted or reduced by the retrieval of the stimulus-go association. All other interactions and main effects were not significant (all p 's $> .17$).

Fig. 2. *Panel A.* Categorization reaction time (*panel a*) and probability of responding (*panel b*) according to training parts and stimulus type. Error bars are the standard errors of the mean.

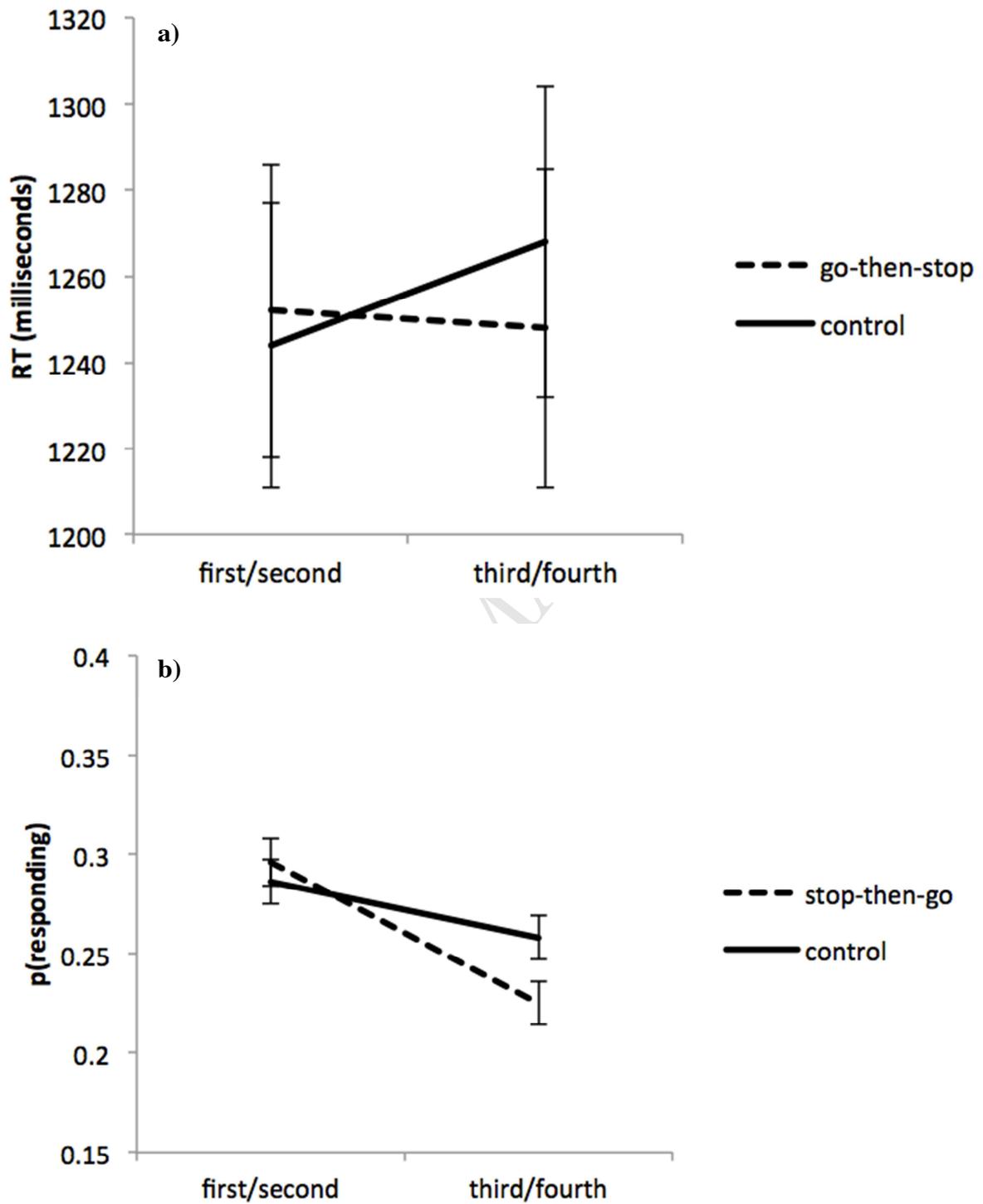


Table 2. Overview of the go data. Probability of an accurate go response [$p(\text{correct})$], probability of a missed go response [$p(\text{miss})$] and average reaction time as a function of stimulus type and stimulus presentation (1-2 and 3-4) and group. Accuracy is the ratio of correct go trials to the number of correct and incorrect go trials (missed trials were excluded); $p(\text{miss})$ is the ratio of omitted responses to the total number of go trials (see Verbruggen & Logan, 2009). M = mean; sd = standard deviation.

Group	Stimulus presentation	Stimulus type	$p(\text{correct})$		$p(\text{miss})$		Reactions times	
			M	sd	M	sd	M	sd
Control	1-2	go-then-stop	0.97	0.03	0.08	0.09	1263	280
	1-2	control	0.97	0.04	0.10	0.08	1256	262
	3-4	go-then-stop	0.96	0.04	0.08	0.09	1271	304
	3-4	control	0.96	0.04	0.10	0.10	1277	286
	5	stop-then-go	0.95	0.04	0.11	0.09	1290	293
	5	control	0.96	0.04	0.10	0.11	1271	296
Alcohol dependent	1-2	go-then-stop	0.94	0.05	0.09	0.08	1238	276
	1-2	control	0.93	0.07	0.09	0.07	1233	281
	3-4	go-then-stop	0.94	0.06	0.09	0.08	1224	301
	3-4	control	0.92	0.07	0.09	0.08	1257	262
	5	stop-then-go	0.92	0.08	0.13	0.12	1259	301
	5	control	0.93	0.07	0.09	0.10	1247	295

3.1.2 Proportion of missed responses according to stimulus type

Due to skewed distribution, we ran Friedman rank-sum tests to examine the effects of stimulus presentation for each stimulus type and each group separately (Table 2). These tests revealed no significant differences (all p 's > .05). Kruskal-Wallis tests revealed no between-groups difference (all p 's > .05).

3.1.3 Probability of responding on stop-signal trials according to stimulus type

We ran another ANOVA with stimulus type (stop-then-go vs. control) and stimulus presentation (one and two vs. three and four) as within-subjects factors and group as a between-subjects factor. We observed a main effect of stimulus presentation, $F(1,64) = 33.88, p < .0001, \eta^2 = .35$, indicating that probability of responding generally decreased throughout the block. Again, a similar pattern was observed in Verbruggen et al. (2014). At the beginning of a block, all words were novel and participants had to learn how to categorize them. It is possible that this increased task demand interfered with stopping (see also e.g. Logan, Cowan, & Davis, 1984). Due to the tracking procedure, probability of responding decreased when stopping failed initially.

Most importantly, the interaction between stimulus type and presentation was significant, $F(1,64) = 11.50, p < .001, \eta^2 = .152$. According to post-hoc pairwise comparisons, participants were better at stopping for stop-then-go stimuli than for control stimuli after some training (that is, during stimulus presentation three and four), $t(65) = -3.70, p < .0001$ (see Fig. 2, panel B and Table 3). SSDs were similar for both stimulus types (see Table 3); consequently, the interaction indicates that stop performance improved for stimuli that were consistently associated with stopping. All other interactions and main effects were not significant (all p 's > .08).

Table 3. Overview of the stop data. Probability of responding on a stop trial [$p(\text{respond}|\text{signal})$] and average SSD as a function of stimulus presentation (1-2, 3-4, and 5), stimulus type and group. M = mean; sd = standard deviation.

Group	Stimulus presentation	Stimulus type	$p(\text{respond} \text{signal})$		Stop-signal delay	
			M	sd	M	sd
Control	1-2	stop-then-go	0.28	0.08	806	310
	1-2	control	0.29	0.08	804	307
	3-4	stop-then-go	0.23	0.10	835	322
	3-4	control	0.25	0.09	833	325
	5	go-then-stop	0.21	0.11	852	331
Alcohol dependent	5	control	0.26	0.10	850	330
	1-2	stop-then-go	0.31	0.10	762	319
	1-2	control	0.30	0.09	761	319
	3-4	stop-then-go	0.23	0.08	787	331
	3-4	control	0.26	0.09	779	327
	5	go-then-stop	0.26	0.12	807	338
	5	control	0.23	0.10	803	337

3.2 Stop-signal task - Test Phase

3.2.1 Go reaction time

We ran an ANOVA with stimulus type (stop-then-go vs. control) as a within-subjects factor and group (alcohol-dependent vs. control) as a between-subjects factor. The effect of stimulus type was marginally significant, $F(1,64) = 3.29$, $p = .075$, $\eta^2 = .05$ (see Table 2 for descriptive statistics). The main effect of group and the stimulus type by group interaction were non-significant; $F(1,64) = 0.14$, $p = .71$, $\eta^2 = .002$, and $F(1,64) = 0.19$, $p = .66$, $\eta^2 = .003$, respectively.

3.2.2 Proportion of missed responses

Due to skewed distribution, we ran Wilcoxon signed ranks tests to examine the effects of stimulus type in each group separately. There was a significant difference between stop-then-go and control stimuli in the alcohol-dependent group (stop-then-go stimuli: *Median* = 0.11, *IQR* = 0.00 to 0.21; control stimuli: *Median* = 0.07, *IQR* = 0.00 to 0.17; $Z = -2.47$, $p = .013$, $r = -0.44$) but not in the control group (stop-then-go stimuli: *Median* = 0.071, *IQR* = 0.00 to 0.18; control stimuli: *Median* = 0.071, *IQR* = 0.00 to 0.18; $Z = -0.45$, $p = .45$). Mann-Whitney U tests revealed no significant between-groups differences (all p 's > .05).

3.2.3 Probability of responding

We ran another ANOVA with stimulus type (go-then-stop vs. control) as a within-subjects factor and group as a between-subjects factor. We observed an effect of stimulus type, $F(1,64) = 4.09$, $p = .047$, $\eta^2 = .06$, indicating that participants had more difficulties to stop their response for go-then-stop stimuli ($M = .27$, $SD = .11$) than for control stimuli ($M = .24$, $SD = .10$). Thus, learning to go in the training phase impaired stopping in the test phase. No other significant result was observed (all p 's > .30). These results further demonstrate intact associative learning in the alcohol-dependent group.

4. Discussion

This study examined automatic inhibition in recently detoxified individuals. In the two groups, we found similar stimulus-stop learning effects in the training phase: the probability of responding on signal trials was significantly lower for stimuli that were associated with stopping compared with the inconsistent control stimuli in the training phase. In the test phase, probability of misses was higher for old stop stimuli than for control stimuli in the alcoholics group. We also found that response latencies tended to be longer for old stop stimuli than for control stimuli in the test phase, although this difference was only marginally significant. Note that the increase in p(miss) for stop-then-go stimuli in the alcohol-dependent group could potentially explain why the main effect of stimulus type failed to reach significance in the RT analyses for the test phase (i.e. the slowest responses were 'captured' by the p(miss) variable rather than the RT variable). Furthermore, it is possible that some participants in both groups learned to associate

items with the stop signal rather than the stop response per se. In Experiment 2 of Verbruggen et al. (2014), learning also influenced $p(\text{respond}|\text{signal})$ in the training phase but not go RTs in the test phase. This pattern of results could indicate that participants learned stimulus-signal associations rather than stimulus-response associations (see Verbruggen et al., 2014, for a detailed discussion of this issue). Finally, go RTs were shorter in the training phase and $p(\text{respond})$ was higher in the test phase for consistent go stimuli than for the inconsistent control stimuli. There were no interactions with group, further demonstrating intact learning in both groups.

Our results support the automatic inhibition hypothesis, which proposes that the stop response or network can be (partly) activated via the retrieval of previously acquired stimulus-stop associations from memory. Importantly, both groups benefited from practicing the stimulus-stop associations, which indicates that associatively mediated or automatic response inhibition is preserved in recently detoxified alcoholics (see also Noël et al., 2013). This contrasts with a profound impairment of non-automatic (intentional) response inhibition in these persons (Goudriaan et al., 2005; Lawrence et al., 2009; Nigg et al., 2006; Noël et al., 2001; Rubio et al., 2008; Smith & Mattick, 2013; Smith et al., 2014; van der Plas et al., 2009). Our finding also contrasts with some studies showing that in the absence of massive memory dysfunction (e.g., Korsakoff's syndrome), individuals with alcoholism exhibit disturbances in various forms of associative learning (De Rosa & Sullivan, 2003; Fortier et al., 2008; McGlinchey, Fortier, Capozzi, & Disterhoft, 2005; Ritz et al., 2014). For instance, alcohol-dependent participants are severely impaired in acquisition in trace eye blink conditioning (McGlinchey et al., 2005). The discrepancy between our finding that alcoholics normally developed automatic response inhibition in a modified version of the SST and those results is interesting but theoretically challenging. Indeed, theoretical analysis suggests an overlap between associative learning in various conditioning paradigms and stimulus-stop learning in response inhibition paradigms (McLaren & Verbruggen, 2016). To our knowledge, no study has directly compared performance of alcohol-dependent patients in various associative learning and inhibition paradigms. Therefore, future research is needed to explore to what extent learning is preserved in various learning and control tasks.

Our findings may open up new avenues for the development of new behavioral treatments.

General stop training and encouraging people to be cautious in stop-signal blocks can reduce risk-taking in gambling tasks (Stevens et al., 2015; Verbruggen, Adams, & Chambers, 2012) and alcohol-seeking (Jones et al., 2011). However, such effects are small and short-lived (Jones et al., 2013; Stevens et al., 2015; Verbruggen et al., 2013), which could potentially explain why some studies failed to observe far-transfer effects (e.g. Redick et al., 2013). Therefore, capitalizing on preserved learning of stimulus-stop associations seems a promising way to achieve better inhibitory control in a real-world context. For instance, in hazardous (non-dependent) alcohol drinkers, training people to stop responding to alcohol cues reduced weekly alcohol intake (for a review, see Jones *et al.* 2013). Similarly, pairing of food-related pictures to stopping in a go/no-go or stop-signal-paradigm reduces subsequent food consumption (Houben & Jansen, 2011; Lawrence, Verbruggen, et al., 2015), and may even lead to weight loss (Lawrence, O'Sullivan, et al., 2015; Veling et al., 2014) (for recent meta-analyses, see Allom et al., 2015; Jones et al., 2016). Possible mechanisms of action modulation include the devaluation of the stop stimuli (Houben et al., 2012; Wessel, O'Doherty, Berkebile, Linderman, & Aron, 2014) and the automatic suppression of inappropriate approach tendencies (Veling et al., 2011; Verbruggen et al., 2014). Our main finding showing that automatic response inhibition develops in recently detoxified patients with alcoholism provides good reasons to be optimistic that learning stimulus-stop associations could be an efficient way for people with alcohol used disorders to (re)gain some control over misuse. Furthermore, clinical interventions aimed at potentiating the automatic suppression of alcohol-going associations and the devaluation of the alcohol-related affective properties, combined with procedures encouraging the *automatic* selection of alternative responses (e.g., intention implementation; Gollwitzer & Sheeran, 2006) could be particularly relevant to treat compulsive drinkers as well as other kinds of substance misuse. However, we like to stress that environmental changes will be required as well to substantially reduce alcohol misuse and other 'inappropriate' behaviors (Granfield & Reinarman, 2014).

This study has several limitations. In order to make the task more engaging and relevant, we used alcohol-related words, but we did not have enough sufficient trials to explore Word Type x Stimulus Type

x Stimulus Count x Group interactions. To keep the experiment as short as possible, the number of trials was low to begin with, and our subjects made more errors than expected and compared to previous studies using a similar task (Verbruggen et al., 2014). Word type and response hand (i.e. dominant vs. non-dominant) were also not counterbalanced. Therefore, we could not perform a meaningful analysis of the interaction between Stimulus Type (go-then-stop, stop-then-go, or control) and Word Type (alcohol-related vs. neutral). Further studies should include two stop-training sessions instead of one, counterbalance the response mapping. Such studies should also use personalized images for the individuals (e.g. images of their favorite drink or venue) that are highly salient and strongly related to affective content (De Houwer & Hermans, 1994), and use multiple stop signals to encourage stimulus-stop learning (instead of stimulus-signal learning; Best, Lawrence, Logan, McLaren, & Verbruggen, 2016). It may also be more appropriate to contrast two distinct but specific semantic categories (e.g., alcohol-related content versus office-related pictures) rather than a specific (alcohol) vs. a general (non-alcohol) category. Finally, our exclusion criteria limit the generalization of the present findings. Indeed, in order to ascertain the relationship between alcohol use disorders and automatic inhibition, participants with other psychiatric syndromes than alcohol dependence were excluded from participation. However, this exclusion criterion eliminates the typical individual with alcoholism, which is intrinsically highly psychiatrically comorbid (e.g., Kessler et al., 1996). For this reason, further studies should ascertain whether the present findings are generalisable to individuals with alcoholism with other psychiatric syndromes. In a similar vein, about 25 percents of our original sample of alcoholics were removed from analyses because of they made too many errors or they responded too slowly. Again, this selection, although justified for the reasons mentioned above, limits the generalisation of our findings and calls for additional empirical data.

In sum, response inhibition improves over practice with consistent stimulus-stop associations in recently detoxified alcoholics, which opens up new avenues of research for the purpose of cognitive training procedures.

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Declaration of interest

None

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Highlights :

- Response inhibition is usually impaired in individuals with alcoholism.
- Response inhibition can become 'automatic' over practice in healthy subjects.
- Stimuli were consistently associated with stopping or going in a stop-signal task.
- Stop performance improved for consistent stop stimuli in healthy controls and alcoholics
- Automatic inhibitory control develops normally in individuals with alcoholism.