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Conflict anticipation in alcohol dependence — A model-based fMRI study of stop signal task

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ABSTRACT

Background: Our previous work characterized altered cerebral activations during cognitive control in individuals with alcohol dependence (AD). A hallmark of cognitive control is the ability to anticipate changes and adjust behavior accordingly. Here, we employed a Bayesian model to describe trial-by-trial anticipation of the stop signal and modeled fMRI signals of conflict anticipation in a stop signal task. Our goal is to characterize the neural correlates of conflict anticipation and its relationship to response inhibition and alcohol consumption in AD.
Methods: Twenty-four AD and 70 age and gender matched healthy control individuals (HC) participated in the study. fMRI data were pre-processed and modeled with SPM8. We modeled fMRI signals at trial onset with individual events parametrically modulated by estimated probability of the stop signal, p(Stop), and compared regional responses to conflict anticipation between AD and HC. To address the link to response inhibition, we regressed whole-brain responses to conflict anticipation against the stop signal reaction time (SSRT).
Results: Compared to HC (54/70), fewer AD (11/24) showed a significant sequential effect — a correlation between p(Stop) and RT during go trials — and the magnitude of sequential effect is diminished, suggesting a deficit in proactive control. Parametric analyses showed decreased learning rate and over-estimated prior mean of the stop signal in AD. In fMRI, both HC and AD responded to p(Stop) in bilateral inferior parietal cortex and anterior pre-supplementary motor area, although the magnitude of response increased in AD. In contrast, HC but not AD showed deactivation of the perigenual anterior cingulate cortex (pgACC). Furthermore, deactivation of the pgACC to increasing p(Stop) is positively correlated with the SSRT in HC but not AD. Recent alcohol consumption is correlated with increased activation of the thalamus and cerebellum in AD during conflict anticipation.
Conclusions: The current results highlight altered proactive control that may serve as an additional behavioral and neural marker of alcohol dependence.

1. Introduction

Alcohol misuse is associated with a wide array of cognitive and affective deficits. Studies showed that amygdalar hyporesponsiveness along with a failure to avoid risky decisions (Glahn et al., 2007), decreased prefrontal, insula/putamen and amygdala activation to emotional stimuli (Heitzeg et al., 2008), and deficits in working memory (Caldwell et al., 2005; Crego et al., 2010; Schweinsburg et al., 2010; Squeglia et al., 2011; Vollstadt-Klein et al., 2010) characterized individual vulnerability to alcohol use disorders. Alcohol dependent patients demonstrated deficits in reward-based probabilistic learning (Jokisch et al., 2014), in procedural learning in conjunction with decreased gray matter volume (GMV) in the caudate nucleus and angular gyrus (Ritz et al., 2014), and in set shifting along with decreased GMV in the inferior frontal cortex (Trick et al., 2014).

In particular, an extensive body of work demonstrated poor impulse control in link with alcohol misuse (Ernst and Paulus, 2005; Everitt and Robbins, 2005; Goldstein and Volkow, 2002; Kalivas and Volkow, 2005; Luijten et al., 2014; Smith et al., 2014). In rodent models, rats under chronic intermittent alcohol exposure exhibited deficits in impulsive control in a five-choice continuous performance task (Irimia et al., 2014). Adolescent alcohol exposure reduces behavioral flexibility, promotes disinhibition, and increases resistance to extinction of ethanol seeking behavior in adulthood (Gass et al., 2014). Monkeys abstinent

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from chronic alcohol consumption demonstrated impairment in response time and accuracy under a distractor condition in a reaction time task (Wright and Taffe, 2014). In humans, behavioral disinhibition is associated with early onset of nicotine, alcohol and illicit drug use in adolescents (Elkins et al., 2006; McGue et al., 2001). Impulsivity distinguished between early and late onset alcoholism (Dom et al., 2006) and is associated with recent alcohol consumption (Mayhew and Powell, 2014). Compared to healthy controls, patients with alcohol use disorders showed greater activations in the medial prefrontal cortex (mPFC) including the supplementary motor area, insula, orbitofrontal gyrus (OFC), and inferior frontal gyrus in a delay discounting task, suggesting widely distributed functional anomalies of impulsive control (Calus et al., 2011). Alcohol consumption confers both acute and chronic effects, and may exacerbate deficits in impulse control and perpetuates alcohol misuse (Bailey et al., 2014; Gan et al., 2014; Houston et al., 2014; Johnston et al., 2013; Townshend et al., 2014; Winward et al., 2014; Worbe et al., 2014). Thus, impulsivity or altered cognitive control contributes to alcohol misuse and constitutes an important focus for the management of alcohol use behaviors (de Wit, 2006; de Wit and Richards, 2004; Everitt and Robbins, 2005; Goldstein and Volkow, 2002; Jentsch and Taylor, 2001; Volkow and Li, 2005; Wilcox et al., 2014).

In the laboratory, the go/no-go task and stop signal task (SST) are widely used to investigate cognitive control in alcohol and substance abusers. In these behavioral tasks, the frequent "go" trials set up a prepotent response tendency that needs to overridden occasionally when the nogo or stop signal appears. By comparing cerebral responses to the nogo or stop trials, when inhibition is required, and responses to go trials, investigators characterized how these processes are altered in alcohol misuse or individuals with a family history of alcohol misuse. For instance, children with a family history of alcoholism showed altered activations in a number of cortical structures, including the ventral caudate, OFC, middle frontal gyrus, posterior cingulate cortex/precuneus, and mPFC in a go/no-go task as compared to the control group. This finding suggested preexisting functional aberrations of impulse control that may increase risk of cognitive impairment and vulnerability to developing alcohol use disorder (Acheson et al., 2014; Anderson et al., 2005; Heitzeg et al., 2010; Schweinsburg et al., 2004). In our previous work heavy drinkers demonstrated prefrontal deficits during response inhibition and post-error adjustment (Li et al., 2009b) and a distinct pattern of reduced cortico-striatal activities during risk taking decisions in the SST (Bednarski et al., 2012; Yan and Li, 2009). Together, although these studies reported a diverse pattern of altered cerebral activation that appeared to depend on behavioral paradigms and contrasts as well as clinical characteristics (Karch et al., 2008), the findings support altered cognitive control as a process critical to the development and maintenance of alcohol misuse.

While extant imaging studies focused on responses to nogo or stop signal in the go/no-go task and SST, a distinct dimension of cognitive control is the ability to anticipate environmental stimuli and adjust behavior accordingly. This ability of proactive control has been studied in the SST by varying the stop signal probability. Previous studies have shown that higher stop likelihood resulted in increased activation in the mPFC and subcortical structures including the caudate and insula, suggesting a neural circuit for proactive inhibitory control (Chikazoe et al., 2009; Jahfari et al., 2010; Vink et al., 2005; Zandbelt et al., 2013). In our recent work, we applied a Bayesian dynamic model to estimate on a trial-by-trial basis the likelihood of the upcoming stop signal based on the history of events (Ide et al., 2013). This estimate allowed us to delineate the neural correlates of conflict anticipation, a critical basis for proactive control (Ide et al., 2013; Yu et al., 2009). To our knowledge, this important aspect of cognitive control has not been examined in association with alcohol misuse. Here, we explored the neural processes of conflict anticipation and examined its link to response inhibition and alcohol use in alcohol dependent individuals. Because alcohol addiction is associated with deficits in top-down executive processes (Brion et al., 2014; Lannoy et al., 2014), we hypothesized altered conflict anticipation in association with impairment in inhibitory control in dependent individuals.

2. Methods

2.1. Participants, assessments, and behavioral task

Twenty-four alcohol dependent (AD; 6 females; 38.7 ± 8 years of age) and seventy healthy control (HC; 27 females; 35.1 ± 10 years of age) individuals, group matched in age ($p = 0.1102$, two-sample t test) and gender ($p = 0.2815$, chi square test), participated in this study.

AD met criteria for current alcohol dependence, as diagnosed by the Structured Clinical Interview for DSM-IV (First et al., 1995); they did not meet current DSM-IV criteria for dependence on other psychoactive substances, except nicotine. Recent use of other illicit substances was ruled out by urine toxicology screens upon admission. Women were excluded from the study if they were using any form of birth control or were either peri- or post-menopausal. In addition, individuals with current depressive or anxiety symptoms requiring treatment or currently being treated for these symptoms were excluded as well. They were drug-free while staying in an inpatient treatment unit prior to the current fMRI study. All participants were physically healthy with no major medical illnesses or current use of prescription medications. None of them reported having a history of head injury or neurological illness. They all signed a written consent after they were given a detailed explanation of the study in accordance with a protocol approved by the Yale Human Investigation Committee.

All participants performed a stop signal task or SST (Hu et al., 2014; Hu and Li, 2012; Li et al., 2005; Li et al., 2009a), in which go and stop trials were randomly intermixed in presentation with an inter-trial-interval of 2 s. A fixation dot appeared on screen to signal the beginning of each trial. After a fore-period varying from 1 to 5 s (uniform distribution), the dot became a circle — the "go" signal — prompting participants to quickly press a button. The circle disappeared at button press or after 1 s if the participant failed to respond. In approximately one quarter of trials, the circle was followed by a 'cross' — the stop signal — prompting participants to withhold button press. The trial terminated at button press or after 1 s if the participant successfully inhibited the response. The time between the go and stop signals, the stop signal delay (SSD), started at 200 ms and varied from one stop trial to the next according to a staircase procedure, increasing and decreasing by 67 ms each after a successful and failed stop trial (Levitt, 1971). With the staircase procedure we anticipated that participants would succeed in withholding the response half of the time. Participants were trained briefly on the task before imaging to ensure that they understood the task. They were instructed to quickly press the button when they saw the go signal while keeping in mind that a stop signal might come up in some trials. In the scanner, they completed four 10-minute sessions of the task, with approximately 100 trials in each session.

2.2. Behavioral data analysis

A critical SSD was computed for each participant that represented the time delay required for the participant to successfully withhold the response in half of the stop trials, following a maximum likelihood procedure (Wetheril et al., 1966). Briefly, SSDs across trials were grouped into runs, with each run being defined as a monotonically increasing or decreasing series. We derived a mid-run estimate by taking the middle SSD (or average of the two middle SSDs when there was an even number of SSDs) of every second run. The critical SSD was computed by taking the mean of all mid-run SSDs. It was reported that, except for experiments with a small number of trials (<30), the mid-run measure was close to the maximum likelihood estimate of X50 (50% positive response; i.e., 50% stop success in the SST, Wetheril et al., 1966). The

stop signal reaction time (SSRT) was computed for each participant by subtracting the critical SSD from the median go trial reaction time (Logan et al., 1984).

2.3. Trial by trial Bayesian estimate of the likelihood of a stop signal

As in our previous work (Ide et al., 2013), we used a dynamic Bayesian model (Yu et al., 2009) to estimate the prior belief of an impending stop signal on each trial, based on prior stimulus history. The model assumes that subjects believe that stop signal frequency r_k on trial k has probability α of being the same as r_{k-1}, and probability $(1-\alpha)$ of being re-sampled from a prior distribution $\pi(r_k)$. Subjects are also assumed to believe that trial k has probability r_k of being a stop trial, and probability $1-r_k$ of being a go trial. With these generative assumptions, subjects are assumed to use Bayesian inference to update their prior belief of seeing a stop signal on trial k, $p(r_k|\boldsymbol{s}_{k-1})$ based on the prior on the last trial $p(r_{k-1}|\boldsymbol{s}_{k-1})$ and last trial's true category ($s_k = 1$ for stop trial, $s_k = 0$ for go trial), where $\boldsymbol{s_k} = \{s_1, \ldots, s_k\}$ is short-hand for all trials 1 through k. Specifically, given that the posterior distribution was $p(r_{k-1}|\boldsymbol{s_{k-1}})$ on trial $k-1$, the prior distribution of stop signal in trial k is given by:

$$p(r_k|s_{\boldsymbol{k-1}}) = \alpha\ p(r_{k-1}|\boldsymbol{s_{k-1}}) + (1-\alpha)\pi(r_k),$$

where the prior distribution $\pi(r_k)$ is assumed to be a beta distribution with prior mean *pm*, and shape parameter *scale*, and the posterior distribution is computed from the prior distribution and the outcome according to the Bayes' rule:

$$p(r_k|s_k) \propto P(s_k|r_k)\ p(r_k|s_{k-1})$$

The Bayesian estimate of the probability of trial k being stop trial, which we colloquially call p(Stop) in this paper, given the predictive distribution $p(r_k|\boldsymbol{s_{k-1}})$ is expressed by:

$$P(s_k = 1|s_{k-1}) = \int P(s_k = 1|r_k)P(r_k|s_{k-1})dr_k = \int r_k P(r_k|s_{k-1})dr_k = \langle\, r_k|s_{k-1}\,\rangle$$

In other words, the probability p(Stop) of a trial k being a stop trial is simply the mean of the predictive distribution $p(r_k|s_{k-1})$. The assumption that the predictive distribution is a mixture of the previous posterior distributions and a generic prior distribution is essentially equivalent to using a causal, exponential, linear filter to estimate the current rate of stop trials (Yu and Cohen, 2009). In summary, for each subject, given a sequence of observed go/stop trials, and the three model parameters {α, *pm*, *scale*}, we estimated p(Stop) for each trial.

2.4. Sequential effect: a parameter set analysis

To obtain the best fit parameters for sequential effect in each individual, we searched for the parameters that maximized the correlation coefficient r between Go RT and p(Stop). The search space of model parameters were set to the following ranges: $\alpha = [0.01, 0.51, \ldots, 1]$, $pm = [0.01, 0.03, \ldots, 1]$, and $sc = [1, 2, \ldots, 20]$. For each subject, we identified the *best model* parameter settings $\{\alpha_{max}, pm_{max}, sc_{max}\}$ that produced r_{max}. We then compared AD and HC participants for α (the weight given to the dynamic, posterior distribution $p(r_k|s_{k-1})$, as opposed to the fixed prior distribution π), *pm* (mean of the beta distribution, which represents the individual's fixed prior of stop trial occurrence), and *sc* (the scale parameter of the beta distribution, which reflects how skewed the distribution is around the mean).

2.5. Imaging protocol and spatial preprocessing of brain images

Conventional T1-weighted spin-echo sagittal anatomical images were acquired for slice localization using a 3 T scanner (Siemens Trio). Anatomical images of the functional slice locations were obtained with spin-echo imaging in the axial plan parallel to the Anterior Commissure–Posterior Commissure (AC–PC) line with TR = 300 ms, TE = 2.5 ms, bandwidth = 300 Hz/pixel, flip angle = 60°, field of view = 220 × 220 mm, matrix = 256 × 256, 32 slices with slice thickness = 4 mm and no gap. A single high-resolution T1-weighted gradient-echo scan was obtained. One hundred and seventy-six slices parallel to the AC–PC line covering the whole brain were acquired with TR = 2530 ms, TE = 3.66 ms, bandwidth = 181 Hz/pixel, flip angle = 7°, field of view = 256 × 256 mm, matrix = 256 × 256, 1 mm^3 isotropic voxels. Functional blood oxygenation level dependent (BOLD) signals were then acquired with a single-shot gradient-echo echo-planar imaging (EPI) sequence. Thirty-two axial slices parallel to the AC–PC line covering the whole brain were acquired with TR = 2000 ms, TE = 25 ms, bandwidth = 2004 Hz/pixel, flip angle = 85°, field of view = 220 × 220 mm, matrix = 64 × 64, 32 slices with slice thickness = 4 mm and no gap. There were three hundred images in each session for a total of 4 sessions.

Data were analyzed with Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, University College London, U.K.). In the pre-processing of BOLD data, images of each participant were realigned (motion-corrected) and corrected for slice timing. A mean functional image volume was constructed for each participant for each run from the realigned image volumes. These mean images were co-registered with the high resolution structural image and then segmented for normalization to an MNI (Montreal Neurological Institute) EPI template with affine registration followed by nonlinear transformation (Ashburner and Friston, 1999; Friston et al., 1995). Finally, images were smoothed with a Gaussian kernel of 8 mm at Full Width at Half Maximum. Images from the first five TRs at the beginning of each trial were discarded to enable the signal to achieve steady-state equilibrium between radio frequency pulsing and relaxation.

2.6. Generalized linear models and group analyses

Our goal is to identify the neural correlates of conflict anticipation or the Bayesian belief of a stop signal. We distinguished four trial outcomes: go success (GS), go error (GE), stop success (SS), and stop error (SE), and modeled BOLD signals by convolving the onsets of the fixation point — the beginning — of each trial with a canonical hemodynamic response function (HRF) and the temporal derivative of the canonical HRF (Friston et al., 1995). Realignment parameters in all 6 dimensions were entered in the model. We included the following variables as parametric modulators in the model: p(Stop) of GS trials, SSD of SS trials, p(Stop) of SS trials, SSD of SE trials, p(Stop) of SE trials, in that order. Inclusion of these variables as parametric modulators improves model fit (Buchel et al., 1996, 1998; Cohen, 1997; Hu and Li, 2012) and, specifically, the parametric modulator of p(Stop) allowed us to examine the neural correlates of conflict anticipation. Serial autocorrelation of the time series was corrected by a first degree autoregressive or AR(1) model (Della-Maggiore et al., 2002; Friston et al., 2000). The data were high-pass filtered (1/128 Hz cutoff) to remove low-frequency signal drifts.

In the first level analysis, we obtained for each participant a contrast "1" (activation) and "-1" (deactivation) each on the parametric modulator "p(Stop)" on GS trials to examine how deviations from the average BOLD amplitude are modulated by trial-by-trial estimate of the likelihood of a stop signal (St Jacques et al., 2011; Wilson et al., 2009). That is, this contrast identified voxels with activation increasing/decreasing with the likelihood — a Bayesian belief — that a stop signal would appear in a go trial. In the second level analysis, all images were evaluated at a voxelwise threshold of $p < .005$, combined with a cluster size threshold of 29 contiguous voxels (783 mm^3). This combined threshold was estimated with a Monte-Carlo simulation using AlphaSim (Douglas Wand, http://afni.nimh.nih.gov/pub/dist/doc/program_help/AlphaSim.html) to yield an overall threshold of $p < .05$, corrected for multiple comparison for the whole brain. One-sample and two-sample *t* tests were

performed each to obtain individual group results and contrasts between AD and HC.

To examine how conflict anticipation is related to stop signal inhibition, we performed a regression of p(Stop) contrast map against SSRT each for AD and HC. Finally, to explore the effects of alcohol use on conflict anticipation in AD, we performed regression analyses of p(Stop) contrast map against the measures of alcohol assumption in AD, including the number of days and amount of alcohol use in the month prior to admission and the years of alcohol use (Table 1).

3. Results

3.1. Behavioral performance

Tables 1 and 2 show demographic information and behavioral performance of the participants. In the SST, the two groups differed significantly in go success rate and go trial reaction time (GORT). We examined the parameters of individual Bayesian models that produced the maximum correlation between RT and p(Stop), indexed by coefficient r_{max}. The parameter α_{max} was significantly lower in AD than in HC, and the parameter pm_{max} was significantly higher in AD than in HC. sc_{max} as not significantly different between the two groups.

To examine the sequential effect, we used the group mean (AD and HC respectively) of each model parameter as a fixed parameter to estimate p(Stop) and compute the correlation between p(Stop) and RT (Camerer and Ho, 1999; Daw et al., 2006; O'Doherty et al., 2004). The correlation between p(Stop) and RT was significantly greater in HC ($r = 0.2111 \pm 0.1358$) as compared to AD ($r = 0.1189 \pm 0.1125$) (regression slope analysis, $t_{(92)} = -3.3268$, $p = 0.0013$) (Fig. 1a). Fifty-four of the 70 HC while only 11 of the 24 AD exhibited a significant sequential effect ($\chi^2 = 8.21$, $p = 0.0042$, chi-square test).

We computed the p(Stop) for each trial for each individual and grouped the RT for p(Stop) binned from 0.1 to 0.8 (equally spaced) for each individual, and averaged RT for each bin (Fig. 1b). We then performed a linear regression each for HC ($r = 0.3511$, $p = 0.0000$) and AD ($r = 0.1177$, $p = 0.0086$). The two linear regressions differed significantly in slope ($p = 0.0048$; Zar, 1999), again suggesting a diminished sequential effect in AD as compared to HC.

To examine the relationship between sequential effect and general performance in the SST, we performed an analysis of variance (ANOVA) on participant groups (HC vs. AD) and sequential effect groups (i.e., SEQ or individuals who showed a sequential effect vs. nSEQ or those who did not demonstrate a significant sequential effect) each for GORT and SSRT. For GORT, the results showed significant main effects of participant ($F_{(1, 90)} = 7.432$, $p = .008$) and sequential effect group ($F_{(1, 90)} = 5.405$, $p = .022$) but not the interaction ($F_{(1, 90)} = 3.130$, $p = .080$). For SSRT, the main effect of participant ($F_{(1, 90)} = 5.315$, $p = .023$) but not the sequential effect group ($F_{(1, 90)} = .803$, $p = .373$) was significant and the interaction was significant ($F_{(1, 90)} = 9.431$, $p = .003$); while SSRT was shorter in the SEQ group in HC, the reverse was true in AD (Fig. 2).

Table 2
Behavioral performance of AD and HC participants in the SST.

	AD ($n = 24$)	HC ($n = 70$)	p-Value
Median GORT (ms)	687 ± 114	603 ± 114	0.0019
SSRT (ms)	190 ± 30	202 ± 40	0.2098
GS %	96.2 ± 1.6	98.3 ± 2.4	0.0007
SS %	53.3 ± 3.6	51.1 ± 3.2	0.3431
α_{max}	0.81 ± 0.29	0.90 ± 0.16	0.0360
pm_{max}	0.57 ± 0.44	0.23 ± 0.34	0.0000
$scale_{max}$	18.04 ± 4.61	18.06 ± 4.97	0.9893

3.2. Regional activations modulated by p(Stop)

We evaluated all imaging results at a voxel threshold of $p < 0.005$, combined with a cluster size threshold of 29 contiguous voxels estimated with a Monte-Carlo simulation using AlphaSim to correct for multiple comparison across the entire brain (see Methods section). In HC, activations to conflict anticipation were found in bilateral inferior parietal lobules (IPLs), right lateral orbital frontal cortex (OFC), midcingulate cortex (MCC), cerebellum, and right pre-SMA in association with increasing p(Stop). Anticipation of the stop signal was also associated with deactivation of multiple brain regions including bilateral superior frontal gyri (SFG), hippocampi, and temporal/occipital cortices (Table 3a; Fig. 3a). In AD, anticipation of the stop signal was associated with activations in the right pre-supplementary motor area (pre-SMA), bilateral lateral OFC, right middle temporal gyrus (MTG), bilateral IPLs, right dorsal lateral prefrontal cortex (DLPFC), and thalamus, and with significant deactivations in bilateral hippocampus gyri, caudate, and precuneus (Table 3b; Fig. 3b). A two-sample t-test showed greater p(Stop) related activation in the right IPL and pre-SMA in AD as compared to HC (Table 3c; Fig. 3c) and less deactivation in multiple brain regions including the mPFC, caudate, right superior temporal gyrus (STG), left hippocampus, and left superior frontal gyrus (SFG) (Table 3d; Fig. 3d).

In considering the issue of unbalanced sample size between the two groups, we selected 24 HC who were individually best matched in age and gender to the 24 AD and performed the identical analyses. The results similarly showed increased activation of the pre-SMA as well as less deactivation of the mPFC and left SFG in AD as compared to HC (Supplementary Fig. 1).

We examined possible behavioral mechanisms of increased pre-SMA and right IPL activation and decreased deactivation of aforementioned regions in relation to the sequential effect. We posited that if the altered activations reflect a compensatory mechanism for proactive control, these differences should show an interaction effect between the participant groups (HC vs. AD) and sequential effect

Table 1
Demographics of alcohol dependent (AD) and health control (HC) participants.

	AD ($n = 24$)	HC ($n = 70$)	p-Value
Men/women	18/6	46/27	0.2815[a]
Age (years)	38.7 ± 8.3	35.1 ± 9.9	0.1102[b]
Ethnicity			0.0807[a]
African American	7 (29.2%)	12 (17.2%)	
Asian/Pacific Islander	0 (0%)	4 (5.7%)	
Caucasian	17 (70.8%)	53 (75.7%)	
Missing information	0 (0%)	1 (1.4%)	
Education (years)	12.5 ± 1.7	15.2 ± 2.5	0.0000[b]
Average number of days of alcohol use/month prior to admission	23.2 ± 9.5	5.9 ± 5.3	0.0000[b]
Average number of drinks/month prior to admission	383.6 ± 348.2	14.1 ± 13.0	0.0000[b]
Years of alcohol use	24.0 ± 9.1	20 ± 12.4	0.2287[b]

Note: Values are mean ± SD.
[a]Chi square test.
[b]2-Sample t-test.

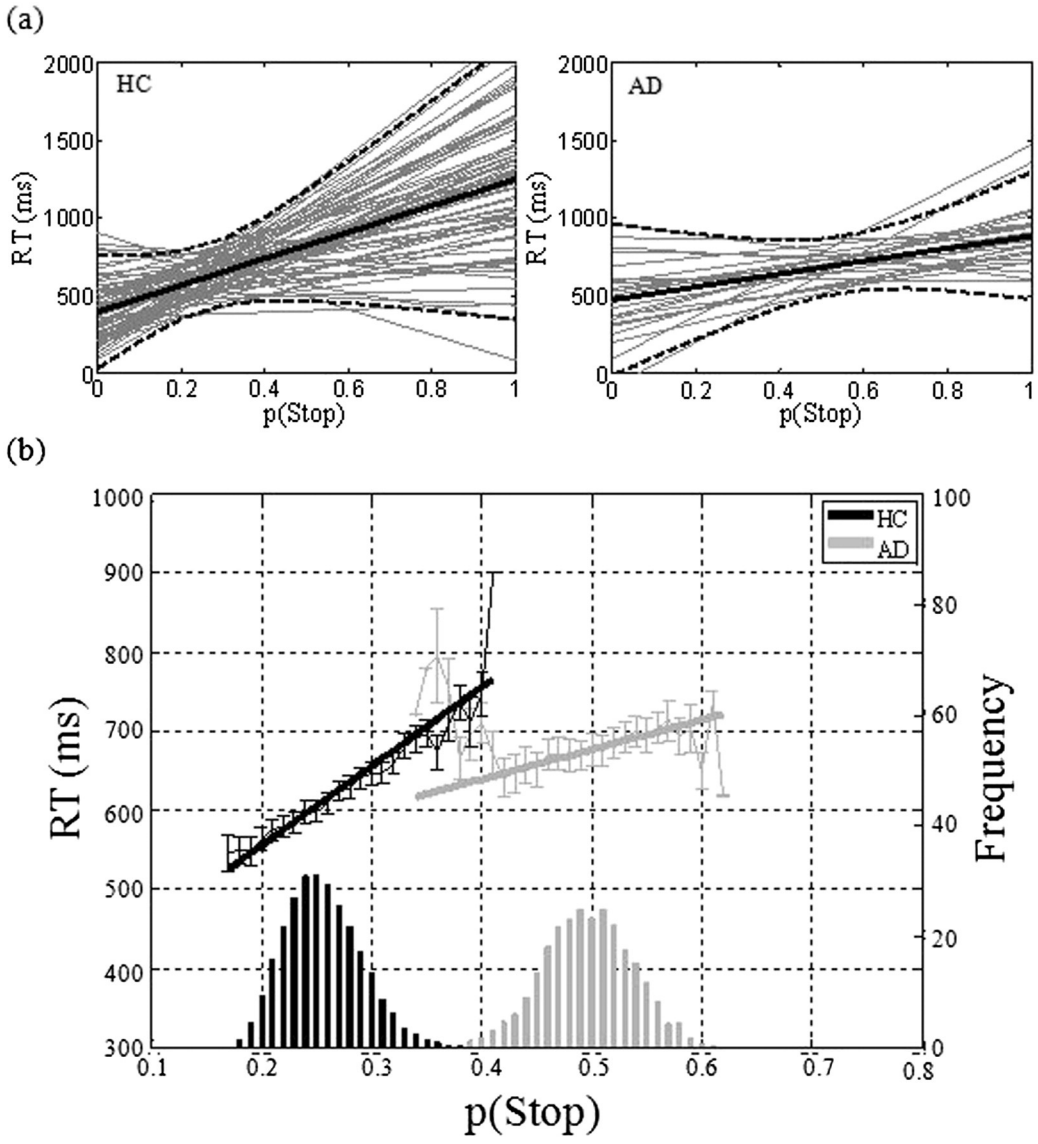

Fig. 1. (a) Sequential effect as measured by the correlation between p(Stop) and RT of all go success trials for individual participants (gray lines). Black solid and dashed lines are the mean and 95% confidence intervals of the regressions. (b) Sequential effect as computed by group parameters (see Methods section). The HC group (black) presents a significantly steeper sequential effect, as measured by the correlation between RT (ms, *y*-axis, left) and p(Stop), when compared to the AD (gray) group ($p = 0.0048$). Error bars indicate standard error of the mean. The standard errors are higher for bins of extreme p(Stop) because there were fewer trials. Histograms at the bottoms show the frequencies (number of go trials per bin of p(Stop), *y*-axis, right) for HC (black) and AD (gray) groups.

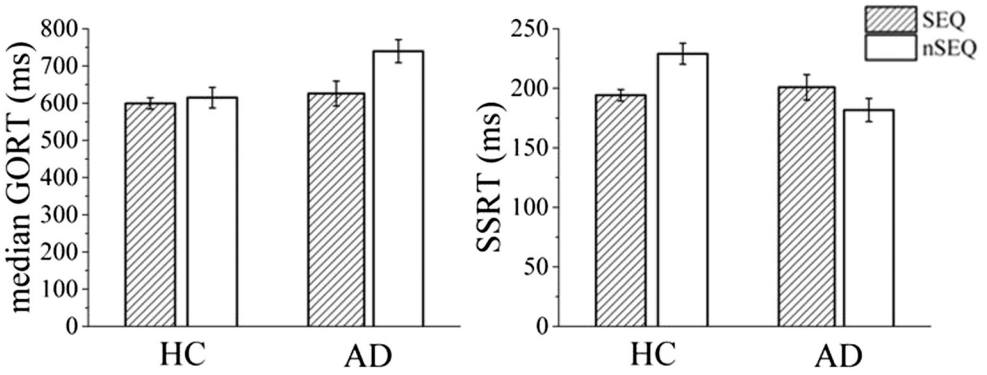

Fig. 2. Median GORT and SSRT (mean ± standard error) in AD and HC broken down for sequential effect: SEQ — with significant sequential effect; nSEQ — without significant sequential effect.

Table 3
Regional activations to stop signal anticipation in alcohol dependents (AD) and healthy controls (HC).

Contrast		Region	Cluster	Peak level	Peak voxel	MNI coordinate (mm)		
			Size	*p*-Value	*Z* value	X	Y	Z
(a) HC	Pos.	R IPL	433	0.000	4.52	60	−46	43
		R lOFC	190	0.000	4.27	36	59	−2
		L IPL	369	0.000	4.13	−57	−46	40
		MCC	92	0.000	4.09	3	−22	28
		L CBL	61	0.000	3.83	−12	−82	−26
		R pre-SMA	65	0.000	3.43	6	23	61
	Neg.	L PHG	5544	0.000	5.89	−30	−37	−11
		L HPC			5.71	−21	−13	−17
		R MTG			5.53	48	−70	1
		L SFG	335	0.000	4.46	−21	14	49
		R Insula/STG	1383	0.000	4.25	54	−1	−8
		R SFG	84	0.000	3.69	24	23	46
(b) AD	Pos.	R pre-SMA	251	0.000	3.85	6	26	61
		R lOFC	31	0.000	3.84	48	29	−14
		R IPL/SMG	188	0.000	3.79	57	−46	25
		R MTG	76	0.000	3.65	63	−22	−11
		R DLPFC	94	0.000	3.54	42	17	31
		L IPL/SMG	85	0.000	3.48	−51	−46	28
		L lOFC	29	0.000	3.41	−42	26	−8
		Thalamus	64	0.000	3.36	−6	−16	1
	Neg.	HPC/PHG	165	0.000	4.08	−18	−43	1
		Caudate	43	0.000	3.43	−3	14	−8
		Precuneus	35	0.000	3.40	−18	−46	25
		PHG	24	0.000	3.19	30	−37	−11
(c) AD > HC	Activation	R IPL	54	0.000	3.68	57	−55	22
		R pre-SMA	97	0.000	3.63	18	38	37
(d) HC > AD	Deactivation	Caudate	401	0.000	3.87	−6	−1	−2
		mPFC	333	0.000	3.77	3	50	22
		L SOG	83	0.000	3.40	−42	−76	22
		R STG	111	0.000	3.35	54	5	−17
		L HPC	156	0.000	3.20	−18	−13	−17
		PCL	49	0.000	3.18	−12	−22	61
		L SFG	275	0.000	3.10	−21	38	43

Note: L: left; R: right. IPL: inferior parietal lobule; lOFC: lateral orbitofrontal cortex; MCC: mid-cingulate cortex; CBL: cerebellum; pre-SMA: pre-supplementary motor area; PHG: parahippocampal gyrus; HPC: hippocampus; MTG: middle temporal gyrus; SFG: superior frontal gyrus; STG: superior temporal gyrus; SMG: supramarginal gyrus; DLPFC: dorsolateral prefrontal cortex; mPFC: medial prefrontal cortex; SOG: superior occipital gyrus; PCL: paracentral lobule.

groups (i.e., SEQ vs. nSEQ). Specifically, the differences would primarily be reflected in a difference between HC and AD in the SEQ group. Thus, we derived the contrast values of these regions of interest (ROI) for AD and HC participants and examined the interaction effects in an ANOVA (HC vs. AD by SEQ vs. nSEQ). The results showed that none of the ROIs showed a significant interaction in the contrast values (Fig. 4a and b).

3.3. Relationship between stop signal anticipation and SSRT

To explore the association of conflict anticipation and stop signal reaction time (SSRT), we performed a linear regression of whole brain activation to p(Stop) against SSRT, each for HC and AD. The results showed that deactivation in the perigenual anterior cingulate cortex (pgACC) to increasing p(Stop) is positively correlated with SSRT in HC but not in AD (Fig. 5a). That is, in HC but not AD, greater deactivation of the pgACC to p(Stop) is associated with prolonged response inhibition. We extracted the contrast value of p(Stop) activity in pgACC for each individual participant and confirmed a positive correlation with SSRT in HC ($r = 0.3679$, $p = 0.0017$) but not AD ($r = 0.1812$, $p = 0.3969$) (Fig. 5b). However, the slopes of the two regressions were not significantly different ($p = 0.2038$).

3.4. Stop signal anticipation and recent alcohol consumption in AD

Among the three regression analyses with the drinking variables, only one showed results associated with proactive control in AD. In the whole-brain regression against the total number of drinks consumed in the prior month, the left thalamus ($x = -15$, $y = -13$, $z = -8$, cluster size = 161, $Z = 4.06$) and right cerebellum ($x = 3$, $y = -64$, $z = -14$, cluster size = 32, $Z = 3.75$) showed greater activation to a higher amount of drinking (Fig. 6a). We extracted the contrast value of p(Stop) activity in these two regions for each individual participant and confirmed the correlations (thalamus: $r = 0.7654$, $p = 0.0000$; cerebellum: $r = 0.6272$, $p = 0.0010$).

3.5. The effects of years of education

AD and HC differed in the number of years of education. Thus, we conducted post-hoc analyses to examine whether the sequential effect and regional activities during conflict anticipation are related to years of education. The results showed that the sequential effect is not correlated with years of education in AD ($p = 0.9932$) or HC ($p = 0.8757$). The contrast value of pre-SMA/right lLP activation to p(Stop) was not correlated with years of education in AD ($p = 0.3191/0.9281$) or HC ($p = 0.6435/0.7539$). The contrast value of pgACC deactivation to p(Stop) was not correlated with years of education in AD ($p = 0.3897$) or HC ($p = 0.3929$). None of these correlations were significant for the combined sample of AD and HC, either (all $p > 0.05$).

4. Discussion

4.1. Neural correlates of proactive control in alcohol dependence

AD individuals did not exhibit differences in stop signal reaction time (SSRT) as compared to HC (Li et al., 2009b). However, Bayesian modeling of the stop signal task performance showed a slower learning rate and higher prior expectation of the stop signal occurrence as well as diminished sequential effects in AD. Furthermore, Bayesian modeling

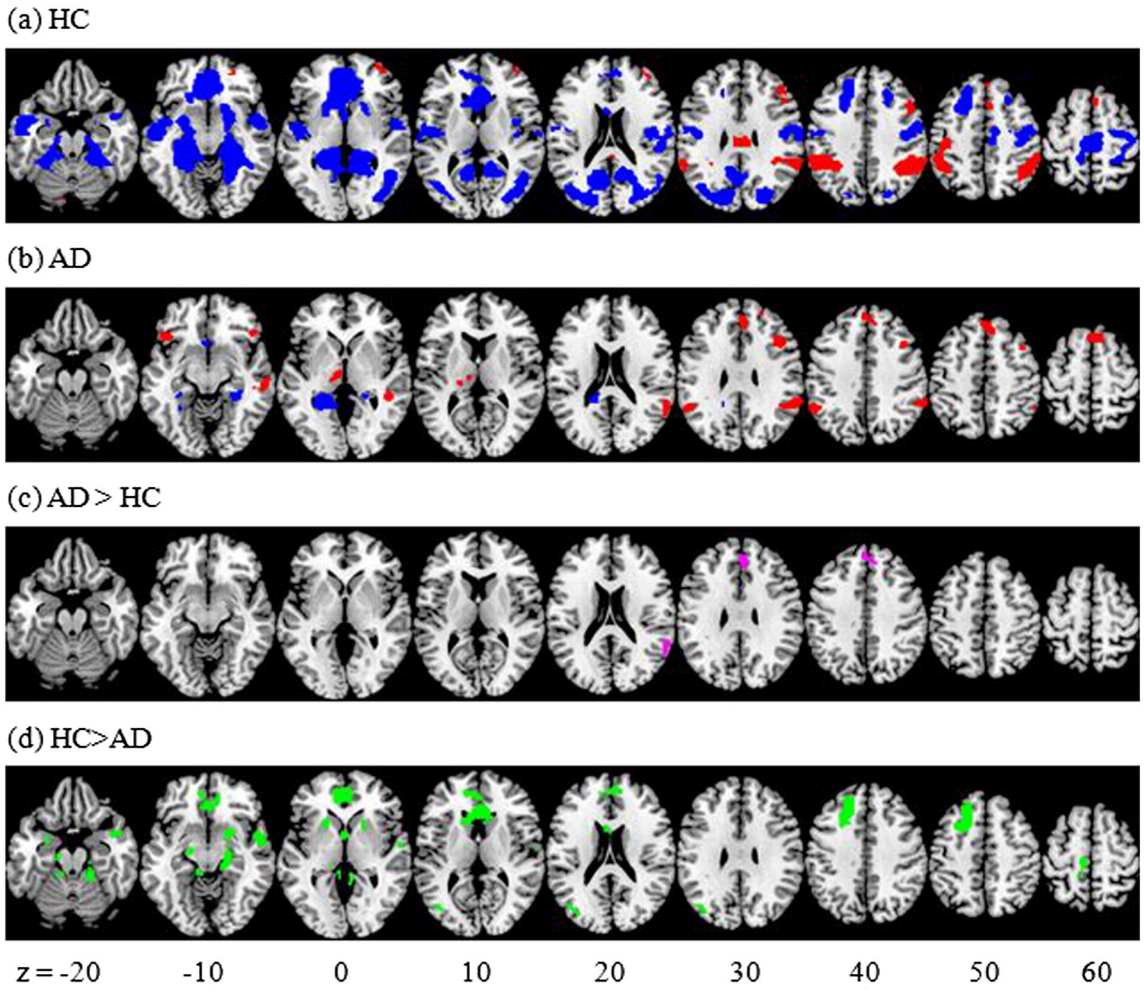

Fig. 3. Regional activations to p(Stop) in (a) HC; and (b) AD (red: positive correlation to p(Stop) and blue: negative correlation to p(Stop)); (c) regions showing greater activation to p(Stop) in AD as compared to HC (purple); and (d) regions showing greater deactivation in HC as compared to AD (green).

distinguished individuals who demonstrate a significant sequential effect and those who do not. While individuals who demonstrated a sequential effect also showed speedier response inhibition in HC, the reverse was true in AD. These findings suggest that alcohol dependence is associated with impairment in proactive control and utilizing contextual experience to guide behavior, in accord with many previous reports (Bailey et al., 2014; Bartholow et al., 2012; Bednarski et al., 2012; Li et al., 2009b; Ridderinkhof et al., 2002; Sjoerds et al., 2013).

Along with this deficit, AD showed greater activations in the anterior pre-supplementary motor area (pre-SMA) and right inferior parietal lobule (IPL) as compared to HC. The dorsomedial prefrontal cortex including the pre-SMA is known to play a critical role in executive control (Brass and Haggard, 2007; Miller and Cohen, 2001; Rushworth et al., 2004; Tabibnia et al., 2014). Transcranial magnetic stimulation (TMS) of the anterior pre-SMA disrupts cognitive control and results in prolonged SSRT in the stop signal task (Chen et al., 2009). Likewise, the IPL is involved in cognitive control (Green and McDonald, 2008; Rushworth and Taylor, 2006) and conflict monitoring (Egner et al., 2007; Luks et al., 2007). TMS of the right IPL disrupts interference control (Soutschek et al., 2013). In a Stroop task, the right IPL demonstrated sustained activity in the high expectancy condition, suggesting its involvement in proactive control (Krug and Carter, 2012).

Along with compromised performance, greater activation of the anterior pre-SMA and right IPL may suggest a compensatory mechanism for cognitive control in AD. However, the data showed that the SEQ (individuals who showed a significant sequential effect) and nSEQ (individuals who did not) groups showed a similar level of anterior pre-SMA and right IPL activation (Fig. 4a), suggesting that compensatory mechanism is not a tenable account. Thus, AD individuals increased activation of these frontal and parietal structures in anticipation of conflict without being able to translate this anticipatory process into action in a sequential effect. This is in contrast to many studies of children with positive history of alcoholism, who increased prefrontal cortical activation to compensate for behavioral performance (Acheson et al., 2014; Dagher, 2014; Hardee et al., 2014; Silveri et al., 2011). On the other hand, one is to note that the current finding may be specific to our paradigm and analysis, as greater cortical activations have been observed for performance compensation in other behavioral tasks in chronic alcohol drinkers (Hatchard et al., 2015; Padilla et al., 2011; Schellekens et al., 2010).

A second set of analysis showed that deactivation of the perigenual anterior cingulate cortex (pgACC) to increasing p(Stop) is positively correlated with SSRT in HC but not AD. As a critical structure of the default mode network (DMN), which deactivates to behavioral engagement, the deactivation of the pgACC to increasing p(Stop) may indicate readiness to withhold response and contribute to speedier SSRT. Thus, the finding of a positive correlation in HC appeared to be counter-intuitive. One possibility is that the mechanism of pgACC activity fluctuating to changing p(Stop), while efficient, hampers one's ability to stop when the estimated p(Stop) is low. In contrast, the pgACC deactivated to a lesser extent in AD as compared to HC and did not show activity to p(Stop) in correlation to SSRT. We speculate that the process with the pgACC as a neural surrogate linking task-entrained preparation for stop signal

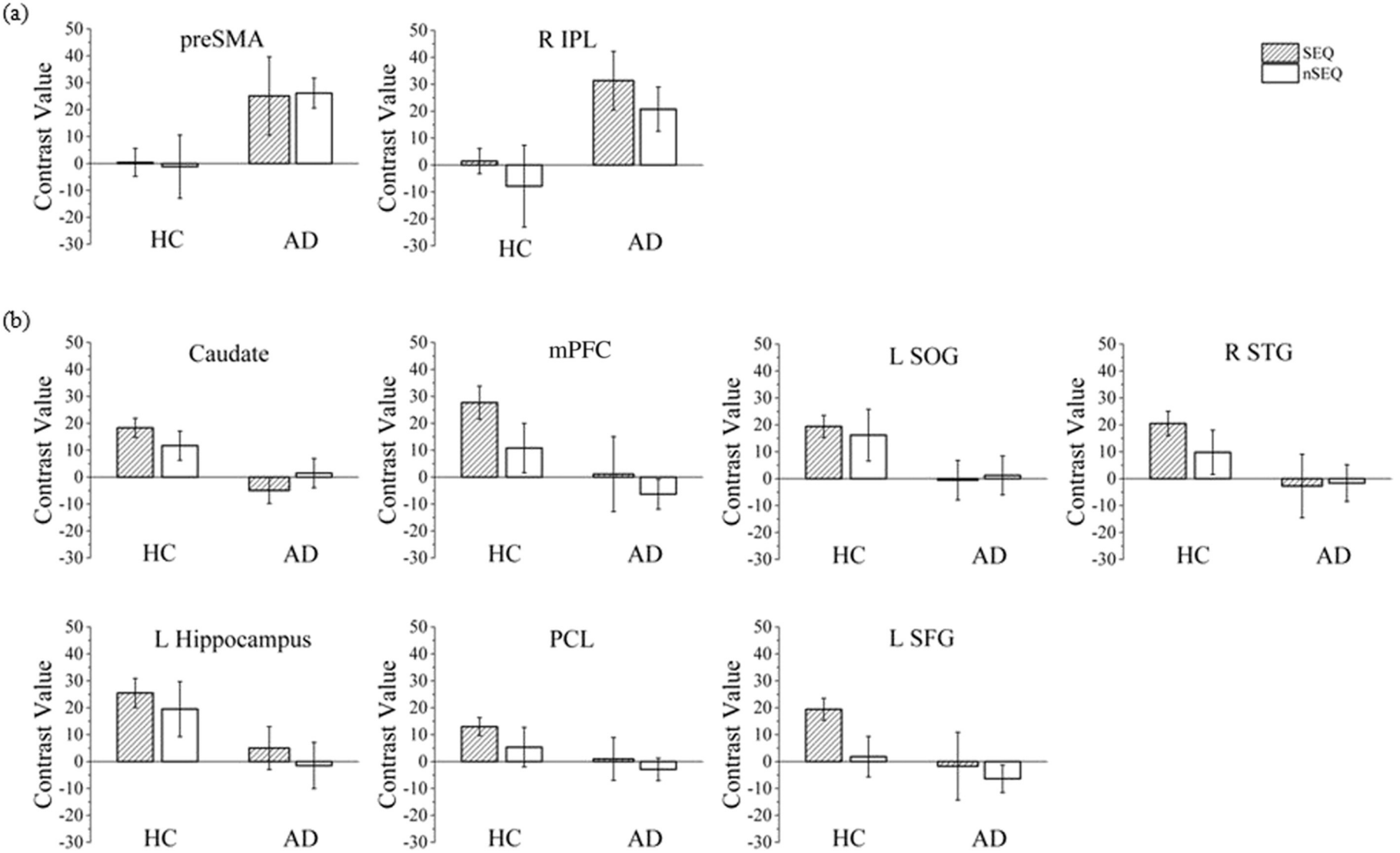

Fig. 4. Contrast values (mean ± standard error) of all regions showing a difference between AD and HC in activation to p(Stop), broken down for sequential effect: SEQ — with significant sequential effect; nSEQ — without significant sequential effect. (a) Regions showing greater activation to p(Stop) in AD as compared to HC; and (b) regions showing greater deactivation to p(Stop) in HC as compared to AD (Table 3).

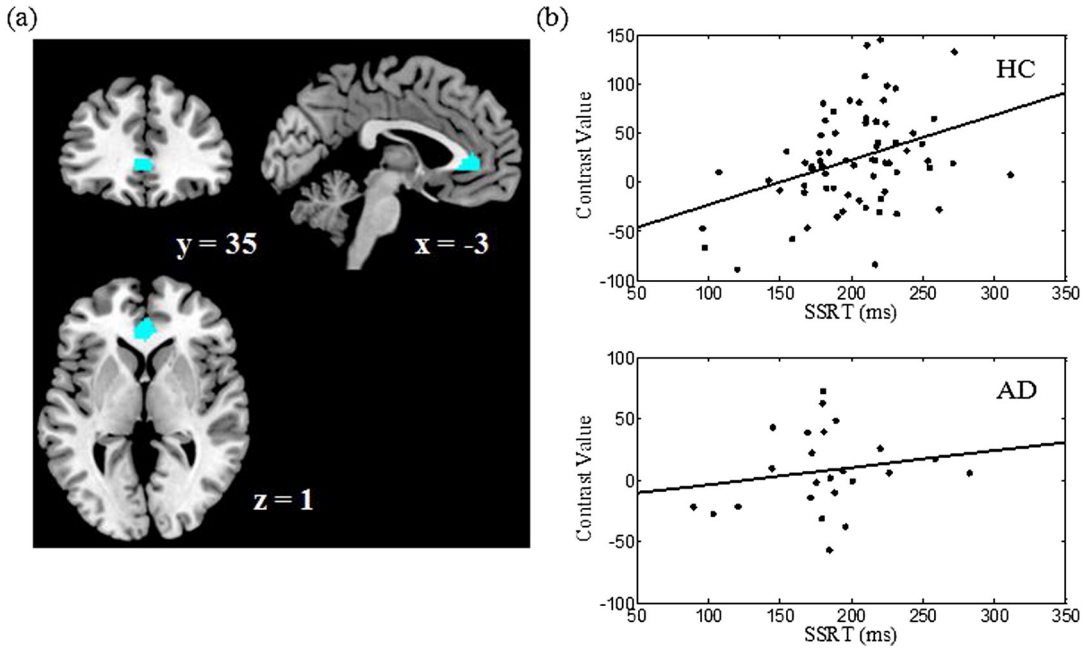

Fig. 5. (a) Regional activity to p(Stop) in association with SSRT: greater deactivation of the perigenual anterior cingulate cortex (pgACC) to increasing p(Stop) is correlated with longer SSRT. (b) p(Stop) activity of the pgACC is correlated to SSRT in HC but not AD.

inhibition is compromised and that this deficit may actually allow more resources to be devoted to response inhibition in alcohol dependence. Considered along with previous imaging studies demonstrating altered activity and functional connectivity of the DMN including the ventromedial prefrontal cortex in individuals with addictive disorders (Ma et al., 2011; Sutherland et al., 2012; Zhang et al., 2014), this issue needs to be investigated further.

The current findings need to be reconciled with several recent reports. Noel et al. (2013) showed that AD individuals are impaired in the ability to suppress prepotent responses, such as those in the Stroop task, but not the control of proactive interference as measured by the correct rate of recall after distractors. In a flanker task, Bailey et al. (2014) reported no event-related potential activities in the medial prefrontal cortex for conflict monitoring and online adjustment following error trials, yet activities were resumed two trials after the immediate error in the group with alcohol consumption. The authors suggested that alcohol does not impair conflict monitoring and behavioral adjustment per se but the recovery from the failure of these control mechanisms. More studies are clearly required to address these discrepancies and to consider differences in behavioral paradigms and clinical characteristics of the participants.

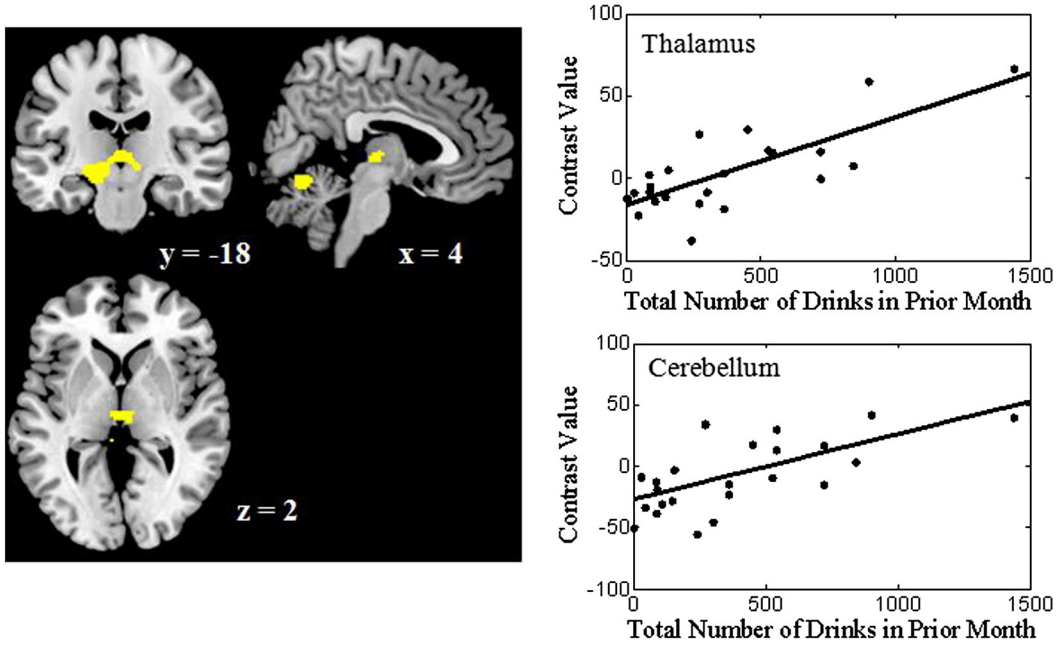

Fig. 6. Regional activation to conflict anticipation and alcohol consumption in AD. The medial thalamus and cerebellum showed increased activation to p(Stop) in association with recent alcohol consumption.

4.2. Effect of alcohol consumption on proactive control in alcohol dependence

Neuroimaging research has documented the vulnerability of the prefrontal cortex, thalamus, and cerebellum to chronic alcohol exposure (Sullivan et al., 2003). There is extensive evidence for reduced gray and white matter volumes in the frontal cortex, thalamus, and cerebellum along with compromised cognitive performance in AD individuals (Chanraud et al., 2007; Sullivan et al., 2003). Adolescents with low-level alcohol consumption showed decreased cortical thickness in the frontal areas in conjunction with compromised integrity of white matter connecting to the caudate and thalamus (Luciana et al., 2013). In a functional study, increased activities of the thalamus, cerebellum, and prefrontal cortex were also found in young adults with regular alcohol consumption than non-alcohol drinkers during performance of a counting Stroop task (Hatchard et al., 2015). The authors interpreted such activity as a manifestation of an early stage of neurocognitive dysfunction as a result of alcohol-induced disruption of the frontocerebellar system (Sullivan, 2003). Thus, the current findings add to the wide literature of cerebellar and thalamic structural/functional changes in chronic alcohol exposure and fetal alcohol syndrome (Cardenas et al., 2014; du Plessis et al., 2014; Fein and Fein, 2013; Grodin et al., 2013; Meintjes et al., 2014).

4.3. Limitations and conclusion

There are a number of limitations to consider in the current study. First, there were a much greater number of HC than AD participants. While this disparity in sample size reflected the strategy to include the largest number of HC participants who are group-matched in age and gender and an additional comparison with more balanced samples yielded similar results, future work is needed to confirm these findings. Second, we did not collect information on life-time alcohol use other than years of drinking, family history of alcoholism or patterns of recent alcohol use. These important variables were not examined in the current work. Third, because of the small sample size of AD we did not examine the influence of gender (Ide et al., 2014; Li et al., 2009c) or personality traits (Farr et al., 2012; Karch et al., 2008; Li et al., 2006) on these behavioral and neural measures.

In conclusion, we showed an impaired ability of proactive control in AD individuals, whose greater fronto-parietal activation fail to compensate for behavioral performance. Unlike HC, AD individuals also did not deactivate the perigenual anterior cingulate cortex during conflict anticipation to facilitate response inhibition. These new findings add to our understanding of the cerebral effects of chronic alcohol consumption, particularly in the domain of self control (Cyders et al., 2014; Kareken et al., 2013).

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2015.03.008.

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