Response inhibition in alcohol dependent patients and patients with depression/anxiety: an fMRI study

Supplementary Information

Supplementary Methods

Detailed task description

An adapted version of the stop signal task (SST) (Logan 1994) was used to assess the ability to inhibit an already initiated response (Heslenfeld and Oosterlaan 2003). Performance on the SST requires a motor response in reaction to a Go-stimulus, only when it is not followed by a Stop-signal. During Go trials the participants had to respond as fast and accurate as possible by pressing a button with their left or right index fingers in response to the appearance of an airplane (Go-stimulus) facing to the left or right respectively (figure S-1, left panel). Occasionally, the Go-stimulus was followed by a Stop-signal, a cross, superimposed over the Go stimulus (figure S-1, right panel) and the participants were instructed to attempt to inhibit the Go response (pressing a button). Before each trial a small plus-sign appeared on the screen for 500 ms to engage eye fixation and attention, immediately followed by the Go-stimulus presented for 1000 ms. The inter-trial interval (ITI) varied between 1 and 2 s. The task consisted of 252 randomized trials, with a Go/Stop ratio of 80/20 (204 Go trials, 48 Stop trials), and took approximately 12 minutes.

The difficulty of stopping was varied by adjusting the interval between the Go-stimulus and the Stop-signal, the Stop Signal Delay (SSD), according to a staircase tracking algorithm based on a horse race model (figure S-2): a failed stop trial reduced the SSD, making it easier to inhibit the Go-response during the next stop trial. A successful Stop increased the subsequent SSD, making it more difficult to succeed during the next Stop trial. This staircase procedure converged upon a critical SSD, which represents the time delay required for a subject to successfully stop a response on approximately 50% of the Stop trials. The time required for the Stop-signal to be successfully processed, the Stop Signal Reaction Time (SSRT), was computed by subtracting the critical SSD from the median Go reaction time. Therefore, the SSRT is the time required for a subject to inhibit his response after seeing the Stop-signal corrected for mean reaction time to Go trials. A short SSRT indicates good response inhibition and a longer SSRT indicates poorer response inhibition.

To become familiarized with the task, participants performed a practice session (30 go trials, 8 stop trials) outside the scanner. Instructions to perform as fast and accurate as possible were repeated right before the task in the scanner started. The task was part of a larger scanning protocol, and preformed as the second task, to ensure concentration was still optimal.

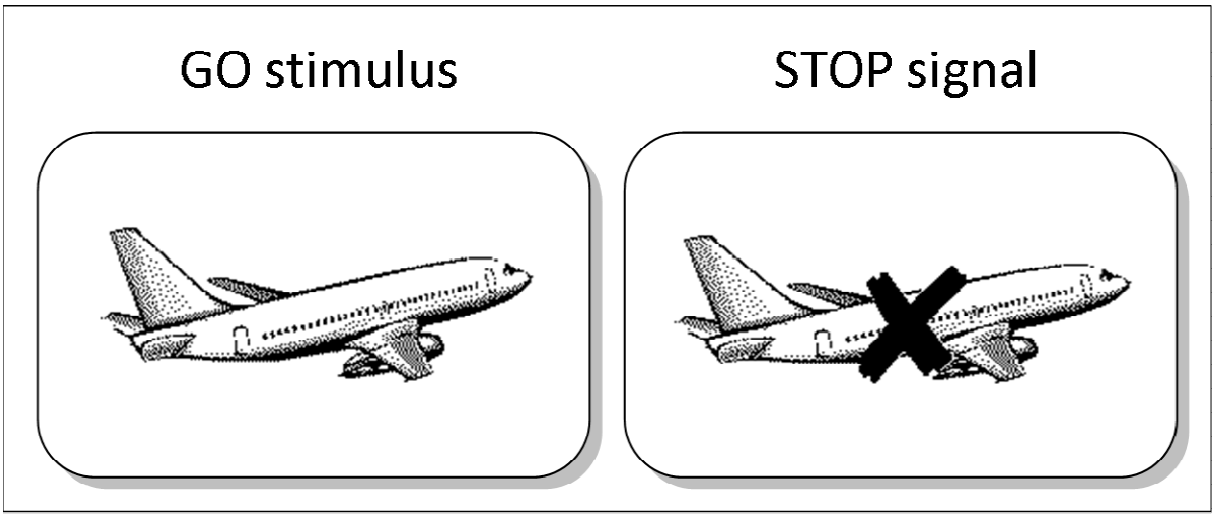

Figure S-1 Stop Signal Task, trial types.
During GO trials, participants had to press a button as fast as possible on the side the airplane points. During STOP trials, a cross followed the airplane after a short interval, indicating participants had to withhold their (sometimes already initiated) response.

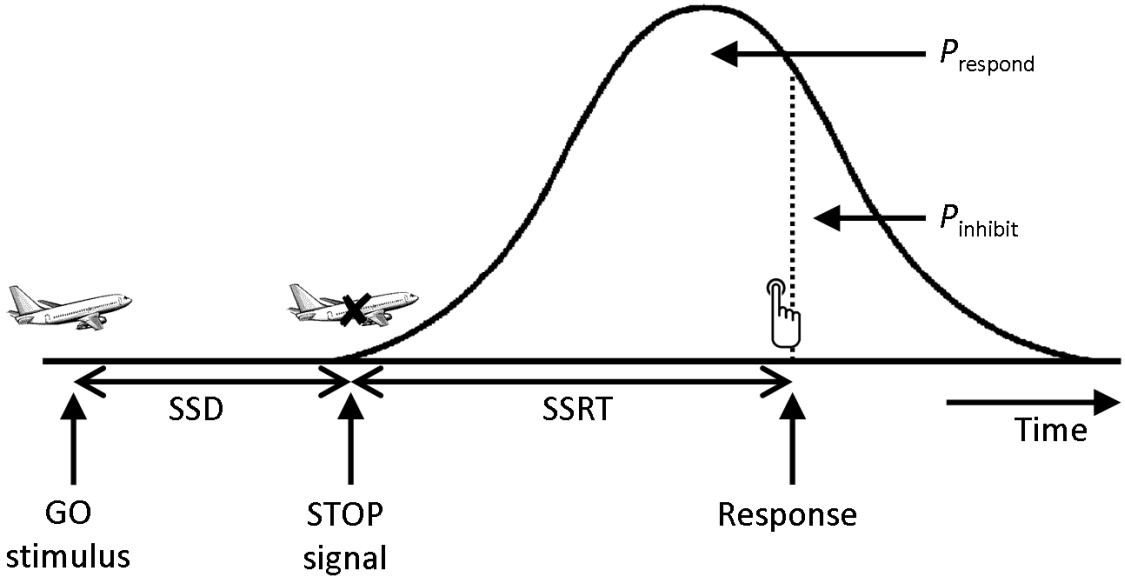

Figure S-2 Graphic representation of the horse race model.
Adapted from a similar figure used by Aron *et al.* (2003). A distribution of Go-stimulus reaction times (RTs) is shown beneath the curve. On stop trials, a cross is superimposed over the Go-stimulus at a particular stop-signal delay (SSD). The stop signal divides the Go-stimulus RT distribution into two probabilities: a left part consisting of responses fast enough to escape inhibition ($P_{respond}$) and a right part corresponding to $P_{inhibit}$. Provided SSD is varied to yield 50% $P_{inhibit}$ (the point of median Go-stimulus RT), SSRT can be calculated by subtracting average SSD from median no-signal RT. Convergence to 50% $P_{inhibit}$ is ensured by using step-up and step-down interleaved staircases. If the subject sucessfully inhibited a stop trial, then inhibition was made more difficult on the next stop trial by increasing the SSD by 50 ms; if the subject did not successfully inhibit response on a stop trial, then SSD was decreased by 50 ms. Average SSD was computed from the values of four staircases after convergence on 50% $P_{inhibit}$.

Supplementary Results

Table S-1, Main Effect of inhibition (SS > Go) over the whole sample, p<0.05 whole brain FWE-corrected.

Area	BA	Side	Clustersize	*Z*	x	y	z
Inferior Frontal Gyrus / Insula		R	152	*6.67*	42	21	-5
	47	R		*5.26*	53	19	3
Insula		L	56	*5.61*	-34	21	-3
		L		*5.28*	-30	28	0
Inferior Parietal Lobule	40	R	465	*6.61*	60	-48	40
	40	R		*6.44*	37	-48	48
		L	43	*5.75*	-32	-59	45
	40	L	22	*5.66*	-57	-50	40
		L	1	*4.76*	-39	-50	45
Superior Occipital Gyrus / Precuneus		R		*6.24*	30	-68	38
Inferior Occipital Gyrus		L	100	*6.44*	-32	-87	-10
	19	L		*6.12*	-34	-89	3
		R	94	*6.11*	35	-87	-3
		R		*5.71*	37	-82	8
Fusiform Gyrus		R	67	*5.91*	44	-59	-18
Inferior Temporal Gyrus		R		*5.48*	48	-61	-10
	20	R		*4.82*	53	-55	-18
		L	42	*5.78*	-46	-68	-10
Superior Temporal Gyrus		R	19	*5.54*	60	-50	8
Middle Frontal Gyrus		R	1	*4.86*	44	31	40
		R	1	*4.79*	46	33	33
Supplementary Motor Area	6	R	1	*4.77*	5	14	50

BA, Brodmann's Area; FWE-corrected, family-wise error corrected; Go, Go-trials; L, left; R, right; SS, Succesful Stop trials; [x y z], MNI-coordinates; Z, z-statistic

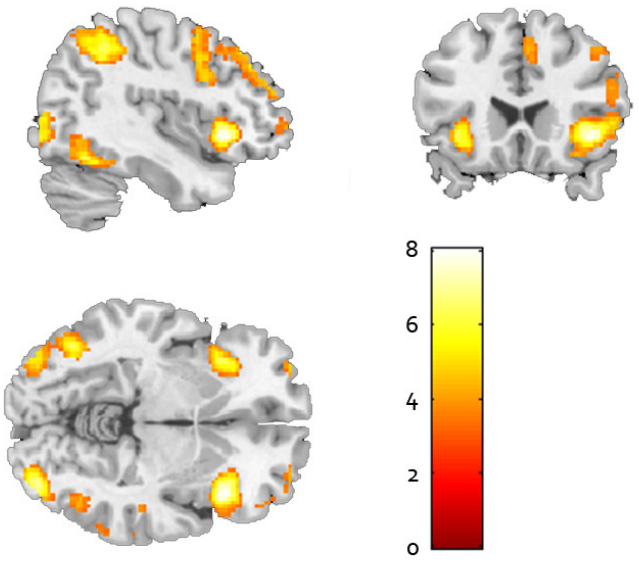

Figure S-3 Main effect of inhibition (SS > GO) over the whole sample.
Displayed at $P_{uncorr.} < 0.001$

Post-hoc analyses

Because groups differed in smoking behavior, and because SSRT scores were positively correlated with the amount of cigarettes smoked within the AD group (however not over the three groups together), a *post-hoc* analysis was performed with the number of cigarettes as a covariate in the ANOVA group comparisons for performance and imaging data. This correction did not influence the performance results, and only slightly lowered significance levels of the imaging results. Since smoking and AUDIT-score were highly correlated ($r_{63} = .541; P < .001$) in the complete sample (however only trend-wise within the AD-group), a small decrease in the power of imaging group comparisons was almost certainly due to removal of variance explained by problematic drinking, after adding smoking as a covariate. No correlations were seen between smoking severity and activation in the putamen, thalamus and SMA within the AD group.

Since AD duration showed an expected positive correlation with age ($r_{29} = .472$; $P = .007$), we tested for additional age-related association with thalamus activation, by entering the two predictors in a multiple regression analysis, which revealed that thalamus activation was independently inversely correlated with AD duration ($P = .014$), but not with age ($P = .308$).

Supplementary reference list

Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW (2003). Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience* **6**, 115-116.

Heslenfeld DJ, Oosterlaan J (2003). Where does the brain stop? Brain areas involved in the inhibition of behavior. *Journal of Psychophysiology* **17**, 138.

Logan, G. D. (1994). On the ability to inhibit thought and action: a user's guide to the stop signal paradigm. In *Inhibitory Processes in Attention, Memory and Language*, (ed. D. Dagenbach and T. H. Carr), pp. 189-239. Academic Press: San Diego, CA.