Supplementary material

Text S1: In- and exclusion criteria for the NESDA-Neuroimaging study

Participants were drawn from the Netherlands Study of Depression and Anxiety (NESDA), a large cohort study (Penninx *et al.* 2008). Out of the 2981 NESDA participants (main sample, baseline measurement), a subset of patients and healthy controls (HCs) aged 18 to 57 years, was selected for magnetic resonance imaging (MRI) scanning during the NESDA-neuroimaging study. Inclusion criteria for patients in the NESDA-neuroimaging study were current major depressive disorder (MDD) and/or anxiety disorder (panic disorder; and/or social anxiety disorder; and/or generalized anxiety disorder) in the past 6 months according to DSM-IV-TR criteria. Diagnoses were established using the structured Composite International Diagnostic Interview (CIDI; WHO lifetime version 2.1) (Robins *et al.* 1988) administered by a trained interviewer.

Exclusion criteria for the patient group were the presence of Axis-I disorders other than MDD or the abovementioned anxiety disorders; any use of psychotropic medication other than a stable use of selective serotonin reuptake inhibitors (SSRIs) or infrequent benzodiazepine use (three times two tablets weekly or within 48 hours before scanning). Exclusion criteria for both patients and HCs were the presence or history of major internal or neurological disorder; dependency or recent abuse (past year) of alcohol or drugs; hypertension (>180/130 mmHg); heavy smoking (>5 cigarettes per day); and general MRI contraindications. The HCs had no lifetime depressive or anxiety disorders, no lifetime alcohol or drug use disorder and were not taking any psychotropic drugs. In total, 301 native Dutch-speaking participants (233 patients and 68 HCs) were included and underwent MR imaging at one of the three participating centers, i.e., Leiden University Medical Center (LUMC), Amsterdam Medical Center (AMC), and University Medical Center Groningen (UMCG). For more information on the exact number of patients included/excluded for various reasons, the reader is referred to the flowchart in Fig. S3.

Text S2: Detailed task description

The emotional word memory (EWM) task and the Tower of London (ToL) task were administered as part of a larger functional and structural imaging study (van Tol *et al.* 2011; 2012), designed and presented using E-prime (Psychological Software Tools, Pittsburgh, PA, USA). The ToL task was administered first and the EWM task as the second task for all participants. Participants' responses and response times were registered by two magnet-compatible button boxes. No feedback regarding the response was provided.

Tower of London Task

We used an event-related parametric version of the ToL task (van den Heuvel *et al.* 2003), which consisted of a planning and a baseline condition (Fig. S4). In the planning condition, participants were presented a starting configuration and a target configuration. In both configurations, three colored beads were placed on three vertical rods, which could accommodate one, two, or three beads, respectively. One bead could be moved at a time and only when there was no other bead on top. Participants were requested to determine the minimum number of steps (ranging from 1 to 5) needed to reach the target configuration by mentally moving beads one at a time. Two possible answers were shown. Subjects had to press the button corresponding to the side (left or right) of the screen where the correct answer was presented. In the baseline condition, subjects were instructed to count the total number of yellow and blue beads, a task that does not require any planning activity. The display was similar to the planning condition, but the number of beads of each color in the two configurations, used for the baseline condition, was unequal, with the aim of preventing planning activity. We used a pseudo-randomized, self-paced design with maximal response duration of 60 seconds for each trial. We adopted a pseudo-randomized design to control for any overflow effects (i.e., persevering of task-related cognitive processes after a difficult trial). Therefore, each trial of three or more moves was followed by a baseline trial. Before the scanning session, subjects received instructions and a standardized training of 10 items, two at each level of difficulty in which errors were corrected. All subjects understood the task rules and instructions.

Emotional Word Memory Task

The EWM task used an event-related, self-paced, implicit word encoding- and recognition paradigm (Daselaar *et al.* 2003) (Fig. S5). During the encoding part, 40 positive, 40 negative and 40 neutral words, and 40 baseline trials were presented in 20 blocks of eight words. Words were presented with an average inter-stimulus interval of 1026 ms (minimum, 1018 ms; maximum, 1035 ms). Within each block, two negative words, two positive words, two neutral words and two baseline trials were presented in randomized order. Across valence (i.e., positive, negative, neutral), words were matched for length (ranging from three to twelve letters) and frequency of occurrence in the Dutch language. The task was paced by the subject, but each word was presented with a maximal duration of 5 seconds. During each stimulus presentation, response options were displayed at the bottom of the screen. Subjects had to indicate whether they thought the word presented was positive, negative, or neutral to them. Baseline words were '<<left', '<<middle>>', and 'right>>' and participants were instructed to press the corresponding button. To protect against *primacy* and *recency* effects three filler (1 positive, 1 negative, 1 neutral) words were presented at the start and end of the encoding task. These filler words were not part of the subsequent recognition task. The recognition test phase consisted of the 120 old encoding target words and 120 new distracter words, and 40 baseline trials. Again, words were presented in a pseudo-randomized order in 20 blocks of 14 words, each block containing two old and two new negative words, two old and two new positive words, two old and two new neutral words, and two baseline trials. 'Old' and 'new' words were matched on complexity, word length, and emotional intensity. Subjects had to indicate whether they ‘have seen’ (i.e., remembered) the words previously, ‘probably have seen it’ (i.e., know), or ‘haven’t seen it’ (rejection). The interval between the encoding and recognition task was 10 minutes. In the retention interval, a neutral image was displayed, to minimize interference effects during the subsequent recognition phase. During the retention interval, the structural image was acquired.

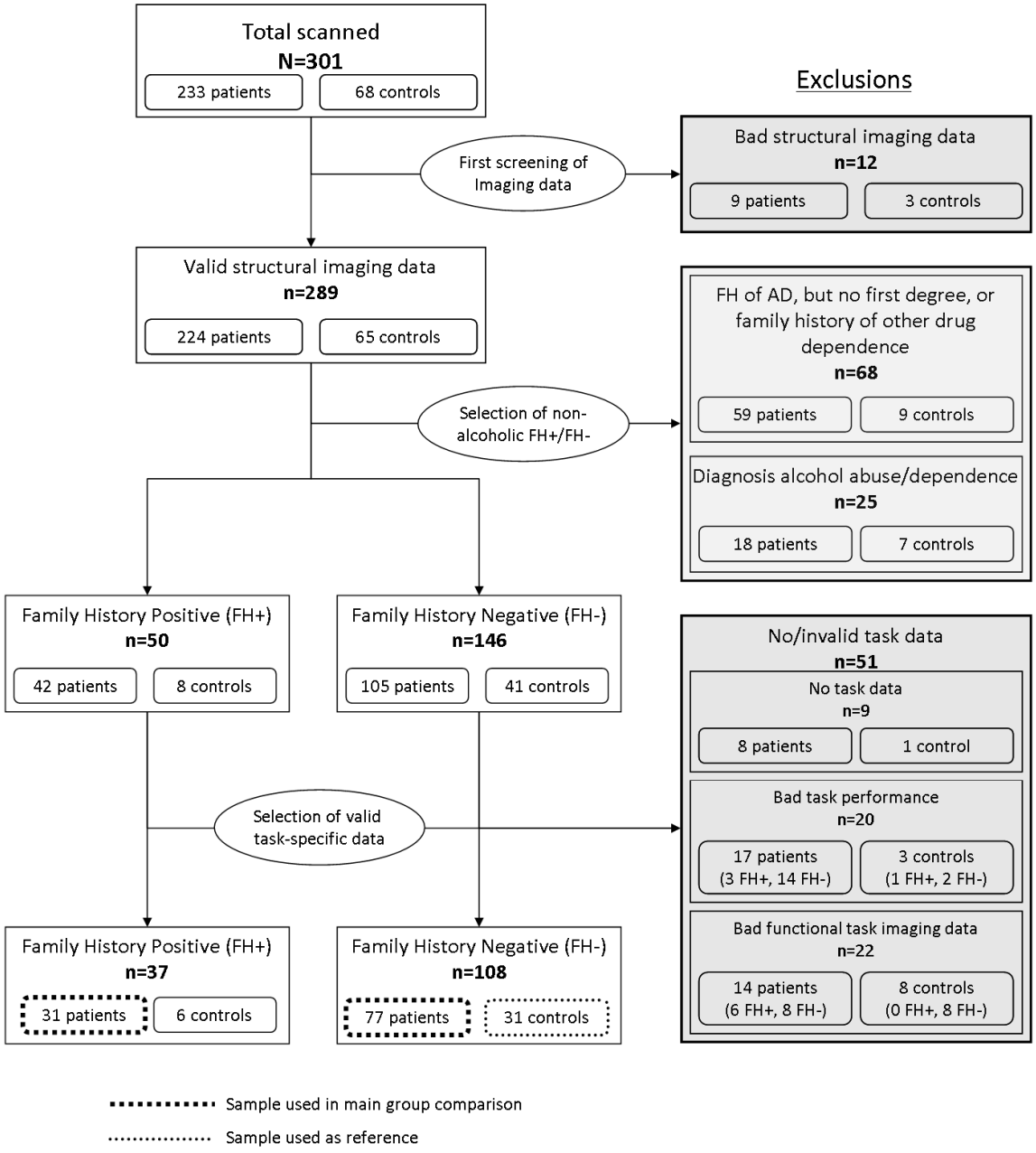

Fig. S3: Flow diagram; inclusion/exclusion from the NESDA-neuroimaging study

After scanning, we excluded participants that did not meet the criteria defined for the current study (non-alcoholic FH+ / FH-), and who had poor task and/or imaging data. Of the original 233 patients, finally 77 met all criteria for the FH- group and 31 for the FH+ group. Of the original 68 healthy controls (HC), finally 31 served as *post hoc* comparison group without a family history of alcohol dependence. Of note, we excluded patients with bad structural imaging data, to start with the same sample as described in Sjoerds *et al. (2012)*.

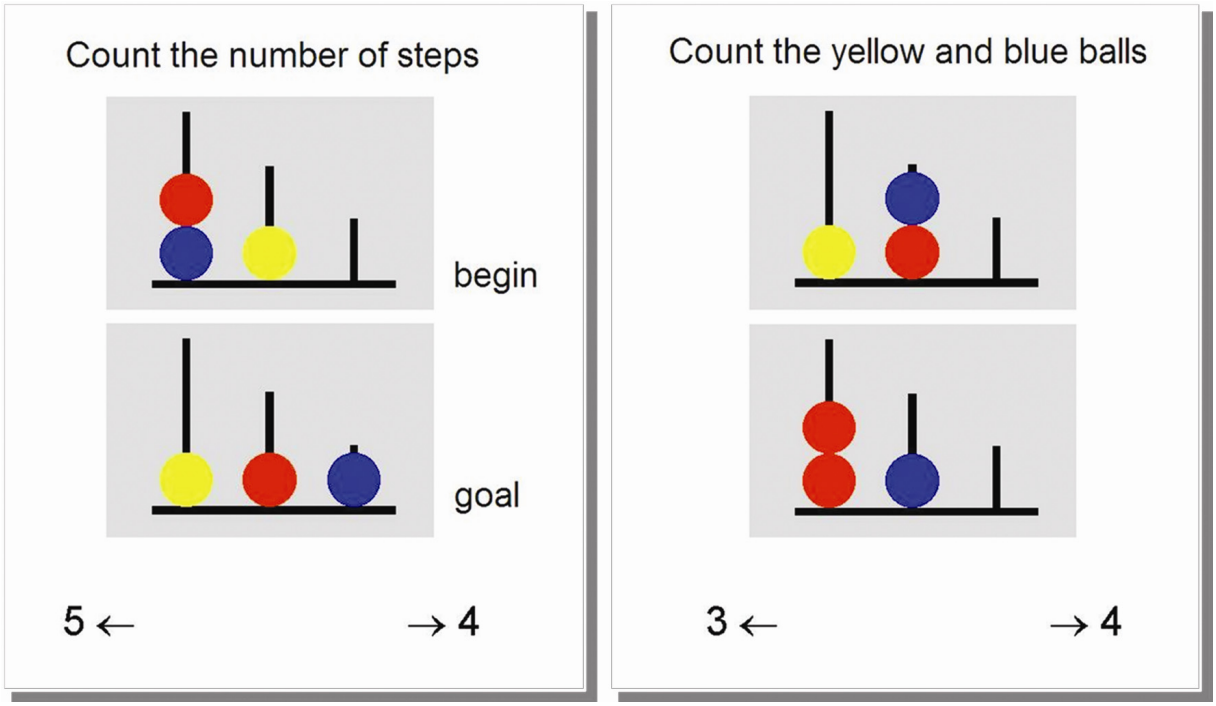

Fig. S4: The Tower of London task (ToL):

A parametric executive functioning test consisting of planning trials, where participants had to compute the minimal number of steps (ranging from 1 to 5) to reach the target situation (left figure), and baseline trials with no planning involved, where participants had to count the yellow and blue balls (right figure).

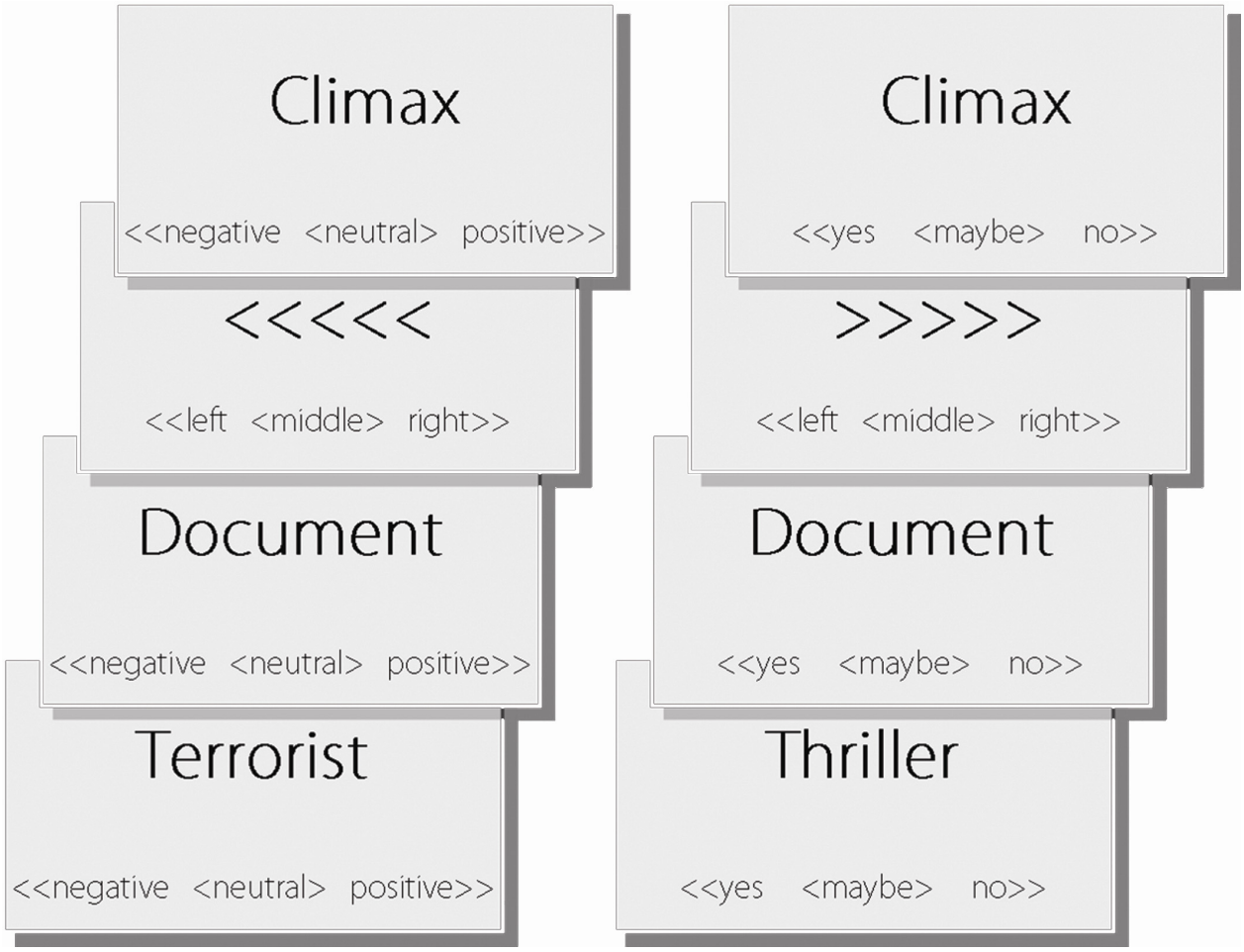

Fig. S5: The Emotional Word Memory task (EWM):

A memory task consisting of an encoding phase, where participants had to indicate whether the word had a positive, negative or neutral valence (left set of words, 40 words per valence and 40 baseline trials), and a recognition phase where participants had to indicate whether they had seen the word during the encoding phase or not (right set of words, 40 old words plus 40 distracter words per valence and 40 baseline trials).

Table S6: Task Performance

		FH-		FH+		HC	
		Mean	SD	Mean	SD	Mean	SD
Emotional word Encoding							
Numbers of words classified							
	Positive	40.50	8.67	40.87	11.04	43.93	8.49
	Negative	41.35	3.92	41.13	3.28	41.13	1.96
	Neutral	43.62	10.22	43.20	12.62	40.63	8.20
Proportion correct subsequently remembered							
	Positive	0.74	0.13	0.71	0.17	0.71	0.17
	Negative	0.70	0.14	0.67	0.18	0.69	0.15
	Neutral	0.70	0.17	0.69	0.17	0.64	0.19
Tower of London							
1-step	Proportion correct	0.95	0.08	0.95	0.08	0.96	0.07
2-step	Proportion correct	0.91	0.13	0.91	0.13	0.93	0.07
3-step	Proportion correct	0.92	0.12	0.90	0.13	0.92	0.08
4-step	Proportion correct	0.83	0.15	0.79	0.21	0.84	0.12
5-step	Proportion correct	0.78	0.18	0.76	0.20	0.79	0.16

Abbreviations: FH-, negative family history of alcohol dependence; FH+, positive family history of alcohol dependence; HC, healthy controls; SD, standard deviation

Table S7. Main effect of the two fMRI-tasks over the two FH patient groups

Tower of London			MNI-coordinates				
Label	Side	BA	x	y	z	*p(FWE)*	Z
Frontal lobe							
Middle Frontal Gyrus	R		27	9	57	*<0.001*	>8
Middle Frontal Gyrus	R	9	39	36	39	*<0.001*	>8
Superior Frontal Gyrus	L	6	-24	3	57	*<0.001*	>8
Inferior Frontal Gyrus	L		-51	6	21	-	3.37
Precentral gyrus	L		-54	-3	39	-	3.31
Parietal lobe							
Precuneus	L	7	-6	-63	48	*<0.001*	>8
Precuneus	R		9	-63	48	*<0.001*	>8
Inferior Parietal Lobule	L	40	-54	-45	42	*<0.001*	7.69
Inferior Parietal Lobule	R	40	57	-42	42	*<0.001*	>8
Angular Gyrus	R	39	45	-72	33	*<0.001*	6.61
Limbic lobe							
Cingulate Gyrus	R		9	-39	42	-	3.12
Sub-Lobar							
Caudate	L		-15	-3	18	*<0.001*	5.58
Insula	L		-33	21	0	*0.017*	4.84
Insula	R		33	21	0	-	4.14

Emotional Word memory Task			MNI coordinates				
Label	Side	BA	x	y	z	*p(FWE)*	Z
Frontal lobe							
Superior Frontal Gyrus	L	9	-9	60	30	*<0.001*	>8
Superior Frontal Gyrus	R		21	33	51	-	3.42
Inferior Frontal Gyrus	L		-48	30	-3	*<0.001*	>8
Inferior Frontal Gyrus	R		33	33	-9	-	4.19
Precentral Gyrus	R		60	-3	15	-	3.84
Occipital lobe							
Middle Occipital Gyrus	L		-15	-96	9	*<0.001*	>8
Middle Occipital Gyrus	R		21	-93	12	*<0.001*	>8
Cuneus	L		-21	-96	-3	*<0.001*	>8
Temporal lobe							
Middle Temporal Gyrus	L		-60	-9	-15	-	3.44
Limbic lobe							
Parahippocampal Gyrus	L		-21	-12	-15	*<0.001*	6.45
Anterior Cingulate Gyrus	R		3	9	-9	*0.007*	5.07
Sub-Lobar							
Caudate	R		9	6	18	-	3.65
Insula	L	47	-30	9	-24	-	3.47
Insula	R		39	-18	21	-	4.22

Abbreviations: BA, Brodmann's area; FH, family history; FWE, family wise error; L, left; MNI, Montreal neurological institute; R, right; Z, z-statistic.

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