Alcohol Approach Bias Is Associated With Both Behavioral and Neural Pavlovian-to-Instrumental Transfer Effects in Alcohol-Dependent Patients

Supplement

Participant recruitment and exclusion criteria

Alcohol-dependent (AD) patients were recruited during detoxification treatment in addiction-specific, psychiatric wards of university hospitals. All participants were aged between 18 to 65, and were fluent in German. Exclusion criteria were: other substance dependence (except nicotine dependence); current substance use (assessed by drug urine test); alcohol intoxication (assessed by alcohol breath test); major psychiatric disorders assessed by M-CIDI; neurological disorders; medications that are known to interact with the central nervous system (less than four half-lives post last intake). Patients had no or low alcohol withdrawal symptoms for 3 days before fMRI as assessed by Clinical Institute Withdrawal Assessment for Alcohol revised version (CIWA-Ar score < 4; 1). The sample sizes for different analyses are shown in Figure S1.

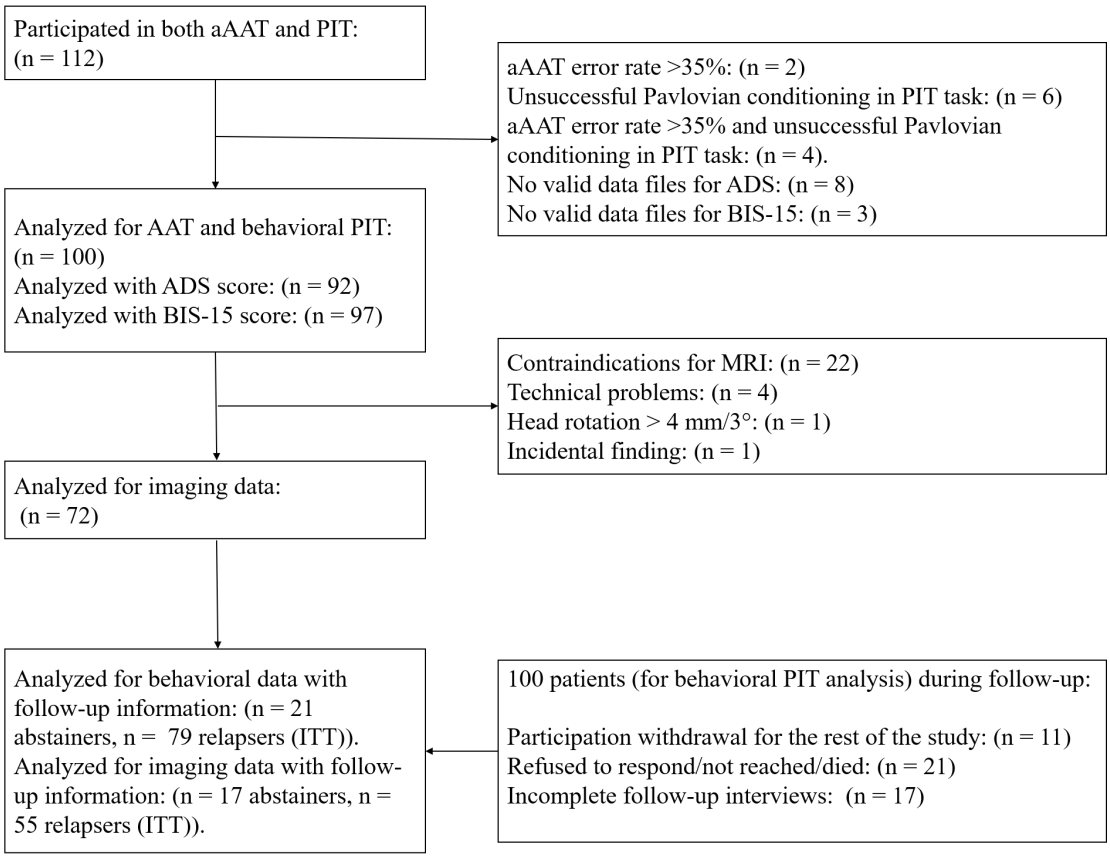

Figure S1: the flow chart of sample sizes for behavioral and imaging analyses. aAAT: alcohol approach/avoidance task; ADS: Alcohol Dependence Scale (2); BIS-15: Short German version of the Barrat Impulsiveness Scale-15 (3); ITT: intention-to-treat; PIT: Pavlovian-to-instrumental transfer task. Details regarding data exclusion based on aAAT and PIT performances are illustrated in the data analysis part in the main text.

Alcohol approach/avoidance task

Twenty-one alcohol drink images and 21 soft drink images were used in this task. In each trial, one of those images randomly presented inclined to the left or to the right on the screen. Pictures of each stimulus category were presented equally often as inclined to either side, and participants responded with a joystick movement according to the inclination of the image. For example, they had to pull the joystick towards themselves (approach) if the image inclined to the left and to push the

joystick away (avoidance) if it inclined to the right (see Figure S2). The correspondence between left/right inclination and push/pull responses was counterbalanced across participants. There was no response time limitation, and participants had to correct their response in case of a wrong action. Only when the trial was accurately responded or corrected, a new trial started. Pulling the joystick enlarged the image while pushing the joystick minimized the image with a zooming motion. Participants conducted 26 practice trials with drink-unrelated neutral images and then 168 experimental trials. The aAAT was conducted outside the fMRI scanner.

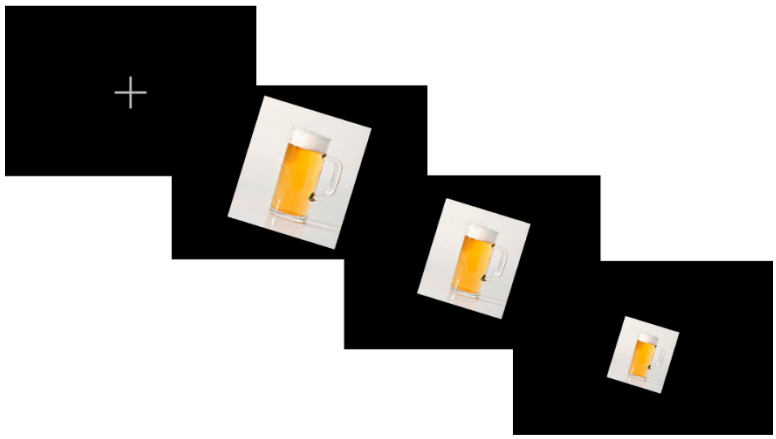

Figure S2: A push trial in alcohol approach/avoidance task (aAAT). An alcohol drink image tilted to the right and thus needed to be pushed away. By pushing the joystick, the picture was minimized.

Pavlovian-to-instrumental transfer task

There were four experimental phases in the PIT task.

(1) Instrumental training. Participants underwent a probabilistic instrumental training and learned to emit a go or a no-go response for each of six instrumental shell

stimuli. For a “good” shell, collecting it (i.e., a “go” response) by repeatly pressing the button for five or more times would lead to a monetary reward of 20 cents in 80% of the trials and a loss of 20 cents in 20% of the trials, while not collecting it (i.e., a “no-go” response) by pressing the button less than five times or no button pressing would lead to the monetary reward with a probablilty of 20% and to the monetary loss with a probability of 80% (Figure S3 (a)). For a “bad” shell, the probability of monetary reward/loss corresponding to a go/no-go action was reversed. Participants should complete a minumum of 60 trials and have 80% correct responses in 16 consecutive trials, or a maximum of 120 trials.

(2) *Pavlovian training.* In each trial, a compound stimulus (conditioned stimulus, CS) consisting of a fractal picture and a pure tone was presented simulatenously with an unconditioned stimulus (US: monetary gain or loss) after a delay of 500 ms. Participants were instructed to passively watch and memorize the pairings. There were 80 trials in the Pavlovian training phase.

(3) *Pavlovian-to-instrumental transfer (PIT)*. In this part, participants performed the same instrumental task as in the first phase. A CS learned from the Pavlovian training or a beverage image (i.e., alcohol drink or water) that was not introduced in the previous phase tiled the background of the instrumental shell in each trial. Ninety trials with Pavlovian CS background and 72 trials with beverage image background were implemented. Trials with beverage image background were out of the scope of the current paper. The instrumental task was independent of the value of the CS. No feedback was given at the end of each trial in this phase to avoid further instrumental

learning. However, participants were instructed that their actions were counted to the final monetary outcome.

(4) *Forced choice task*. The forced choice task was used to exmaine the efficacy of the Pavlovian training. In each trial, participants chose one CS over another between two CSs that presented sequentially. All possible CS pairings were presented three times in randomized order. Each choice trial was pesented for 2 sec.

Three phases (i.e., instrumental training, pavlovian training and forced choice task) were conducted outside the fMRI scanner, while the transfer part was conducted inside the scanner.

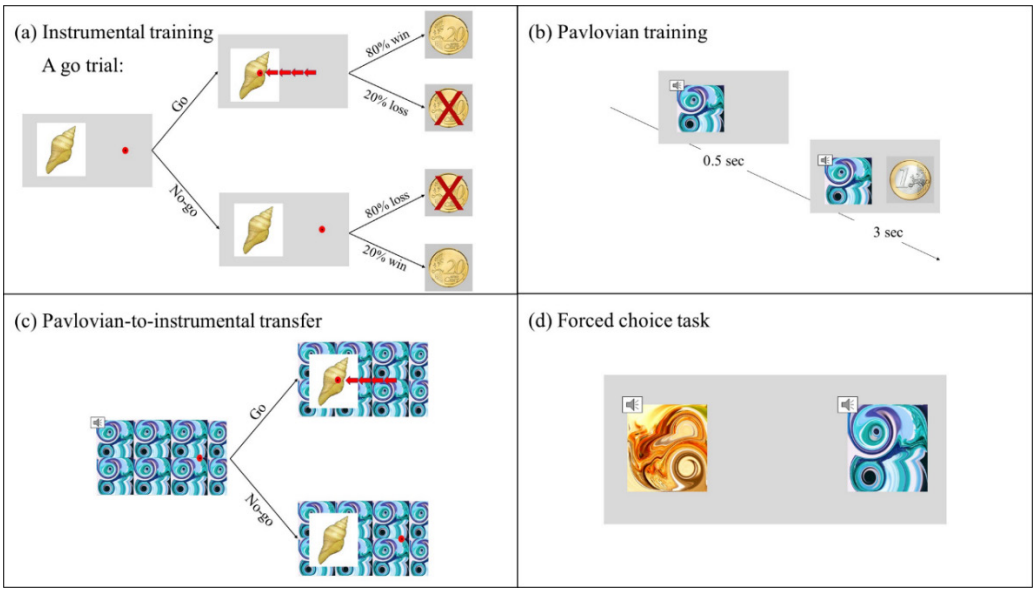

Figure S3. Pavlovian-to-instrumental transfer (PIT) task. (a): Instrumental training: participants learn to collect "good" shells (go trials) and leave "bad" shells (no-go trials) with probabilistic outcomes. A go trial was depicted in the figure. Collecting the shell would lead to a reward of 20 cents with 80% probability and to a loss of 20 cents with 20% probability, while vice versa for not collecting it. The probability of reward/loss after an action of go/no-go was reversed for a "bad" shell (not depicted here). (b): Pavlovian training: a Pavlovian conditioned stimulus (CS) consisting of a fractal and a pure tone was paired with an unconditioned cue (US), i.e., a picture of

coin (-2€, -1€, 0€, +1€, +2€). Negative USs were presented as coins with a superimposed red cross. Participants passively viewed the trials and remembered the pairings. (c): Pavlovian-to-instrumental transfer: participants were instructed to perform the instumental actions as learned from instrumental training with a Pavlovian CS tiling the backgroud. (d): Forced choice task: two Palovian CSs simulatenously presented on the screen and participants were instructed to choose the most appealing one.

Neural PIT effect – whole brain analyses

Table S1. Explorative whole-brain analyses: activations for the PIT effect at p_{unc} < .001 with cluster extend k > 20.

		Cluster			Peak					
		k	*p (FWE corrected)*	*p (unc)*	*t*	MNI-Coordinates			*p (FWE corrected)*	*p(unc)*
						x	y	z		
BA11- Anterior cingulate and paracingulate gyri	L	441	.02	.004	4.19	-6	40	-6	.33	< .001
					4.05	8	48	-4	.44	< .001
					3.69	-6	46	8	.77	< .001
BA21- Superior temporal gyrus	R	105	.42	.12	4.07	66	-28	4	.43	< .001
					3.79	60	-20	4	.68	< .001
BA22- Superior temporal gyrus	L	31	.83	.39	3.81	-64	-32	12	.67	< .001
BA54- ParaHippocampal gyrus	L	54	.69	.26	3.63	-32	-36	-8	.83	< .001
					3.49	-40	-26	2	.91	< .001
					3.47	-40	-34	-4	.92	< .001
BA24- Anterior cingulate and paracingulate gyri	L	21	.89	.49	3.52	-2	32	14	.90	< .001

Note. BA, Brodmann area; FWE, family-wise error; L, left hemisphere; MNI, Montreal Neurological Institute; R, right hemisphere.

Visual inspection of behavioral PIT slopes and D-diff scores

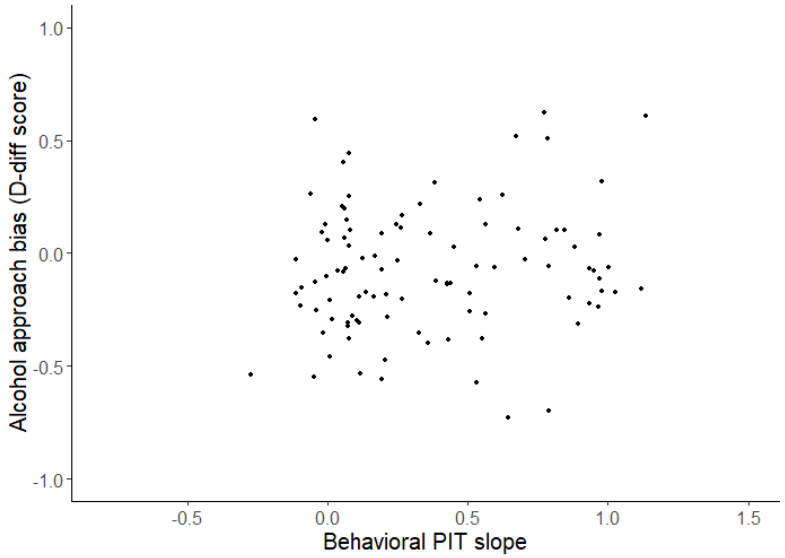

Figure S4. Scatter plot for behavioral PIT slopes and D-diff scores

Note. The behavioral PIT slopes were the extracted slopes from a generalized linear mixed-effects model used for the behavioral PIT analysis to reflect the strength of the individual PIT effect.

The correlation between alcohol dependence severity and trait impulsivity

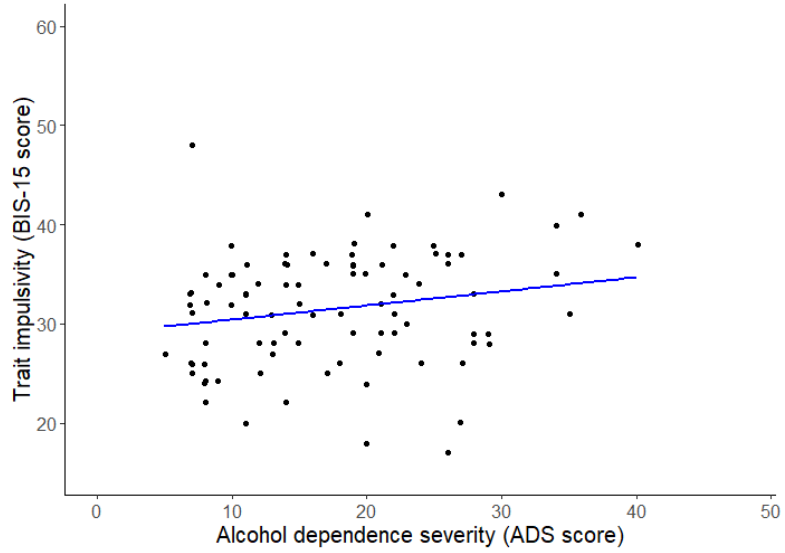

Figure S5. The correlation between the ADS score and the BIS-15 score

Note. ADS: Alcohol Dependence Scale (2), possible score range is 0 to 48; BIS-15: Barrat Impulsiveness Scale-15 (3), possible score range is 15 to 60. The blue line shows the linear correlation between the ADS score and the BIS-15 score (rho = .24, p = .026, Spearman rank correlation).

Exploratory analyses including only patients with clear relapse status

Behavioral result

When including only patients with clear relapse status (n = 21 abstainers and 30 relapsers; n = 49 with unclear relapse status were removed here) into analysis, there was no significant interaction of Pavlovian CS value, aAAT D-diff score, and relapse group (estimate = -0.03, z = -0.81, p = .418), which did not support a difference between abstainers and relapsers in the association between the alcohol approach bias and the behavioral PIT effect.

fMRI results

When only patients with clear relapse status were included into analysis, as found before, there was no significant group differences in the association between the alcohol approach bias and the neural PIT effect in either the right NAcc or the left NAcc (right NAcc (relapsers > abstainers: x = 6, y = 8, z = -8, t (32) = 0.95, $p_{svc\text{-}FWE}$ = .694; abstainers > relapsers: x= 16, y = 14, z = -12, t (32) = 1.13, $p_{svc\text{-}FWE}$ = .630; left NAcc (relapsers > abstainers: x = -14, y = 2, z = -12, t (32) = -0.25, $p_{svc\text{-}FWE}$ = .892; abstainers > relapsers: x= -10, y = 10, z = -12, t (32) = 2.34, $p_{svc\text{-}FWE}$ = .156).

Supplemental References

1. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM (1989): Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict*. 84:1353-1357.

2. Skinner HA, Horn JL (1984): *Alcohol dependence scale (ADS): User's guide*.

Addiction Research Foundation.

3. Meule A, Vögele C, Kübler A (2011): Psychometrische evaluation der deutschen Barratt impulsiveness scale–Kurzversion (BIS-15). *Diagnostica*.