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Fighting against fear

Novel approaches to understanding, modifying, and manipulating maladaptive memories

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Publication date

2020

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Citation for published version (APA):

Elsey, J. W. B. (2020). *Fighting against fear: Novel approaches to understanding, modifying, and manipulating maladaptive memories*. [Thesis, fully internal, Universiteit van Amsterdam].

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Appendices

Appendix 1 - Supplementary Materials for Chapter 2

Medical Screening

Participants underwent a medical screening to determine any contraindications for taking propranolol, and some generic exclusion criteria for participation in our research, namely: screening for heart conditions in first degree relatives; a medical history of heart, circulatory, lung, liver, or kidney problems that would contraindicate the use of propranolol; use of contraindicated medications (e.g., use of other medications that affect the heart/blood pressure); current use of psychoactive medication; current diagnosis of a psychiatric disorder; checking heart rate (HR > 60, or >55 if reports regular vigorous physical activity) and blood pressure (>90/60); pregnancy; active asthma.

MANOVA for emotional change and distress with respective ANOVAs

Supplementary Table S1a. Estimate of mean for emotional induction MANOVA

	Prop-Placebo		Placebo-Prop		Placebo-Placebo	
	Change	Distress	Change	Distress	Change	Distress
Estimate of mean	8.463	53.957	22.154	64.458	18.340	64.200

Supplementary Table S1b. Prior variance-covariance matrix for MANOVA on emotional induction

		Prop-Placebo		Placebo-Prop		Placebo-Placebo	
		Change	Distress	Change	Distress	Change	Distress
Prop-Placebo	Change	213.198	116.502	-	-	-	-
	Distress	116.502	358.532	-	-	-	-
Placebo-Prop	Change	-	-	213.198	116.502	-	-
	Distress	-	-	116.502	358.532	-	-
Placebo-Placebo	Change	-	-	-	-	213.198	116.502
	Distress	-	-	-	-	116.502	358.532

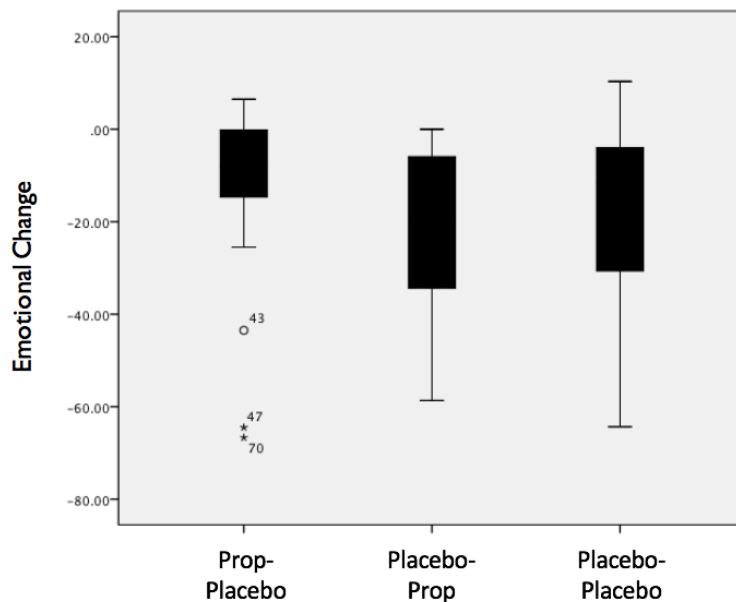
Supplementary Table S1c. Posterior variance-covariance matrix for MANOVA on emotional induction

		Prop-Placebo		Placebo-Prop		Placebo-Placebo	
		Change	Distress	Change	Distress	Change	Distress
Prop-Placebo	Change	12.359	6.754	-	-	-	-
	Distress	6.754	20.784	-	-	-	-
Placebo-Prop	Change	-	-	11.844	6.472	-	-
	Distress	-	-	6.472	19.918	-	-
Placebo-Placebo	Change	-	-	-	-	11.371	6.213
	Distress	-	-	-	-	6.213	19.122

Change scores (pre vs. post rating) were used in the above MANOVA for emotional change, rather than conducting a repeated measures analysis for emotional change and a one-way ANOVA for distress separately. As propranolol would have been active in the Prop-Placebo group when pre-movie emotion ratings were given, we here supplement this analysis with a frequentist mixed-measures analysis of variance with Time (pre-movie vs. post-movie) as a within and Condition (Prop-Placebo vs. Placebo-Prop and Placebo-Placebo combined) as a between groups variable. The Placebo-Prop and Placebo-Placebo groups were combined to match the form of the informative hypotheses in the MANOVA, and because the Placebo-Prop and Placebo-Placebo groups are simply both ‘Placebo’ groups at the time of emotion ratings. This ANOVA indicated that our interpretation of emotional change scores indicating a lower emotional induction from the movie in the prop-placebo group was not confounded by initial differences in emotion ratings from the group receiving propranolol beforehand. There was a significant main effect of time ($F(1,70) = 45.50$, $p < .001$, $\eta^2 = .370$), no significant main effect of group ($F(1,70) = 1.02$, $p = .317$, $\eta^2 = .014$), and a significant time*group interaction ($F(1,70) = 7.64$, $p = .007$, $\eta^2 = .062$). Post-hoc tests suggest no significant differences between groups in negative emotions before the movie ($t(70) = .81$, $p = .421$, $d = .205$), but significantly lower levels of negative emotions in the prop-placebo group after the movie ($t(57.95 - \text{unequal variances adjustment}) = 2.06$, $p = .044$, $d = -.465$).

Robust Bayesian ANOVA for emotional change scores

As can be seen in supplementary Figure S3, two extreme outlying values were observed in the prop-placebo group, and were removed from further analyses in the main paper. An alternative approach to removing outliers is to compute 20% trimmed means and their variances (Meijerink-Bosman & Hoijsink, 2018; Mair & Wilcox, 2018) to make estimates of group parameters more robust to the influence of the outliers, while not rejecting them completely. Supplementary Table S2 depicts the trimmed means and variances of emotional change scores for each group. Results for this ANOVA are presented in the main text, Figure 2c and Table 3c.



Supplementary Figure S1. Two extreme outliers in emotional change scores are present in the prop-placebo group.

Supplementary Table S2. Prior and posterior variances and 20% Trimmed means and for robust ANOVA on emotional change.

	Prior Variance	Posterior Variance	Estimated Mean	<i>n</i>
Prop-Placebo	383.058	10.215	7.61	25
Placebo-Prop	774.547	21.515	20.084	24
Placebo-Placebo	654.655	17.457	14.589	25

ANOVA for Intrusions

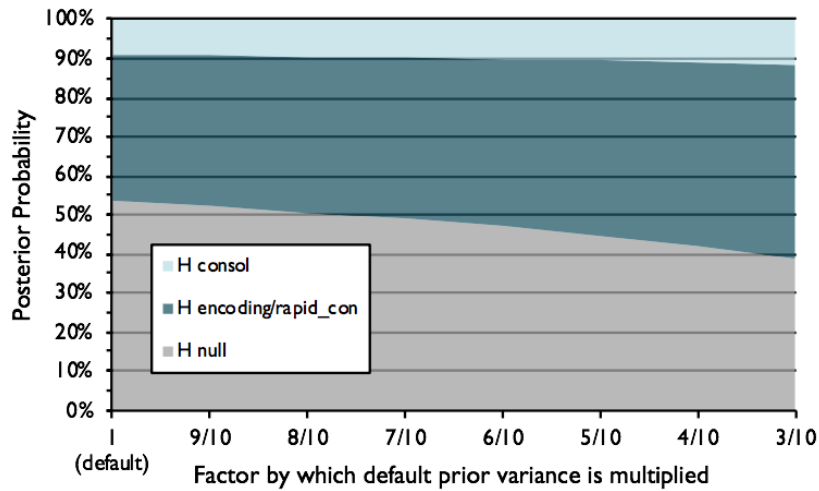
Supplementary Table S3. Prior and posterior variances and rates for ANOVA on intrusions.

	Prior Variance	Posterior Variance	Estimated rate	<i>n</i>
Prop-Placebo	0.784	0.023	0.649	23
Placebo-Prop	0.571	0.016	0.965	24
Placebo-Placebo	0.647	0.017	0.841	25

ANOVA for intrusions after day 1

Supplementary Table S4. Prior and posterior variances and rates for ANOVA on intrusions after day 1.

	Prior Variance	Posterior Variance	Estimated rate	<i>n</i>
Prop-Placebo	1.150	0.033	0.266	23
Placebo-Prop	0.818	0.023	0.606	24
Placebo-Placebo	0.937	0.025	0.47	25



Supplementary Figure S2. Posterior probabilities associated with each hypothesis across the sensitivity analysis of ANOVA for intrusions after day 1.

ANOVA for log-transformed Impact of Events Scale

Supplementary Table S5. Prior and posterior variances and means for ANOVA on Impact of Events Scale.

	Prior Variance	Posterior Variance	Mean	<i>n</i>
Prop-Placebo	1.135	0.033	1.833	23
Placebo-Prop	1.135	0.032	2.214	24
Placebo-Placebo	1.135	0.030	2.056	25

Non-parametric assessments of Impact of Events Scale

Given the non-normal distribution of the raw data for IES scores, we supplemented our Bayesian analyses with non-parametric Kruskal-Wallis and Jonckheere-Terpstra tests on raw IES scores. In alignment with the Bayesian analyses, the Kruskal-Wallis test did not provide evidence that we should reject the null of no differences between groups ($\chi^2(2) = 1.658, p = .437$). The Jonckheere-Terpstra test allows one to specify a proposed ordering of ranked scores across groups. We

conducted two separate tests for each variable. For one test, we collapsed the Placebo-Prop and Placebo-Placebo groups together, proposing that the Prop-Placebo group would have lower scores than this combination of groups (i.e., the *encoding/rapid consolidation hypothesis*). For the other test, we collapsed the Prop-Placebo and Placebo-Prop groups together, proposing that this combination of groups would score lower than the Placebo-Placebo group (i.e., the *consolidation hypothesis*). As with our Bayesian analyses, the Jonckheere-Terpstra test of $H_{encoding/rapid_con}$ did not provide evidence in favor of rejecting the null ($T_{JT} = 619.500$, $z = .677$, $p = .498$), nor could the null be rejected for our Jonckheere-Terpstra equivalent of H_{consol} ($T_{JT} = 536.000$, $z = -.610$, $p = .542$).

MANOVA for visual and verbal declarative memory

Supplementary Table S6a. Estimate of mean for declarative memory MANOVA

	Prop-Placebo		Placebo-Prop		Placebo-Placebo	
	Verbal	Visual	Verbal	Visual	Verbal	Visual
Estimate of mean	0.299	1.114	0.424	1.162	0.279	1.414

Supplementary Table S6b. Prior variance-covariance matrix for MANOVA on declarative memory

		Prop-Placebo		Placebo-Prop		Placebo-Placebo	
		Verbal	Visual	Verbal	Visual	Verbal	Visual
Prop-Placebo	Verbal	0.239	0.168	-	-	-	-
	Visual	0.168	0.451	-	-	-	-
Placebo-Prop	Verbal	-	-	0.239	0.168	-	-
	Visual	-	-	0.168	0.451	-	-
Placebo-Placebo	Verbal	-	-	-	-	0.239	0.168
	Visual	-	-	-	-	0.168	0.451

Supplementary Table S6c. Posterior variance-covariance matrix for MANOVA on declarative memory

		Prop-Placebo		Placebo-Prop		Placebo-Placebo	
		Verbal	Visual	Verbal	Visual	Verbal	Visual
Prop-Placebo	Verbal	0.014	0.01	-	-	-	-
	Visual	0.01	0.026	-	-	-	-
Placebo-Prop	Verbal	-	-	0.013	0.009	-	-
	Visual	-	-	0.009	0.025	-	-
Placebo-Placebo	Verbal	-	-	-	-	0.013	0.009
	Visual	-	-	-	-	0.009	0.025

Analyses restricted to women

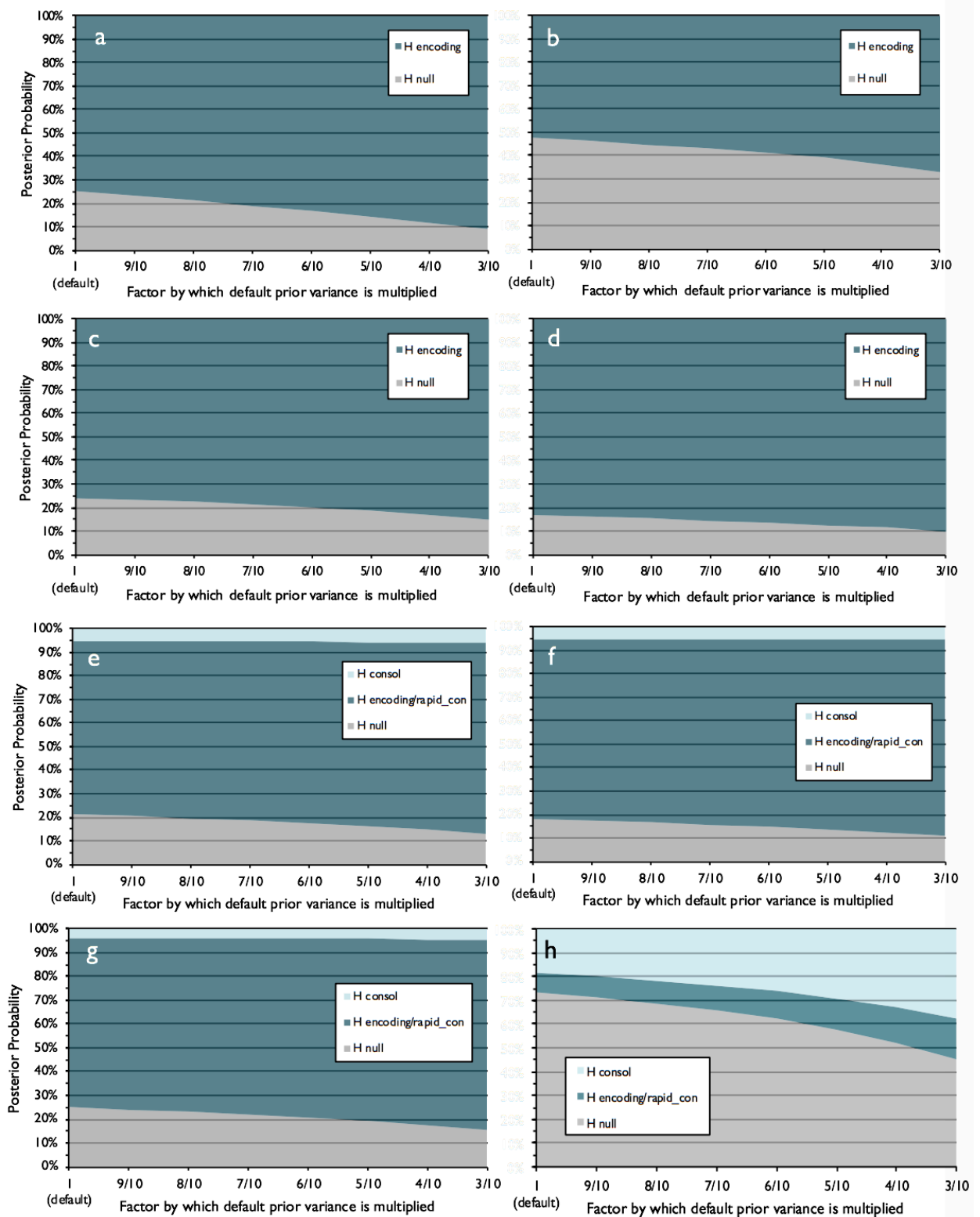
The study was not sufficiently powered to examine gender differences, but given the larger number of women in the sample it was possible to run supplementary analyses to determine whether similar patterns of results were present when women were analyzed in isolation. Hypothesis comparisons were quite similar to those in the overall analysis, though with some deviations that could be followed up on using another sample of just women (Supplementary Table S7, Supplementary Figure S3). In the MANOVA for initial impact, $H_{encoding}$ was favored relative to H_0 . For the subsequent ANOVAs, $H_{encoding}$ was favored for distress but evidence was quite equivocal at the default prior for Emotional Change. Notably, the two outliers in the overall sample were not extreme outliers in just the women (though still around 2 standard deviations above the mean), and so were not removed from analyses. The robust ANOVA for Emotional Change, which can reduce the influence of such outlying values, indeed favored $H_{encoding}$.

Interestingly, Bayesian ANOVAs assessing intrusions and the Impact of Events scale did provide evidence in favor of $H_{encoding/rapid_con}$ (Supplementary Table S7e, f, & g, as well as Supplementary Figure S3e, f, and g). H_{consol} received very little support. H_0 was again favored in the analysis of declarative memory. Of possible note, while heart rate changes between groups only reached marginal significance in the sample overall, they were statistically significant in women ($F(2,49) = 3.822, p = .029$, uncorrected, $\eta^2 = .135$), with the greatest change apparent in the propranolol-placebo group. Blood pressure changes still were not statistically significantly different between groups, however ($p > .25$).

Supplementary Table S7. Bayes factors for each of the hypotheses compared in each Bayesian analysis, restricted to women.

S7a. MANOVA for Emotional Change and Distress	
Hypotheses compared	BF
$H_{encoding}$ vs. H_0	2.997
S7b. ANOVA for Emotional Change	
Hypotheses compared	BF
$H_{encoding}$ vs. H_0	1.103
S7c. Robust ANOVA for Emotional Change	
Hypotheses compared	BF
$H_{encoding}$ vs. H_0	3.124
S7d. ANOVA for Distress	
Hypotheses compared	BF
$H_{encoding}$ vs. H_0	4.931
S7e. ANOVA for Intrusions	
Hypotheses compared	BF
$H_{encoding/rapid_con}$ vs. H_0	3.432
H_0 vs. H_{consol}	3.99
$H_{encoding/rapid_con}$ vs. H_{consol}	13.693
S7f. ANOVA for Intrusions after D1	
Hypotheses compared	BF
$H_{encoding/rapid_con}$ vs. H_0	4.212
H_0 vs. H_{consol}	3.523
$H_{encoding/rapid_con}$ vs. H_{consol}	14.853
S7g. ANOVA for log transformed IES	
Hypotheses compared	BF
$H_{encoding/rapid_con}$ vs. H_0	2.816
H_0 vs. H_{consol}	6.329
$H_{encoding/rapid_con}$ vs. H_{consol}	17.824
S7h. MANOVA for Verbal and Visual Declarative Memory	
Hypotheses compared	BF
H_0 vs. $H_{encoding/rapid_con}$	8.733
H_0 vs. H_{consol}	3.965
H_{consol} vs. $H_{encoding/rapid_con}$	2.203

BF = Relative Bayes factor favoring the first hypothesis vs. the second; H_0 = null hypothesis; H_{consol} = the consolidation hypothesis; $H_{encoding}$ = the encoding hypothesis, used when assessing initial emotional responsiveness; $H_{encoding/rapid_con}$ = the encoding and rapid consolidation hypotheses, which specify the same pattern of means as $H_{encoding}$, but used for long-term assessments where consolidation can have played a role; IES = Modified Impact of Events Scale



Supplementary Figure S3. Posterior probabilities associated with each hypothesis across the sensitivity analyses in women. a) MANOVA for emotional change and distress. b) ANOVA for emotional change. c) Robust ANOVA for emotional change.

d) ANOVA for distress. e) ANOVA for intrusions. f) ANOVA for intrusions after day 1. g) ANOVA for log-transformed impact of events scale. h) MANOVA for verbal and visual declarative memory.

Alcohol Consumption and Emotional and Declarative Memory

Though we requested that participants refrain from drinking alcohol on the night of the study session, it became apparent that some participants were drinking alcohol on the evening after taking part in session 1. We thus requested that participants also start recording whether or not they had consumed alcohol in their diaries (N = 58, 21 did consume alcohol). A chi-square test indicated that there was no evidence of a difference between the groups in the proportion of participants who had consumed alcohol ($\chi^2 = 2.820, p = .244$). Furthermore, we found that those participants who had consumed alcohol did not score significantly differently on IES scores or declarative memory to those who did not in *t*-tests or Mann-Whitney *U* tests (see Supplementary Table S6). Bayes Factors also provided evidence in favor of the null hypothesis, relative to an alternative hypothesis that groups scored differently. Likewise, a generalized linear model predicting intrusions from alcohol consumption showed that intrusion rates were not significantly different between groups (*p* value for dummy coded alcohol consumption variable vs. intercept = .42).

Supplementary Table S8. Comparison between participants who did vs. did not consume alcohol on the evening of the first study session.

		<i>t</i> (<i>df</i>)	<i>p</i>	<i>U Z-score</i>	<i>p</i>	<i>BF₀₁</i>
	Log IES	-0.115 (56)	0.909	-0.745	0.456	3.62
Declarative	Visual	-0.559 (55)	0.579	-0.820	0.412	3.18
Memory	Verbal	-0.212 (55)	0.833	-0.596	0.551	3.56

p = 2-tailed *p*-value; *U Z-score* = standardized Mann-Whitney *U* test score, *BF₀₁* = Bayes factor for null hypothesis

Supplementary References

- Meijerink-Bosman, M., & Hoijtink, H. (2018). Robust Bayes factors for Bayesian ANOVA: overcoming adverse effect of non-normality and outliers. Unpublished manuscript.
- Mair, P., & Wilcox, R. (2018). Robust Statistical Methods Using WRS2.

Appendix 2. Supplementary Materials for Chapter 4.

Medical inclusion/exclusion criteria for propranolol administration

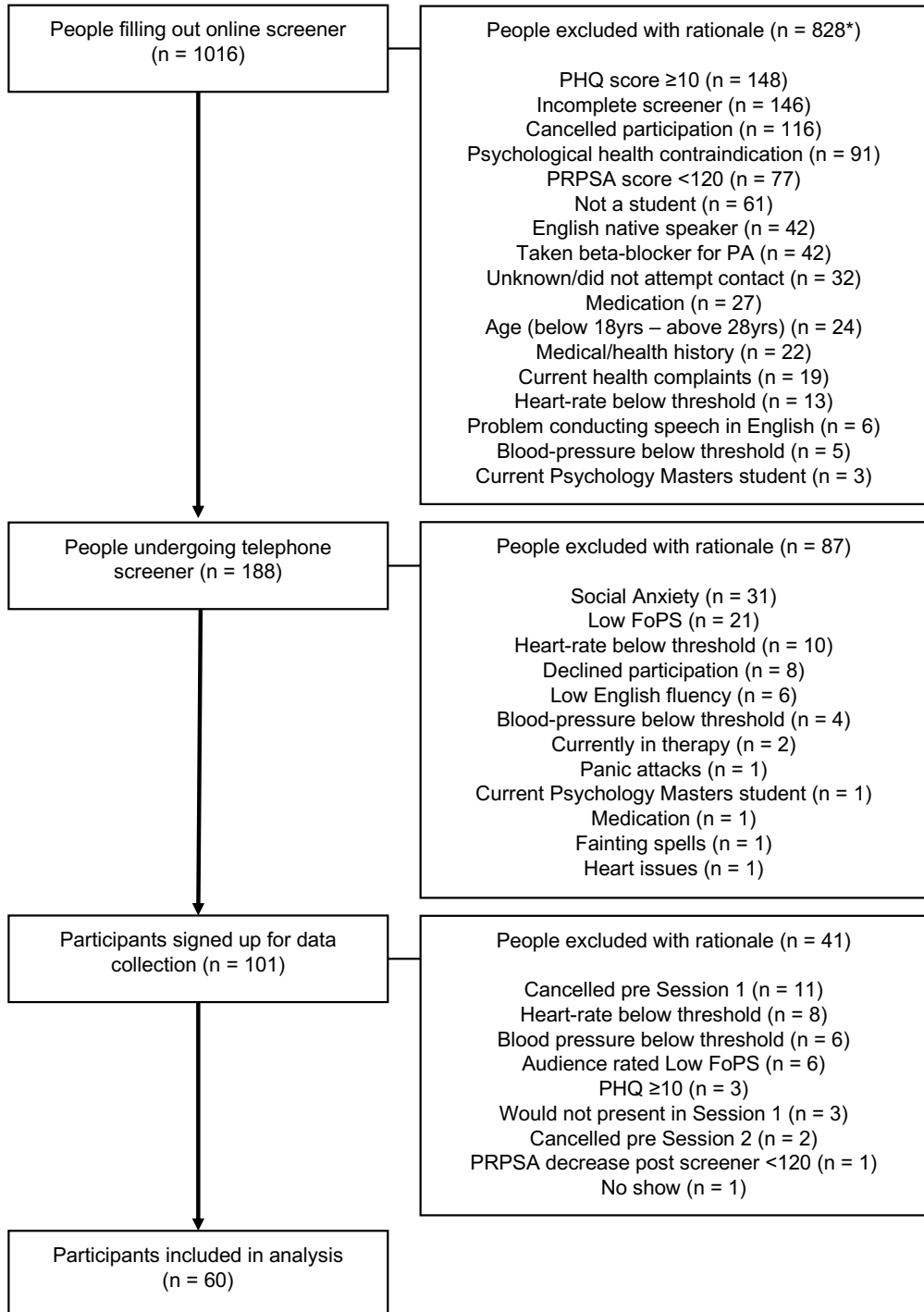
Participants underwent a medical screening to confirm the safe use of propranolol, namely: screening for heart conditions in first degree relatives; a medical history of heart, circulatory, lung, liver, or kidney problems that would contraindicate the use of propranolol; use of contraindicated medications (e.g., use of other medications that affect the heart/blood pressure); heart rate <60, blood pressure <100/60; pregnancy; active asthma. A flow chart of all reasons for exclusion is presented on the following page (Figure S1).

Questionnaire Information

Personal Report of Public Speaking Anxiety (PRPSA: McCroskey, 1970). The PRPSA is a 34-item self-report scale for measuring a respondent's fear of public speaking. Participants respond using a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Scores can range from 34-170, with higher scores indicating greater PSA. The scale has shown excellent internal consistency ($\alpha = .94$), with high test-retest reliability ($r = .84$) making it suitable for repeated measurements (McCroskey, 1970).

Subjective units of distress/discomfort (SUDS, cf. Wolpe & Lazarus, 1966). The SUDS is a brief self-report instrument used to quickly and relatively unobtrusively determine a participant's subjective state of distress. Participants are required to rate their distress from 0 (no distress) to 100 (extreme distress). SUDS scales have shown convergent validity with other measures of distress/anxiety, and also proven sensitive to intervention effects (Foa, Riggs, Massie, & Yarczower, 1995; Kim, Bae, & Park, 2008; Soeter & Kindt, 2015a; Tanner, 2012).

Public Speaking Study – Exclusion Flow



Note. PHQ = Patient Health Questionnaire; PRPSA = Personal Report of Public Speaking Anxiety; FoPS = Fear of public speaking; PA = performance anxiety; * = Reasons contain duplicate for exclusion per candidate

Figure S1. Complete inclusion/exclusion information.

Global Perception of Speech Performance - Self-rating (GPSP: Rapee & Lim, 1992). The GPSP is a brief self-report measure in which respondents assess the general impression they believe they have made upon an audience (e.g., 'Appeared confident'), with items rated from 0 ('Not at all') to 4 ('Very much'). Scores are summed, with higher scores (after reverse scoring items) indicating poorer performance. Internal consistency for the scale is acceptable-to-good ($\alpha = .79$) (Rapee & Lim, 1992).

Liebowitz Social Anxiety Scale - Self-report (LSAS: Baker, Heinrichs, Kim, & Hofmann, 2002; Heimberg et al., 1999). The LSAS is a self-report scale assessing a respondent's social anxiety. Respondents answer how much fear they would have of (from 0 = "none", to 3 = "severe"), and how often they would avoid (from 0 = "never", to 3 = "usually") 24 social situations. These fear and avoidance subscales have shown good internal consistency ($\alpha = .85-.91$, Baker et al., 2002; Fresco et al., 2001) and test-retest reliability ($r = .79$ & $.83$ respectively, Baker et al., 2002).

Patient Health Questionnaire 9 (PHQ-9: Kroenke, Spitzer, & Williams, 2001). The PHQ-9 is a 9 item self-report scale for assessing depression severity. Participants indicate how much they have experienced 9 depressive symptoms over the past 2 weeks, from 0 ("not at all"), to 3 ("nearly every day"). The scale is deemed a valid measure of depression severity and shows good agreement with diagnoses and other measures of depression (Martin, Rief, Klaiberg, & Braehler, 2006). The official Dutch version of the PHQ-9 was given to Dutch participants.

Anxiety Sensitivity Index (ASI: Reiss, Peterson, Gursky, & McNally, 1986). The ASI is a 16-item self-report scale measuring the degree to which a respondent fears feelings and behaviors associated with anxiety (i.e., anxiety sensitivity). Respondents rate how much they agree with statements reflecting anxiety sensitivity from 0 (very little) to 4 (very much). The robust psychometric properties of the ASI are reported in a review and the scale manual (Peterson & Plehn, 1999; Peterson & Reiss, 1992). Dutch participants were given a validated Dutch translation of the questionnaire with good internal consistency ($\alpha = .83$: Vujanovic, Arrindell, Bernstein, Norton, & Zvolensky, 2007).

Rosenberg Self-Esteem Scale (RSES: Rosenberg, 1965). The RSES is a 10 item self-report scale assessing a respondent's sense of self-worth. Respondents indicate the degree to which they agree with statements about satisfaction with their self, from 1 ("strongly disagree") to 4 ("strongly agree"), with higher scores indicating

greater self-esteem. The scale has good internal consistency ($\alpha = .88$, Gray-Little, Williams, & Hancock, 1997) and correlates with related constructs (Schmitt & Allik, 2005). A validated Dutch translation (Franck, De Raedt, Barbez, & Rosseel, 2008) with good internal consistency ($\alpha = .86$) was used for Dutch participants.

Spielberger State-Trait Anxiety Index (STAI: Spielberger, Gorsuch, & Lushene, 1970). The STAI is a self-report questionnaire, consisting of two 20-item subscales that measure state (STAI-S) and trait (STAI-T) anxiety. For the STAI-T, respondents answer how frequently they experience anxiety-related phenomena on a scale, from 1 ("almost never") to 4 ("almost always"). For the STAI-S, participants indicate how much they are currently experiencing feelings/thoughts related to anxiety, from 1 ("not at all") to 4 ("very much so"). The subscales have shown good internal consistency (ranging from .83-.92), and the STAI-T shows good test-retest reliability ($r = .81$) (Foa, Riggs, Dancu, & Rothbaum, 1993). A validated Dutch translation of the STAI was given to Dutch participants (van der Ploeg, 1980).

Saliva analysis procedure

Quantification of salivary analytes was performed by Dresden LabService GmbH. Information on the analysis process was provided by Prof. Dr Clemens Kirschbaum. All samples were kept frozen at -20°C until analysis. Once thawed, salivettes were centrifuged at 3000rpm for 5 minutes, producing a clear, low viscosity supernatant. For cortisol, concentrations were measured using a high sensitivity, commercially available chemiluminescence immunoassay (IBL International, Hamburg, Germany). The intra and interassay coefficients for cortisol were below 7%.

Alpha-amylase concentrations were determined using an enzyme kinetic method. A Genesis RSP8/150 liquid handling system (Tecan, Crailsheim, Germany) was used to process the saliva. This handling system first dilutes (1:625) the saliva with double-distilled water. Twenty microliters of diluted saliva and standard were then transferred to standard transparent 96-well microplates (Roth, Karlsruhe, Germany). "Calibrator f.a.s" solution (Roche Diagnostics, Mannheim, Germany) was used to prepare standard with the following concentrations: 326, 163, 81.5, 40.75, 20.38, 10.19, and 5.01 U/l alpha-amylase. Double distilled ('bidest') water was used as zero standard. A multichannel pipette was then used to pipette 80ml of substrate reagent (alpha-amylase EPS Sys; Roche Diagnostics, Mannheim, Germany) into each well. The microplate with sample and substrate was when incubated in a waterbath

for 90 seconds to reach 37°C. Immediately following this, a standard ELISA reader (Anthos Labtech HT2, Anthos, Krefeld, Germany) was used to obtain a first interference measurement, at a 405nm wavelength. A second measurement at 405nm was then taken after incubating the plate in the waterbath at 37°C for another 5 minutes. Increases in absorbance were calculated for unknowns and standards. Linear regression calculated for each microplate was used to transform increases of absorbance of diluted samples to alpha-amylase concentrations (Graphpad Prism 4.0c for MacOSX, Graphpad Software, San Diego, CA). Intra and interassay coefficients for amylase were below 9%.

***brms* physiological prior specification**

Analyses of physiological data in *brms* did not converge using default priors. We retained default priors on variance parameters, and specified priors for the Intercept and predictors that represent a deflection from that intercept. Priors for all such parameters for HR and log-cortisol are presented in Table S1. Log-cortisol values have been multiplied by 10 for ease of specification and reading output.

Table S1. Prior specifications for *brms* physiological analyses

Variable	Parameter	Family	Specification
HR	Intercept	Normal	80, 10
HR	Time = Preparation	Student t	5, 15, 7.5
HR	Time = Speech	Student t	5, 30, 15
HR	Session = S2	Student t	5, 0, 10
HR	Session = S1, Time = Baseline, Placebo	Student t	5, 0, 10
HR	Session = S1, Time = Baseline, Prop	Student t	5, 0, 10
HR	Session = S1, Time = Preparation, Prop	Student t	5, 0, 10
HR	Session = S1, Time = Preparation, Placebo	Student t	5, 0, 10
HR	Session = S1, Time = Speech, Placebo	Student t	5, 0, 10
HR	Session = S1, Time = Speech, Prop	Student t	5, 0, 10
HR	Session = S2, Time = Baseline, Placebo	Student t	5, 0, 10
HR	Session = S2, Time = Baseline, Prop	Student t	5, 0, 10
HR	Session = S2, Time = Preparation, Prop	Student t	5, 0, 10
HR	Session = S2, Time = Preparation, Placebo	Student t	5, 0, 10
HR	Session = S2, Time = Speech, Placebo	Student t	5, 0, 10
HR	Session = S2, Time = Speech, Prop	Student t	5, 0, 10
Cortisol	Intercept	Normal	9, 1.5
Cortisol	Time = Post1	Student t	5, 3, 2

Cortisol		Time = Post2	Student t	5, 3, 2
Cortisol		Session = S2	Student t	5, 0, 2
Cortisol	Session = S1, Time = Baseline, Placebo		Student t	5, 0, 2
Cortisol	Session = S1, Time = Baseline, Prop		Student t	5, 0, 2
Cortisol	Session = S1, Time = Post1, Prop		Student t	5, 0, 2
Cortisol	Session = S1, Time = Post1, Placebo		Student t	5, 0, 2
Cortisol	Session = S1, Time = Post2, Placebo		Student t	5, 0, 2
Cortisol	Session = S1, Time = Post2, Prop		Student t	5, 0, 2
Cortisol	Session = S2, Time = Baseline, Placebo		Student t	5, 0, 2
Cortisol	Session = S2, Time = Baseline, Prop		Student t	5, 0, 2
Cortisol	Session = S2, Time = Post1, Prop		Student t	5, 0, 2
Cortisol	Session = S2, Time = Post1, Placebo		Student t	5, 0, 2
Cortisol	Session = S2, Time = Post2, Placebo		Student t	5, 0, 2
Cortisol	Session = S2, Time = Post2, Prop		Student t	5, 0, 2

Normal = Mean, SD, Student t = Degrees of freedom, Mean, SD

Note that specified prior families represent distributions of the search space, not for the actual outcome variables. For heart rate, a normal heart rate is between 60-100bpm (<https://www.heart.org/en/health-topics/high-blood-pressure/the-facts-about-high-blood-pressure/all-about-heart-rate-pulse#.Wg1mcBO0OCU>). We set the Intercept to 80 with an SD of 10, as values very close to 60 are also unlikely given that this is set as a lower bound for study inclusion. All other priors use a t distribution with 5 degrees of freedom. The t distribution is similar to the normal, only having larger tails (coming closer to the normal distribution as degrees of freedom increase). Use of this distribution means that we can set reasonable bounds on the probable parameter values, but allow the search space to consider large values should they arise in the data. In reviewing 10 years of research on the TSST, Kudielka, Hellhammer, & Kirschbaum (2007) indicate that HR can be expected to increase from between 15-25bpm. Given that we are investigating anxious individuals and taking the first minute of their speech where HR can be expected to be higher, we chose a slightly higher value of 30 with standard deviations and degrees of freedom that allow much lower or higher values to be considered. We select half this value for the preparation period. For all interaction terms, the mean is set to 0, with degrees of freedom and standard deviations enabling potentially sizable interactions to be accepted, while considering a null effect as most plausible.

For cortisol, we used approximate starting values for cortisol levels in previous studies (e.g., Kirschbaum, Pirke, & Hellhammer, 1993), which seem to be

between 6 and 10. Log 8 is 0.9, so we take this as a starting point for the intercept. Kudielka et al. (2007) suggest that typical responses in women (which predominate in our sample) are for cortisol increases of 50-150%. Doubling 8 gives 16, and log 16 is 1.2, giving a difference on the log scale of 0.3, which we thus take as the likely deviation around which to search for values in the post-stress period. Again we give sufficient degrees of freedom and standard deviations such that considerably higher or lower values will be considered. As with HR, we set interactions to a mean of 0, with degrees of freedom and standard deviations allowing sizable positive or negative effects, with the null being given the most initial plausibility.

Manipulation check

Table S2. Means for manipulation check

Variable	Time	Condition	Mean (SD)	n
HR	Start	Placebo	70.89 (6.71)	20
		Propranolol	71.11 (10.75)	40
	End	Placebo	62.67 (7.22)	20
		Propranolol	55.27 (8.22)	40
BP _{Systolic}	Start	Placebo	117.1 (6.67)	20
		Propranolol	117.9 (10.15)	40
	End	Placebo	111.9 (6.70)	20
		Propranolol	108.1 (9.33)	40
BP _{Diastolic}	Start	Placebo	72.58 (13.67)	20
		Propranolol	73.43 (8.16)	40
	End	Placebo	71.15 (6.93)	20
		Propranolol	67.18 (9.83)	40
Amylase	Start	Placebo	1.83 (0.35)	20
		Propranolol	1.87 (0.41)	37*
	End	Placebo	1.71 (0.35)	20
STAI-S	Start	Placebo	1.44 (0.32)	37*
		Propranolol	40.25 (9.68)	20
	End	Propranolol	43.55 (8.61)	40
		Placebo	30.95 (7.72)	20
		Propranolol	31.65 (6.02)	40

* saliva/amylase could not be assayed from 3 samples

Table S2. $BF_{Inclusion}$ of Session (S), Condition (C), Duration (D), and their interaction (*).

		$BF_{Inclusion}$					
		PRPSA	LSAS _{Fear}	LSAS _{Avoid}	Distress (Ant)	Distress (Max)	GPSP
RM ANOVA	S	7.08e +8	7424.54	26.1	1099.51	2.64e +8	2.54e +9
	C	0.29	0.45	0.47	0.39	0.70	0.35
	S*C	0.11	0.11	0.28	0.35	0.50	0.33
Regression on change scores	D	0.22	0.20	0.24	0.20	2.35	0.61
	C	0.19	0.22	0.31	0.18	0.53	0.32
	C*D	0.19	0.24	0.34	0.19	0.60	0.35

RM ANOVA = Bayesian repeated measures ANOVA; $BF_{Inclusion}$ = Bayes factor for inclusion of respective model component, Ant = Anticipatory distress

Ordered probit models for questionnaire responses

Recent discussions argue that most questionnaires, being aggregations of ordinal Likert items, are not optimally analysed using metric models (Bürkner & Vuorre, 2019; Liddell & Kruschke, 2018). We thus additionally analysed GPSP and PRPSA responses using an ordered probit model in *brms*, to supplement the standard analyses. These models additionally tested the inclusion of a varying slope for the effect of Session across participants.

Results of cross-validation analyses for these probit models are presented in Figure S2. Corroborating the key take-aways from the more typical regression analyses, ordered probit models for GPSP and PRPSA items similarly indicate that adding Session improves predictions, with further predictors yielding negligible gains. Including a varying impact of Session across participants further improves model predictions, again with no evidence favouring additional predictors.

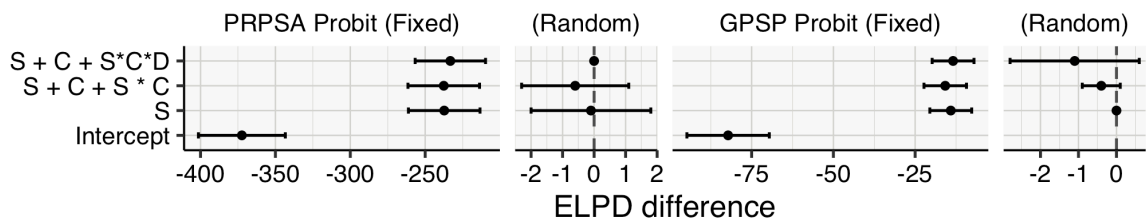


Figure S2. Model performance in leave-one-out cross validation for each primary and secondary outcome variable, indicating improvement of model performance with the inclusion of Session and no benefit of additional predictors. ELPD = expected log pointwise predictive density vs. best model. (Fixed) = probit model with fixed effects of session; (Random) = probit model with random/varying effects of session. S = Session, C = Condition, D = Duration, * = interaction between predictors.

Fitted means for Physiological Analyses

Analyses of physiological outcome variables indicated that timepoint was the only meaningful predictor for HR, and no predictors were sufficiently informative to be included in a model for log-cortisol responses. We nevertheless report in Table S4 the fitted means (estimates using the regression equation and posterior parameter estimates) in each condition at each time point, for HR and cortisol, for the Session*Condition*Timepoint model.

Table S4. Fitted means for physiological outcomes

Variable	Condition	Session	Timepoint	Mean [95% PDI]
HR	Placebo	S1	Baseline	71.23 [65.27-77.20]
HR	Propranolol	S1	Baseline	71.33 [66.93-75.70]
HR	Placebo	S1	Preparation	89.76 [83.89-95.80]
HR	Propranolol	S1	Preparation	93.53 [89.10-97.83]
HR	Placebo	S1	Speech	108.40 [102.15-114.66]
HR	Propranolol	S1	Speech	116.45 [111.92-120.85]
HR	Placebo	S2	Baseline	72.13 [66.23-78.22]
HR	Propranolol	S2	Baseline	74.76 [70.35-79.18]
HR	Placebo	S2	Preparation	89.93 [83.98-95.90]
HR	Propranolol	S2	Preparation	94.90 [90.44-99.31]
HR	Placebo	S2	Speech	110.92 [104.87-117.05]
HR	Propranolol	S2	Speech	117.90 [113.45-122.39]
Cortisol	Placebo	S1	Baseline	0.731 [0.619-0.846]
Cortisol	Propranolol	S1	Baseline	0.758 [0.674-0.841]
Cortisol	Placebo	S1	Post 1	0.748 [0.634-0.864]
Cortisol	Propranolol	S1	Post 1	0.789 [0.707-0.871]
Cortisol	Placebo	S1	Post 2	0.810 [0.695-0.924]
Cortisol	Propranolol	S1	Post 2	0.818 [0.733-0.900]
Cortisol	Placebo	S2	Baseline	0.725 [0.611-0.839]
Cortisol	Propranolol	S2	Baseline	0.776 [0.691-0.859]
Cortisol	Placebo	S2	Post 1	0.746 [0.631-0.861]
Cortisol	Propranolol	S2	Post 1	0.883 [0.801-0.967]
Cortisol	Placebo	S2	Post 2	0.718 [0.604-0.831]
Cortisol	Propranolol	S2	Post 2	0.906 [0.822-0.989]

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Appendix 3. Supplementary Materials for Chapter 6.

Table S1. Questionnaire scores and group comparisons

	High Fear				Low Fear				χ^2 M:F*Group			Mann-Whitney test		
	<i>n</i>	<i>M:F</i>	<i>Mean [SD]</i>	<i>Med</i>	<i>n</i>	<i>M:F</i>	<i>Mean [SD]</i>	<i>Med</i>	χ^2 (<i>df</i> = 1)	<i>p</i>	<i>BF</i> ₁₀	<i>Statistic</i>	<i>p</i>	<i>BF</i> ₊₀
Spiders FSQ	34	01:33	80.32 [18.78]	80.5	20	09:11	19.70 [2.00]	19	14.76	<.001	313.6	680	<.001	39291.37
Heights AQ_An timer	26	14:12	45.15 [11.94]	43.5	13	04:09	9.00 [4.78]	9	1.857	0.173	0.956	338	<.001	32815.14
Heights AQ_Avoid	26	14:12	8.85 [4.97]	8	13	04:09	1.53 [1.13]	2	-	-	-	316	<.001	1297.94
Needles IPS	36	10:26	40.67 [18.78]	40.5	16	08:08	6.38 [4.15]	6.5	2.417	0.12	1.099	576	<.001	18653.22

Med = median; M:F = male:female ratio; BF₁₀ = Bayes factor for alternative hypothesis of genders not being distributed evenly across high vs. low fear groups, *Statistic* = Mann-Whitney U statistic from JASP, BF₊₀ = Bayes factor for high fear group showing higher fear questionnaire scores than low fear group; FSQ = Fear of Spiders Questionnaire; AQ = Acrophobia Questionnaire; IPS = Injection Phobia Scale.

Experiment 1: Fear-relevant items

General items for self in situation:

1. I will be so afraid that I will have a heart attack
2. I will faint/pass out
3. I will be so scared that it just feels absolutely terrible

General items for patients in situation:

How many [specific fear] phobic patients do you predict...

1. ...will have a heart attack, or other heart complication?
2. ...will faint/pass out/black-out?
3. ...will find the experience completely awful (patients will be asked to report their feelings shortly afterwards)?

Spider items for self in situation:

1. The spider will jump on me
2. The spider will bite me
3. The spider will run on me and not come off

Spider items for patients in situation:

1. What number of patients do you predict the spider will jump on?
2. How many spider phobic patients do you predict will be bitten by the spider?
3. For what number of patients do you predict the spider will climb on them?

Heights items for self in situation:

1. I will lose control of my body and fall or even jump from the ladder
2. I will completely freeze and be unable to get down from the ladder without being carried down
3. The ladder will collapse or fall from the building

Heights items for patients in the situation:

1. How many height phobic patients do you predict will lose control and fall or jump from the ladder?
2. How many height patients do you predict will totally freeze, and need to be brought down from the ladder by someone else?
3. For how many patients do you predict the ladder will fall away from the building, or break?

Needles/injections for self in situation:

1. The injection will be intolerably painful
2. For some reason, the needle will miss the target vein and my arm will be damaged or I will bleed a lot
3. I will lose control of my body, causing the needle to stab me in the wrong place

Needles/injections for patients in the situation:

1. How many needle phobic patients do you predict will find the injection to be unbearably painful (patients will be asked to rate the experience shortly afterwards)?
2. For what number of patients do you think the needle will slip past or out of the intended vein, making them bleed a lot, or otherwise injure them?
3. How many patients do you think will lose control and move so much that the needle hits them in the wrong place?

Experiments 2 and 3: Fear-relevant items

1. The spider will jump on me
2. The spider will climb up the brush and onto my hand
3. I will be so afraid that I have a heart attack
4. The spider will run onto my bare feet
5. The spider will bite me

Spider Probability Scale

Spider items

1. You are trying to find some old clothes in the back of a closet. When you pull your hand out you realise a spider has gotten onto your arm.
2. You kill a spider in your living room, but you find that this has only attracted another even bigger spider.
3. You accidentally leave your shoes outside overnight. When you go to pick them up in the morning, a spider comes out of them and bites your hand.
4. You are sitting on the toilet when a big black spider comes under the door and moves towards you.
5. There is a spider on the wall of a corridor in your house and you need to get past. When you try to walk by, the spider jumps at you.
6. You go out camping with friends. In the morning, you wake up and realise a spider has come into the tent with you.

7. You are on holiday in Thailand hiking in a forest. A huge spider falls from a tree and lands on your back.

Analytic approach

For our proof of concept study (Experiment 1), we performed multiple comparisons of High and Low Fear participants' responses to Belief and Bet items. Bayesian Mann-Whitney U tests, performed in *JASP* (JASP team, 2019), were used because the outcome variables typically violated normality assumptions. These analyses were performed 1-tailed and uncorrected, favoring the detection of higher ratings among High vs. Low Fear participants that most people might expect to observe. *JASP* provides Bayes Factors (BFs), which indicate a ratio of evidence in favor of one hypothesis versus another. For example, a BF of 10 for the alternative hypothesis indicates a 10:1 ratio in favor of that alternative hypothesis versus the null, whereas a BF of 0.1 would indicate a 10:1 ratio in favor of the null over the alternative. A BF of or near 1 indicates equivocal evidence for either hypothesis. The BF should ideally be interpreted as a scale of evidence tending to favor one hypothesis over another with increasing certainty, and arbitrary cutoffs for interpretation of the presence or absence of an effect may lead to 'BF hacking'. However, as a general guide to interpretation to aid the unfamiliar reader, it has been suggested at the extremes that a ratio favoring one hypothesis over another of approximately 3:1 or less might be considered 'not worth more than a bare mention', whereas Bayes factors exceeding 100 could be deemed 'decisive' (Jeffreys, 1961; Kass & Raftery, 1995). For all Bayesian Mann-Whitney U tests in *JASP*, analyses were repeated 10 times using 10000 samples each, and the median BF was taken, to correct for slight instability in the BF owing to sampling.

Data from the two behavioral experiments – Experiment 2 (Exp2) and Experiment 3 (Exp3) were combined for analyses. Emotion ratings, Beliefs, and Bets were all analyzed using Bayesian hierarchical regression models in *R* v3.5.3 (R Core Team, 2013), using *RStudio* v1.2.1335 (RStudio Team, 2015), and the *R* package *brms* (Bürkner, 2017), with repeated observations of any variable nested within subjects. Response variables were measured using a scale bounded at 0-100, and were typically not normally distributed, as is common for such response formats (Smithson & Verkuilen, 2006). Such variables can be analyzed using a 'beta regression', where the responses are seen to reflect a beta distribution bound between 0 and 1. Following Smithson and Verkuilen (2006), we thus divided the responses by 100 to get them into a 0-1 range, and transformed the data as follows to avoid zeros or ones, as required by this form of analysis:

$$y^n = [y'(N - 1) + \frac{1}{2}] / N$$

Independent variables entered into the regression were used to predict the mean (or *mu*) and precision (or *phi*) of the beta distribution underpinning the observed data. The mean reflects the general central tendency from 0-1 of the distribution. Precision can be seen to reflect the spread around this mean, with higher numbers indicating a distribution more peaked at the mean, and lower numbers suggesting wider dispersion of responses around the mean. The mean was predicted by Group (Low Fear, High Fear_{Exp2}, and High Fear_{Exp3}), Proximity (Distal vs. Proximal from threat), and their interaction. STAI and Age were also included, to control for possible confounds between conditions (discussed in the next paragraph). Precision was predicted by Group (Low vs. High Fear – comprising all High Fear participants).

BFs provided by *JASP* were used to compare groups on Baseline questionnaire measures in a pooled analysis presented in the main text (Table 1), and separate comparisons of each subgroup (see **Baseline comparisons of High vs. Low Fear groups across Experiments 2 and 3** below), to assess the presence of any clear confounds. The results suggest some evidence of differences in Age, STAI-T and ROQ scores between groups/subgroups. ROQ scores were measured to determine whether levels of risk-taking propensity might affect betting behavior. Given the slightly higher ROQ scores of the High Fear participants, it could be that their bets gravitate towards risk averse decisions (i.e., always betting 50, so as to risk the minimum amount of money and guarantee moderate winnings). In the section **Multiple Regression with ROQ** below, we demonstrate that this does not seem to be the case using a Bayesian multiple regression in *JASP*, with ROQ, Fear Group, and their interaction as predictors under Proximal and Distal conditions. There was no evidence in favor of the idea that we can predict participants' absolute deviations from a bet of 50 using ROQ scores. Hence, we did not include ROQ scores in our analyses. Age and STAI scores were mean-centered and included in the hierarchical regression analyses of Emotion ratings, Beliefs, and Bets.

Brms generates a posterior distribution of estimates for the regression coefficients, which can be used to make estimates of each cell in the design (e.g., “*Low Fear, Proximal*”, or “*High Fear, Proximal, in Experiment 2*”) by adding the appropriate regression coefficients together. One thus generates informative estimates as to the range of plausible parameters underpinning the observed data in each group/condition. In addition, the relative strength of evidence in favor of differences between groups/conditions can be assessed by comparing the posterior distributions for a particular condition with another (e.g., estimates of the difference

in means for Low Fear, Proximal participants, with the High Fear, Proximal participants in Experiment 2). One then receives a posterior distribution of possible differences between the conditions that were compared. As with Bayes Factors, the posterior distribution does not strictly give an arbitrary yes/no criterion for the determination of whether an effect is present, but a probabilistic distribution of possible effects. However, if we are to be confident that two groups/conditions differ, then we would expect the vast bulk of the most probable values of the posterior distribution of the differences between them to exclude 0. This can be assessed by determining not only a point estimate for the posterior distribution (we use the mean), but also a 95% highest density interval (HDI) around it, which reflects the 95% most probable values for the value estimated in the posterior (cf. Kruschke, 2014, p87-89). For comparisons involving Low Fear Distal vs. High Fear Distal, posterior distributions for the two Distal, High Fear groups were averaged together (weighted according to sample size), as these groups are procedurally equivalent and almost exactly replicated one another. All parameters in each hierarchical regression showed good convergence diagnostics and effective sampling (effective sample sizes of at least 2000, and Rhat values of 1.00).

A final question was the degree to which participants' Beliefs, Emotion ratings, and Bets correlated with one another. Responses from High Fear participants were pooled for these analyses. Given non-normal distributions of the correlated variables, we used a non-parametric Bayesian Kendall's *tau* correlation in *JASP*. Pairwise correlations were run to determine associations between Beliefs and Bets, Beliefs and Emotions, and Emotions and Bets, separately for High and Low fear participants, under Distal and Proximal conditions. All analyses used the default priors provided by the analysis package, described in Wagenmakers et al. (2018) and Bürkner (2017) for *JASP* and *brms* respectively.

Multiple Regression with ROQ

Regressions were run to predict absolute deviance from 50 in Bets, predicted from Group, ROQ, and Group*ROQ. The Bayes Factors for each overall model, and for inclusion of different predictors ($BF_{Inclusion}$), all give at most equivocal evidence for including ROQ scores. In each case, the favored model typically just includes Group, and $BF_{Inclusion}$ values for ROQ or its interaction with group never exceed 1.5. These findings indicate no clear reason to include ROQ scores as a possible confound in analyses of bets.

Table S2a. Distal Models

Models	P(M)	P(M data)	BF _M	BF ₁₀	R ²
Group	0.08	0.31	4.82	1.00	0.14
Group * ROQ	0.08	0.14	1.76	0.45	0.12
Group + ROQ + Group*ROQ	0.25	0.14	0.48	0.15	0.15
ROQ + Group*ROQ	0.08	0.13	1.71	0.44	0.15
Group + ROQ	0.08	0.13	1.70	0.44	0.15
Group + Group*ROQ	0.08	0.10	1.21	0.32	0.15
Null model	0.25	0.04	0.11	0.04	0.00
ROQ	0.08	0.02	0.21	0.06	0.06

Table S2b. Proximal Models

Models	P(M)	P(M data)	BF _M	BF ₁₀	R ²
Group	0.08	0.20	2.82	1.00	0.10
Group + ROQ + Group*ROQ	0.25	0.19	0.72	0.32	0.13
ROQ + Group*ROQ	0.08	0.16	2.16	0.80	0.13
Group + ROQ	0.08	0.12	1.55	0.61	0.12
Group*ROQ	0.08	0.12	1.47	0.58	0.09
Null model	0.25	0.09	0.30	0.15	0.00
Group + Group*ROQ	0.08	0.06	0.76	0.32	0.10
ROQ	0.08	0.04	0.48	0.21	0.06

Table S2c. Bayes Factors for inclusion of predictors

Predictor	<i>BF</i> _{Inclusion}	
	Distal	Proximal
Intercept	1.00	1.00
Group	2.07	1.42
ROQ	0.74	1.10
Group * ROQ	1.03	1.18

P(M) = prior probability for model, P(M|data) = probability for model given the data

Baseline comparisons of High vs. Low Fear groups across Experiments 2 and 3.

Table S3a. Baseline comparisons for Low Fear (Exp 2) vs. High Fear (Exp 2).

	Fear	Mean [SD]	Med	Test	Stat	<i>p</i>	<i>BF</i> ₁₀
Age	Low	19.88 [1.57]	20.00	<i>t</i> (47)	0.73	0.467	0.36
	High	19.52 [1.81]	19.00	<i>M-W</i>	35.00	0.299	0.46
FSQ	Low	22.13 [3.06]	22.00	<i>t</i> (47)	-22.47	< .001	1.87e+23
	High	85.80 [13.55]	81.00	<i>M-W</i>	0.00	< .001	80347.94
SPSs	Low	19.33 [14.32]	16.63	<i>t</i> (47)	-4.83	< .001	1140.84
	High	39.66 [15.15]	36.25	<i>M-W</i>	106.00	< .001	204.85
SPS+	Low	12.18 [9.40]	10.60	<i>t</i> (47)	-1.38	0.173	0.62
	High	16.42 [11.82]	14.20	<i>M-W</i>	237.50	0.215	0.58
SPS-	Low	13.21 [14.05]	8.14	<i>t</i> (47)	-0.56	0.577	0.32
	High	15.41 [13.38]	8.14	<i>M-W</i>	263.00	0.465	0.34
ROQ	Low	4.77 [0.80]	4.92	<i>t</i> (47)	3.34	0.002	20.81
	High	4.09 [0.62]	4.17	<i>M-W</i>	450.50	0.003	21.60
PHQ	Low	6.29 [3.56]	5.00	<i>t</i> (47)	0.31	0.759	0.30
	High	6.00 [3.06]	6.00	<i>M-W</i>	310.00	0.848	0.30
STAI-T	Low	39.58 [11.59]	38.00	<i>t</i> (47)	-0.99	0.325	0.43
	High	42.56 [9.30]	40.00	<i>M-W</i>	235.00	0.197	0.46

Table S3b. Baseline comparisons for Low Fear (Exp 2) vs. High Fear, Distal (Exp 3).

	Fear	Mean [SD]	Med	Test	Stat	<i>p</i>	<i>BF</i> ₁₀
Age	S1 Low	19.88 [1.57]	20.00	<i>t</i> (45)	-4.10	< .001	138.06
	S2 Dist	22.26 [2.36]	21.00	<i>M-W</i>	98.00	< .001	214.38
FSQ	S1 Low	22.13 [3.06]	22.00	<i>t</i> (45)	-28.75	< .001	9.474e+26
	S2 Dist	96.35 [12.27]	96.00	<i>M-W</i>	0.00	< .001	17723.71
SPSs	S1 Low	19.33 [14.32]	16.63	<i>t</i> (44)	-5.43	< .001	5971.42
	S2 Dist	48.35 [21.54]	49.38	<i>M-W</i>	70.50	< .001	612.10
SPS+	S1 Low	12.18 [9.40]	10.60	<i>t</i> (44)	-0.19	0.847	0.30
	S2 Dist	12.71 [9.10]	10.90	<i>M-W</i>	254.00	0.834	0.30
SPS-	S1 Low	13.21 [14.05]	8.14	<i>t</i> (44)	-1.36	0.182	0.61
	S2 Dist	19.2 [15.97]	14.43	<i>M-W</i>	190.00	0.106	0.79
ROQ	S1 Low	4.77 [0.80]	4.92	<i>t</i> (45)	2.25	0.029	2.15
	S2 Dist	4.29 [0.68]	4.08	<i>M-W</i>	380.00	0.027	1.70
PHQ	S1 Low	6.29 [3.56]	5.00	<i>t</i> (45)	1.71	0.095	0.93
	S2 Dist	4.72 [2.68]	4.00	<i>M-W</i>	350.50	0.113	0.92
STAI-T	S1 Low	39.58 [11.59]	38.00	<i>t</i> (45)	0.87	0.391	0.39
	S2 Dist	37.04 [8.13]	38.00	<i>M-W</i>	297.00	0.662	0.36

Table S3c. Baseline comparisons for Low Fear (Exp 2) vs. High Fear, Proximal (Exp 3).

	Fear	Mean [SD]	Med	Test	Stat	<i>p</i>	<i>BF</i> ₁₀
Age	S1 Low	19.88 [1.57]	20.00	<i>t</i> (47)	0.73	0.144	0.70
	S2 Prox	20.64 [2.00]	20.00	<i>M-W</i>	35.00	0.131	0.80
FSQ	S1 Low	22.13 [3.06]	22.00	<i>t</i> (47)	-22.47	< .001	2.070e +30
	S2 Prox	93.28 [10.21]	95.00	<i>M-W</i>	0.00	< .001	40890.39
SPSs	S1 Low	19.33 [14.32]	16.63	<i>t</i> (44)	-4.83	< .001	2270.74
	S2 Prox	44.53 [19.05]	45.00	<i>M-W</i>	106.00	< .001	381.17
SPS+	S1 Low	12.18 [9.40]	10.60	<i>t</i> (44)	-1.38	0.584	0.33
	S2 Prox	14.08 [13.66]	9.20	<i>M-W</i>	237.50	0.982	0.30
SPS-	S1 Low	13.21 [14.05]	8.14	<i>t</i> (44)	-0.56	0.39	0.40
	S2 Prox	16.4 [10.42]	13.50	<i>M-W</i>	263.00	0.088	0.64
ROQ	S1 Low	4.77 [0.80]	4.92	<i>t</i> (47)	3.34	0.182	0.60
	S2 Prox	4.47 [0.75]	4.50	<i>M-W</i>	450.50	0.17	0.54
PHQ	S1 Low	6.29 [3.56]	5.00	<i>t</i> (47)	0.31	0.765	0.30
	S2 Prox	6 [3.23]	6.00	<i>M-W</i>	310.00	0.833	0.31
STAI-T	S1 Low	39.58 [11.59]	38.00	<i>t</i> (47)	-0.99	0.4	0.38
	S2 Prox	42.2 [9.93]	42.00	<i>M-W</i>	235.00	0.28	0.41

Table S3d. Baseline comparisons for High Fear (Exp 2) vs. High Fear, Distal (Exp 3).

	Fear	Mean [SD]	Med	Test	Stat	<i>p</i>	<i>BF</i> ₁₀
Age	S1 High	19.52 [1.81]	19.00	<i>t</i> (46)	-4.54	< .001	484.45
	S2 Dist	22.26 [2.36]	21.00	<i>M-W</i>	97.50	< .001	288.09
FSQ	S1 High	85.8 [13.55]	81.00	<i>t</i> (46)	-2.82	0.007	6.37
	S2 Dist	96.35 [12.27]	96.00	<i>M-W</i>	154.00	0.006	9.77
SPSs	S1 High	39.66 [15.15]	36.25	<i>t</i> (45)	-1.62	0.113	0.83
	S2 Dist	48.35 [21.54]	49.38	<i>M-W</i>	190.50	0.073	0.94
SPS+	S1 High	16.42 [11.82]	14.20	<i>t</i> (45)	1.19	0.24	0.52
	S2 Dist	12.71 [9.10]	10.90	<i>M-W</i>	322.50	0.316	0.43
SPS-	S1 High	15.41 [13.38]	8.14	<i>t</i> (45)	-0.89	0.38	0.40
	S2 Dist	19.2 [15.97]	14.43	<i>M-W</i>	232.50	0.37	0.40
ROQ	S1 High	4.09 [0.62]	4.17	<i>t</i> (46)	-1.05	0.301	0.45
	S2 Dist	4.29 [0.68]	4.08	<i>M-W</i>	265.50	0.657	0.39
PHQ	S1 High	6 [3.06]	6.00	<i>t</i> (46)	1.54	0.13	0.75
	S2 Dist	4.72 [2.68]	4.00	<i>M-W</i>	357.00	0.152	0.78
STAI-T	S1 High	42.56 [9.30]	40.00	<i>t</i> (46)	2.18	0.034	1.90
	S2 Dist	37.04 [8.13]	38.00	<i>M-W</i>	387.00	0.041	1.82

Table S3e. Baseline comparisons for High Fear (Exp 2) vs. High Fear, Proximal (Exp 3).

	Fear	Mean [SD]	Med	Test	Stat	p	BF ₁₀
Age	S1 High	19.52 [1.81]	19.00	<i>t</i> (48)	-2.08	0.043	1.61
	S2 Prox	20.64 [2.00]	20.00	<i>M-W</i>	198.50	0.024	3.34
FSQ	S1 High	85.8 [13.55]	81.00	<i>t</i> (48)	-2.20	0.032	1.98
	S2 Prox	93.28 [10.21]	95.00	<i>M-W</i>	192.50	0.02	2.48
SPSs	S1 High	39.66 [15.15]	36.25	<i>t</i> (45)	-0.98	0.334	0.43
	S2 Prox	44.53 [19.05]	45.00	<i>M-W</i>	216.50	0.216	0.44
SPS+	S1 High	16.42 [11.82]	14.20	<i>t</i> (45)	0.63	0.532	0.34
	S2 Prox	14.08 [13.66]	9.20	<i>M-W</i>	325.00	0.291	0.42
SPS-	S1 High	15.41 [13.38]	8.14	<i>t</i> (45)	-0.28	0.78	0.30
	S2 Prox	16.4 [10.42]	13.50	<i>M-W</i>	234.50	0.394	0.37
ROQ	S1 High	4.09 [0.62]	4.17	<i>t</i> (48)	-1.96	0.055	1.33
	S2 Prox	4.47 [0.75]	4.50	<i>M-W</i>	197.00	0.025	1.92
PHQ	S1 High	6 [3.06]	6.00	<i>t</i> (48)	0.00	1	0.28
	S2 Prox	6 [3.23]	6.00	<i>M-W</i>	315.50	0.961	0.29
STAI-T	S1 High	42.56 [9.30]	40.00	<i>t</i> (48)	0.13	0.895	0.29
	S2 Prox	42.2 [9.93]	42.00	<i>M-W</i>	328.00	0.771	0.29

Table S3f. Baseline comparisons for High Fear, Distal (Exp 3) vs. High Fear, Proximal (Exp 3).

	Fear	Mean [SD]	Med	Test	Stat	p	BF ₁₀
Age	S2 Dist	22.26 [2.36]	21.00	<i>t</i> (46)	2.58	0.013	3.90
	S2 Prox	20.64 [2.00]	20.00	<i>M-W</i>	413.00	0.009	6.82
FSQ	S1 Dist	96.35 [12.27]	96.00	<i>t</i> (46)	0.95	0.35	0.41
	S2 Prox	93.28 [10.21]	95.00	<i>M-W</i>	317.50	0.542	0.38
SPSs	S2 Dist	48.35 [21.54]	49.38	<i>t</i> (42)	0.62	0.537	0.35
	S2 Prox	44.53 [19.05]	45.00	<i>M-W</i>	257.00	0.734	0.33
SPS+	S1 Dist	12.71 [9.10]	10.90	<i>t</i> (42)	-0.39	0.699	0.32
	S2 Prox	14.08 [13.66]	9.20	<i>M-W</i>	248.00	0.897	0.30
SPS-	S2 Dist	19.2 [15.97]	14.43	<i>t</i> (42)	0.69	0.494	0.36
	S2 Prox	16.4 [10.42]	13.50	<i>M-W</i>	251.00	0.842	0.32
ROQ	S1 Dist	4.29 [0.68]	4.08	<i>t</i> (46)	-0.90	0.371	0.40
	S2 Prox	4.47 [0.75]	4.50	<i>M-W</i>	220.00	0.166	0.50
PHQ	S2 Dist	4.72 [2.68]	4.00	<i>t</i> (46)	-1.49	0.143	0.71
	S2 Prox	6 [3.23]	6.00	<i>M-W</i>	221.00	0.17	0.64
STAI-T	S1 Dist	37.04 [8.13]	38.00	<i>t</i> (46)	-1.96	0.056	1.33
	S2 Prox	42.2 [9.93]	42.00	<i>M-W</i>	200.00	0.072	1.38

SPSs = SPS spider items; SPS+ = SPS positive items; SPS- = SPS negative items; Med = median; BF₁₀ = Bayes factor for alternative hypothesis of a difference between groups; CI = confidence interval; Stat = statistic for respective test, SD = standard deviation, M-W = Mann-Whitney U test, t = independent groups t-test

Table S4a. Full regression table for beta-regression of emotions

Family: beta

Links: mu = logit; phi = log

emotion ~ 1 + Proximity + Group + Proximity:Group + STAI + Age + (1 | PPN)

	Estimate	Est.Error	l-95% CCI	u-95% CCI	Eff.Sample	Rhat
sd(Intercept)	0.61	0.10	0.41	0.82	2636.00	1.00
Population-Level Effects						
	Estimate	Est.Error	l-95% CCI	u-95% CCI	Eff.Sample	Rhat
Intercept	-1.96	0.23	-2.43	-1.51	4840.00	1.00
phi Intercept	2.18	0.27	1.62	2.70	6123.00	1.00
Proximity = Proximal	0.67	0.24	0.21	1.13	6015.00	1.00
Group = High Fear, Experiment 2	2.81	0.29	2.25	3.39	4828.00	1.00
Group = High Fear, Experiment 3	2.86	0.31	2.27	3.48	4808.00	1.00
STAI	0.00	0.01	-0.01	0.02	6571.00	1.00
Age	0.02	0.05	-0.07	0.11	6613.00	1.00
Proximity = Proximal*Group = High Fear, Experiment 2	0.22	0.29	-0.36	0.80	6336.00	1.00
Proximity = Proximal*Group = High Fear, Experiment 3	0.31	0.36	-0.40	1.00	5448.00	1.00
phi High Fear	0.54	0.33	-0.07	1.20	7725.00	1.00

Table S4b. Full regression table for beta-regression of beliefs
belief ~ 1 + Proximity + Group + Proximity:Group + STAI + Age + (1 | PPN)

	Estimate	Est.Error	l-95% CCI	u-95% CCI	Eff.Sample	Rhat
sd(Intercept)	0.83	0.11	0.62	1.06	3580.00	1.00
Population-Level Effects						
	Estimate	Est.Error	l-95% CCI	u-95% CCI	Eff.Sample	Rhat
Intercept	-0.39	0.22	-0.81	0.04	4686.00	1.00
phi Intercept	2.39	0.31	1.76	2.96	5185.00	1.00
Proximity = Proximal	-0.13	0.18	-0.49	0.23	9679.00	1.00
Group = High Fear, Experiment 2	1.86	0.34	1.21	2.53	4894.00	1.00
Group = High Fear, Experiment 3	2.07	0.37	1.34	2.81	4649.00	1.00
STAI	0.01	0.01	-0.02	0.03	4983.00	1.00
Age	-0.06	0.06	-0.18	0.06	5035.00	1.00
Proximity = Proximal*Group = High Fear, Experiment 2	-0.40	0.30	-0.98	0.19	9215.00	1.00
Proximity = Proximal*Group = High Fear, Experiment 3	0.48	0.42	-0.34	1.31	6401.00	1.00
phi High Fear	-0.35	0.35	-1.02	0.35	7276.00	1.00

Table S4c. Full regression table for beta-regression of beliefs

$$bet \sim 1 + Proximity + Group + Proximity:Group + STAI + Age + (1 | PPN)$$

	Estimate	Est.Error	l-95% CCI	u-95% CCI	Eff.Sample	Rhat
sd(Intercept)	0.87	0.13	0.61	1.12	2012.00	1.00
Population-Level Effects						
	Estimate	Est.Error	l-95% CCI	u-95% CCI	Eff.Sample	Rhat
Intercept	-1.05	0.29	-1.64	-0.48	7913.00	1.00
phi Intercept	1.15	0.23	0.69	1.60	9979.00	1.00
Proximity = Proximal	0.11	0.30	-0.49	0.70	10246.00	1.00
Group = High Fear, Experiment 2	0.72	0.37	0.00	1.46	7248.00	1.00
Group = High Fear, Experiment 3	0.76	0.40	-0.01	1.55	6932.00	1.00
STAI	0.00	0.01	-0.03	0.02	8074.00	1.00
Age	-0.08	0.06	-0.19	0.04	8425.00	1.00
Proximity = Proximal*Group = High Fear, Experiment 2	-0.12	0.35	-0.81	0.56	10968.00	1.00
Proximity = Proximal*Group = High Fear, Experiment 3	-0.44	0.45	-1.32	0.44	7752.00	1.00
phi High Fear	1.26	0.35	0.57	1.95	3710.00	1.00

CCI = 'central credible interval': 95% of the posterior distribution between the 2.5 and 97.5 percentiles; STAI = Trait Anxiety Index

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White Papers

- Harris, J. L., O'Brien, K., **Elsey, J.W.B.**, Gross, R., & LoDolce, M. (2014). *Rudd Center Report on Targeted Marketing to Communities of Color*. Rudd Center white paper.
- Harris, J. L., Gross, R., & LoDolce, M. **Elsey, J.W.B.**, *et al.* (2014). *Sugary Drink FACTS: Food Advertising to Children and Teens*. Rudd Center white paper.

Authorship Contributions

Chapter 2.

Elsey, J.W.B., Bekker, T.A., De Bree, A.M., & Kindt, M. (2019 *in press*). Encoding or consolidation? The effects of pre-and post-learning propranolol on the impact of an emotional scene. *Journal of Behavior Therapy and Experimental Psychiatry*.

JE and MK designed the study. TB and AdB collected the data. JE analyzed the results and wrote the manuscript. MK supervised and provided feedback on the writing.

Chapter 3.

Elsey, J.W.B., & Kindt, M. (2016). Manipulating human memory through reconsolidation: Ethical implications of a new therapeutic approach. *AJOB Neuroscience*, 7(4), 225-236.

JE wrote the manuscript. MK supervised and provided feedback on the writing.

Chapter 4.

Elsey, J.W.B., Filmer, A.I., Galvin, H.R., Kurath, J.D., Vossoughi, L., Thomander, L.S., Zavodnik, M., & Kindt, M. (*under review in Translational Psychiatry*). Reconsolidation-based treatment for fear of public speaking: A systematic pilot study using propranolol.

JE and MK planned the study, and JE, MK, AF, and LV designed the protocol. AF, HG, JK, LV, LT, and MZ ran participants. JE analyzed the data and wrote the manuscript. MK supervised and provided feedback on the writing.

Chapter 5.

Elsey, J.W.B., Van Ast, V. A., & Kindt, M. (2018). Human memory reconsolidation: A guiding framework and critical review of the evidence. *Psychological Bulletin*, 144(8), 797-848.

The concept was discussed by JE, VvA, and MK. JE wrote the manuscript and screened the studies. MK and VvA supervised the process and provided feedback on the writing. MK and VvA confirmed/checked included studies and their assessment.

Chapter 6.

This chapter is in preparation for publication. The idea developed out of discussions between JE and MK about patients' fear-related beliefs. Marieke Effting helped formalize the study and supervise students for Experiments 1 and 2 with JE. Two student groups helped generate Dutch versions of the protocols and tested participants. For Experiments 1 and 2, these were Donna Knoop, Nella Schrijver, Lena van den Nieuwenhof, and Suraya Gangadien. For Experiment 3, these were Elias Geiser, Marta Jakschik, Esperanza Visbeek, and Casper Enkelaar.

JE analyzed the data and wrote the manuscript. MK has additionally provided feedback on the manuscript.

Summary

It is strange to think that someone may be more afraid of the act of entering an MRI scanner than of what the results of the scan might tell them, but that was exactly how Joanna felt. As she explained to us, she was required to go every two years for an MRI scan, which would tell her whether or not an aggressive form of tumor she had previously fought off had returned. Strikingly, every other year, she underwent an alternative form of scan which did not involve entering the small space of the MRI machine. This was no problem at all. Yet, each time before she was required to undergo her MRI scan, she was sick with dread. Two years previously, after multiple failed attempts to undergo the required check, doctors had resorted to completely sedating her. That didn't help the anxious anticipation of her upcoming scan this time around. Joanna reached out to us, and asked if we might be able to help her tackle her fear.

We constructed a treatment session in which Joanna was required to enter a mock scanner for an undisclosed but short length of time. The experience was so frightening for her that at one point she almost threw up. Upon exiting the scanner after what had no doubt seemed like an eternity (but was in fact approximately three minutes), Joanna was visibly sweating, and her glasses had misted over. Encouraging her that she had done a great job facing her fear and simultaneously wondering whether I had subjected someone to three minutes of torture, I led Joanna to another room, and gave her a small tablet: propranolol, 40mg. Ninety minutes later, I checked her blood pressure and heart rate, and sent her home to rest.

The following week, Joanna returned for a test session. She didn't know whether the treatment had been successful, but felt less tense and somewhat curious about how she might find the experience this time around. I again led her to the mock scanner, and watched with some trepidation as she disappeared into the small, cylindrical bore of the machine. Two minutes in and she hadn't said a word, so I asked through the scanner intercom:

“So...how's it going in there?”

“Well, I suppose it's a bit like lying down in a tube, isn't it?” came the muffled reply.

Indeed it is, to someone who is not claustrophobic. Joanna remained in the machine for a further 10 minutes while we tested some different scanner noises, and performed some other checks of her anxiety responses. It seemed that we had dramatically reduced Joanna's fear. This possibility was confirmed when, at her real scan several weeks later, she reportedly was so relaxed that she fell asleep in the machine.

Apparently then, tackling intense fears and anxiety disorders might be as simple as scaring someone half to death, then having them quickly pop a pill. If treatment is so easy,

then why do millions of people across the globe suffer intensely from all manner of fears and traumatic experiences? Furthermore, if we have the power to manipulate people's 'emotional memories' in this way, is it something we should champion, or worry about? Finally, how do we know what processes underpin such effects, and how can they be understood in relation to existing treatments? These were the questions that we set out to answer with my PhD work (see Chapter 1). For those who (perhaps wisely) wish to skip the preceding 300 pages, the answers are as follows:

1. These treatments are not so simple. There are many intricacies to translating novel insights from experiments on memory modification into legitimate clinical interventions (see Chapters 2, 4, and 7)
2. If we can harness these approaches, then we should champion them, while carefully considering the boundaries between proper use, misuse, and abuse (see Chapter 3).
3. There are numerous ways of testing the effects observed in experiments and clinical interventions that can help us to elucidate the most likely candidate explanations for the observed effects, but there are currently relatively few studies that perform such tests (see Chapter 5).
4. I propose that many novel developments in the treatment of trauma-related and anxiety disorders – whether pharmacological, behavioral, or cognitive – may broadly be understood within a framework emphasizing competition between adaptive and maladaptive representations ('memories') of the feared stimuli. In treatment, we seek to enhance existing and generate new adaptive representations. Simultaneously, we hope to reduce the retrievability and motivational power of maladaptive ones (see Chapters 6 and 7).

Each of the Chapters in this dissertation deals in some way with these issues. In Chapter 1, I briefly outline how we have come to understand many mental health problems as disorders of emotional memory. Accordingly, we hope to leverage cutting-edge advances in our neurobiological understanding of memory formation and change as a means of tackling the emotional memories that underpin maladaptive behavior. The primary approach taken in the *Amsterdam Emotional Memory Lab* is that of pharmacological manipulation, specifically using propranolol.

In Chapter 2, I report an experiment in healthy volunteers that was intended to model the potential prophylactic use of propranolol in the aftermath of a traumatic experience.

Participants watched a disturbing set of movie clips and received either propranolol or placebo. Propranolol was intended to reduce the impact of stress-related hormones/neurotransmitters resulting from the experience, and thereby prevent them from generating a strong, negative memory trace. We found that propranolol in fact showed little efficacy in reducing intrusive memories over the following week, but it should also be stressed that an overall low emotional impact of the movie scenes may have prevented us from observing such effects.

In Chapter 3, I make the case that aiming to interfere with already existing maladaptive memories, rather than preventing their initial formation, may not only open the scope of such novel interventions up to a wider range of mental health problems (such as phobias, or treating people who already have post-traumatic stress disorder), but also sidesteps a number of ethical concerns of a prophylactic approach. While considering several possibilities for the misuse and abuse of memory-modifying techniques, I argue that concerns in the media or among bioethicists have been largely overblown and divorced from reality.

In Chapter 4, I present the results of an attempt to perform just such a ‘memory-modifying’ treatment in volunteers with a subclinical but nevertheless severe fear of public speaking. Participants were required to undergo a stress-inducing public speaking task, after which they received 40mg propranolol. While we have observed striking effects of similar interventions employed to tackle a whole host of fears in individual cases, we were unable to produce such an effect under these controlled conditions. Participants did on average experience a decline in their fear of public speaking, but this appeared to be the result of non-specific placebo or exposure effects. However, participants did not typically experience the very dramatic changes that we have seen in some patients (or in a previous controlled trial for fear of spiders), suggesting that simple placebo effects are unlikely to fully explain these other observations. Possible reasons for these null findings are discussed in the chapter as well as in Chapter 7.

Chapter 5 focuses on the concept of ‘reconsolidation’ – the idea that memories can, under certain circumstances, become unstable after reactivation, and must be actively restabilized in order to persist. Drawing upon fundamental research in animal models, we formalize and put to use several criteria for determining whether reconsolidation represents a good explanation for effects observed in a large number of experimental and clinical studies in humans. We find that while there is considerable (and arguably justified) excitement around the idea of reconsolidation and its clinical potential, relatively few researchers have performed critical tests that can help determine whether reconsolidation is a plausible

candidate for effects they observe. Nevertheless, we argue that aiming at the clinical translation of reconsolidation-based research can be a goal that unites researchers.

The final empirical study presented in Chapter 6 developed out of observations of striking effects in patients undergoing treatments in our lab. Mechanistically, dramatic changes in fear such as that of Joanna described above are hard to square with a number of influential models of anxiety disorders, which argue that irrational beliefs about threats posed by feared stimuli underpin a patient's excessive fear. Yet, many patients recognize there is no justification for their fear, and it did not seem that we needed to change Joanna's beliefs about the danger of being enclosed in a small space in order to transform her fear. One possibility is that patients hold multiple representations of their feared stimuli – some of which may be more maladaptive, emotionally laden, and irrational, and others which reflect their grasp on reality but which may have little motivational force under normal circumstances. We aimed to demonstrate that fearful individuals might have these multiple representations by having them engage in a task where they had to firstly indicate what negative outcomes they thought might happen upon exposure to their feared stimulus – potentially eliciting a rapid or 'emotional' assessment of the situation – but then additionally required them to place bets on whether those outcomes would actually happen – thereby placing consequences on their expressed beliefs and possibly causing them to draw upon a more realistic representation of threat. We indeed found that fearful individuals showed much higher initial beliefs about unpleasant things happening when faced with their fear than non-fearful people. However, they appeared far less willing to actually endorse these events really happening when required to place bets on them. Hence, it does seem that people's fear-related beliefs are in some way multidimensional. A key question is how we can best leverage this understanding to enable people to engage more with their adaptive representations.

This issue, as well as the unfortunate null findings of Chapters 2 and 4, are taken up in the final discussion chapter. I emphasize how novel insights into the malleability of memory may be understood as operating through similar overarching principles as existing therapies: affecting the retrievability and motivational power of adaptive and maladaptive representations stored in the brain. While we remain far from the idealized vision of a novel intervention in which intense fears can be silenced by a simple procedure and swallowing a magic pill, I hope that the modest insights gained from my research – and the further work I now intend to carry out – can get us incrementally closer to helping the many people who remain debilitated by their fears.

Samenvatting

Het idee dat iemand banger is om in een MRI-scanner te liggen dan om te horen wat de uitkomst van zo'n scan kan zijn, is best gek, maar toch was dat precies het gevoel dat Joanna had. Ze vertelde ons dat ze om het jaar werd opgeroepen voor een MRI-scan, om te horen of een agressieve soort tumor die eerder succesvol behandeld was, wel of niet was teruggekeerd. In de tussenliggende jaren onderging ze steeds een alternatief soort scan, waarbij ze níét in zo'n krappe ruimte als een MRI-scanner hoefde te gaan liggen. Dit doorstond ze steeds zonder problemen. Maar elke keer dat ze werd opgeroepen voor de MRI-scan stond ze doodsangsten uit. Twee jaar daarvoor, na een aantal mislukte pogingen om het vereiste onderzoek te ondergaan, besloten de artsen haar volledig te verdoven. Dat nam overigens haar angst voorafgaand aan de scan geenszins weg. Joanna nam contact met ons op met de vraag of wij haar van haar angst af konden helpen.

We ontwierpen een behandeling voor haar specifieke klacht, waarbij Joanna gedurende een niet nader gedefinieerde, maar korte tijdspanne werd gevraagd in een nepscanner te gaan liggen. Deze ervaring was zo beangstigend voor haar dat ze op een gegeven moment bijna moest overgeven. Toen ze uit de scanner kwam na wat ongetwijfeld een eeuwigheid moet hebben geleken, maar wat in werkelijkheid ongeveer drie minuten had geduurd, was Joanna zichtbaar bezweet en was haar bril beslagen. Ik prees haar hoe geweldig het was dat ze haar angst onder ogen had durven zien en vroeg me tegelijkertijd af of ik niet iemand had onderworpen aan drie minuten marteling. Vervolgens bracht ik Joanna naar een andere kamer en gaf haar een pil, 40 mg propranolol. Anderhalf uur later controleerde ik haar bloeddruk en hartslag, en daarna mocht ze naar huis om uit te rusten.

In de daaropvolgende week kwam Joanna terug voor een testsessie. Ze wist niet of de behandeling was geslaagd, maar voelde zich niet meer zo gespannen en was nieuwsgierig hoe ze het deze keer zou ervaren. Ik nam haar weer mee naar de nepscanner en keek met enige spanning toe hoe zij verdween in het krappe, ronde gat van het apparaat. Toen ze na twee minuten nog geen woord had gezegd, vroeg ik via de intercom:

‘En... hoe gaat het daarbinnen?’

‘Nou ja, het voelt een beetje alsof je in een buis ligt, hè?’ klonk het gedempte antwoord.

Zo is het inderdaad voor iemand die niet claustrofobisch is. Joanna bleef vervolgens nog tien minuten in het apparaat liggen, terwijl wij op verschillende

manieren angst bij haar probeerden op te roepen, bijvoorbeeld door scanner geluiden te laten horen. Zo te zien was Joanna's angst aanzienlijk afgenomen. Dit werd bevestigd toen ze enkele weken daarna een echte scan onderging en naar eigen zeggen zo ontspannen was geweest dat ze in het apparaat in slaap was gevallen.

Het lijkt er dus op dat het aanpakken van fobieën en angststoornissen heel simpel is: eerst iemand de stuipen op het lijf jagen en vervolgens snel een pil laten innemen. Als het zo gemakkelijk is, waarom lijden dan miljoenen mensen overal ter wereld aan allerlei vormen van angst en de gevolgen van traumatische ervaringen? Bovendien, als we het 'emotionele geheugen' van mensen op deze manier kunnen manipuleren, is dat dan iets wat we moeten omarmen of juist iets waar we ons zorgen over moeten maken? En welke processen liggen dan aan zulke effecten ten grondslag en hoe moeten we die zien in het licht van bestaande behandelingen? Dit waren de vragen waarop we door middel van mijn promotieonderzoek een antwoord probeerden te vinden (zie hoofdstuk 1). Voor degenen die (misschien niet eens zo heel onverstandig) de voorgaande 300 pagina's liever overslaan, de antwoorden luiden als volgt:

1. Dit soort behandelingen zijn niet bepaald eenvoudig. Nieuwe inzichten die voortkomen uit experimenten op het gebied van geheugenverandering kunnen niet zomaar vertaald worden naar werkzame klinische interventies (zie de hoofdstukken 2, 4 en 7).
2. Als we deze methode kunnen toepassen moeten we dat zeker doen, maar we moeten wel zorgvuldig nagaan wat de grenzen tussen juist gebruik, verkeerd gebruik en misbruik zijn (hoofdstuk 3).
3. Onderzoek naar de effecten die worden waargenomen bij experimenten en klinische interventies zou ons kunnen helpen een beter zicht krijgen op de meest waarschijnlijke verklaringen voor deze observaties. Dit kan op talloze manieren, maar er zijn nog altijd relatief weinig studies die dit hebben gedaan (hoofdstuk 5).
4. Ik zou willen stellen dat veel nieuwe ontwikkelingen op het gebied van de behandeling van traumagerelateerde en angststoornissen – ongeacht of de behandeling farmacologisch, gedragsmatig of cognitief is – kunnen worden verklaard in termen van een competitie tussen functionele en disfunctionele geheugenrepresentaties ('herinneringen') van de gevreesde stimuli. Bij een behandeling proberen we bestaande functionele geheugenrepresentaties te

versterken en nieuwe te genereren. Tegelijkertijd hopen we dat de disfunctionele representaties uit het geheugen worden verzwakt en daarmee minder makkelijk terugkeren (hoofdstukken 6 en 7).

In elk hoofdstuk van dit proefschrift komen deze kwesties op tot op zekere hoogte aan de orde. In hoofdstuk 1 zet ik kort uiteen hoe we veel psychische problemen zijn gaan beschouwen als stoornissen van het emotionele geheugen. In dat licht bezien hopen we de allernieuwste ontwikkelingen op het gebied van onze neurobiologische kennis van de vorming en het veranderen van het geheugen optimaal te kunnen benutten en daarmee disfunctioneel gedrag aan te pakken. De belangrijkste methode die wordt toegepast in het *Amsterdam Emotional Memory Lab* is farmacologische manipulatie, in het bijzonder het gebruik van propranolol.

In hoofdstuk 2 doe ik verslag van een experiment dat werd uitgevoerd bij gezonde vrijwilligers, om het profylactische gebruik van propranolol in de nasleep van een traumatische ervaring te testen. Proefpersonen bekeken een aantal angstaanjagende filmfragmenten en kregen propranolol of een placebopil. Er werd verondersteld dat propranolol de impact van stressgerelateerde hormonen/neurotransmitters zou verminderen en op die manier zou voorkomen dat zij een sterk, negatief geheugenspoor achterlieten. We ontdekten echter dat propranolol gedurende de daaropvolgende week nauwelijks effect had op het aantal intrusieve herinneringen, al kunnen we niet uitsluiten dat een geringe emotionele impact van de filmfragmenten er misschien voor heeft gezorgd dat wij zulke effecten niet konden waarnemen.

In hoofdstuk 3 beargumenteer ik waarom we veel beter kunnen ingrijpen op reeds bestaande disfunctionele geheugenrepresentaties in plaats van te voorkomen dat ze überhaupt ontstaan. Niet alleen hebben interventies die op bestaande geheugensporen ingrijpen de potentie om toegepast te worden bij een breed scala aan psychische problemen (zoals fobieën of het behandelen van mensen die al een posttraumatische stressstoornis hebben), maar tevens omzeilen we dan een aantal ethische vragen die een profylactische benadering oproepen. Hoewel ik zeker oog heb voor de manieren waarop geheugenveranderende technieken verkeerd gebruikt of misbruikt zouden kunnen worden, ben ik van mening dat de zorgen hierover in de media of onder bio-ethici sterk overtrokken zijn en niets te maken hebben met de werkelijkheid.

In hoofdstuk 4 beschrijf ik resultaten van een poging om zo'n 'geheugenveranderende' behandeling uit te voeren bij vrijwilligers met een subklinische, maar niettemin ernstige angst voor spreken in het openbaar. Proefpersonen werd gevraagd een betoog voor publiek te houden, wat stress bij hen opleverde, waarna zij 40 mg propranolol kregen. Hoewel een vergelijkbare behandeling bij allerlei mensen met verschillende angsten succesvol was, lukte het niet om zo'n effect te vinden onder deze gecontroleerde omstandigheden. Over het algemeen ervoeren de proefpersonen een vermindering van hun angst voor spreken in het openbaar, maar dit leek eerder het resultaat te zijn van een niet-specifiek placebo-effect of louter een effect van de blootstelling. Proefpersonen lieten echter niet de spectaculaire veranderingen zien die we eerder zagen bij sommige andere patiënten (of bij een eerder gecontroleerd onderzoek onder mensen met een spinfobie). Het is derhalve onwaarschijnlijk dat een simpel placebo-effect deze andere waarnemingen volledig verklaart. Mogelijke redenen voor het uitblijven van een behandel-effect worden zowel in dit hoofdstuk als in hoofdstuk 7 besproken.

In hoofdstuk 5 ga ik wat dieper in op het concept 'reconsolidatie': het idee dat herinneringen, wanneer ze worden opgehaald – en alleen onder bepaalde omstandigheden – tijdelijk openstaan voor verandering en actief opnieuw moeten worden gestabiliseerd teneinde in stand te blijven. Geïnspireerd door dieronderzoek hebben we verscheidene criteria opgesteld waarmee we kunnen vaststellen of reconsolidatie een goede verklaring vormt voor effecten die zijn waargenomen bij een groot aantal experimentele en klinische studies bij mensen. We constateren dat er weliswaar een aanzienlijk (en beslist gerechtvaardigd) enthousiasme bestaat rond het idee van reconsolidatie en de klinische mogelijkheden ervan, maar dat vooralsnog relatief weinig onderzoekers de lakmoestest voor reconsolidatie hebben uitgevoerd. Niettemin zijn we van mening dat het streven naar een klinische vertaling van op reconsolidatie gebaseerd onderzoek ertoe kan leiden dat onderzoekers beter gaan samenwerken.

De laatste empirische studie, die wordt beschreven in hoofdstuk 6, is gebaseerd op opvallende, succesvolle behandelingen van patiënten uit ons lab. Technisch gezien zijn dergelijke plotselinge veranderingen van angst, zoals bij Joanna, niet eenvoudig te verklaren met de gangbare modellen van angststoornissen. Deze modellen stellen immers dat irrationele overtuigingen met betrekking tot vermeend gevaar, opgewekt door gevreesde stimuli, ten grondslag liggen aan de

excessieve angst van een patiënt. Maar toch erkennen veel patiënten dat hun angst irrationeel is. Het leek dan ook niet nodig te zijn om Joanna's gedachten over het gevaar om in een nauwe ruimte opgesloten te worden te veranderen om haar angst effectief te kunnen behandelen. Het zou kunnen dat patiënten uiteenlopende geheugenrepresentaties hebben van de door hen gevreesde stimuli: sommige zijn wellicht vooral disfunctioneel, emotioneel geladen en irrationeel, terwijl andere weliswaar een reële weerspiegeling zijn van de werkelijkheid, maar onder normale omstandigheden weinig uithalen. We hebben geprobeerd deze uiteenlopende geheugenrepresentaties bij angstige personen aan te tonen, door hen te vragen wat voor negatieve gevolgen ze verwachtten als ze werden blootgesteld aan de door hen gevreesde stimulus, hetgeen mogelijk een snelle of 'emotionele' inschatting van de situatie teweeggebracht. Vervolgens vroegen wij hen een geldbedrag in te zetten op de vraag of ze dachten dat deze gevolgen ook echt zouden plaatsvinden – waarbij dus consequenties werden verbonden aan de door hen uitgesproken verwachtingen en zij ertoe werden aangezet zich een realistischere voorstelling van de dreigende situatie te maken. We zagen inderdaad dat angstige personen in eerste instantie veel vaker verwachtten dat er onplezierige dingen zouden gebeuren als ze met hun angst geconfronteerd zouden worden dan niet-angstige mensen. Zij bleken echter uiteindelijk veel minder bereid te zijn deze verwachting te bevestigen als hun werd gevraagd er een geldbedrag op in te zetten. Het lijkt er dus op dat de ideeën die mensen over hun angsten hebben eigenlijk niet zo eendimensionaal zijn. De belangrijkste vraag is hoe we dit inzicht maximaal kunnen benutten om ervoor te zorgen dat de functionele geheugenrepresentaties, meer dan de disfunctionele, het gedrag gaan bepalen.

Deze kwestie en de teleurstellende nuleffecten in de hoofdstukken 2 en 4 worden besproken in het laatste hoofdstuk, de discussie. Daarin benadruk ik de gelijkens tussen innovatie op het gebied van de veranderbaarheid van geheugen en de principes waarop bestaande therapieën gestoeld zijn: uiteindelijk hebben alle therapieën als doel meer grip te krijgen op de mate waarin functionele en disfunctionele geheugenrepresentaties in ons brein toegankelijk zijn en ons gedrag bepalen. Hoewel het ideaalbeeld van een nieuwe interventie waarmee ernstige angsten het zwijgen opgelegd kunnen worden door middel van een simpele methode en het slikken van een wonderpil voorlopig nog utopisch is, hoop ik dat de bescheiden inzichten die uit mijn onderzoek zijn voortgekomen – en mijn huidige

werkzaamheden – ons steeds beter in staat zullen stellen de vele mensen te helpen die nog altijd gebukt gaan onder hun angsten.

Acknowledgments

First and foremost I thank my supervisor Merel Kindt, without whom none of this work would have been possible. It is only as a result of her contributions to translating experimental work on reconsolidation into clinical interventions that I was inspired to undertake a PhD, and that these lines of research are even open. I cannot imagine another lab in which I would have been conducting experimental research one day and wrapping a snake around my supervisor's neck the next. The freedom and trust Merel gave to me in this environment has led to a challenging but formative experience over the past several years. I'm extremely grateful for that, and your honest and forthright feedback and insights.

My co-promoter Arnold has always been open to helping me wherever possible, facilitating recruitment of patients, and rapidly giving feedback on designs for studies involving clinical interventions. Your positive and laid back attitude has certainly been a calming influence when I've been stressed! Arnoud Arntz was also involved in discussions of several designs during the early stage of my PhD, and I thank him for the stimulating clinical discussions and statistical knowledge he provided. Special thanks also goes to Herbert Hoijtink, who helped tremendously with interpreting the results of Bayesian hypothesis testing presented in Chapter 2.

During the time of this PhD the amount of others working on projects in the lab has grown tremendously – from Renee and Vanessa returning to Amsterdam to all the new PhD candidates, postdocs, and research assistants. I want to thank everyone of the Amsterdam Emotional Memory Lab for helping to make these past years not merely bearable, but enjoyable. It is inspiring to be around a group of people who are both fun to be around and hugely interested in science – truly a rare mix. That being said, I still do not want to play table football.

I would especially like to acknowledge my two paranymphs – Sascha and Olivier. Though we certainly hope that it will, it is quite possible none of our research will ever have any tangible impact on mental health. Rest assured, however, that your presence has helped at least mine. Sascha, I still am not quite sure where your idea to start skateboarding came from, but it was an unbelievably good one. Olivier, how do we have so many random things from our pasts in common? Your taste in music alone has enriched the many hours spent cleaning data sets, not to speak of your guitar skills. Wikipedia informs me that your roles are “ceremonial” and that: “A paranymph nowadays is therefore not required to have any knowledge of the subject matter”. Yet, on top of the experiences we've had together, I am confident in both of

your capabilities to take over my defense, should I pass out. Both of you are not only great friends, but also talented aspiring researchers – I look forward to seeing your own dissertations in due time, and I'll be there if you need me!

For the past five (!) years I have also been blessed with a stream of great office mates, from Anna Kunze who helped me settle in way back in 2015, through Bennett and Manon, up to Lotte, Carlijn, and Sascha. Thank you all for tolerating my Tupperware lunches, annoying questions, and messy desk. Whenever I have found myself flagging and unable to focus, I have usually been able to look over and see one of you diligently hammering away at something on your laptop, marking a student's work, or reading a paper. You've been a source of inspiration and energy even if you did not know it.

Reaching yet further back into the past, I would like to thank several teachers, tutors, and professors who encouraged my development and helped put the building blocks in place to enable me to undertake a PhD: Ms Pitchforth (Chilton Foliat primary school!), Mr Cowdry, Ms Harrigan, and Mrs Barber (all from John O'Gaunt), Helene Joffe, Eamon McCrory, and Essi Viding (of UCL), and Marc Potenza (Yale).

Thank you to all the students and assistants who helped slave away at data collection – without your help I might have ended up with a PhD composed entirely of review articles! It has been a pleasure to work with many of you, and I know I will be working closely with some of you in the future as you take the next steps in your careers. I was also lucky to also be able to work with members of the PsyPoli (initially led by Arnold van Emmerik and now Jaap Lancee), who helped recruit, screen, and treat patients. Thanks also of course to all the participants who took part in these experiments, and in particular those who were willing not only to spend their time in a lab, but to confront their fears without any guarantee of benefit.

Last but certainly not least, I would like to express my thanks to those closest to me for all their love and support. Mum and Dad, though we've been living in separate countries for a long time now, you have always been there if I needed to talk. Thank you for all your care and encouragement, not only during the PhD. Lauren, you have been an amazing source of support and my companion throughout this process, no matter how stressed or annoying I have been. You have not only helped me personally but inspired and motivated me with your approach to work. For these things, and for bringing a strange, white fluff-ball called Ralph into our lives, thank

you. While this PhD has been about the power of aversive memories, you have taught me about the power of the positive.