Appendix

Chapter 2

Table 1: buspirone groups well matched for age gender and baseline mood

Supplementary Table 1: Demographics and psychometrics of participants

	Buspirone (N = 31)	Placebo (N = 31)
Gender, N female:male	17:14	17:14
Age (years), mean (S.D.)	25.19 (6.00)	27.28 (8.72)
BDI[a], mean (S.D.)	3.03 (3.03)	2.19 (2.71)

[a] BDI = Becks Depression Inventory

Table 2: side effect and mood ratings at baseline, 1 hour and 4 hr post intervention

Rating	**Allocation**	**Timepoint**		
		Baseline	1 hour	4 hours
Happy	Buspirone	65.7 (18)	60.4 (19.5)	68.7 (13.8)
	Placebo	70.4 (19.1)	73.6 (17.5)	75.2 (14.6)
Calm	Buspirone	79.1 (20.1)	72.5 (21.9)	80.1 (14.2)
	Placebo	77.5 (19.2)	80.9 (14.6)	77.9 (15.6)
Energetic	Buspirone	59.6 (17.6)	41.9 (19.9)	51.8 (17.5)
	Placebo	63.2 (21.5)	65.5 (18.4)	59.4 (24.3)
Nausea	Buspirone	1.9 (5.7)	5.7 (12)	3.3 (10.7)
	Placebo	0.9 (2.8)	0.7 (2.4)	0.2 (0.7)
Lightheadedness	Buspirone	4.6 (12.2)	26.4 (28)	5.7 (14.4)
	Placebo	1 (3.6)	2.2 (4.7)	1.7 (4.7)
Restless	Buspirone	3.8 (13)	5.8 (15.5)	5.5 (13.8)
	Placebo	4.2 (15.5)	1.5 (3.5)	1.9 (4.5)
Sleepy	Buspirone	13.2 (16.5)	21.7 (26.7)	14.6 (19.8)
	Placebo	6.6 (12)	6.5 (8.6)	14.7 (16)

Table 3: Correlation coefficient between mood and side effects score at 1-hour post intervention

Mood	Side effect	*r* value	*p value*
Calm	Nausea	-0.48	0.0033
Calm	Light-headedness	-0.43	0.0119
Calm	Restless	-0.39	0.0327
Calm	total	-0.42	0.0175
Energetic	Light-headedness	-0.49	0.0016
Energetic	Sleepy	-0.57	0.0001
Energetic	total	-0.52	0.0005
total	Light-headedness	-0.44	0.0096
total	total	-0.44	0.0096

Table 4: Side effect correlation with time point (all subjects)

Rating	*r* value	*p value* (2-tailed)	*df*
Energetic	-0.21	0.0224	116
Sleepy	0.157	0.0836	120
Happy	0.144	0.124	113
Light-headedness	0.0447	0.625	120
Calm	0.0378	0.683	117
Nausea	0.0271	0.767	120
Restless	-0.018	0.844	120

Correlations between side effect scores and time point (pre, 1-hour and 4-hour) were calculated for each side effect using a repeated-measures correlation function in R (rmcorr), which gave correlation value similar to Pearson's r but without assuming all measurements are independent, thus mitigating the risk of Type I error.

Figure 1: Line plot of average change from baseline temperature over time, grouped by allocation group. Error bars = +/- 1 S.E.M.

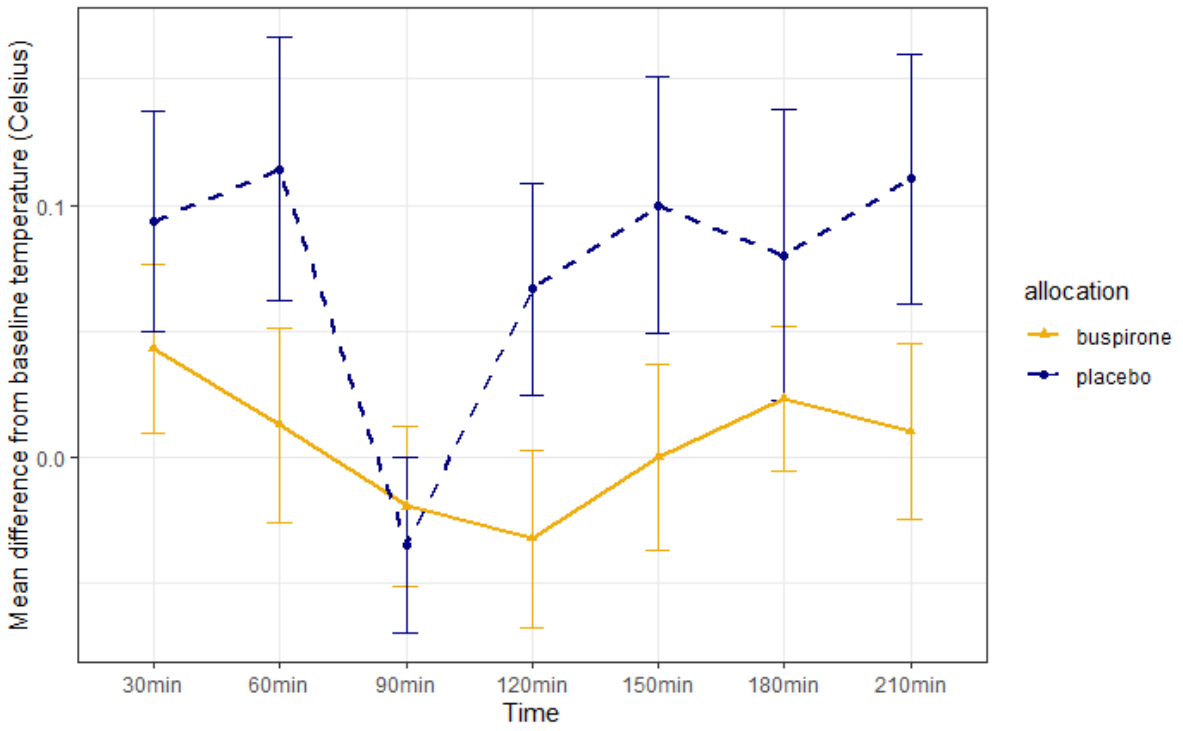
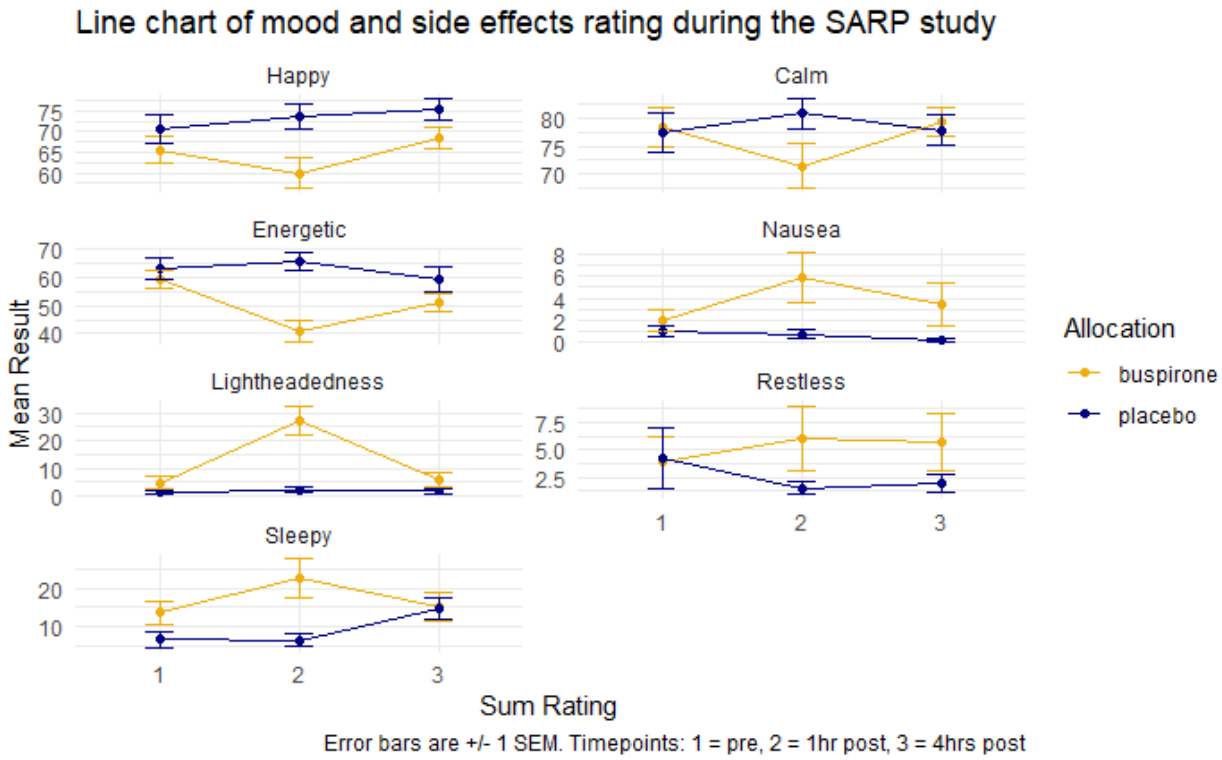


Figure 2:



Methods: Behavioural testing: Statistical testing and degrees of freedom note

Similar to mood and side effect testing, after data cleaning, some groups were unbalanced, as well as including repeated measures. Therefore, data were analysed using a linear mixed-effects model. Each model included a random intercept for participant. To approximated degrees of freedom for fixed effects, Satterthwaite's (or Kenward–Roger's) methods were used. The rationale for this is it provides the optimal balance between statistical validity and

interpretability. It keeps every datapoint available, is suitable for mixed-effects models for sampling variance, controls for false positive risk by calculating unique variances for each group in each unique test.

Chapter 3:

Table 1: results of model fit for taste task

Taste	Formula	Adj. R^2	R SE	AIC	BIC
Sweet	post_Pleasure ~ pre_Pleasure + Nausea2 + allocation * post_Intensity * post_Anticipation	0.6222	11.29	410.5945	432.0582
Sweet1	post_Pleasure ~ pre_Pleasure + allocation + Nausea2 + post_Intensity * post_Anticipation	0.5679	12.08	415.1665	430.7765
Sweet2	post_Pleasure ~ pre_Pleasure + allocation + Nausea2 + post_Intensity + post_Anticipation	0.5596	12.20	415.3057	428.9644
Sweet3	post_Pleasure ~ pre_Pleasure + allocation * post_Intensity * post_Anticipation	0.5934	11.72	413.6397	433.1521
Sweet4	post_Pleasure ~ pre_Pleasure + allocation + post_Intensity * post_Anticipation	0.4923	13.09	422.6964	436.3551
Sweet5	post_Pleasure ~ pre_Pleasure + allocation + post_Intensity + post_Anticipation	0.4734	13.34	423.7212	435.4286
Sour	post_Pleasure ~ pre_Pleasure + Nausea2 + allocation * post_Intensity * post_Anticipation	0.762	10.61	404.134	425.598
Sour1	post_Pleasure ~ pre_Pleasure + allocation + Nausea2 + post_Intensity * post_Anticipation	0.736	11.18	407.147	422.756
Sour2	post_Pleasure ~ pre_Pleasure + allocation + Nausea2 + post_Intensity + post_Anticipation	0.741	11.06	405.186	418.845
Sour3	post_Pleasure ~ pre_Pleasure + allocation * post_Intensity * post_Anticipation	0.753	10.81	405.210	424.722
Sour4	post_Pleasure ~ pre_Pleasure + allocation + post_Intensity * post_Anticipation	0.704	11.82	412.084	425.743
Sour5	post_Pleasure ~ pre_Pleasure + allocation + post_Intensity + post_Anticipation	0.710	11.72	410.256	421.963
Salt	post_Pleasure ~ pre_Pleasure + Nausea2 + allocation * post_Intensity * post_Anticipation	0.5402	12.57	421.7451	443.2088
Salt1	post_Pleasure ~ pre_Pleasure + allocation + Nausea2 + post_Intensity * post_Anticipation)	0.5584	12.32	417.2300	432.8400
Salt2	post_Pleasure ~ pre_Pleasure + allocation + Nausea2 + post_Intensity + post_Anticipation)	0.561	12.29	416.0689	429.7277
Salt3	post_Pleasure ~ pre_Pleasure + allocation * post_Intensity * post_Anticipation)	0.5509	12.43	419.7453	439.2578
Salt4	post_Pleasure ~ pre_Pleasure + allocation + post_Intensity * post_Anticipation)	0.5674	12.2	415.3053	428.9640
Salt5	post_Pleasure ~ pre_Pleasure + allocation + post_Intensity + post_Anticipation)	0.5701	12.16	414.1001	425.8076
Bitter	bitter_model ~ pre_Pleasure + Nausea2 + allocation * post_Intensity * post_Anticipation	0.533	11.77	414.85	436.32

Bitter1	post_Pleasure ~ pre_Pleasure + allocation + Nausea2 + post_Intensity * post_Anticipation	0.523	11.89	413.50	429.11
Bitter2	post_Pleasure ~ pre_Pleasure + allocation + Nausea2 + post_Intensity + post_Anticipation	0.514	12.01	413.67	427.33
Bitter3	post_Pleasure ~ pre_Pleasure + allocation * post_Intensity * post_Anticipation	0.536	11.73	413.77	433.28
Bitter4	post_Pleasure ~ pre_Pleasure + allocation + post_Intensity * post_Anticipation	0.532	11.78	411.69	425.35
Bitter5	post_Pleasure ~ pre_Pleasure + allocation + post_Intensity + post_Anticipation	0.522	11.90	411.91	423.62

	β Estimate	Std. Error	$t_{(42)}$ value	p value
(Intercept)	9.502	8.091	1.174	0.247
Pre-Pleasurableness	0.705	0.134	5.244	<0.005
Post-Nausea	-0.521	0.252	-2.069	0.045
Allocation	3.916	13.114	0.299	0.767
Post-Intensity	-0.432	0.250	-1.723	0.092
Post-Anticipation	0.028	0.283	0.098	0.922
Allocation : Post-Intensity	0.438	0.355	1.234	0.224
Allocation : Post-Anticipation	-0.341	0.423	-0.805	0.426
Post-Intensity : Post-Anticipation	0.013	0.008	1.620	0.113
Allocation : Post-Intensity : Post-Anticipation	-0.003	0.011	-0.296	0.769

Table 2: results of linear regression model for sweet taste. 'Pre–' prefix indicates pre-intervention rating and 'post-' prefix indicates post-intervention rating. Model is as follows: post-intervention pleasurableness ~ $\beta 0 + \beta_1$(pre-intervention pleasurableness) + β_2(post-intervention intensity) + β_3(allocation) + β_4(post-intervention anticipation) + β_5(post-intervention nausea) + β_6(post-intervention intensity x allocation) + β_7(post-intervention anticipation x allocation) + β_8(post-intervention intensity x post-intervention anticipation) + β_9(post-intervention intensity x post-intervention anticipation x allocation)

	β Estimate	Std. Error	$t_{(42)}$ value	p value
(Intercept)	10.897	9.728	1.120	0.269
Pre-Pleasurableness	0.331	0.142	2.330	0.025
Post-Nausea	-0.383	0.240	-1.600	0.117
Allocation	-8.782	11.372	-0.772	0.444
Post-Intensity	-0.060	0.205	-0.291	0.773
Post-Anticipation	1.068	0.481	2.218	0.032
Allocation : Post-Intensity	0.055	0.230	0.241	0.811
Allocation : Post-Anticipation	-0.497	0.547	-0.910	0.368
Post-Intensity : Post-Anticipation	-0.013	0.010	-1.302	0.200
Allocation : Post-Intensity : Post-Anticipation	0.016	0.011	1.429	0.160

Table 3: results of linear regression model for sour taste. 'Pre–' prefix indicates pre-intervention rating and 'post-' prefix indicates post-intervention rating. Model is as follows: post-intervention pleasurableness ~ $\beta 0 + \beta_1$(pre-intervention pleasurableness) + β_2(post-intervention intensity) +

β_3(allocation) + β_4(post-intervention anticipation) + β_5(post-intervention nausea) + β_6(post-intervention intensity x allocation) + β_7(post-intervention anticipation x allocation) + β_8(post-intervention intensity x post-intervention anticipation) + β_9(post-intervention intensity x post-intervention anticipation x allocation)

	β Estimate	Std. Error	$t_{(47)}$ value	p value
(Intercept)	1.409	4.365	0.323	0.748
Pre-Pleasurableness	0.807	0.119	6.776	< 0.005
Allocation	0.971	3.515	0.276	0.783
Post-Intensity	0.010	0.085	0.118	0.907
Post-Anticipation	0.075	0.110	0.686	0.496

Table 4: results of linear regression model for salt taste. 'Pre–' prefix indicates pre-intervention rating and 'post-' prefix indicates post-intervention rating. Model is as follows: post-intervention pleasurableness ~ β0 + β_1(pre-intervention pleasurableness) + β_2(post-intervention intensity) + β_3(allocation) + β_4(post-intervention anticipation)

	β Estimate	Std. Error	$t_{(44)}$ value	p value
(Intercept)	-3.661	4.198	-0.872	0.388
Pre-Pleasurableness	0.213	0.139	1.526	0.134
Allocation	7.563	3.561	2.124	0.039
Post-Intensity	-0.210	0.083	-2.520	0.015
Post-Anticipation	0.398	0.106	3.740	0.001

Table 5: results of linear regression model for bitter taste. 'Pre–' prefix indicates pre-intervention rating and 'post-' prefix indicates post-intervention rating. Model is as follows: post-intervention pleasurableness ~ β0 + β_1(pre-intervention pleasurableness) + β_2(post-intervention intensity) + β_3(allocation) + β_4(post-intervention anticipation)

Chapter 4

Table 1: Inclusion and exclusion criteria

1. Inclusion Criteria
• Participant is willing and able to give informed consent for participation in the research • Not currently taking any medications (except the contraceptive pill) • Aged between 18 to 65 years • Sufficient knowledge of English language to understand and complete study tasks

2. Exclusion criteria

The participant may not enter the study if ANY of the following apply:

- Current or past probable diagnosis of significant psychiatric disorder, according to DSM-5 criteria, including but not limited to psychosis, bipolar disorder, major depression, OCD, PTSD, substance abuse disorder or any eating disorder
- Current or past diagnosis of any significant personality disorder (e.g. borderline personality disorder) according to self-report
- Current use of medication that might interact with the effects of citalopram
- Known contraindication to citalopram including: past allergic reaction to citalopram or any other medicines, diagnosis of a cardiovascular condition, glaucoma, type 1 or type 2 diabetes, diagnosis of epilepsy, previous diagnosis of angle-closure glaucoma, or current use of any other medication whose use interacts with citalopram (according to BNF guidance) e.g. associated with prolonged QT-interval
- Any other current or past medical conditions which in the opinion of the study medic may interfere with the safety of the participant or the scientific integrity of the study including epilepsy/seizures, brain injury, hepatic or renal disease, diabetes, severe gastro-intestinal problems, Central Nervous System (CNS) tumours, neurological conditions
- First-degree relative with a diagnosis of schizophrenia-spectrum or other psychotic disorder, or bipolar disorder
- Severely underweight or overweight in a manner that renders them unsuitable for the study in the opinion of the study medic
- Heavy use of cigarettes (smoke > 20 cigarettes per day)
- Heavy use of caffeine (drink > 4 250ml cups/cans of coffee/energy drinks per day)
- Lactose intolerance (due to the study involving administration of a lactose placebo tablet)
- Pregnancy (as determined by urine pregnancy test taken during the Part 2 screening visit), breast feeding
  or plans to become pregnant
- past history of dependence on illegal substances or illegal substance use within previous three months
- previous participation in a study involving the tasks used in this study or involving use of citalopram in the last year
- physical (including visual and auditory) or language impairment that would make complying with the study protocol challenging
- ongoing deficit in sense of smell or taste e.g. following Covid-19 infection
- Participant is unlikely to comply with the clinical study protocol or is unsuitable for any other reason, in the opinion of the Investigator
- Not suitable for MRI neuroimaging e.g. claustrophobia, difficulty remaining still for duration of scan
- Any MRI contraindications outlined in FMRIB 3 Tesla scanning safety form

Chapter 5

Table 1: WBA activation of several clusters

Appendix Table 1. Main effect of task (whole brain analysis)					
contrast	Cluster size	MAX	MNI	T score	Brain area at peak voxel (Harvard-Oxford)
win outcome	31651	1	-10, -78, -44	3.25	Occiptal lobe, cerebellum, Supramarginal gyrus, Middle & superior temporal gyrus
	280	0.98	48, 12, 32	5.17	Precentral gyrus (right), middle frontal gyrus,

					inferior frontal gyrus
	278	0.981	46, 38, 24	5.25	Frontal pole, Middle frontal gyrus
	232	0.976	-44, 4, 24	4.88	Precentral gyrus (left), Inferior frontal gyrus
	156	0.994	32, 22, -2	7.56	Insular cortex (right) Orbito-frontal cortex
loss outcome	28883	1	-34, -72, -54	3.19	Cerebellum, Occipital lobe, Middle & superior temporal gyrus
	1942	0.999	48, 14, 30	6.34	Inferior frontal gyrus (right) Middle frontal gyrus Frontal pole
	1152	0.993	-48, -40, 2	5.27	Middle temporal gyrus, posterior (left) Superior temporal gyrus, posterior (left)
	398	1	34, 20, -6	7.48	Insular (right), Orbito-frontal cortex
	150	0.98	-44, 14, 26	6.03	Inferior frontal gyrus (left) Middle frontal gyrus
	130	0.971	6, 36, 40	5.19	Paracingulate gyrus, Superior frontal gyrus
	81	0.962	32, -70, -50	4.15	Cerebellum (right)
	33	0.957	25, 56, -2	4.36	Frontal pole (right)
	14	0.954	4, 20, 44	4.74	Paracingulate gyrus
	13	0.97	2, -24, 28	7.02	Cingulate gyrus (posterior)
win anticipation	59085	37	16, -66, -56	3.27	Cerebellum, Occipital cortex Cingulate gyrus (anterior & posterior), thalamus, Insular (BL) Orbito-frontal cortex (BL) Putamen (BL) Caudate (BL)
loss anticipation	55733	1	12, -74, -48	3.23	Cerebellum, Occipital cortex, Cingulate cortex (anterior & posterior) Paracingulate gyrus, Cingulate gyrus (anterior). Superior frontal gyrus, Middle frontal gyrus, Inferior frontal gyrus, frontal pole (BL) insular cortex (BL) caudate (BL) putamen (BL)
	195	0.981	-6, -24, 28	5.64	Cingulate cortex (posterior)
no win outcome	22830	1	40, -36, -30	4.96	Occipital lobe
no loss outcome	30795	1	-26, -76, -52	3.53	Occipital lobe, Insular cortex (right)
	1179	0.998	46, 42, 24	6.00	Frontal pole, Middle frontal gyrus (right),
	308	0.978	-42, 6, 30	4.95	Precentral gyrus (left), Middle frontal gyrus,

					Inferior frontal gyrus
	38	0.982	32, 22, -4	7.25	Insular cortex (right)
loss anticipation > win anticipation	44	0.971	-40, -58, 46	5.68	Angular gyrus (left), Occipital lobe
win outcome > no win outcome	1583	0.986	-20, 14, -10	5.34	Putamen (BL) Caudate (BL) Accumbens (BL), Anterior cingulate cortex
	164	0.974	6, -88, -2	5.27	Lingual cortex Occipital lobe
	66	0.963	-16, -94, -6	4.56	Occipital lobe (left)
	41	0.961	18, -20, -8	4.26	Right cerebral white matter (Amygdala, hippocampus, thalamus)
	28	0.958	-2, 60, 18	4.25	Frontal pole
loss outcome > no loss outcome	104	0.977	-14, -94, 0	6.16	Occipital pole
	88	0.977	50, -26, -4	6.05	Middle temporal gyrus Superior temporal gyrus
win outcome > loss outcome	54	0.978	-12, 10, -6	6.78	Accumbens (left) Caudate (left)
loss outcome > win outcome	63	0.967	4, 34, 52	5.19	Superior frontal gyrus
	11	0.957	0, 44, 30	5.30	Paracingulate gyrus
	10	0.956	18, 14, 64	5.37	Superior frontal gyrus
Clusters < 10 voxels in size are not reported					

Table 2: RoI Main effect of task

Appendix Table 2: Main effect of task (RoI)							
Contrast	Region of interest	Voxels	t value	MNI152			p value
win outcome	Insula	116	4.66	32	18	-10	< 0.0001
	Insula	28	4.12	-36	18	-4	0.016
	Left accumbens	51	4.18	-12	10	-8	0.002
	Left putamen	43	4.6	-14	10	-8	0.008
	Orbito-frontal cortex	68	6.15	34	24	-6	< 0.0001
	Right accumbens	41	3.54	12	18	-4	0.007
	Right caudate	25	4.33	14	16	0	0.009
	Right putamen	47	4.76	18	14	-2	0.003
loss outcome	Insula	115	5.13	34	18	-8	< 0.0001
	Insula	62	6.18	-34	16	-4	< 0.0001

	Anterior cingulate cortex	38	5.77	2	-14	32	0.003
	Orbito-frontal cortex	143	4.47	34	20	-14	< 0.0001
	Orbito-frontal cortex	26	4.27	-32	20	-14	0.012
win anticipation	Insula	46	4.57	-34	20	0	0.005
	Insula	39	4.99	34	22	0	0.001
	Anterior cingulate cortex	323	4.68	-6	16	34	0.002
	Left accumbens	9	3.67	-12	8	-8	0.017
	Left caudate	57	4.51	-14	14	-2	0.002
	Left putamen	566	4.67	-24	6	-6	< 0.0001
	Right putamen	300	4.15	28	8	-4	< 0.0001
loss anticipation	Insula	65	4.88	34	22	-4	< 0.0001
	Insula	64	4.27	-34	18	0	< 0.0001
	Anterior cingulate cortex	20	4.92	-4	18	36	0.012
	Anterior cingulate cortex	10	5.29	6	14	38	0.01
	Left accumbens	24	3.35	-12	8	-10	0.005
	Left caudate	149	5.88	-14	14	-2	< 0.0001
	Left putamen	412	5.89	-16	10	-4	< 0.0001
	Orbito-frontal cortex	9	4.82	34	26	-4	0.022
	Right caudate	98	4.31	16	18	0	0.002
	Right putamen	302	5.69	22	10	-2	< 0.0001
no win outcome	Insula	17	4.49	34	20	-2	0.01
no loss outcome	Insula	80	4.96	34	18	-6	< 0.0001
	Insula	13	4.5	-34	20	-2	0.012
	Orbito-frontal cortex	42	5.11	34	24	-10	0.001
win anticipation vs loss anticipation	Anterior cingulate cortex	21	3.73	-4	8	34	0.027
	Fronto-medial cortex	252	4.73	2	54	-14	0.002
	Orbito-frontal cortex	17	4.65	28	32	-16	0.018
	Orbito-frontal cortex	6	3.94	-28	16	-16	0.039
loss anticipation vs win anticipation	Left caudate	18	3.29	-10	12	10	0.033
	Right caudate	42	4.19	18	20	2	0.005
win outcome vs no win outcome	Anterior cingulate cortex	286	4.08	-2	44	6	0.003
	Anterior cingulate cortex	9	2.65	-2	30	18	0.048
	Left accumbens	64	3.99	-12	14	-8	0.001
	Left caudate	64	4.67	-12	12	-4	0.002
	Left putamen	136	4.81	-20	8	-10	< 0.0001
	Orbito-frontal cortex	60	4.87	34	24	-10	0.004
	Right accumbens	56	4.73	12	8	-10	0.001
	Right caudate	71	3.83	10	18	-2	0.011
	Right putamen	142	4.72	18	6	-10	0.001

loss outcome vs no loss outcome	Insula	83	4.28	-34	12	-14	0.004
	Insula	54	5.25	36	20	-6	0.001
	Anterior cingulate cortex	7	4.23	0	-14	30	0.036
No loss outcome vs loss outcome	Left caudate	18	3.69	-8	4	8	0.028
	Orbito-frontal cortex	134	5.27	30	20	-16	0.001
	Orbito-frontal cortex	69	4.3	-34	16	-18	0.008
	Right caudate	92	4.41	10	6	8	0.003
	Fronto-medial cortex	25	3.59	4	42	-14	0.024
	Left accumbens	41	3.73	-8	10	-6	0.005
	Right accumbens	18	3.1	12	10	-8	0.020
win outcome vs loss outcome	Fronto-medial cortex	137	3.26	4	42	-16	0.017
	Left accumbens	66	4.43	-12	8	-10	< 0.0001
	Left putamen	63	5.45	-14	8	-8	0
	Right accumbens	55	5.2	12	8	-10	0
	Right caudate	41	5.23	12	18	0	0.002
	Right putamen	42	4.85	14	8	-10	0.002
loss outcome vs win outcome	Right caudate	9	3.56	12	2	16	0.033