Social Cognitive and Affective Neuroscience, 2024, **19**(1), nsae075

DOI: https://doi.org/10.1093/scan/nsae075
Advance Access Publication Date: 18 October 2024
Original Research – Neuroscience

Brain encoding during perceived control as a prospective predictor of improvement in quality of life

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Abstract

Perceived control is strongly related to mental health and well-being. Specifically, lack of perceived control has been associated with learned helplessness and stress-related disorders, such as depression and anxiety. However, it is unknown whether brain activation to control and its protective effect against stress can predict changes in quality of life. To address this gap, we examined the neural underpinning of controllability in healthy females ($N = 40$) performing the Value of Control task in an functional magnetic resonance imaging scanner. Quality of life and perceived stress were assessed at baseline and 6-month follow-up. Increased brain activation for control was found within the putamen, insula, thalamus, mid-cingulate, dorsolateral prefrontal cortex, motor cortex, and cerebellum. In contrast, increased brain activation for lack of control was found within the posterior cingulate and prefrontal cortices. In an exploratory analysis, an elastic-net algorithm was used to identify brain predictors of quality of life 6 months later. The right putamen's activation to control was selected as the best prospective predictor of improvement in life enjoyment and satisfaction and this association was mediated by changes in perceived stress. Our findings suggest that neural responsiveness to control may have utility as a potential marker of quality of life and resilience to adversity.

Keywords: fMRI; perceived control; prediction; quality of life; reward; stress

Introduction

The perception of control over events describes the belief that an individual's actions can influence the environment in a desired manner (Leotti et al. 2010). Perceived control is a highly adaptive construct linked to better psychosocial functioning, well-being, and physical and mental health (Skinner 1992, Eklund and Bäckström 2006). For example, occupational performance improves when an individual has a greater sense of control (Kielhofner 2002). Similarly, among patients with schizophrenia, perceived control was positively related to quality of life and negatively related to affective symptoms (Bengtsson-Tops 2004). Conversely, lack of perceived control has been linked to increased risk for psychiatric disorders, particularly depression and anxiety (Benassi et al. 1988, Ryff 2013, Gallagher et al. 2014).

Perceived control has a protective effect against stressors. In animal research, the presence of control was shown to inhibit the impact of current stressors and mitigate the outcomes of future stressors (Maier et al. 2006). The mechanism behind this phenomenon has been postulated to involve top-down modulation from the ventromedial prefrontal cortex (vmPFC) which detects control, to limbic and brainstem regions that respond to stressors, such as the dorsal raphe nucleus (Maier and Seligman 2016). Human studies on stressor controllability found that perceived control can reduce the experience of pain (Mohr et al. 2012) and restore avoidance behavior from aversive stimuli (Wang and Delgado 2021).

The neural underpinnings of controllability have been hypothesized to involve subcortical-cortical circuits, centering on the striatum and prefrontal cortices (Leotti et al. 2015, Baratta et al. 2023). Recently, Wang and Delgado developed the Value of Control (VOC) task (Wang and Delgado 2019) to characterize the behavioral and neural preference for control. This study introduced a computational metric—the point of equivalence—to quantify the subjective value of perceived control, namely, the extent to which having control is preferred over gaining reward. The authors found that while the striatum responded to the presence of control, the vmPFC was associated with the subjective value of control.

Understanding the neural encoding of control has important implications. First, it promises to identify mechanisms potentially

Received: 16 January 2024; **Revised**: 14 August 2024; **Accepted**: 17 October 2024

associated with resilience to childhood adversity or stressful life events (Grote et al. 2007, Elliot et al. 2018). Second, the perception of control is pivotal in decision-making (Wang et al. 2021b). Controllability was suggested to shape our decisions in several ways, including boosting approach behavior (Bobadilla-Suarez et al. 2017), motivating us to exert effort (White 1959), and reducing maladaptive responses in aversive environments (Maier and Seligman 2016). Notably, it has been argued that the preference for control is innate and has a biological motivation (Leotti et al. 2010).

There are several knowledge gaps regarding the neural correlates of control. First, controllability in humans was mostly studied with respect to stressors, and only a handful of studies examined the encoding of control per se. This distinction is important since the literature has pointed to different mechanisms of control in the presence versus absence of stressors. For example, the vmPFC was shown to respond to controllable stressors but not to controllable neutral stimuli (Kerr et al. 2012). Second, despite the established relationship between perceived control and well-being, it is unknown whether brain activation to control can map to measures of quality of life. Since brain activation to control was suggested as a mechanism of resilience to life adversity (Skinner and Zimmer-Gembeck 2011), its utility in predicting quality of life merits investigation.

To address these gaps, the present study had the following goals. First, we aimed to probe the neural underpinnings of perceived control in humans in the absence of an adverse context. The encoding of control was examined using the VOC task (Wang and Delgado 2019) in two settings: (i) active ("mixed") condition: the participant can choose to exert control or lend control; and (ii) passive ("baseline") condition: the control or lack of control is dictated by the task. We sought to replicate previous findings by Delgado and colleagues and hypothesized to extend them to identify a broader brain network of control, by using a larger and more powered sample. Second, an exploratory analysis was conducted to identify putative brain predictors of prospective quality of life. We hypothesized that brain response to control in the striatum or prefrontal cortex would prospectively predict improvement in life enjoyment and satisfaction at a 6-month follow-up. Last, based on the documented effects of control against stressors, we hypothesized that the relationship between brain activation to control and changes in quality of life would be mediated by experienced daily life stress.

Materials and Methods

Participants and study design

A sample of 40 healthy female participants (ages: 20–32) was recruited from the Center for Depression, Anxiety and Stress Research at McLean Hospital. Only women were included as this study was part of a parent project focusing on the effects of childhood abuse on depression risk among women. Before inclusion, participants underwent a clinical evaluation session, including the Structured Clinical Interview for DSM-V (SCID-5-RV) (First et al. 2015) (see Supplementary data for inclusion/exclusion criteria).

Eligible participants completed two study visits: (i) an functional magnetic resonance imaging (fMRI) session; and (ii) a clinical 6-month follow-up. During the fMRI scan, participants completed the VOC task (Wang and Delgado 2019) followed by an appraisal questionnaire ("VOC appraisal") administered in the magnetic resonance imaging (MRI) scanner. In addition, after the scan, participants filled out the Locus of Control (LOC) Scale (Rotter 1966). To prospectively evaluate quality of life and perceived stress, participants filled out the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q) (Endicott et al. 1993) and the Perceived Stress Scale (PSS) (Cohen et al. 1983) at baseline before the fMRI scan and at 6-month follow-up. The study was approved by the Partners Human Research Committee and participants provided written informed consent before enrollment.

VOC task

The VOC task was previously introduced by Delgado and colleagues (Wang and Delgado 2019, Wang et al. 2021a) (Fig. 1). Briefly, each trial included a "choice" and a "game" phase. During the "choice" phase, the participant decided who would play the game (themselves or the computer) by selecting between two options. Each option was associated with points (i.e. monetary rewards) that could be earned in the "game" phase. During the "game" phase, a card hiding a number was presented and the participant/computer (depending on which option had been selected in the choice phase) guessed if the number was greater or less than 5. If the participant played the game, they guessed by pressing "up" (>5) or "down" (<5). If the computer played the game, the participant pressed "left" and the computer guessed. The participant was not informed of the outcome (i.e. if they won or not).

The "choice" phase included two conditions: (i) Mixed: the participant chose if they want to have control and play the game ("self" option) or have the computer play the game for them ("computer" option). Notably, the options differed in both control and rewards. (ii) Baseline: the participant chose between two self (controllable) or two computer (uncontrollable) options. Namely, the options differed in associated rewards but not in control.

In the mixed condition, the self-option was fixed at 10 points, whereas the computer option was associated with a balanced distribution of 0–20 points (mean: 10 points). In the baseline condition, one option was fixed at 10 points and the other had a balanced distribution of 0–20 points (mean: 10 points). Points earned were awarded to the participant (i.e. the computer was playing for them). In addition, points could be earned but not lost.

The VOC task included 4 runs: 2 runs of the mixed condition interleaved with 2 runs of the baseline condition, each run comprising 20 trials. The baseline condition included a balanced amount of controllable and uncontrollable trials. Of note, the primary difference between the conditions is that the mixed condition allows participants to integrate both reward and control, whereas in the baseline condition options differ only in rewards. This was important for the behavioral analysis of the point of equivalence; however, in terms of brain activation, both conditions enable examination of the impact of control.

VOC appraisal

Following the VOC task, participants rated their subjective experience on visual analog scales presented in the MRI scanner. Each question was rated on a continuous sliding scale between 0 and 100, with zero indicating "not at all" and 100 indicating "extremely". The first two questions were designed to assess the extent to which the participant thought that controllability influenced their gain of reward, whereas the last two questions assessed how much the participant liked having control in the game. The following questions were rated: (i) "When YOU played the card guessing game, how likely do you think you won and earned the points?" (ii) "When the COMPUTER played the card

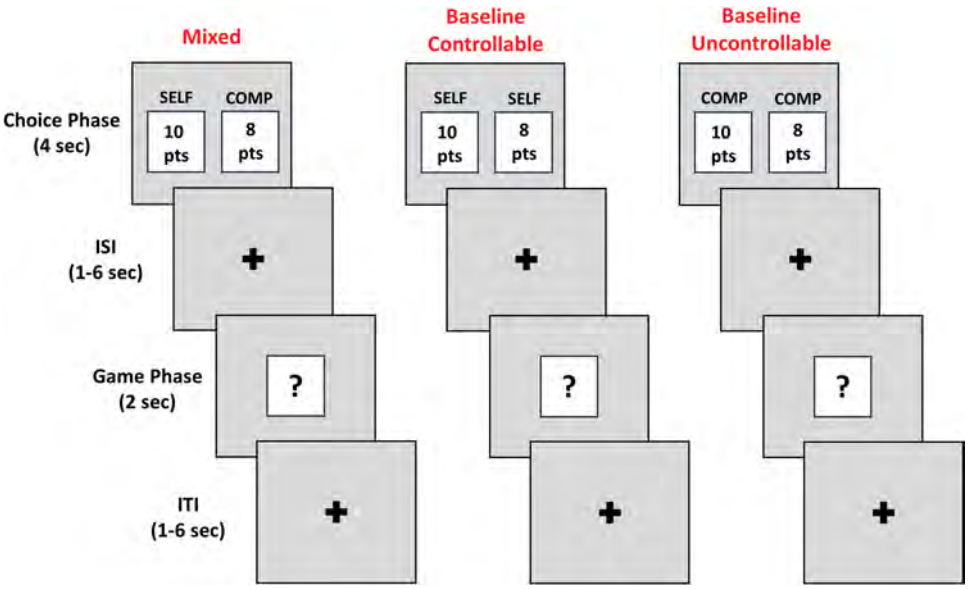


Figure 1. Illustration of the VOC task; modified after Wang and Delgado (2019). ISI, interstimulus interval; ITI, intertrial interval.

guessing game for you, how likely do you think you won and earned the points?" (iii) "How much did you like playing the game for YOURSELF in order to try and earn the points?" (iv) "How much did you like having the COMPUTER play the game for you in order to earn the points?" Note that a subject report was not administered in previous VOC studies.

MRI data acquisition and preprocessing

MRI data were collected at the McLean Imaging Center on a 3T Siemens Prisma using a 64-channel head coil (Supplementary Methods). Preprocessing of fMRI data was done using fMRIPrep (Esteban et al. 2019) (Supplementary Methods).

Behavioral data analysis

All analyses examined the choice phase in which participants were requested to select between two options. Two main metrics were extracted: Point of Equivalence (POE) and reaction time.

(i) Point of equivalence

The interplay between controllability and reward on the participants' choices was captured by computing the POE, as introduced in Wang and Delgado (Wang and Delgado 2019). The POE is a computational metric that estimates the subjective value that an individual attributes to having control in the task. For the mixed condition, the POE calculates for every participant the difference in points between the self (controllable) and computer (uncontrollable) options that makes the participant equally likely to select between them. For example, a POE of 3 indicates that the participant is equally likely to choose between self and computer options when the computer option has 3 more points than the self-option. Thus, the subjective value of control for that participant would be estimated as 3.

For the baseline condition, the POE calculates the difference in points between the fixed- and varied-value options, which makes the participant equally likely to select between them. Since the expected value of both options was the same and the options differed only in their points and not in controllability, if a participant is making choices according to the points, the POE should be zero. Thus, the baseline condition served as a control to verify that the participant's choices complied with the task's instructions (i.e. choices should be made according to points and controllability).

Computationally, the POE was derived for each individual using the following steps: (i) Calculating the proportion of self-choices for each point-difference between the two options. (ii) Fitting a logistic function for the relationship between the proportion of self-choices (P_{self}) and the point-differences (x): $P_{self} = \frac{1}{1+e^{\beta_0-\beta_1 x}}$, where β_0, β_1 are the parameters of the logistic function. (iii) The POE can be obtained from the previous equation as the value of x when the proportion of self-choices equals 0.5. Inserting $P_{self} = 0.5$ to the equation and solving for x, leads to the following derivation: $POE = \frac{\beta_0}{\beta_1}$. The POE of the mixed and baseline conditions were compared using a two-sided Wilcoxon signed-rank test.

Participants were excluded from all analyses (behavioral and imaging) if their behavioral data indicated poor compliance with the task ($n = 3$; see "Results" section). Specifically, if the behavioral data could not be fitted to a logistic function, it indicated that choices were not made according to reward or controllability. For example, selecting according to the side of the presentation on the screen. The fit of the baseline condition, in particular, served as a control to ensure that participants were making choices according to reward (since the baseline options did not differ on controllability).

(ii) Reaction time

The impact of controllability (mixed, baseline controllable, baseline uncontrollable) and run order (first, second) on participants' reaction time was tested by a two-way repeated-measures ANOVA model implemented by a general linear model (GLM) in SPSS v.23 (SPSS Inc., Chicago, IL, USA).

VOC appraisal analysis

The interplay between controllability and reward was further evaluated using the participants' subjective reports. A two-way repeated-measures ANOVA model with controllability (self, computer) and experience (liked, earned rewards) as two within-subject factors was implemented by a GLM in SPSS v.23 (SPSS Inc., Chicago, IL). *Post hoc* pairwise comparisons were conducted using Sidak correction.

Functional MRI data analysis

Similarly to the behavioral analyses, imaging analyses were conducted on the choice phase. Subject- and group-level analyses were conducted in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12). Subject-level analysis included a GLM model with the following regressors: (i) Mixed: self-choices, computer choices, game phase; (ii) Baseline: controllable trials, uncontrollable trials, game phase. Regressors were convolved with a canonical hemodynamic response function and the six motion parameters were included as covariates of no interest. For each participant, whole-brain contrast maps of the beta values of the convolved regressors were derived for the following contrasts: "control > no control" and "no control > control."

At the group level, one-sample *t*-tests were conducted on the contrasts of "control > no control" and "no control > control." A statistical threshold of voxel-level $P < .001$, false discovery rate (FDR) cluster-extent corrected at $P < .05$ for multiple comparison was applied. MRIcroGL (Rorden et al. 2007) was used for visualization of the results. Note that analyses were conducted for the mixed and baseline conditions separately, as our main aim was to identify neural activation patterns for prediction. Results from a flexible factorial model examining the main effect of control and condition-by-control interaction can be found in the Supplementary data.

Quality of life and perceived stress evaluation

Quality of life was evaluated using the Q-LES-Q (Endicott et al. 1993). The Q-LES-Q is a 16-item self-report questionnaire assessing overall enjoyment and satisfaction across the following domains: physical health, mood, work, household and leisure activities, social and family relationships, daily functioning, sexual interest, and economic status. As recommended by the scale developers, the first 14 items were summed to create a total score (possible range: 14–70), where higher scores indicate greater life enjoyment and satisfaction. Perceived stress was assessed using the PSS (Cohen et al. 1983), which measures the extent to which situations experienced over the past month were appraised as stressful. Items are summed together to obtain a total score where higher values indicate greater perceived stress.

Predicting changes in quality of life from brain activation to control

An elastic-net algorithm was used to select predictors of quality of life among the brain regions that showed significant activation to control or lack of control. Namely, the significant brain clusters identified at the group-level fMRI analyses (i.e. the results of the contrasts: control > no control, no control > control) for mixed and baseline conditions, were pooled together, yielding a total set of 18 variables (i.e. different brain clusters) that were included in the elastic-net model as possible predictors. For each individual and brain cluster, the average beta contrast from the subject-level GLM (e.g. beta for the contrast "self minus computer") was extracted and used in the model.

Elastic-net is a regularized regression method that combines lasso and ridge regression and can identify the important predictors from a large set of variables (Zou and Hastie 2005). It allows for correlations among variables, thus suitable for the current purpose. Elastic-net was implemented in MATLAB using *Glmnet* (http://hastie.su.domains/glmnet_matlab/) (Qian et al. 2013). Hyperparameters were optimized using cross-validation for all possible combinations of alpha (elastic net penalty, ranging from 0 to 1 in steps of 0.05) and lambda (controls the overall strength of penalty). The model with the pair of alpha–lambda that minimized the cross-validated error was selected. In the next step, brain predictors were ranked according to the standardized regression coefficients, and the predictor with the largest regression coefficient was considered the most important one.

Mediation analysis

Following the results of elastic-net, the best brain predictor was identified and included in a mediation model to test whether a change in perceived stress (PSS at 6-month follow-up relative to baseline) mediated the relationship between brain activation to perceived control and change in life satisfaction (as measured by Q-LES-Q) from baseline to 6-month follow-up. A bootstrapped mediation analysis was performed using SPSS PROCESS macro (Hayes 2013), and the significance of the indirect effect was tested using bootstrapped 95% confidence intervals with 10 000 resamples.

Locus of control, stress, and quality of life: an alternative approach

As an alternative model, we tested whether changes in quality of life or perceived stress could be predicted from the subjective report of locus of control (using the LOC) rather than brain response to control (Supplementary Methods).

Results

Sample characteristics

Table 1 summarizes the sample's demographics, LOC, quality of life, and perceived stress at baseline and 6-month follow-up. PSS and LOC scores were missing from two participants at baseline and PSS was missing for one at follow-up. One participant was lost to follow-up, i.e. did not complete the 6-month visit. Supplementary Table S1 presents the correlations among scales over time.

Table 1. Demographic and clinical characteristics of the sample

Demographics	
Age, years, mean ± SD (range)	25.9 ± 3.5 (20–32)
Female, *n* (%)	40 (100)
Education, years, mean ± SD (range)	17.1 ± 1.9 (15–24)
Race and ethnicity	
Asian, *n* (%)	5 (12.5)
Black, *n* (%)	2 (5)
White, *n* (%)	28 (70)
More than one race, *n* (%)	5 (12.5)
Hispanic, *n* (%)	4 (10)
Marital status	
Never married, *n* (%)	30 (75)
Married/living with someone as if married, *n* (%)	8 (20)
Divorced or annulled, *n* (%)	1 (2.5)
Not reported, *n* (%)	1 (2.5)
LOC Scale	
Baseline, mean ± SD (range)	11.9 ± 4.0 (2–19)
PSS Scale	
Baseline, mean ± SD (range)	12.9 ± 5.0 (4–31)
6-month follow-up, mean ± SD (range)	11.5 ± 5.6 (1–27)
Q-LES-Q	
Baseline, mean ± SD (range)	63.3 ± 4.6 (55–70)
6-month follow-up, mean ± SD (range)	62.9 ± 5.2 (50–70)

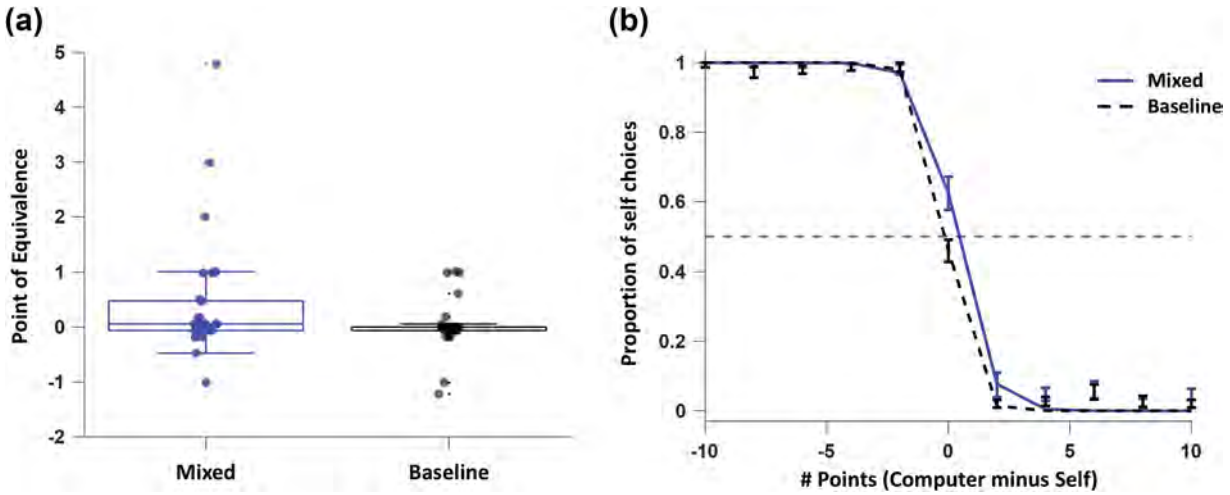


Figure 2. POE: participants favored reward over control.

Controllability and reward

Three participants were excluded due to poor compliance with the task, as indicated by their behavioral choices. The final analyzed sample included 37 participants.

(i) Point of equivalence computational metric

The POE did not differ between the mixed and baseline conditions ($z = 1.53$, $P = .125$, Wilcoxon signed-rank test) (Fig. 2a). The means, standard errors, and ranges were as follows: (i) POE mixed: 0.38 ± 1.01 (−1.00–4.77); (ii) POE baseline: 0.01 ± 0.40 (−1.21–1.01). Figure 2b presents for the mixed condition, the proportion of self-choices as a function of the point-difference between the computer (uncontrollable) and self (controllable) options. The left half indicates more points (i.e. rewards) associated with the self-option, whereas the right side indicates more points for choosing the computer option. For the baseline condition, the proportion of fixed-value choices is presented as a function of the difference in points between the varied- and fixed-value options. Means and standard errors are indicated by the error bars and the fits to a logistic function are indicated by lines. As shown, participants' choices were made primarily according to rewards (i.e. selecting the option with greater points) without choosing to have control over gaining rewards. This finding contrasts with previous reports that used the VOC (Wang and Delgado 2019, Chantland et al. 2022).

(ii) Subjective report

In the subject report ("VOC appraisal"), controllability was found to influence liking to play the game but did not affect the perceived likelihood of earning rewards [interaction effect: $F(1,38) = 6.61$, $P = .014$] (Fig. 3). *Post hoc* analyses indicated that participants enjoyed playing the game more when they had control ($P = .010$ Sidak corrected) but did not consider control to affect their chances of gaining rewards ($P = .532$ Sidak corrected).

Reaction time

There were no effects of *Condition* (mixed, baseline controllable, baseline uncontrollable), *Run order*, or *Condition*-by-*Run* interaction on reaction time (all $Fs < 2.7$, $Ps > .09$), as expected and in accordance with previous VOC studies (Wang and Delgado 2019, Chantland et al. 2022) (Supplementary Fig. S1).

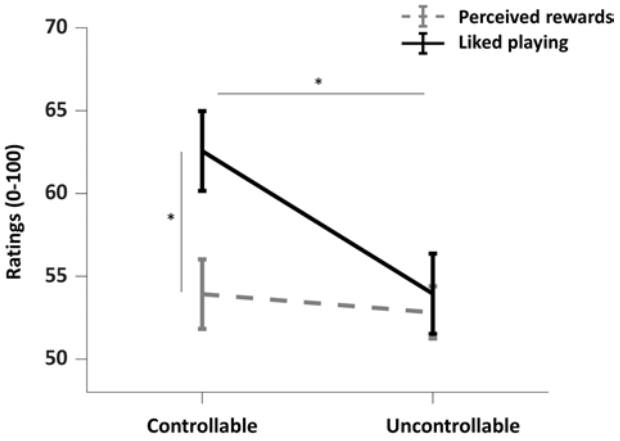


Figure 3. Interaction between controllability and reward (self-report); the asterisk (*) indicates Sidak corrected *post hoc* pairwise comparisons.

Brain activation to control

For both mixed and baseline conditions, widespread brain activation for control (control > no control) was found (Fig. 4 and Table 2). Brain clusters showing greater response to control included the bilateral motor cortex, mid-cingulate cortex, bilateral putamen, bilateral insula (Fig. 4a and d); left thalamus (Fig. 4b and e); cerebellum (Fig. 4c and f); and dorsolateral prefrontal cortex (DLPFC) (all $P < .05$ FDR cluster corrected for multiple comparisons). The same results were found across conditions using a flexible factorial model (Supplementary Fig. S2 and Supplementary Table S2).

Brain activation to lack of control

For the mixed condition, increased brain activation when choosing not to have control (no control > control) was found within the posterior cingulate cortex (PCC) (Fig. 5a), left ventrolateral prefrontal cortex (VLPFC) (Fig. 5b), left DLPFC (Fig. 5c), bilateral middle occipital gyri, and left inferior parietal lobule (all $P < .05$ FDR cluster corrected). For the baseline condition, increased brain activation for lack of control (no control > control) emerged within the PCC (Fig. 5d), vmPFC (Fig. 5e), left middle temporal gyrus, right cuneus, and left lateral occipital cortex (all $P < .05$ FDR cluster corrected; Fig. 5 and Table 3). When using a flexible factorial model,

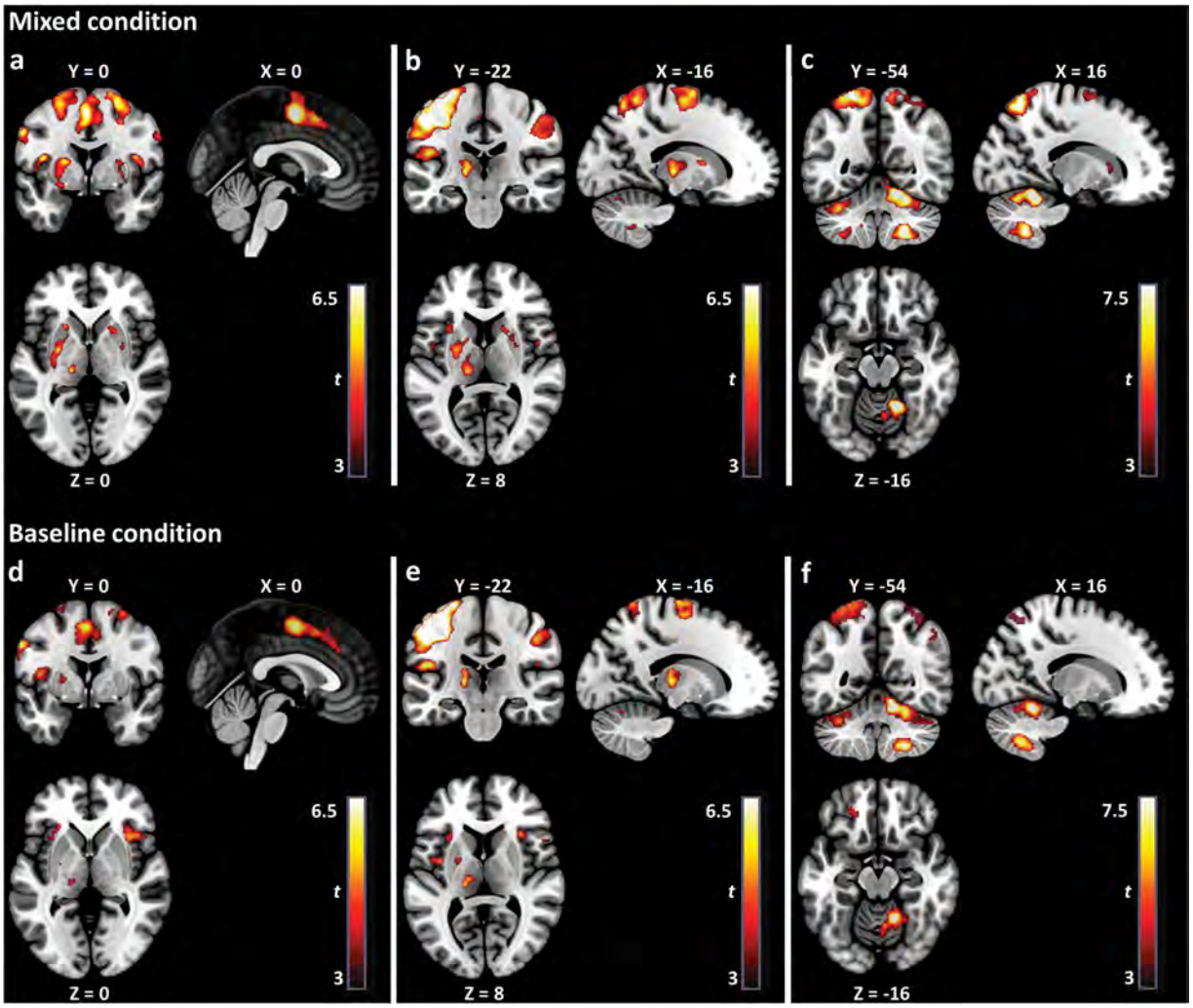


Figure 4. Brain clusters exhibiting greater response to control (control > no control) during the mixed condition (top row) and baseline condition (bottom row).

the PCC was the only region showing increased response to lack of control across mixed and baseline conditions (Supplementary Fig. S3).

Brain activation to control predicted changes in quality of life

The following brain regions were selected by elastic-net as prospective predictors of changes in life satisfaction, listed according to their ranked weights, from largest (most important) to smallest: right putamen, left thalamus, left VLPFC, and left DLPFC (Table 4). Note that a hyper-parameter of alpha = 1 was chosen indicating that elastic-net approached lasso regression (i.e. a small number of variables was used in the predictive model). Prediction accuracy of the elastic-net model was quantified as: $R^2 = 0.38$; Pearson's correlation between predicted and observed scores: $r(34) = 0.64$, $P < 10^{-4}$.

Perceived stress mediated the association between brain activation to control and quality of life

The right putamen was identified as the most important predictor of changes in life satisfaction (see "brain activation to control predicted changes in quality of life"), and thus was included in the mediation model to examine the relationship between brain activation to control, perceived stress, and changes in quality of life. Right putamen activation was correlated with a change in Q-LES-Q [$r(34) = 0.492$, $P = .002$] (Fig. 6a) and a change in PSS [$r(31) = -0.410$, $P = .017$] (Fig. 6b). Changes in PSS and Q-LES-Q were negatively correlated [$r(31) = -0.605$, $P = 1.9 \cdot 10^{-4}$] (Fig. 6c). A significant mediation effect of perceived stress on the relationship between the putamen's activation to control and improvement in life satisfaction was found [standardized indirect effect = 0.197, SE(boot) = 0.094, 95% CI = (0.036, 0.399)] (Fig. 6d).

Locus of control, stress, and quality of life: alternative model

The LOC was not associated with changes in PSS [$r(29) = 0.021$, $P = .908$], changes in Q-LES-Q [$r(32) = 0.125$, $P = .479$] or the right putamen's activation to control [$r(33) = 0.030$, $P = .860$].

Discussion

The presence of control recruited an extensive subcortical–cortical–cerebellar network of regions, including the striatum, insula, motor cortices, and DLPFC. In contrast, lack of control

Table 2. Brain activation to control (control> no control).

Brain cluster	Peak MNI (mm) x	y	z	Cluster P value (FDR corrected)	Cluster size (voxels)
Mixed condition					
L precentral and postcentral gyri, L and R supplementary motor areas, mid-cingulate cortex	−40	−28	52	$<10^{-4}$	8823
R cerebellum, anterior and posterior lobes	16	−54	−16	$<10^{-4}$	2286
R precentral and postcentral gyri	16	−64	60	$<10^{-4}$	3322
L insula	−40	−4	16	.001	132
L thalamus	−16	−22	2	$<10^{-4}$	294
R precentral gyrus	34	−12	58	$<10^{-4}$	1182
L putamen	−22	−2	12	$<10^{-4}$	478
L precentral gyrus	−60	2	36	$<10^{-4}$	242
L cerebellum, anterior and posterior lobes	−34	−54	−30	$<10^{-4}$	569
L insula	−32	14	6	.005	87
L superior and middle frontal gyri (L DLPFC)	−30	42	32	$<10^{-4}$	208
L cerebellum, posterior lobe	−28	−56	−52	$<10^{-4}$	220
R middle frontal gyrus (R DLPFC)	38	28	34	$<10^{-4}$	508
R putamen	18	14	8	$<10^{-4}$	234
L superior and middle frontal gyri (L DLPFC)	−32	48	16	.009	74
R insula	48	−26	18	.024	54
Baseline condition					
L precentral and postcentral gyri, L and R supplementary motor areas, mid-cingulate cortex	−36	−22	52	$<10^{-4}$	7405
R cerebellum, anterior lobe	14	−52	−18	$<10^{-4}$	1280
R cerebellum, posterior lobe	24	−56	−52	$<10^{-4}$	595
R precentral gyrus	34	−12	60	$<10^{-4}$	753
L insula	−42	−4	12	.001	154
L thalamus	−18	−24	6	.001	151
L precentral gyrus	−60	2	36	$<10^{-4}$	227
L cerebellum, anterior and posterior lobes	−34	−54	−30	$<10^{-4}$	336
R precentral and postcentral gyri	58	−14	40	$<10^{-4}$	2004
R insula	32	22	10	$<10^{-4}$	272
L insula	−26	26	2	.001	125
R inferior and middle frontal gyri	60	8	26	$4.9 \cdot 10^{-4}$	159
L inferior frontal gyrus	−24	46	−14	.045	50
R middle frontal gyrus (R DLPFC)	38	44	20	$<10^{-4}$	229
L putamen	−22	−2	8	.038	54
R middle frontal gyrus (R DLPFC)	38	34	42	.011	79

L, left; R, right.

was associated with increased activation within the PCC and prefrontal cortices, including the vmPFC. Utilizing an elastic-net algorithm, we identified prospective brain predictors of improvement in quality of life, with the right putamen being the strongest predictor. Importantly, perceived stress emerged as a mediator of the relationship between putamen activation to control and changes in life satisfaction and enjoyment.

Controllability was associated with greater neural response in the subcortex (putamen, insula, thalamus), cortex (mid-cingulate, motor, DLPFC), and cerebellum. These brain circuits were consistently associated with perceived control across different task conditions: actively choosing control or having the presence of control dictated by the task. Previous work has highlighted a key role of the striatum in the detection of control (Amat et al. 2014, Moscarello and Hartley 2017). In addition, these regions were previously implicated in agency. Agency is a concept closely related to perceived control and refers to the sense of controlling one's own actions or the felt capacity to act (Bandura 1982). The insula has been strongly implicated in the experience of agency (Farrer and Frith 2002, Craig 2009, Sperduti et al. 2011) as well as the premotor and motor cortices (Haggard 2017). For example, self-determined choices, as opposed to forced ones, were found to elicit greater activations in the insula and motor cortices (Murayama et al. 2015).

Lack of control was associated with greater neural response in the PCC and the prefrontal cortices: the DLPFC, VLPFC, and vmPFC. Recent studies on the brain mechanisms of agency have implicated the lateral and medial prefrontal cortices in response to external agency, i.e. lack of control (Sperduti et al. 2011). Increased activity in the vmPFC was found when participants could not choose whether to exert control (Cosme et al. 2018). The PCC was found to be more active when anticipating uncontrollable relative to controllable pain (Salomons et al. 2007). Moreover, the PCC and DLPFC were implicated in illusions of control, the belief that an individual can influence chance events (Shao et al. 2016).

Notably, increased activity in the vmPFC was not found in the presence of control. While this may seem to contrast with animal research on stressor controllability, it can be explained by different neural mechanisms underlying controllability in the presence vs. absence of stressors. In agreement with this notion, previous work in humans found that the vmPFC was not active to controllable neutral stimuli (Kerr et al. 2012). This finding highlights the importance of future work to advance our knowledge on the neural underpinnings of control in the absence of adverse contexts.

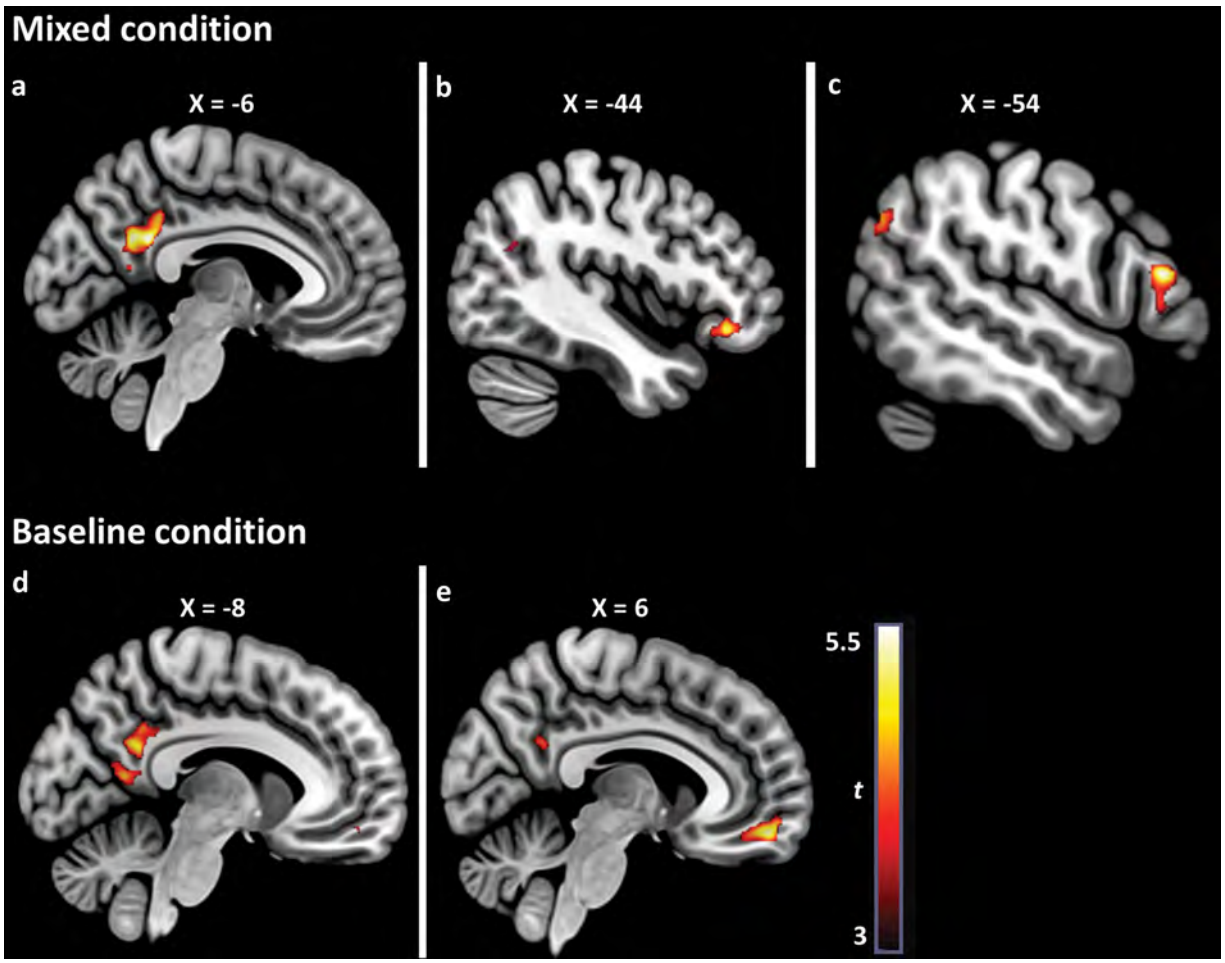


Figure 5. Brain clusters exhibiting greater response to lack of control (no control > control) during the mixed condition (top row) and baseline condition (bottom row).

Table 3. Brain activation to lack of control (no control> control).

	Peak MNI (mm)			Cluster P value	Cluster size
Brain cluster	**x**	**y**	**z**	**(FDR corrected)**	**(voxels)**
Mixed condition					
L inferior frontal gyrus (L DLPFC)	−54	28	16	.005	121
Posterior cingulate cortex	−6	−48	26	$<10^{-4}$	354
R middle occipital gyrus	28	−84	20	.004	144
L inferior frontal gyrus (L VLPFC)	−44	32	−10	.004	131
L middle occipital gyrus	−26	−82	18	.005	116
L inferior parietal lobule	−54	−68	34	.004	135
Baseline condition					
Medial frontal gyrus (vmPFC)	6	52	−14	$<10^{-4}$	272
Posterior cingulate cortex	−8	−52	26	$<10^{-4}$	493
L middle temporal gyrus	−62	−8	−10	.013	94
R cuneus	16	−84	28	.002	141
L lateral occipital cortex	−40	−76	30	.018	83

L, left; R, right.

The activation of the vmPFC, together with the PCC, during the absence of control in the baseline (passive) condition may reflect the task-negative effects of the default mode network (DMN). The DMN is known to be more active during self-referential processes (Buckner et al. 2008) and attenuated during effortful cognitive processing such as engaging in a task (Raichle et al. 2001). When there is no future control in playing the game/task, task demands are lower and more focus can be directed to self-processing, and thus, recruiting the DMN.

Our findings contrast with previous work utilizing the VOC task (Wang and Delgado 2019, Chantland et al. 2022). First, at the behavioral level, participants did not favor control over gaining rewards. Notably, the same task scripts, instructions, and practice were used. Nevertheless, differences between studies

Table 4. Brain predictors of changes in quality of life.

Brain region	Standardized regression coefficient (beta)	Task contrast	Condition
R putamen	0.432	Control > no control	Mixed
L thalamus	−0.186	Control > no control	Baseline
L VLPFC	−0.117	No control > control	Mixed
L DLPFC	0.057	Control > no control	Mixed

L, left; R, right

in participants' behavior can result from sample characteristics, such as clinical or subthreshold symptoms (previous work did not administer the SCID-5-RV), education, race, ethnicity, age, or sex. We also note the larger sample size in the current study. Future work with larger and more diverse samples can shed more light on the relationship between individual differences and the interplay between reward and control. Second, in terms of brain activation, we identified a broader set of regions activated in response to control compared to Delgado and colleagues (Wang and Delgado 2019). This may be partly explained by differences in the fMRI scanning protocols (in addition to sample sizes): multi-band fMRI utilized here versus single-band used by Delgado and colleagues. Multi-band increases power by collecting more brain volumes during a given scan time. It was suggested that multi-band may compromise the detection of mesolimbic activation (Sriranganarajan et al. 2021); however, we were able to detect significant activations in the striatum.

A novel finding emerging from the current study is that the neural correlates of perceived control were associated with prospective changes in well-being, specifically, life enjoyment and satisfaction. Person-centered outcome measurements focus on assessing an individual's subjective experience of quality of life and evaluate diverse domains of health and well-being, including physical, mental, and social aspects (Smith et al. 2016). In mental health, such measures provide important clinical information that is mostly not captured by disease-specific scales (Broderick et al. 2013, Lavallee et al. 2016). However, person-centered outcomes have been rarely integrated into psychiatric neuroimaging research. Rather, much of the focus has been given to identifying associations between neural measures and clinical symptoms. Changing the focus from targeting specific symptoms to more holistic measures of functioning that incorporate an individual's perceptions and values may identify neural mechanisms of well-being and promote novel targets for interventions.

Of note, perceived stress mediated the association between the putamen's activation to control and quality of life. Specifically, stronger activation to control was associated with reduced stress at 6-month follow-up and improvement in life enjoyment and satisfaction. Experienced stress is tightly and inversely related to quality of life (Treharne et al. 2007, Slavich 2016). Previous work indicated that perceived life stress is an important mediator between the impact of treatment interventions, psychological characteristics, and well-being (Segrin et al. 2007, Valikhani et al. 2020). Several studies have associated the putamen's activation with stress. In adolescence, trait anxiety was associated with

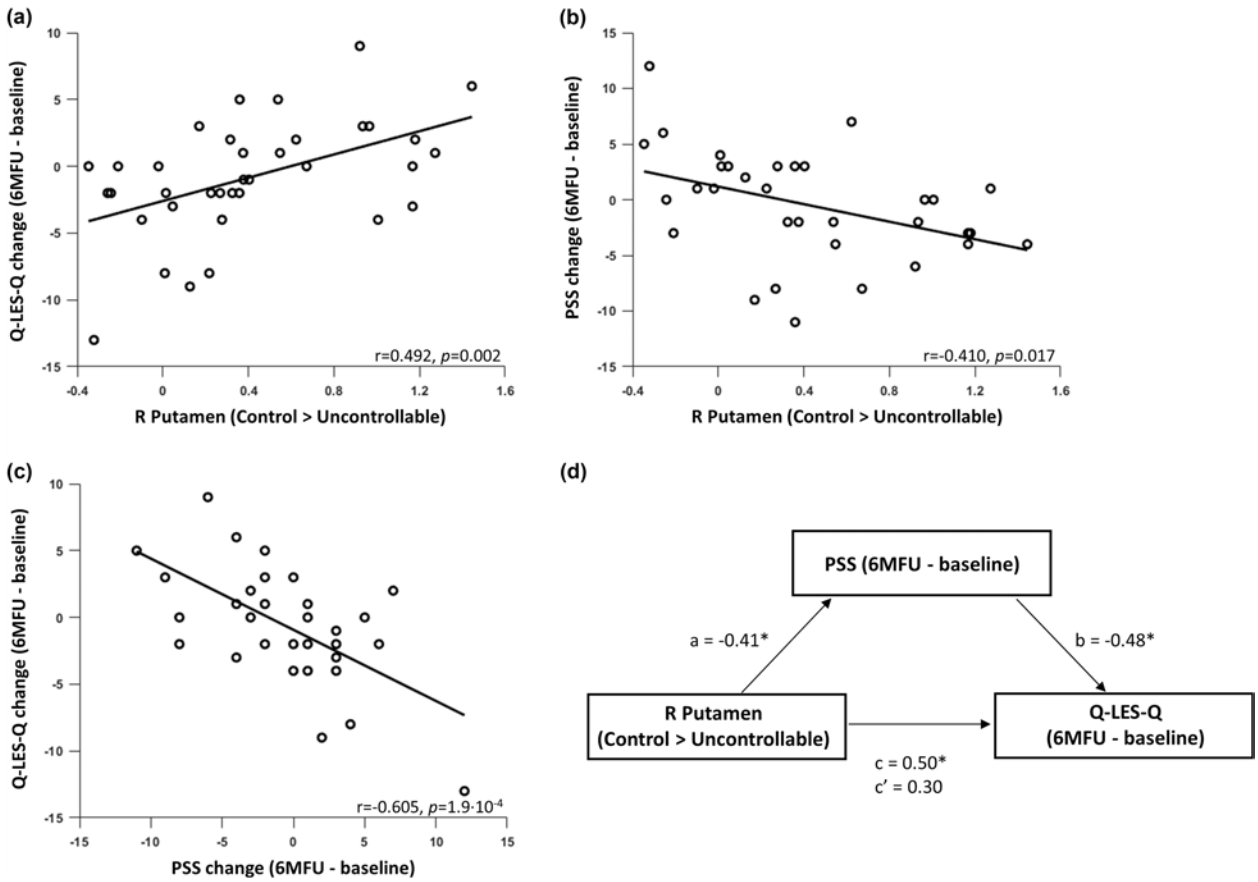


Figure 6. The relationship between putamen activation to control and changes in life enjoyment and satisfaction was mediated by perceived stress. The asterisk (*) indicates $P < .05$. 6MFU, 6-month follow-up; R, right.

decreased putamen activity during stress manipulation (Corr et al. 2021). In individuals with high childhood stress, reduced putamen activation was found during the anticipation of loss (Birn et al. 2017) or reward (Boecker et al. 2014).

While alternative explanations may exist regarding the relationship among putamen reactivity, stress, and quality of life, we note that there was no association between putamen's response to control and baseline PSS [$r(33) = -6.6 \cdot 10^{-4}$, $P = .997$] or baseline Q-LES-Q [$r(35) = -0.156$, $P = .355$]. This strengthens the role of the putamen's reactivity to control as a prospective marker of improvement/resilience rather than reflecting current stress. Moreover, an alternative model utilizing the LOC instead of brain reactivity to control was unsuccessful in predicting changes in perceived stress or quality of life. Notably, the LOC is a self-report trait-like measure and thus can capture different aspects of controllability than state-like brain activation.

Several limitations should be noted. First, this study examined only female participants and future work studying possible sex effects is needed. Second, our sample was quite highly educated. The influence of education, among other demographic, clinical, and cultural variables on the interplay between control and reward merits further investigation. Third, participants reported an overall high quality of life, with only 15.0%–22.5% showing potentially clinically meaningful changes in Q-LES-Q across 6 months, as indicated by 8%–12% change in the normalized scores (Wyrwich et al. 2011). Additionally, approximately two-thirds of the sample reported low perceived stress and a third indicated moderate stress. Of note, in clinical populations, perceived stress is typically higher and quality of life is generally lower and less stable.

Fourth, perceived stress and quality of life were measured prospectively, whereas brain response to control was assessed at baseline. In future studies, repeated brain measurements during a follow-up period could aid in understanding the possible reciprocal relationships among stress, quality of life, and brain reactivity. Fifth, the subject report did not directly evaluate the participants' perception of having control but rather how much they believed it influenced their rewards. Future work should more directly assess the subjective perceived control, for example, by adding questions to the VOC appraisal. Last, the construct of control encompasses several closely related concepts, including perceived control, agency, self-efficiency, LOC, and illusion of control. Future work can illuminate if the relationships found here are common to these various facets of controllability.

Conclusions

The neural correlates of perceived control emerged as prospective predictors of changes in quality of life, specifically, life enjoyment and satisfaction at 6-month follow-up, and this relationship was mediated by daily life stress. Important avenues for future research include investigations in clinical populations to evaluate the utility of the perceived control paradigm to identify neural correlates of resilience to life adversity.

Acknowledgements

The authors thank Dr Mauricio R. Delgado and Dr Sally K. Wang for their assistance with the VOC task, including providing task materials and scripts.

Author contributions

Rotem Dan (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing - original draft, Writing – review & editing), Aliza R. Brown (Investigation, Project administration, Resources, Writing – review & editing), Lauren Hutson (Investigation, Project administration, Resources, Writing – review & editing), Emily L. Belleau (Conceptualization, Methodology, Resources, Software, Writing – review & editing), Shiba M. Esfand (Investigation, Project administration, Resources, Writing – review & editing), Valerie Ruberto (Investigation, Project administration, Resources), Emily Johns (Investigation, Project administration, Resources, Writing – review & editing), Kaylee E. Null (Investigation, Project administration, Resources), Fei Du (Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing), Diego A. Pizzagalli (Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing).

Supplementary data

Supplementary data is available at *SCAN* online.

Conflict of interest

Over the past 3 years, D.A.P. has received consulting fees from Boehringer Ingelheim, Compass Pathways, Engrail Therapeutics, Karla Therapeutics, Neumora Therapeutics (formerly BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Sama Therapeutics, and Takeda; he has received honoraria from the Psychonomic Society, Springer, and American Psychological Association (for editorial work) and from Alkermes; he has received research funding from the Bird Foundation, Brain and Behavior Research Foundation, Dana Foundation, Millennium Pharmaceuticals, NIMH, and Wellcome Leap; he has received stock options from Compass Pathways, Engrail Therapeutics, Neumora Therapeutics, and Neuroscience Software. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors. All other authors have no conflicts of interest or relevant disclosures.

Funding

The study was supported by the National Institute of Mental Health (NIMH) (Grant No. R01 MH095809 to D.A.P. and F.D.). R.D. is an Awardee of the Weizmann Institute of Science – Israel National Postdoctoral Award Program for Advancing Women in Science. E.L.B. is supported by funding from the National Institute of Mental Health (K23MH122668) and the Klingenstein Third Generation Foundation.

Data and code availability

The data utilized in this study are available on the NIMH Data Archive (NDA) at https://nda.nih.gov/study.html?id=2451. All measures used in the broader project can be found in NDA Collection #3821: "Early Life Stress and Depression: Molecular and Functional Imaging Approaches." Unthresholded SPM *t*-statistic maps were uploaded to NeuroVault: https://identifiers.org/neurovault.collection:17313. The scripts for the VOC task and its analysis are publicly available at: https://github.com/delgado-lab/Value_of_Control. We thank Drs Delgado and Wang for providing these codes.

References

Amat J, Christianson JP, Aleksejev RM *et al*. Control over a stressor involves the posterior dorsal striatum and the act/outcome circuit. *Eur J Neurosci* 2014;**40**:2352–58. https://doi.org/10.1111/ejn.12609

Bandura A. Self-efficacy mechanism in human agency. *Am Psy* 1982;**37**:122–47. https://doi.org/10.1037/0003-066X.37.2.122

Baratta MV, Seligman MEP, Maier SF. From helplessness to controllability: toward a neuroscience of resilience. *Front Psychiatry* 2023;**14**:1170417. https://doi.org/10.3389/fpsyt.2023.1170417

Benassi VA, Sweeney PD, Dufour CL. Is There a relation between locus of control orientation and depression?. *J Abnormal Psychol* 1988;**97**:357–67. https://doi.org/10.1037/0021-843X.97.3.357

Bengtsson-Tops A. Mastery in patients with schizophrenia living in the community: relationship to sociodemographic and clinical characteristics, needs for care and support, and social network. *J Psychiatric Mental Health Nurs* 2004;**11**:298–304. https://doi.org/10.1111/j.1365-2850.2003.00718.x

Birn RM, Roeber BJ, Pollak SD *et al*. Early childhood stress exposure, reward pathways, and adult decision making. *Proc Natl Acad Sci USA* 2017;**114**:13549–54. https://doi.org/10.1073/pnas.1708791114

Bobadilla-Suarez S, Sunstein CR, Sharot T. The intrinsic value of choice: the propensity to under-delegate in the face of potential gains and losses. *J Risk Uncertainty* 2017;**54**:187–202. https://doi.org/10.1007/s11166-017-9259-x

Boecker R, Holz NE, Buchmann AF *et al*. Impact of early life adversity on reward processing in young adults: EEG-fMRI results from a prospective study over 25 years. *PLoS ONE* 2014;**9**:e104185. https://doi.org/10.1371/journal.pone.0104185

Broderick J, DeWit EM, Rothrock N *et al*. Advances in patient reported outcomes: the NIH PROMIS measures. *eGEMs*. 2013;**1**:12.

Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann NY Acad Sci* 2008;**1124**:1–38. https://doi.org/10.1196/annals.1440.011

Chantland ECM, Wang KS, Delgado MR *et al*. Control preference persists with age. *Psychol Aging* 2022;**37**:843–47. https://doi.org/10.1037/pag0000708

Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Social Behav* 1983;**24**:385–96. https://doi.org/10.2307/2136404

Corr R, Pelletier-Baldelli A, Glier S *et al*. Neural mechanisms of acute stress and trait anxiety in adolescents. *NeuroImage Clin* 2021;**29**:102543. https://doi.org/10.1016/j.nicl.2020.102543

Cosme D, Mobasser A, Zeithamova D *et al*. Choosing to regulate: does choice enhance craving regulation?. *Soc Cognit Affective Neurosci* 2018;**13**:300–09. https://doi.org/10.1093/scan/nsy010

Craig AD. How do you feel - now? The anterior insula and human awareness. *Nat Rev Neurosci* 2009;**10**:59–70. 10.1038/nrn2555

Eklund M, Bäckström M. The role of perceived control for the perception of health by patients with persistent mental illness. *Scand J Occup Ther* 2006;**13**:249–56. https://doi.org/10.1080/11038120600928823

Elliot AJ, Turiano NA, Infurna FJ *et al*. Lifetime trauma, perceived control, and all-cause mortality: results from the midlife in the United States study. *Health Psychol* 2018;**37**:262–70. https://doi.org/10.1037/hea0000585

Endicott J, Nee J, Harrison W *et al*. Quality of life enjoyment and satisfaction questionnaire: A new measure. *Psychopharmacol Bull* 1993;**29**:321–26.

Esteban O, Markiewicz CJ, Blair RW *et al*. fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nat Methods* 2019;**16**:111–16. https://doi.org/10.1038/s41592-018-0235-4

Farrer C, Frith CD. Experiencing oneself vs another person as being the cause of an action: The neural correlates of the experience of agency. *NeuroImage* 2002;**15**:596–603. https://doi.org/10.1006/nimg.2001.1009

First M, Williams J, Karg R *et al*. *Structured Clinical Interview for DSM-5—Research Version (SCID-5 for DSM-5, Research Version; SCID-5-RV)*. Arlington, VA: American Psychiatric Association, 2015.

Gallagher MW, Bentley KH, Barlow DH. Perceived control and vulnerability to anxiety disorders: a meta-analytic review. *Cognitive Ther Res* 2014;**38**:571–84. https://doi.org/10.1007/s10608-014-9624-x

Grote NK, Bledsoe SE, Larkin J *et al*. Stress exposure and depression in disadvantaged women: the protective effects of optimism and perceived control. *Social Work Res* 2007;**31**:19–33. https://doi.org/10.1093/swr/31.1.19

Haggard P. Sense of agency in the human brain. *Nat Rev Neurosci* 2017;**18**:197–208. https://doi.org/10.1038/nrn.2017.14

Hayes AF. *Introduction to Mediation, Moderation and Conditional Process Analysis: A regression-based approach*. New York: Guilford Press, 2013, 1–20.

Kerr DL, McLaren DG, Mathy RM *et al*. Controllability modulates the anticipatory response in the human ventromedial prefrontal cortex. *Front Psychol* 2012;**3**:557. https://doi.org/10.3389/fpsyg.2012.00557

Kielhofner G. *A model of human occupation: Theory and application*, Vol. 53, 3rd edn. In: Julet T (ed.), Philadelphia, PA, US: Lippincott Williams & Wilkins, 2002, 231.

Lavallee DC, Chenok KE, Love RM *et al*. Incorporating patient-reported outcomes into health care to engage patients and enhance care. *Health Affairs* 2016;**35**:575–82. https://doi.org/10.1377/hlthaff.2015.1362

Leotti LA, Cho C, and Delgado MR. The neural basis underlying the experience of control in the human brain. In: Haggard P and Eitam B (eds.), *The Sense of Agency*. New York: Oxford University Press, 2015, 145–76.

Leotti LA, Iyengar SS, Ochsner KN. Born to choose: the origins and value of the need for control. *Trends Cognit Sci* 2010;**14**:457–63. https://doi.org/10.1016/j.tics.2010.08.001

Maier SF, Amat J, Baratta MV *et al*. Behavioral control, the medial prefrontal cortex, and resilience. *Dialog Clin Neurosci* 2006;**8**:397–406. https://doi.org/10.31887/DCNS.2006.8.4/smaier

Maier SF, Seligman MEP. Learned helplessness at fifty: Insights from neuroscience. *Psychol Rev* 2016;**123**:349–67. https://doi.org/10.1037/rev0000033

Mohr C, Leyendecker S, Petersen D *et al*. Effects of perceived and exerted pain control on neural activity during pain relief in experimental heat hyperalgesia: a fMRI study. *Eur J Pain* 2012;**16**:496–508. https://doi.org/10.1016/j.ejpain.2011.07.010

Moscarello JM, Hartley CA. Agency and the calibration of motivated behavior. *Trends Cognit Sci* 2017;**21**:725–35. https://doi.org/10.1016/j.tics.2017.06.008

Murayama K, Matsumoto M, Izuma K *et al*. How Self-determined choice facilitates performance: a key role of the ventromedial prefrontal cortex. *Cereb Cortex* 2015;**25**:1241–51. https://doi.org/10.1093/cercor/bht317

Qian J, Hastie T, Friedman J *et al*. Glmnet for Matlab. 2013.

Raichle ME, MacLeod AM, Snyder AZ *et al*. A default mode of brain function. *Proc Natl Acad Sci USA* 2001;**98**:676–82. https://doi.org/10.1073/pnas.98.2.676

Rorden C, Karnath H-O, Bonilha L. Improving lesion-symptom mapping. *J Cognitive Neurosci* 2007;**19**:1081–88. https://doi.org/10.1162/jocn.2007.19.7.1081

Rotter JB. Generalized expectancies for internal versus external control of reinforcement. *Psychol Monogr* 1966;**80**:1–28. https://doi.org/10.1037/h0092976

Ryff CD. Psychological well-being revisited: advances in the science and practice of eudaimonia. *Psychother Psychosom* 2013;**83**:10–28. https://doi.org/10.1159/000353263

Salomons TV, Johnstone T, Backonja MM *et al*. Individual differences in the effects of perceived controllability on pain perception: critical role of the prefrontal cortex. *J Cognitive Neurosci* 2007;**19**:993–1003. https://doi.org/10.1162/jocn.2007.19.6.993

Segrin C, Hanzal A, Donnerstein C *et al*. Social skills, psychological well-being, and the mediating role of perceived stress. *Anxiety Stress Coping* 2007;**20**:321–29. https://doi.org/10.1080/10615800701282252

Shao R, Sun D, Lee TMC. The interaction of perceived control and Gambler's fallacy in risky decision making: an fMRI study. *Human Brain Mapp* 2016;**37**:1218–34. https://doi.org/10.1002/hbm.23098

Skinner EA. Perceived control: motivation, coping, and development. In: Schwarzer R (ed.), *Self-Efficacy*. New York: Taylor & Francis, 1992, 91–106.

Skinner EA, Zimmer-Gembeck MJ. Perceived control and the development of coping. In: Folkman S (ed.), *The Oxford Handbook of Stress, Health, and Coping*. New York: Oxford University Press, 2011.

Slavich GM. Life stress and health: a review of conceptual issues and recent findings. *Teach Psychol* 2016;**43**:346–55. https://doi.org/10.1177/0098628316662768

Smith AW, Mitchell SA, De Aguiar K *et al*. News from the NIH: person-centered outcomes measurement: NIH-supported measurement systems to evaluate self-assessed health, functional performance, and symptomatic toxicity. *Transl Behav Med* 2016;**6**:470–74. https://doi.org/10.1007/s13142-015-0345-9

Sperduti M, Delaveau P, Fossati P *et al*. Different brain structures related to self- and external-agency attribution: a brief review and meta-analysis. *Brain Struct Funct* 2011;**216**:151–57. https://doi.org/10.1007/s00429-010-0298-1

Srirangarajan T, Mortazavi L, Bortolini T *et al*. Multi-band FMRI compromises detection of mesolimbic reward responses. *NeuroImage* 2021;**244**:118617. https://doi.org/10.1016/j.neuroimage.2021.118617

Treharne GJ, Lyons AC, Booth DA *et al*. Psychological well-being across 1 year with rheumatoid arthritis: coping resources as buffers of perceived stress. *Br J Health Psychol* 2007;**12**:323–45. https://doi.org/10.1348/135910706X109288

Valikhani A, Kashani VO, Rahmanian M *et al*. Examining the mediating role of perceived stress in the relationship between mindfulness and quality of life and mental health: testing the mindfulness stress buffering model. *Anxiety Stress Coping* 2020;**33**:311–25. https://doi.org/10.1080/10615806.2020.1723006

Wang KS, Delgado MR. Corticostriatal circuits encode the subjective value of perceived control. *Cereb Cortex* 2019;**29**:5049–60. https://doi.org/10.1093/cercor/bhz045

Wang KS, Delgado MR. The protective effects of perceived control during repeated exposure to aversive stimuli. *Front Neurosci* 2021;**15**:625816. https://doi.org/10.3389/fnins.2021.625816

Wang KS, Kashyap M, Delgado MR. The influence of contextual factors on the subjective value of control. *Emotion* 2021a;**21**:881–91. https://doi.org/10.1037/emo0000760

Wang KS, Yang YY, Delgado MR. How perception of control shapes decision making. *Curr Opin Behav Sci* 2021b;**41**:85–91. https://doi.org/10.1016/j.cobeha.2021.04.003

White R. Motivation reconsidered: the concept of competence. *Psychol Rev* 1959;**66**:297. https://doi.org/10.1037/h0040934

Wyrwich KW, Harnam N, Revicki DA *et al*. Assessment of quality of life enjoyment and satisfaction questionnaire-short form responder thresholds in generalized anxiety disorder and bipolar disorder studies. *Int Clin Psychopharmacol* 2011;**26**:121–29. https://doi.org/10.1097/YIC.0b013e3283427cd7

Zou H, Hastie T. Regularization and variable selection via the elastic net. *J R Stat S Soc Ser B* 2005;**67**:301–20. https://doi.org/10.1111/j.1467-9868.2005.00503.x

Social Cognitive and Affective Neuroscience, 2024, 19(1), nsae075, DOI: https://doi.org/10.1093/scan/nsae075, Advance Access Publication Date: 18 October 2024, Original Research – Neuroscience

Received: 16 January 2024; **Revised**: 14 August 2024; **Accepted**: 17 October 2024

Brain encoding during perceived control as a prospective predictor of improvement in quality of life

Supplemental Information

Supplemental Methods

Supplemental Results

Supplemental Methods

Inclusion/exclusion criteria

Inclusion criteria included: 20-32 years old, female, right-handed, no current or past use of psychotropic medications, absence of any current/past medical, neurological, or psychiatric illness (including alcohol/substance abuse), absence of first-degree relatives with a history of psychiatric illness, absence of childhood maltreatment, no history of significant head injury or concussion, and no MRI contraindications. Recruitment was completed mainly using online advertisements. Study data were collected and managed using REDCap electronic data capture tools (Harris *et al.*, 2009).

MRI data acquisition

Functional MRI data were acquired during the VOC task using a multiband GE-EPI sequence with the following parameters: TR=800 msec, TE=37 msec, image matrix=104×104, in-plane field of view=208x208 mm, flip angle=52°, 2.0 mm isotropic voxels, 72 interleaved slices with a multiband factor of 8. The VOC task included 4 runs, each of 300 measurements (i.e., a total of 1200 measurements were collected). Anatomical images were acquired using a high-resolution T1-weighted multi-echo MPRAGE sequence with TR=2530 msec, TE= 1.69, 3.55, 5.41, 7.27 msec, in-plane field of view=256x256 mm, voxel size=1x1x1 mm, 176 slices. The T1-weighted images were acquired for coregistration and normalization of the functional images.

MRI data preprocessing

Preprocessing of MRI data was performed using fMRIPrep 20.2.1 (Esteban *et al.*, 2019). The following description was taken from the custom language generated by fMRIPrep, which is recommended for use in publications and has been released under the CC0 license.

Anatomical data preprocessing: The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al. 2010), distributed with ANTs 2.3.3 (Avants et al. 2008, RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference

was then skull-stripped with a Nipype implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL 5.0.9, RRID:SCR_002823, Zhang, Brady, and Smith 2001). Brain surfaces were reconstructed using recon-all (FreeSurfer 6.0.1, RRID:SCR_001847, Dale, Fischl, and Sereno 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (RRID:SCR_002438, Klein et al. 2017). Volume-based spatial normalization to two standard spaces (MNI152NLin2009cAsym, MNI152NLin6Asym) was performed through nonlinear registration with antsRegistration (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: ICBM 152 Nonlinear Asymmetrical template version 2009c [Fonov et al. (2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym], FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration Model [Evans et al. (2012), RRID:SCR_002823; TemplateFlow ID: MNI152NLin6Asym].

Functional data preprocessing: First, a reference volume and its skull-stripped version were generated by aligning and averaging 1 single-band references (SBRefs). A deformation field to correct for susceptibility distortions was estimated based on fMRIPrep's fieldmap-less approach. The deformation field is that resulting from co-registering the BOLD reference to the same-subject T1w-reference with its intensity inverted (Wang et al. 2017; Huntenburg 2014). Registration is performed with antsRegistration (ANTs 2.3.3), and the process regularized by constraining deformation to be nonzero only along the phase-encoding direction, and modulated with an average fieldmap template (Treiber et al. 2016). Based on the estimated susceptibility distortion, a corrected EPI (echo-planar imaging) reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using bbregister (FreeSurfer) which implements boundary-based registration (Greve and Fischl 2009). Co-registration was configured with six degrees of freedom. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation

parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 5.0.9, Jenkinson et al. 2002). BOLD runs were slice-time corrected using 3dTshift from AFNI 20160207 (Cox and Hyde 1997, RRID:SCR_005927). First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. The BOLD time-series were resampled onto the following surfaces (FreeSurfer reconstruction nomenclature): fsaverage. The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. These resampled BOLD time-series will be referred to as preprocessed BOLD in original space, or just preprocessed BOLD. The BOLD time-series were resampled into standard space, generating a preprocessed BOLD run in MNI152NLin2009cAsym space. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. Automatic removal of motion artifacts using independent component analysis (ICA-AROMA, Pruim et al. 2015) was performed on the preprocessed BOLD on MNI space time-series after removal of non-steady state volumes and spatial smoothing with an isotropic, Gaussian kernel of 6mm FWHM (full-width half-maximum). Corresponding "non-aggressively" denoised runs were produced after such smoothing.

Locus of control, stress, and quality of life: an alternative approach

As an alternative model, we tested whether changes in perceived stress or quality of life could be predicted from the subjective report of locus of control rather than brain response to control. Locus of control was measured using the Locus of Control Scale (LOC) (Rotter, 1966). The LOC is a 29-item questionnaire that evaluates an individual's sense of internal vs. external control, that is, how much they perceive events as dependent on their own behavior. Items were summed together to obtain a total score (possible range: 1 to 23), where higher scores indicate an external locus of control and lower scores indicate an internal locus of control.

Supplemental Results

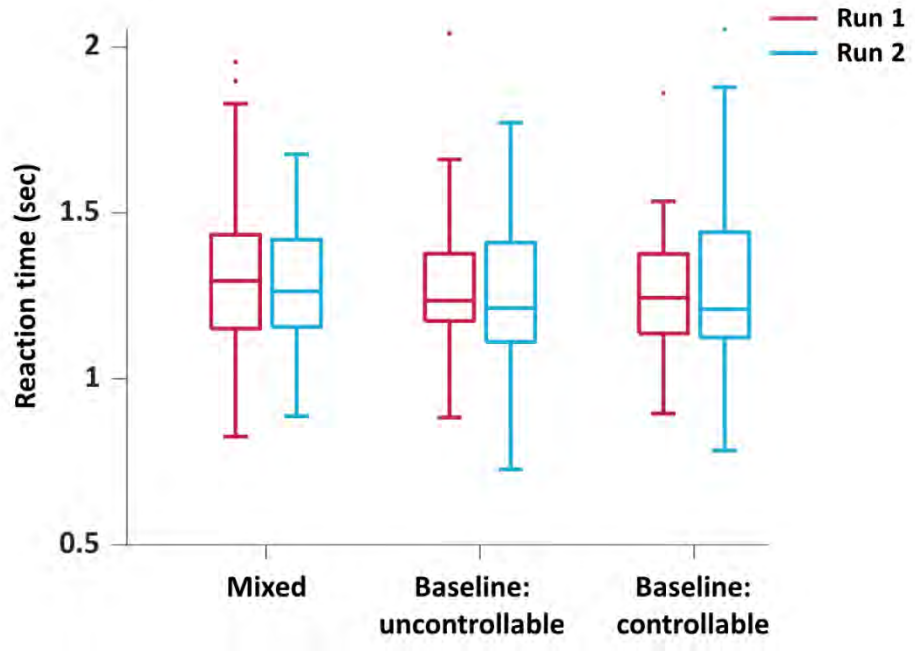
Supplemental Table 1. Correlations among scales over time

The table below presents Pearson's correlations between the Locus of Control Scale (LOC) (Rotter, 1966) at baseline, Perceived Stress Scale (PSS) (Cohen *et al.*, 1983) at baseline and 6-month follow-up (6M), and Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q) (Endicott *et al.*, 1993) at baseline and 6M.

	Locus of control baseline	**PSS baseline**	**PSS 6M**	**Q-LES-Q baseline**	**Q-LES-Q 6M**
Locus of control baseline	1	0.22	0.17	-0.17	-0.01
PSS baseline	0.22	1	0.57*	-0.43*	-0.33
PSS 6M	0.17	0.57*	1	-0.34	-0.70*
Q-LES-Q baseline	-0.17	-0.43*	-0.34	1	0.57*
Q-LES-Q 6M	-0.01	-0.33	-0.70*	0.57*	1

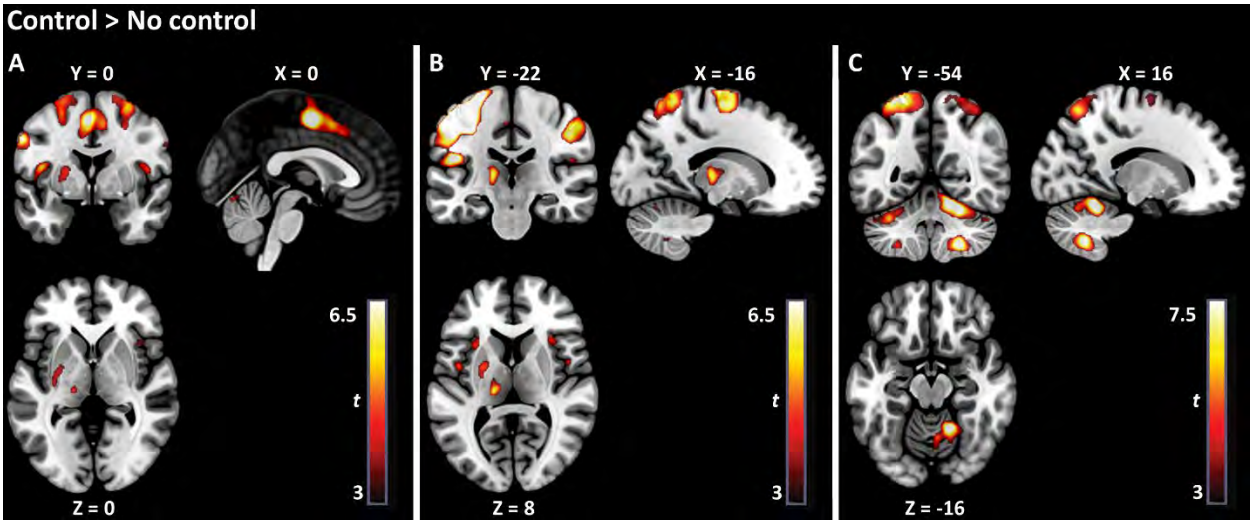
*$p<0.05$

Supplemental Figure 1. Controllability and run order did not impact reaction time



The boxplot presents the reaction time as a function of the condition (mixed, baseline uncontrollable, baseline controllable) and run order (first run indicated in red, second in blue). There were no effects of *Condition*, *Run*, or *Condition*-by-*Run* interaction [(i) main effect of *Condition*: $F(1.64,59.26)=1.76$, $p=0.17$, $\eta_p^2=0.04$, Greenhouse-Geisser corrected; (ii) main effect of *Run*: $F(1,36)=0.01$, $p=0.89$, $\eta_p^2=0.001$; (iii) *Condition*-by-*Run* interaction: $F(1.54,55.56)=2.61$, $p=0.09$, $\eta_p^2=0.06$, Greenhouse-Geisser corrected].

Supplemental Figure 2. Brain activation to control: across mixed and baseline conditions



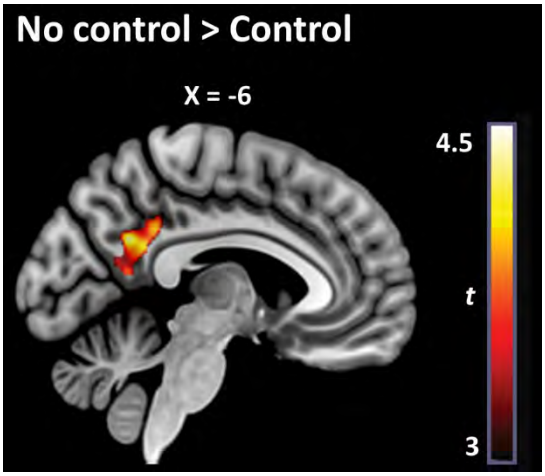
Brain clusters showing greater response to control (control > no control) across mixed and baseline conditions. For comparison, the same MNI coordinates were used as in Figure 4. Brain clusters included: **(A)** bilateral motor cortex, mid-cingulate cortex, left putamen, and bilateral insula; **(B)** left thalamus; **(C)** bilateral cerebellum. *t* values are indicated by the color bar. Uncorrected voxel-level $p<0.001$, FDR cluster-extent corrected for multiple comparisons at $p<0.05$.

Supplemental Table 2. Brain activation to control: across mixed and baseline conditions

Brain cluster (control > no control)	Peak MNI (mm)			Cluster *p* value	Cluster size
	x	y	z	(FDR corrected)	(voxels)
L precentral and postcentral gyri, L and R supplementary motor areas, mid-cingulate cortex	-36	-26	58	$<10^{-4}$	9011
R cerebellum, anterior and posterior lobes	16	-52	-18	$<10^{-4}$	1384
R cerebellum, posterior lobe	24	-54	-50	$<10^{-4}$	737
R precentral gyrus	30	-8	58	$<10^{-4}$	1252
R postcentral gyrus	58	-14	38	$<10^{-4}$	3371
L precentral gyrus	-60	2	36	$<10^{-4}$	292
L insula	-42	-4	14	0.001	151
L cerebellum, anterior and posterior lobes	-34	-54	-30	$<10^{-4}$	493
L thalamus	-16	-22	6	$3.05 \cdot 10^{-4}$	169
L cerebellum, posterior lobe	-28	-52	-52	0.001	132
L putamen	-24	-2	10	$<10^{-4}$	240
R inferior frontal gyrus	46	0	10	0.012	69
L insula	-32	14	6	0.002	116
R middle frontal gyrus (R DLPFC)	36	48	18	$<10^{-4}$	482
R insula	32	20	8	0.002	114
L middle frontal gyrus (L DLPFC)	-40	42	30	0.047	41

Abbreviations: DLPFC, dorsolateral prefrontal cortex; L, left; R, right.

Supplemental Figure 3. Brain activation to lack of control: across mixed and baseline conditions



The posterior cingulate cortex showed greater response to lack of control (no control > control) across mixed and baseline conditions (MNI peak coordinates: [-6 -56 28], cluster size: 362, cluster *p* value FDR corrected: $<10^{-4}$). Coordinates are presented in MNI space and *t* values are indicated by the color bar. Uncorrected voxel-level $p<0.001$, FDR cluster-extent corrected for multiple comparisons at $p<0.05$.

References

Cohen, S., Kamarck, T., Mermelstein, R. (1983). A global measure of perceived stress. *Journal of health and social behavior*, **24**, 385–96

Endicott, J., Nee, J., Harrison, W., et al. (1993). Quality of life enjoyment and satisfaction questionnaire: A new measure. In: *Psychopharmacology Bulletin*. p. 321–26.

Esteban, O., Markiewicz, C.J., Blair, R.W., et al. (2019). fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nature Methods*, **16**, 111–16

Harris, P.A., Taylor, R., Thielke, R., et al. (2009). Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, **42**, 377–81

Rotter, J.B. (1966). Generalized expectancies for internal versus external control of reinforcement. *Psychological Monographs*, **80**, 1–28