OXFORD

Cerebral Cortex, May 2020;30: 3116–3129

doi: 10.1093/cercor/bhz298
Advance Access Publication Date: 14 December 2019
Original Article

ORIGINAL ARTICLE

Subjective Uncontrollability over Aversive Events Reduces Working Memory Performance and Related Large-Scale Network Interactions

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Abstract

Lack of control over significant events may induce a state of learned helplessness that is characterized by cognitive, motivational, and affective deficits. Although highly relevant in the pathogenesis of several mental disorders, the extent of the cognitive deficits induced by experiences of uncontrollability and the neural mechanisms underlying such deficits in humans remain poorly understood. Using functional magnetic resonance imaging **(fMRI), we tested here whether uncontrollability over aversive events impairs subsequent working memory performance and, if so, which neural processes are involved in such deficits. We assessed working memory and the involved neurocircuitry in the MRI scanner before and after participants underwent a task in which they could either learn to avoid electric shocks or had no instrumental control over shocks. Our results show that subjective, but not objective, uncontrollability over aversive events impaired working memory performance. This impact of subjective uncontrollability was linked to altered prefrontal and parahippocampal activities and connectivity as well as decreased crosstalk between frontoparietal executive and salience networks. Our findings show that the perceived uncontrollability over aversive events, rather than the aversive events themselves or the actual, objective control over them, disrupts subsequent working memory processes, most likely through altered crosstalk between prefrontal, temporal, and parietal areas.**

Key words: learned helplessness, parahippocampal gyrus, perceived controllability, prefrontal cortex, stress

Introduction

Stressful experiences are ubiquitous in our daily life and can have serious effects on our health and well-being (McEwen 1998). There are, however, psychological processes that may buffer the adverse consequences of such experiences. In particular, the feeling of control over aversive events alleviates the deleterious effects of these events. In contrast, lack of control over events in the environment may induce a state of *learned helplessness* that is characterized by severe cognitive, emotional, and motivational deficits (Overmier and Seligman 1967; Seligman and Maier 1967) and may ultimately contribute to psychopathology (Miller and Seligman 1975). Indeed, learned helplessness is thought to be a key factor in several mental disorders, including major depression, anxiety disorders, and posttraumatic stress disorder (PTSD; Abramson et al. 1978; Overmier and Hellhammer 1988; Foa et al. 1992; Hammack et al. 2012). Moreover, learned helplessness is a major model of anxiety and mood disorders in preclinical animal research that is sensitive to both anxiolytic and antidepressant drugs (Short and Maier 1993; Reines et al. 2008; Hammack et al. 2012).

Accordingly, a large body of research in nonhuman animals was directed at understanding the neural underpinnings of learned helplessness. Early studies showed that uncontrollable aversive events activate serotonergic neurons in the dorsal raphe nucleus far more than equal controllable events and that this activation is both necessary and sufficient to evoke the behavioral changes associated with learned helplessness (Grahn et al. 2000; Maier et al. 1993; Maswood et al. 1998). Furthermore, a series of experiments in rats provided compelling evidence that the ventromedial prefrontal cortex detects control over aversive

events and subsequently inhibits activation of serotonergic neurons within the dorsal raphe nucleus and hence prevents the release of serotonin and symptoms of learned helplessness (Amat et al. 2005; Amat et al. 2006; Amat et al. 2008).

Although initially demonstrated in dogs (Overmier and Seligman 1967; Seligman and Maier 1967), learned helplessness has been established in humans as well. For instance, participants exposed to inescapable noise or unsolvable discrimination problems later failed to escape noise or solve anagrams (Abramson et al. 1978; Miller and Norman 1979). However, the neural mechanisms underlying cognitive deficits after exposure to uncontrollable events in humans are largely unknown. The few studies that aimed to assess the neural underpinnings of learned helplessness in humans so far lacked an appropriate test of the core feature of learned helplessness, i.e., cognitive or behavioral alterations after an experience of (un)controllability over aversive events (Schneider et al. 1996; Fretska et al. 1999; Bauer et al. 2003; Salomons et al. 2004; Salomons et al. 2007; Diener et al. 2009). Moreover, most of these studies employed a cross-over design, which precludes the possibility to study learned helplessness effects (Pryce et al. 2011).

In the present experiment, we examined, for the first time, the impact of (un)controllability over aversive events on subsequent working memory performance, a fundamental cognitive process that is sensitive to stress (Qin et al. 2009; Arnsten et al. 2012) and impaired in many stress-related mental disorders (Goldman-Rakic 1994; Snyder 2013; Honzel et al. 2014), and used functional magnetic resonance imaging (fMRI) to elucidate the underlying neural mechanisms. We used the classic "triadic" design, in which participants were assigned to one of three experimental groups: (i) a *controllability* group, which could learn how to avoid electric shocks; (ii) a yoked *uncontrollability* group, which received exactly the same number of shocks as participants in the controllability group, yet noncontingent to the own behavior, i.e., without instrumental control; and (iii) a *no-shock control* group that did not receive any shocks and served as a control group. Working memory performance was assessed, in the MRI scanner, both before and after this manipulation of controllability. As working memory performance has been found to rely on a range of distributed brain regions (Cohen et al. 1997; Rottschy et al. 2012; Eriksson et al. 2015; Christophel et al. 2017) and network interactions (Gordon et al. 2012; Liang et al. 2016), we also examined whether (un)controllability affected large-scale network interactions during the working memory task. Because appraisal processes are known to play an important role in the development of learned helplessness (Abramson et al. 1978), we measured also the subjectively experienced control over aversive events through a rating questionnaire immediately after the MRI session. Based on the averaged controllability ratings, we subdivided participants into high and low subjective controllability subjective controllability groups in order to distinguish effects of subjective and actual (un)controllability over aversive events on working memory and its neural underpinnings, a distinction that is not feasible in preclinical animal studies.

Methods and Materials

Participants and Experimental Design

Seventy-five healthy, right-handed men and women with normal or corrected-to-normal vision participated in this experiment. The sample size was determined based on pilot testing and an a priori power calculation (Faul et al. 2007) showing that this sample size is sufficient to detect a medium-sized effect with a power of 0.95. Exclusion criteria were checked in a standardized interview and comprised a lifetime history of any neurological or psychiatric disorders, medication intake or drug abuse, and any MRI contraindications. Seven participants had to be excluded from analysis either because no electric shocks were delivered due to technical failure ($n = 2$), because they did not learn to avoid shocks in the controllability condition (criterion: > 40 out of 50 possible shocks and no or fewer than 5 consecutive shock-avoiding button presses; $n = 4$) or because they performed below 65% accuracy on the n-back task in the baseline session ($n = 2$), resulting in a sample of 67 participants (33 women; age (years): $M = 24.10$, $SD = 3.31$) for behavioral analyses. Four additional participants had to be excluded due to excessive head motion in the scanner, thus leaving a sample of 63 participants (32 women; age (years): $M = 24.17$, $SD = 3.31$) for the fMRI analyses. A post hoc power analysis confirmed that this final sample size was still sufficient to detect a medium-sized effect with a power of.94. All participants provided written informed consent before testing and received a monetary compensation for participation. The study protocol was approved by the local ethics committee (PV5120).

In order to test the impact of uncontrollability on working memory, we used a mixed-design in which working memory was assessed both before and after the manipulation of controllability, and participants were randomly assigned to one of three controllability groups: a controllability group ($n = 22$), a yoked uncontrollability group ($n = 23$), or a no-shock group ($n = 22$).

Working Memory Assessment

To assess working memory performance before and after the manipulation of controllability, we used the n-back task (Kirchner 1958), a well-established measure of working memory that has been shown to be sensitive to cognitive deficits in several mental disorders (Goldman-Rakic 1994; Snyder 2013; Honzel et al. 2014) as well as to stress manipulations in healthy individuals (Qin et al. 2009). In this task, participants saw a series of one-digit numbers one after another on a screen and were instructed to indicate for each number whether the number was identical to the number shown in n trials before or not by pressing one of two buttons ("yes"/"no") in a cylindrical button box (Current Designs Inc., Philadelphia, USA). Prior to MRI scanning, participants performed a brief training session involving short blocks (4×12 trials) of each n-back level used in the task later on. If overall accuracy during training was below 60%, the training was repeated. In the scanner, participants first performed a baseline session involving four 18-trial blocks of n-back levels 0, 2, and 3 (i.e., 12 blocks in total), presented in a pseudo-randomized order in order to ensure that consecutive blocks did not involve the same n-back level and that each block type was present at the beginning, middle, and end of the session. While 2- and 3-back tested working memory performance at different loads, the 0-back condition served as a control for working memory processes. Here, participants were asked to decide whether the number on the screen was different from zero or not. The basic trial procedure was identical for all n-back levels and consisted of a stimulus presentation (number between 0 and 9) for 500 ms, a response window (including stimulus presentation) of 1500 ms and an intertrial interval of 1500 ms (Fig. 1). To ensure that participants responded in time and did not confuse the button-response assignment, a rectangle appeared around the

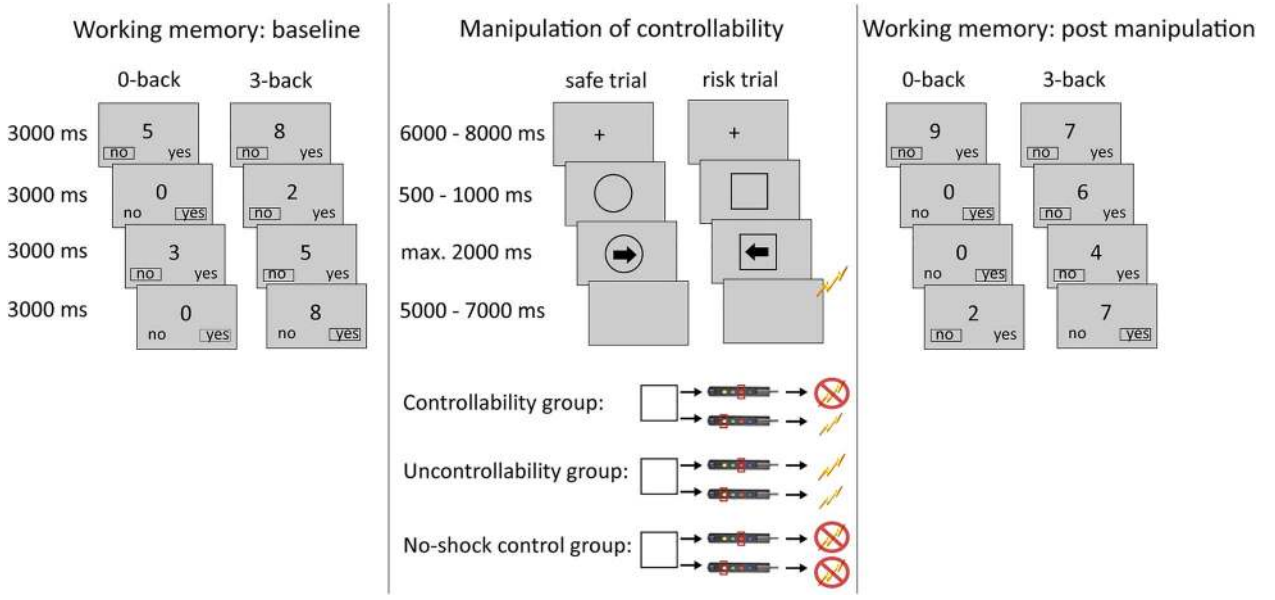

Figure 1. Experimental design. Participants performed an n-back task, probing working memory, in the MRI scanner before and after a manipulation of controllability. In the n-back task, participants were requested to indicate whether a shown number was identical to the number shown in three trials before (3-back) or whether it was 0 (0-back), with the 0-back trials serving as visual-motor control trials. In the manipulation of controllability, each trial started with a fixation cross, followed by a frame (circle or square) signaling risk of shock or safety. Participants were instructed to press one out of four buttons when an arrow pointing to the left or right appeared within the frame. Depending on the experimental group and individual response, participants could receive a brief (100 ms) electric shock. Participants in the experimental controllability group could learn to avoid shocks in risk trials by pressing the third button on a four-button response box (upper image of response box), whereas they received a shock whenever they pressed no button or one of the other three buttons within the 2000 ms response window (e.g., when they pressed the first button, as depicted in the lower response box image). Participants in the uncontrollability group were yoked to a participant in the controllability group and were exposed to exactly the same sequence of experimental trials and shock deliveries. Thus, they received the same number of shocks at the exact same time points as their yoked counterpart in the controllability group but had no instrumental control over shock delivery. The no-shock control group received no shocks and served as control group.

selected response alternative on the screen after each button press made within the response window. Between blocks a fixation cross was presented for 13 s, which was followed by a 5 s-announcement of the n-back level of the next block.

After the manipulation of controllability (see below), participants performed a second n-back session, again in the MRI scanner, which was identical to the first one, except that n-back levels 0, 3, and 4 were used. We chose different n-back levels for the two sessions because we aimed to avoid feelings of distress and helplessness during the baseline session, and, at the same time, aimed at a higher level of difficulty in the second working memory test session because we expected practice effects after the baseline session (Bogdanov and Schwabe 2016). Leaving levels 0 and 3 constant across sessions, we ensured that working memory performance could be compared between the pre- and postmanipulation sessions.

Manipulation of Controllability

After the baseline working memory session, participants underwent a manipulation of controllability, which differed critically between groups (Fig. 1). Participants in the *controllability* group could learn a behavioral response to avoid electric shocks, whereas participants in the (yoked) *uncontrollability* group received an identical number of shocks at the exact same timings as their counterpart in the controllability group, but without instrumental control over shock delivery. Participants in the *no-shock control* group received no shocks and served as control group. Before the task, shock electrodes were placed at the lower leg of participants in the controllability and uncontrollability groups, and we individually determined a shock level that was perceived to be "unpleasant, but not yet painful" using a standard workup procedure starting from 20 V. For the controllability and uncontrollability group, the task comprised 50 safe trials and 50 risk trials, whereas all trials were neutral for the no-shock control group. Each trial started with a black fixation cross (6000–8000 ms) presented on a light gray background, followed by a frame (circle or square) signaling risk or safety. After 500–1000 ms, an arrow pointing to the left or right appeared within that frame. Frame and arrow stayed on the screen until participants pressed one out of four buttons, with a maximum response time of 2000 ms. Next, a blank screen was shown for 5000–7000 ms, which was followed by a brief (100 ms) electric shock depending on experimental condition and participants' behavioral response. We instructed participants of all groups to press one out of four buttons whenever an arrow appeared on the screen in both safe and risk trials. Participants in the controllability group could learn to avoid electric shocks in risk trials by pressing the third button on a four-button response box when the arrow appeared within the frame, irrespective of the direction the arrow pointed to. Accordingly, participants in the controllability group received a shock in risk trials in which they gave a wrong or no behavioral response. In addition, they received a shock in 10% of risk trials irrespective of their actual response to prevent a clear-cut end of risk trials with and without shocks in the yoked uncontrollability group. Participants in the uncontrollability group were yoked to a participant in the controllability group. More specifically, we replayed the exact sequence of experimental trials and shock deliveries from a participant of the controllability group

for a participant of the uncontrollability group. Thus, while participants in the controllability and uncontrollability groups were matched with respect to shock number and timing, there was no contingency between behavioral response and shock delivery in the uncontrollability group, but participants in the uncontrollability group received an electric shock whenever their counterpart in the controllability group had received an electric shock. Whether circle or square signaled risk and safety, respectively, was counterbalanced across participants. To ensure that participants in the controllability and uncontrollability condition could learn to differentiate between safe and risk trials from the beginning of the task, the first three risk trials were always followed by a shock. Furthermore, to prevent a clear-cut end of electric shocks after learning the required response in the controllability group, and as a consequence an illusory control in the uncontrollability group, participants randomly received an electric shock in 1 out of 10 trials irrespective of their behavioral response. To avoid that this would affect their perception of controllability, participants in the controllability group were explicitly instructed that they could "significantly decrease the risk of receiving a shock when performing the correct response," whereas participants in the uncontrollability group were instructed that they could "reliably avoid shocks when performing the correct response." The trial order was pseudo-randomized to avoid that more than three trials of the same type (risk vs. safe) occur in a row. After the second n-back session, participants rated the two n-back sessions and the controllability manipulation task on controllability, helplessness, stress, and motivation on a scale from 0 to 100 using a 12-item rating questionnaire for each experimental session (see Supplemental Table 3 for averaged ratings on the controllability manipulation task).

Control Variables

In order to control for potential group differences in state and trait anxiety, depressive mood, chronic stress level, and attributional style, participants completed German versions of the State-Trait Anxiety Inventory (STAI; Spielberger et al. 1970), Beck's Depression Inventory (BDI; Beck and Steer 1987), Trier Inventory of Chronic Stress (TICS; Schulz et al. 2004), and the Attributional Style Questionnaire for adults (ASF-E; Poppe et al. 2005). We further collected saliva samples before the experiment to explore potential differences in baseline cortisol and measured blood pressure at the beginning and the end of the experiment as a measure of physiological arousal.

Behavioral Analysis

To assess changes in working memory performance after the manipulation of controllability, we used a mixed-design ANOVA with group (controllability vs. uncontrollability vs. no-shock control) as between-subject factor and session (baseline vs. post- manipulation) and n-back level (0-back vs. 3-back) as within-subject factors. In order to correlate changes in performance with other variables, such as controllability ratings, we calculated differential performance scores for the n-back levels 0-back and 3-back by subtracting accuracy during the baseline session from accuracy after the manipulation. All analyses were performed both for the groups as experimentally designed and for groups based on their subjective controllability ratings. Specifically, we performed a median split based on the controllability ratings for the controllability manipulation task, separately for the experimental controllability and uncontrollability group. After exploring potential interaction effects between objective and subjective controllability on n-back performance, participants in the experimental controllability and uncontrollability group scoring high on controllability (above the experimental group median) were assigned to a subjective controllability (SubCON) group, and those scoring below the median were assigned to a subjective uncontrollability (SubUNCON) group. We performed separate median splits for the two groups because they were given slightly different instructions regarding the controllability of electric shocks. Participants in the controllability group knew that they could control the majority but not all electric shocks, and thus, we expected that this might result in an anchoring effect and slightly shift their subjective controllability scale towards the maximum. The two group medians ($Med_{Uncon} = 65$, $Med_{Con} = 75$) did, however, differ only minimally from the total median ($Med_{total} = 70$). Consequently, defining subjective (un-) controllability groups based on the total median would have resulted in virtually the same group assignment. Although we believe that our approach to assign participants into subjective (un-)controllability groups is more appropriate, as it accounts for a potential anchoring bias, we performed an additional analysis in which we split participants into subjective controllability and uncontrollability groups based on the overall median ($Med_{total} = 70$). Importantly, using the overall median left the pattern of results largely unchanged (see supplemental material). The experimental no-shock control group was used as a control group for both types of analyses (experimental controllability and subjective controllability). Behavioral analyses reported here include the full behavioral sample, but analyses including the fMRI subsample only yielded basically identical results (see supplemental material). Data analysis was performed using SPSS 22 (IBM, New York, USA), and all reported *P* values are two-tailed.

Acquisition and Analysis of fMRI Data

MRI data were acquired using a 3 T Siemens Prisma Scanner, equipped with a 64-channel head coil. The MRI session consisted of three functional runs, a high-resolution T1-weighted anatomical image collected at the beginning of each session (TR = 2500 ms, TE = 2.12 ms, 256 slices, voxel size = 0.8 × 0.8 × 0.9 mm^3), and a magnetic (B0) field map to unwarp the functional images (TR = 634 ms, $TE_1 = 4.92$ ms, $TE_2 = 7.38$ ms, 40 slices, voxel size = 2.9 × 2.9 × 3.0 mm^3). For the functional scans, interleaved T2∗-weighted gradient-echo echo planar imaging sequences were used to obtain 60 2-mm-thick oblique axial slices (TR = 2000 ms, TE = 30 ms, flip angle = 60°, FOV = 224). Participants viewed the screen via a mirror mounted on the head coil. We analyzed fMRI data using scripted batches in SPM12 (The Wellcome Trust Center for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), running under MATLAB R14a (The MathWorks Inc., Natick MA, USA). We discarded the first four volumes to allow for magnetic field (T1) equilibration. The images were first spatially realigned and unwarped using the FieldMap Toolbox in SPM12 and then coregistered to the structural image. After normalization to Montreal Neurological Institute (MNI) space, data were finally smoothed with an 8 mm full-width half-maximum Gaussian kernel.

Preprocessed images were then analyzed using a two-level general linear modeling approach as implemented in SPM12. The first-level model contained a 54 s boxcar function for the

onset of each n-back condition (0-back, 2-back, and 3-back in the baseline session; 0-back, 3-back, and 4-back in the postmanipulation session) as regressors of interest, each convolved with the hemodynamic response function. We created linear contrast maps for the contrast "3-back vs. 0-back", which were then subjected to a second-level full factorial model including the factors group and session. We performed a hypothesis-driven regions of interest (ROI) analysis using regions that have previously been associated with n-back performance (e.g., Allen et al. 2006; Harvey et al. 2005) and altered working memory after exposure to stressful events (Qin et al. 2009), with a particular focus on prefrontal areas, which have been identified as key regions in working memory (D'Esposito et al. 1995, 1998; McCarthy et al. 1996; Barbey et al. 2013). Thus, our analysis included the insular cortex, inferior frontal gyrus, middle frontal gyrus, parahippocampal gyrus (PHG), precuneus, superior frontal gyrus, superior parietal lobule, caudate, pallidum, putamen, and thalamus. The referring brain masks were taken from the Harvard-Oxford Atlas with a probability threshold of 50%. We additionally used masks for the left and right dorsolateral prefrontal cortex (dlPFC) created with MARINA (http://www.bion.de/eng/MARINA.php). We applied a small-volume correction (SVC) for these ROIs, and the threshold for these analyses was set at a corrected voxel threshold of $P < 0.05$ (family wise error (FWE) corrected). All clusters reported include $k > 5$ voxels.

Using the MarsBar Toolbox (Brett et al. 2002), we then created spheres (radius: 5 mm) around peak values from a previous study showing stress-induced changes in working memory (Qin et al. 2009) and extracted percent signal change (PCT) for the regressors 0-back and 3-back, which were then combined to a pre-post measure (by subtracting baseline from postmanipulation estimates) and correlated with controllability ratings and differential n-back performance. In addition, we created 5-mm spheres around peak activations obtained for the working memory task at baseline (whole-brain level, FWE-corrected) in the present study.

We additionally performed a functional connectivity analysis based on the contrast "3-back > 0-back" using a psychophysiological interactions (PPI) approach as implemented in SPM12. In addition to our regressors, a PPI interaction term and the time course from the seed region was entered into our first-level PPI model. We then performed a full-factorial second-level PPI analysis based on the contrast PPI "3-back" > PPI "0-back" and applied a small-volume correction to our predefined ROIs to determine group differences in connectivity between these regions from baseline to postmanipulation. The seed region was defined as a sphere with a 6 mm radius around our peak level coordinates from the univariate analysis ([16 -36 -12], PHG).

To elucidate the impact of an experience of (un)controllability on network interactions, we further analyzed large-scale network interactions using the CONN Toolbox version 18b (Whitfield-Gabrieli and Nieto-Castanon 2012; http://www.nitrc.org/projects/conn). We used the implemented network atlas to parcellate structural brain images into eight networks (default mode, sensorimotor, visual, salience/cingulo-opercular, dorsal attention, frontoparietal/central executive, language, cerebellar) consisting of several ROIs each. Next, we extracted a mean time series of neuronal activation for each ROI to assess functional communication between ROIs. Raw time series were normalized to PCT, and we used a high-pass filter (0.008 Hz) to remove potential nuisance signals, white matter, and cerebrospinal fluid. We focused on networks that have been consistently reported to show changes in functional connectivity with changes in working memory load and performance (Gordon et al. 2012; Liang et al. 2016), in particular the frontoparietal executive and salience network and also the default mode network. We performed first- and second-level general linear modeling analyses including the predefined ROIs/networks and finally calculated within- and between-network connectivities for the pre- and postmanipulation sessions. Resulting P values were converted so that they represented two-tailed, false discovery rate (FDR) corrected values. We further extracted individual within- and between-connectivity values for both the baseline and postmanipulation session and entered them into a 3-way (group × condition (3-back > 0-back) x session (baseline vs. postmanipulation) ANOVA. We additionally correlated individual connectivity values with controllability ratings and working memory performance.

Results

Subjective, but not Objective, Uncontrollability over Aversive Events Reduces Working Memory Performance

Participants in the controllability and uncontrollability groups received a moderate number of shocks during the manipulation of controllability ($M = 19.89$; $SD = 7.91$; range: 11–43). Importantly, participants in the controllability group showed, across the task, a significant increase in performing the instrumental response that prevented the delivery of a shock in risk trials ($F(4,18) = 24.946$, $P < 0.001$; Fig. 2), suggesting that they learned how to avoid the shock, whereas there was no significant change in response selection in the yoked uncontrollability group ($F(4,19) = 1.711$, $P = 0.189$) or no-shock controls ($F(4,18) = 1.395$, $P = 0.275$). Subjective controllability ratings, however, varied considerably across participants (overall: $M = 65.556$; $SD = 23.890$; range: 0–95; controllability group: $M = 70.000$; $SD = 21.931$; range: 5–95; yoked uncontrollability group: $M = 61.304$; $SD = 25.371$; range: 0–95) and did not differ between groups ($t(43) = 1.228$, $P = 0.226$), underlining that the subjective experience of (un)controllability may be clearly distinct from the actual (objective) control over events.

In order to assess whether objective or subjective controllability over aversive events affects working memory performance, we compared the change in working memory performance from the baseline to the postmanipulation session in (i) our three experimental groups and (ii) high- vs. low-controllability groups based on the subjectively reported controllability vs. the no-shock control group. Overall, working memory performance increased from baseline to postmanipulation ($t(66) = -3.733$, $P < 0.001$, $d = -0.919$), as observed previously (Bogdanov and Schwabe 2016). Most interestingly, however, we obtained a significant subjective controllability ×session×n-back level interaction ($F(2,59) = 3.984$, $P = 0.024$, $\eta^2 = 0.119$), indicating that participants who experienced the shock delivery as uncontrollable were impaired in the 3-back condition, but not in the 0-back condition, in the postmanipulation session compared to participants who perceived the delivery of the shocks as controllable (change in 3-back performance from baseline to postmanipulation: $t(38) = 2.870$, $P = 0.007$, $d = 0.931$; change in 0-back performance from baseline to postmanipulation: $t(38) = 0.335$, $P = 0.739$, $d = 0.109$; baseline session: all $t < 0.815$, all $P > 0.392$, Fig. 2). Moreover, subjective ratings of controllability in the groups that received shocks were significantly correlated with differential 3-back performance ($r = 0.400$, $P = 0.007$), but not with 0-back performance ($r = 0.052$, $P = 0.736$). While these

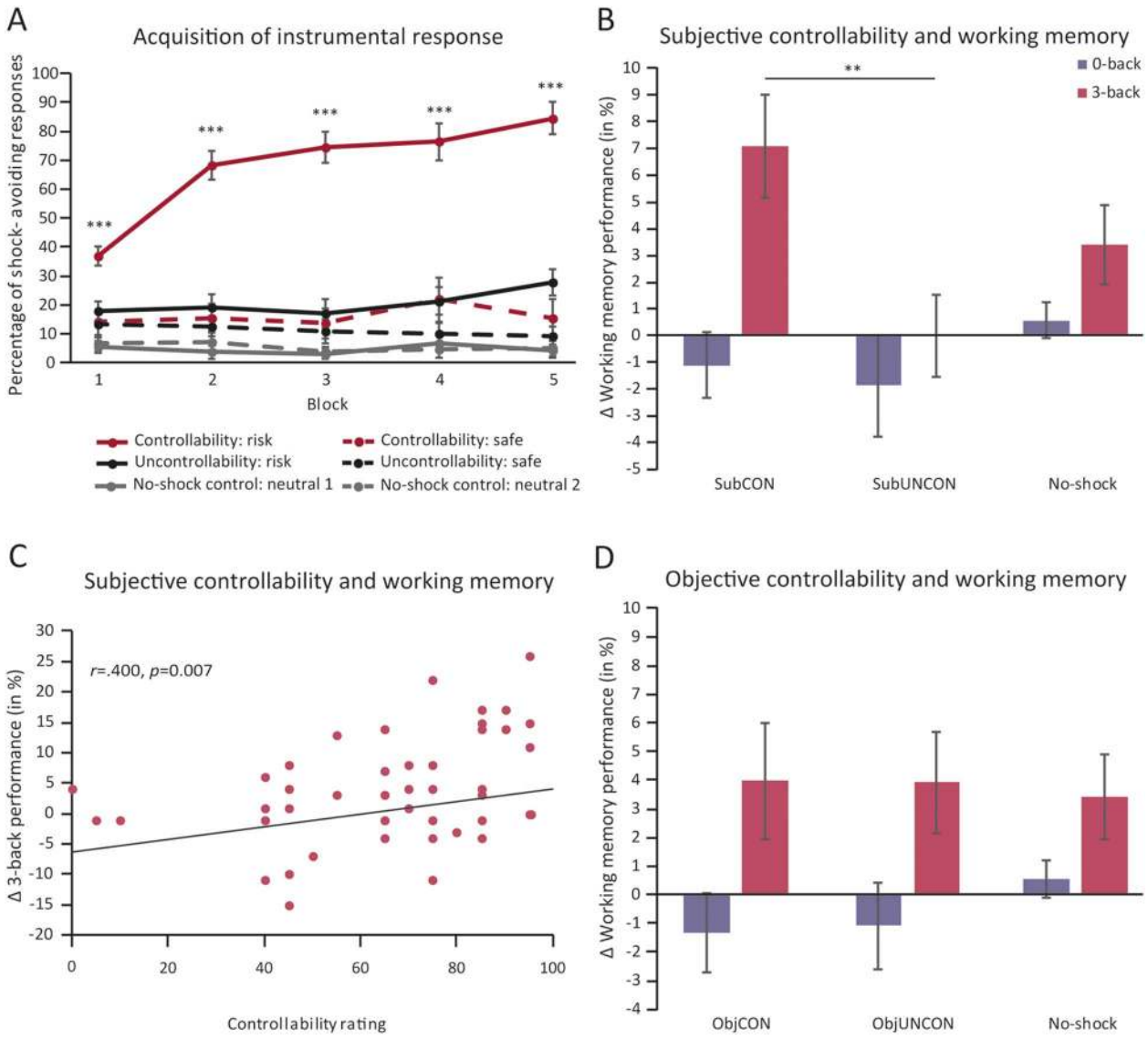

Figure 2. Behavioral results. (*A*) Percentage of shock-avoiding responses for experimental groups and trial types. These instrumental responses increased across 10 trial blocks in the experimental controllability group, indicating that they learned how to avoid the shock. (*B*) Differential working memory performance defined as change in accuracy from baseline to postmanipulation for the SubCON, SubUNCON, and no-shock control (no-shock) groups. SubUNCON was associated with significantly reduced differential 3-back, but not 0-back performance when compared to the SubCON group. (*C*) Subjective controllability was positively correlated with differential 3-back performance defined as change in the accuracy from baseline to postmanipulation. (*D*) No difference in differential working memory performance defined as change in accuracy from baseline to postmanipulation was seen between the ObjCON, ObjUNCON, and no-shock groups. Error bars represent standard errors of the mean. ** $P < 0.01$, *** $P < 0.001$.

data show a detrimental impact of subjective uncontrollability on working memory performance, objective (un)controllability, as reflected in our experimental group assignment, left working memory unaffected ($F(2,64) = 0.586$, $P = 0.560$, $\eta^2 = 0.018$, Fig. 2).

It might be argued that this detrimental influence of subjective uncontrollability over aversive events on working memory may be due to differences between individuals with high vs. low subjective controllability in the number of shocks received. We could, however, rule out this possibility. First, an analysis of covariance confirmed that subjective uncontrollability impaired working memory performance even when controlling for the influence of the number of shocks received ($F(1,37) = 5.333$, $P = 0.027$, $\eta^2 = 0.126$). Second, when we focused on a subsample of participants including only participants of the controllability group that experienced the delivery of shocks as controllable and their yoked twins from the uncontrollability group who experienced the shock delivery as uncontrollable ($n = 7$ each), i.e., in groups that had received an identical number of shocks, uncontrollability was still associated with an impairment of working memory performance (group×session×n-back level interaction: $F(1,12) = 8.845$ $P = 0.012$; driven by differential 3-back performance: $t(12) = 2.034$, $P = 0.065$, $d = 1.174$). Together, these behavioral data indicate that the subjective experience of uncontrollability over aversive events reduces working memory performance, irrespective of the actual instrumental control.

Table 1 Brain regions related to working memory (3-back > 0-back) during the baseline session

Brain regions	Cluster size	T value	MNI 152 coordinates x y z
Bilateral DLPFC/middle frontal gyrus Bilateral inferior frontal gyrus Bilateral superior frontal gyrus Cingulate gyrus Bilateral insula Bilateral precentral gyrus Left caudate Left putamen Left pallidum	12 267	12.29	2 18 50
Bilateral inferior parietal lobule Bilateral precuneus Bilateral superior parietal lobule Bilateral angular gyrus Bilateral supramarginal gyrus Bilateral postcentral gyrus	4965	12.02	46–36 46
Left cerebellum	1986	10.99	−34-64-30
Right cerebellum	1283	10.67	42–66-30
Left cerebellum	49	6.88	−10-56-52
Middle frontal gyrus Superior frontal gyrus	31	6.86	−20 46–14
Right caudate	127	6.58	16 4 18
Brain stem	78	6.38	6 -16-14
Right middle temporal gyrus Right inferior temporal gyrus	90	6.25	56–52-12
Right pallidum	21	5.59	14 4 2
Left thalamus	6	5.24	−6-18 16

Only clusters significant at $p_{FWE} < 0.05$, whole-brain corrected, are reported.

Neural Basis of Reduced Working Memory Performance Following Subjective Uncontrollability over Aversive Events

We next aimed to elucidate the neural underpinnings of the disruptive influence of subjective uncontrollability on working memory. First, we identified brain regions involved in working memory across groups. In line with previous research (Cohen et al. 1997; Rottschy et al. 2012; Eriksson et al. 2015; Christophel et al. 2017), a whole-brain analysis revealed significantly higher activation in 3-back vs. 0-back trials in a number of regions, including the bilateral dlPFC, inferior frontal gyrus, and caudate nucleus (all $p_{FWE} < 0.05$; see Table 1). Moreover, pre-post PCT estimates were negatively correlated with differential 3-back performance in the right dlPFC ($r = -0.228$, $P = 0.072$; for controllability and uncontrollability groups only: $r = -0.356$, $P = 0.021$), indicating that a decrease of activation in the right dlPFC from the pre- to the postmanipulation session was associated with an increase in 3-back performance.

In order to identify the neural basis of the observed reduction in working memory performance due to subjective uncontrollability over aversive events, we next performed a full factorial model based on the contrast 3-back vs. 0-back with the factors subjective controllability and session. This analysis yielded a significant subjective controllability × session interaction in the posterior division of the PHG ([16-36-12], $p_{SVC} = 0.012$, FWE-corrected), a region that has been implicated in working memory processes before (Luck et al. 2010; Libby et al. 2014; Schon et al. 2016). Follow-up tests showed that this effect in the posterior PHG was driven by decreased activities in the SubUNCON group as compared to the SubCON group in the postmanipulation session ([18-28-18], $p_{SVC} = 0.021$, FWE-corrected; Fig. 3).

In line with our behavioral findings, no systematic treatment-related activations were observed when analyzing the impact of the objective controllability objective controllability over aversive events (i.e., the actual experimental groups) on working memory-related brain activities.

Next, we sought to elucidate the association between subjective controllability ratings and brain areas implicated in working memory, harnessing the substantial individual variability in subjective controllability in a correlational analysis. Due to a large number of studies pointing to a key role of prefrontal regions in working memory (D'Esposito et al. 1995, 1998; McCarthy et al. 1996; Barbey et al. 2013), we focused first on prefrontal areas. We identified peaks of prefrontal activation based on coordinates reported in previous studies on stress and working memory (Harvey et al. 2005; Allen et al. 2006; Qin et al. 2009) and based on contrast maps for 3-back vs. 0-back in the baseline session of the present study. Interestingly, these analyses revealed a significant negative correlation between the controllability ratings and pre-post changes in activities in the right dlPFC ($r = -0.329$, $P = 0.033$), right middle frontal gyrus ($r = -0.341$, $P = 0.027$), and left inferior frontal gyrus ($r = -0.334$, $P = 0.031$; Fig. 4). Beyond the PFC, subjective controllability ratings correlated significantly with activities in the left insula ($r = -0.317$, $P = 0.041$).

Subjective Uncontrollability over Aversive Events Alters Functional Connectivity Between Areas of the Working Memory Network

To investigate whether subjective (un)controllability over aversive events affects the crosstalk between brain regions known to be involved in working memory, we first performed a functional connectivity analysis using a PPI. We chose the right posterior PHG as the seed region (6 mm sphere around peak level coordinates from our univariate analyses [16-36-12]) as this region showed an uncontrollability-related change from baseline to postmanipulation in our full-factorial model. This PPI analysis showed that the subjective controllability, but not the actual control over aversive events, affected the functional

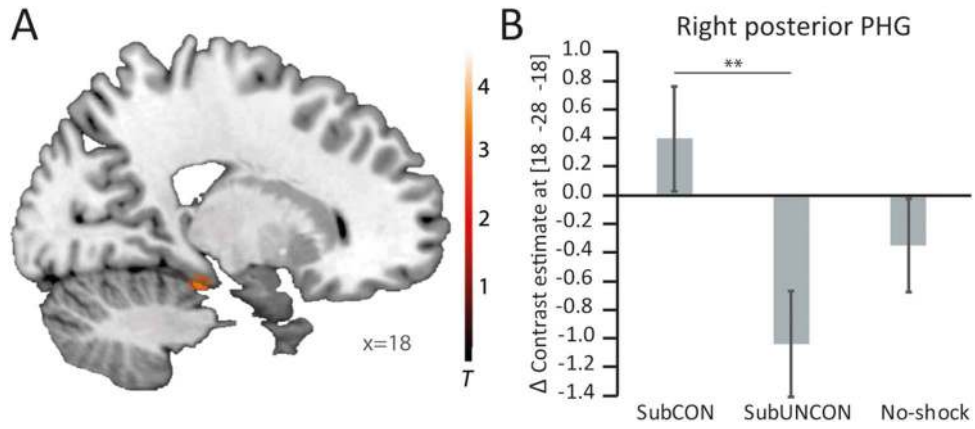

Figure 3. Activities changes of the right posterior PHG after perceived lack of control. (A) Results of a univariate analysis in the PHG for SubCON > SubUNCON based on the contrast 3-back > 0-back in the postmanipulation session, peak level: $x = 18$, $y = -28$, $z = -18$, for visualization purposes displayed at $P = 0.005$, uncorrected. (B) Differential contrast estimate defined as change in contrast estimate from baseline to postmanipulation at [18-28-18] for the SubCON, SubUNCON, and no-shock control (no-shock) group. SubUNCON showed significantly reduced activation when compared to SubCON. Error bars represent standard errors of the mean. ** $P < 0.01$.

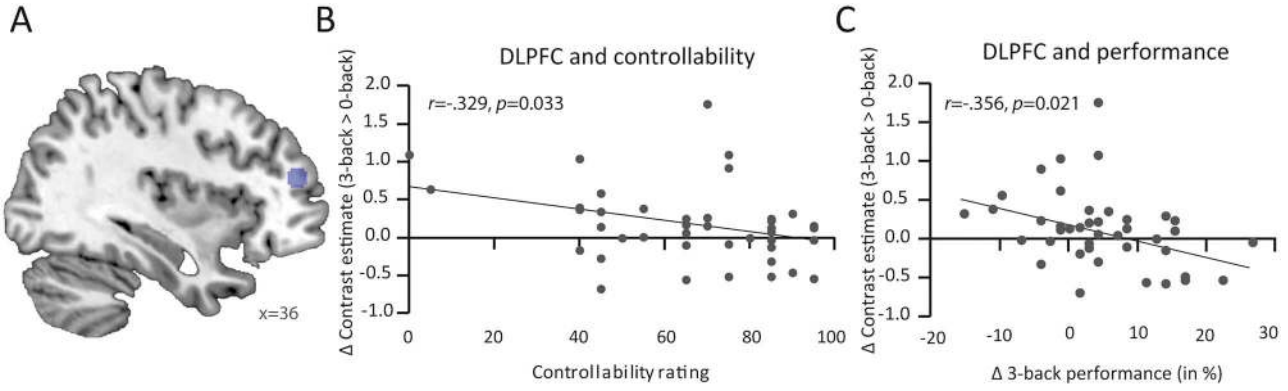

Figure 4. Correlations between DLPFC activities and behavioral parameters. (A) Data was extracted from a 5 mm sphere in the right DLPFC centered at [36 48 18]. Differential contrast estimate defined as change in average contrast estimate from baseline to postmanipulation for the contrast 3-back > 0-back correlated negatively with (B) subjective controllability and (C) differential 3-back performance defined as change in 3-back accuracy from baseline to postmanipulation.

connectivity between the posterior PHG and the right dlPFC ([18 50 26], $p_{SVC} = 0.017$, FWE-corrected), left inferior frontal gyrus ([−54 32 2], $p_{SVC} = 0.006$, FWE-corrected), left thalamus ([−8-22 4], $p_{SVC} = 0.011$, FWE-corrected), and dorsal striatum (left caudate: [−8 14 10], $p_{SVC} = 0.041$, FWE-corrected; right pallidum: [20-8 4], $p_{SVC} = 0.023$, FWE-corrected; Fig. 5). Follow-up tests showed that the SubCON group, compared to the SubUNCON group, showed significantly increased connectivity between the posterior PHG on the one hand and the right dlPFC ([20 46 22], $p_{SVC} = 0.017$, FWE-corrected) and left caudate ([−16–8 24], $p_{SVC} = 0.007$, FWE-corrected) on the other hand in the postmanipulation session. Compared to both the SubCON group and the no-shock control group, the SubUNCON group showed decreased functional connectivity between the right posterior PHG on the one hand and the left inferior frontal gyrus ([−54 30 4], $p_{SVC} = 0.056$, FWE-corrected) and right pallidum ([26-8-4], $p_{SVC} = 0.020$, FWE-corrected) on the other hand after the manipulation.

Subjective Uncontrollability over Aversive Events Alters the Crosstalk Between Large-Scale Networks Implicated in Working Memory

While the PPI analysis focused on the connectivity between two brain areas and its modulation by subjective (un)controllability, we finally sought to shed light on the large-scale network dynamics related to subjectively experienced uncontrollability over aversive events. To this end, we focused—based on the literature (Gordon et al. 2012; Liang et al. 2016)—on the interaction between frontoparietal executive, salience, and default mode networks. Our analyses revealed a significant subjective controllability ×condition×session interaction for the connectivity between the frontoparietal executive network and the salience network ($F(2,56) = 3.877$, $P = 0.026$), which was specific to the postmanipulation session ($F(2,56) = 5.923$, $p_{FDR} = 0.028$). As shown in Figure 6, this interaction effect was due to a significantly reduced working memory-related (3-back > 0-back) between-network connectivity in the SubUNCON group compared to the SubCON group ($t(36) = 3.295$, $p_{FDR} = 0.007$, $d = 1.098$), and we further observed a strong trend for reduced between-network connectivity in the SubUNCON group compared to the no-shock control group ($t(36) = 2.362$, $p_{FDR} = 0.070$, $d = 0.787$).

Importantly, when we performed these analyses for the objective (un)controllability (i.e., with the factor experimental group), no network connectivity changes were observed (all $Fs < 0.700$, all $p_{FDR} > 0.340$), suggesting again that changes in working memory-related networks were driven specifically by the subjective experience that the delivery of aversive

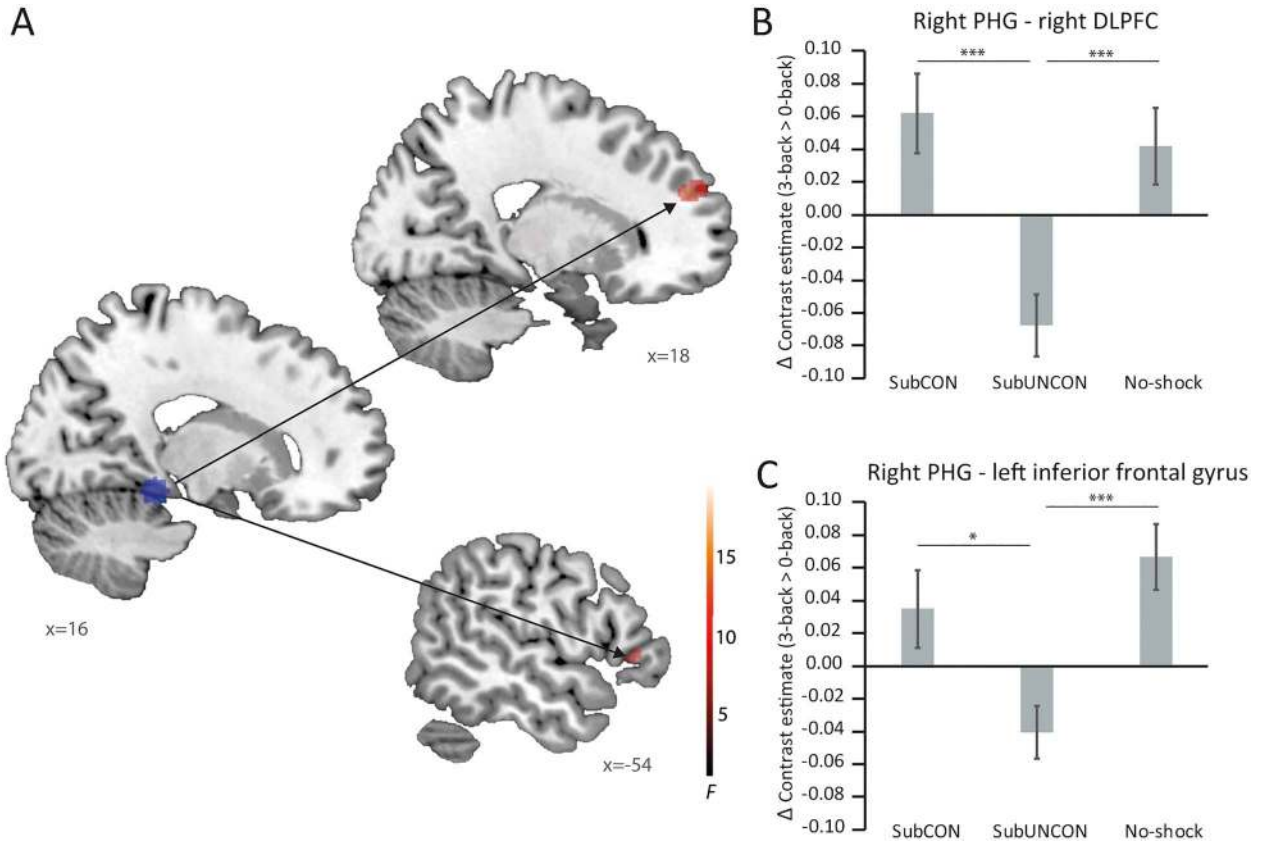

Figure 5. Functional connectivity between the right PHG and prefrontal regions. (*A*) Visualization of functional connectivity between the right posterior PHG and the right DLPFC (upper part) and the left inferior frontal gyrus (lower part). Blue area represents a 6 mm sphere around peak level coordinate from the univariate analysis [16-36-12], red represents activation in the right DLPFC (upper part) and in the left inferior frontal gyrus (lower part) for the F-contrast subjective group × session of PPI interactions based on the contrast 3-back > 0-back with the right PHG as seed, for visualization purposes displayed at $P = 0.005$, uncorrected. (*B*) Differential parameter estimate defined as change in average contrast estimate from baseline to postmanipulation in the cluster around peak voxel [18 50 26] for the SubCON, SubUNCON and no-shock control (no-shock) group. The SubUNCON group showed reduced functional connectivity between the right PHG and right dlPFC from baseline to postmanipulation when compared to both the SubCON and no-shock group. (*C*) Differential parameter estimate defined as change in average contrast estimate from baseline to postmanipulation in the cluster around peak voxel [−54 32 2]. The SubUNCON group showed reduced functional connectivity the right PHG and right inferior frontal gyrus from baseline to postmanipulation when compared to both the subjective SubCON and no-shock group. Error bars represent standard errors of the mean. * $P < 0.05$, *** $P < 0.001$.

events cannot be controlled. This was further reflected by a significant correlation between subjective controllability and differential between-network connectivity in the postmanipulation session ($r = 0.433$, $P = 0.004$). Additionally, higher differential between-network connectivity was associated with better 3-back performance ($r = 0.306$, $P = 0.015$; Fig. 6).

Control Variables and Reaction Times

Before the scanning session, participants completed several questionnaires to control for potential differences between groups. We further collected saliva samples at the beginning of the experiment and measured blood pressure before and after the scanning session to control for potential group differences in baseline cortisol and physiological arousal. The experimental groups did not differ with regard to levels of chronic stress, depressive mood, state, or trait anxiety (all $Ps > 0.613$). Similarly, there were no significant differences in these variables between groups based on subjective controllability ratings (all $Ps > 0.618$). The objective and subjective groups did not further differ with regard to individual shock intensity (subjective: $t(16) = -1.461$, $P = 0.163$; objective: $t(31) = 0.430$, $P = 0.966$), pulse or blood pressure measured at the beginning and end of the experiment (all $Ps > 0.283$), and baseline cortisol levels (all $Ps > 0.743$). There were further no baseline differences between groups based on objective and subjective controllability regarding their attributional style on the internality dimension for both positive (subjective: $P = 0.303$; objective: $P = 0.344$) and negative events (subjective: $P = 0.537$; objective: $P = 0.496$), an attributional dimension that has been associated with the etiology of learned helplessness (Abramson et al. 1978).

To further explore whether any of these control variables could explain to some extent the level of subjective (un)controllability in our experimental groups, we additionally compared these variables in participants with high vs. low subjective controllability in the objective controllability and uncontrollability groups, respectively. There were no significant differences between the two subgroups of our experimental groups (objective controllability (ObjCON): all $Ps > 0.235$; objective uncontrollability (ObjUNCON): all $Ps > 0.088$), except that participants in the controllability group who experienced the aversive events as subjectively controllable scored lower on the internality dimension for positive events than participants in the controllability group with a subjective perception of

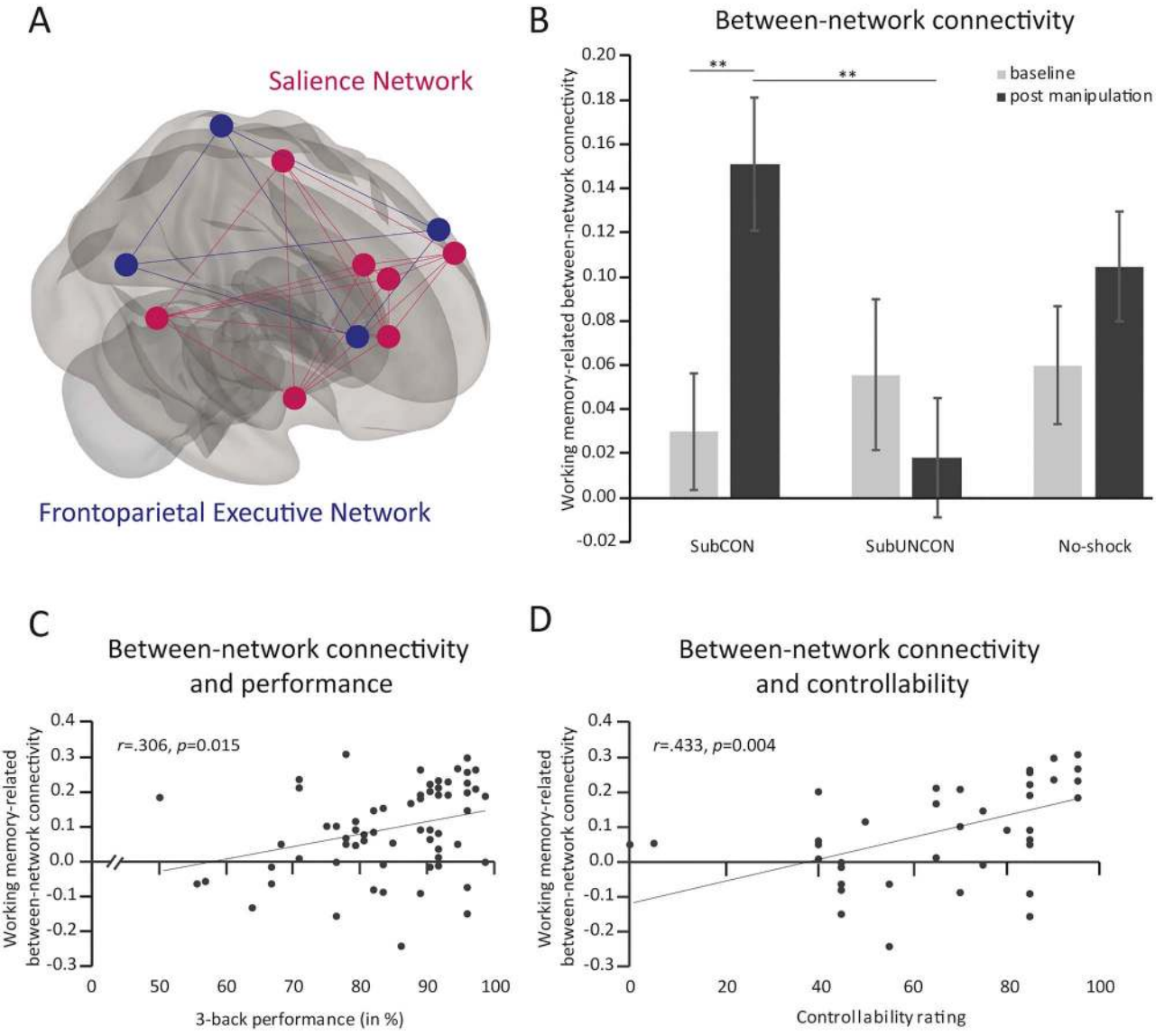

Figure 6. Large-scale network connectivity affected by subjective uncontrollability over aversive events. (*A*) Visualization of the salience network comprising seven nodes (anterior cingulate cortex, bilateral anterior insula, bilateral rostral prefrontal cortex and bilateral supramarginal gyrus; depicted in red) and the frontoparietal executive network with four nodes (bilateral lateral prefrontal cortex, bilateral posterior parietal cortex; depicted in blue). (*B*) Working memory-related (3-back > 0-back) between-network connectivity for the SubCON, SubUNCON and no-shock control (no-shock) groups in the baseline and postmanipulation session. The SubCON group showed significantly decreased working memory-related (3-back > 0-back) between-network connectivity in the postmanipulation session as compared to the SubUNCON group. Working memory-related (3-back > 0-back) between-network connectivity in the postmanipulation session correlated positively with (*C*) 3-back performance in the postmanipulation session. (*D*) subjective controllability. Error bars represent standard errors of the mean. ** $P < 0.01$.

uncontrollability ($t(17) = -2.333$, $P = 0.032$, see supplemental Table 2). This difference, however, needs to be interpreted with caution as the sample sizes of our subgroups are rather small.

Finally, there were no significant differences in reaction times between groups (group×session×n-back level interaction, subjective (un)controllability groups $F(2,59) = 0.663$, $P = 0.519$; objective (un)controllability groups: $F(2,64) = 0.840$, $P = 0.436$).

Discussion

Learned helplessness is a fundamental process of human behavior, a key concept in psychiatry and clinical psychology, and a major model of mood and anxiety disorders in preclinical animal research. However, the extent of the cognitive deficits after an experience of uncontrollability, the hallmark feature of learned helplessness, and how such deficits are represented in the human brain remained largely elusive. Here, we demonstrate for the first time that the subjective experience of uncontrollability over aversive events impairs working memory performance, measured as change relative to the individual baseline. This working memory deficit was paralleled by altered prefrontal and parahippocampal activity after subjectively experiencing uncontrollability and altered connectivity between large-scale executive control and salience networks known to be involved in working memory. Importantly, none of these changes

were induced by the actual, objective uncontrollability over aversive events but solely by the subjectively perceived lack of control.

We show here that the experience of uncontrollability may disrupt later performance in an entirely unrelated task. More specifically, we demonstrate here, to the best of our knowledge, for the first time that subjective uncontrollability over aversive events may disrupt working memory, a fundamental cognitive process that is thought to be impaired in several stress-related mental disorders (Goldman-Rakic 1994; Snyder 2013; Honzel et al. 2014). Although previous studies showed already that stress may interfere with working memory and its neural basis (Qin et al. 2009; Schoofs et al. 2009; Arnsten et al. 2012), the present study extends these earlier reports in critical ways. While these previous studies showed that aversive events impair working memory, our results provide additional evidence for related changes in functional connectivity and large-scale network interactions. Even more importantly, our data indicate that working memory is not impaired by aversive events per se but by the perceived lack of control over such events. The present results even show that the number of aversive events does not affect working memory, as long as individuals experience control over these events.

One of our most striking findings is that the objective (un)controllability over aversive events is not sufficient to affect working memory but that it is the subjective experience of (un)controllability that changes subsequent cognitive performance. This finding is well in line with the reformulated theory of learned helplessness that emphasized the role of individual attributions (Abramson et al. 1978; Miller and Norman 1979). At this point, it is also important to note that our results do not point to a disruption of working memory after an experience of uncontrollability alone but rather to opposite effects of perceived controllability versus uncontrollability over aversive events. Compared to the no-shock control group, the SubUNCON group tended to be impaired and the SubCON group to be enhanced in working memory performance relative to no-shock controls, and a similar pattern was obtained at the brain level for parahippocampal activities and between-network connectivity. This "mastery effect" might be explained by the release of the neurotransmitter dopamine after experiences perceived as controllable (Cabib and Puglisi-Allegra 2012), which is known to play an important role in working memory (D'Esposito and Postle 2015).

Another striking finding is that a substantial number of participants in the controllability group experienced the aversive events as subjectively uncontrollable although they showed a clear and robust increase of the instrumental response, suggesting that they had effectively learned how to prevent the aversive event. A similar pattern can also be observed in psychopathologies, such as depression (Beck 1979), PTSD (Dunmore et al. 1999), obsessive-compulsive disorder (McLaren and Crowe 2003), and other nonpathological real-life situations in which humans underestimate their ability to exert control. While the present study was not designed to identify specific traits or factors that affected participants' subjective perceptions of controllability, future studies should employ a more extensive set of additional measures to shed light on the factors underlying the subjective sense of controllability. Corroborating earlier studies on the neural underpinnings of working memory (McCarthy et al. 1996; Curtis and D'Esposito 2003; Barbey et al. 2013), our fMRI data showed overall a key role of prefrontal areas in working memory. Interestingly, changes in these areas from the baseline to the postmanipulation session were negatively correlated with increases in working memory performance. Although this negative correlation might be surprising at first glance, a negative relationship between dlPFC activities and working memory performance has been reported before (Mehta et al. 2000; Karlsgodt et al. 2009) and might reflect increased neural efficiency or suppression of distracting processes. Accordingly, ratings of subjectively perceived controllability over aversive events correlated negatively with changes in neural activities from baseline to postmanipulation during working memory performance in a range of prefrontal areas, including the dlPFC. The direction of these correlations might also be owing to differential dopaminergic and serotonergic contributions to working memory after experienced uncontrollability, which are thought to exert opposite effects on prefrontal activities (Luciana et al. 1998; Ellis and Nathan 2001).

In addition to prefrontal areas, there was a reduction in activities of the right posterior PHG from baseline to postmanipulation selectively in the subjective uncontrollability group. Interestingly, temporal regions, and particularly the PHG, have recently been identified as being involved in working memory maintenance and have been suggested to fulfill the role of an "episodic buffer" (Luck et al. 2010; Libby et al. 2014; Schon et al. 2016). Yet, how many perceptions of (un)controllability affect subsequent parahippocampal activities during a working memory task? Animal models have demonstrated that exposure to uncontrollable aversive events leads to increased neural activities in the dorsal raphe nucleus, resulting in increased serotonergic firing along the serotonergic pathway (Maier et al. 1993; Maswood et al. 1998). In addition to animal studies showing serotonergic projections from the dorsal raphe nucleus to the PHG (Saunders and Aggleton 2007), there is also good evidence for a serotonergic pathway between the dorsal raphe nucleus and PHG in humans (Beliveau et al. 2015), suggesting that the changes we obtained after subjective lack of control might indeed be due to serotonergic projections originating from the dorsal raphe nucleus.

Moreover, beyond activities changes in single prefrontal or temporal areas, our data show that perceived (un)controllability over aversive events affects also the crosstalk between the PHG and prefrontal as well as dorsal striatal areas belonging to the working memory network (Cohen et al. 1997; D'Esposito et al. 1998; Eriksson et al. 2015). More specifically, the SubUNCON group showed significantly decreased functional connectivity between these areas after the manipulation when compared to the SubCON and no-shock control groups, indicating decreased communication between the PHG as a putative episodic buffer and a range of other brain regions crucially involved in working memory execution. Most interestingly, large-scale network analyses further demonstrated that the perceived lack of control over aversive events reduced working memory-related functional connectivity between the frontoparietal executive and salience network as compared to the SubCON and no-shock control group. This finding suggests a reduced integration of large-scale neural circuits which are assumed to be essential for working memory performance (Stanley et al. 2014; Braun et al. 2015; Cohen and D'Esposito 2016; Liang et al. 2016).

In contrast to animal studies, participants were explicitly instructed that it is possible to control (i.e., to prevent) the aversive events. Although this instruction was required as otherwise learning was unlikely to occur in the experimental controllability group within a restricted time window, in the uncontrollability group this instruction was incorrect and may have led to

further negative affect in this group. However, considering the fact that subjective, but not objective, (un)controllability affected working memory performance and decreased crosstalk between relevant brain regions, it appears unlikely that this aspect of the experimental instruction had a strong effect on our results.

In sum, our findings show that subjective uncontrollability over aversive events reduces subsequent working memory performance and that this cognitive deficit was linked to altered prefrontal and parahippocampal activities as well as reduced crosstalk between these areas. Our large-scale network analyses further indicate that the experience of uncontrollability affected primarily the communication between the frontoparietal executive and salience networks. Importantly, both the behavioral and neural changes were induced by the subjective experience of uncontrollability over aversive events, irrespective of the actual instrumental control over these events. Thus, these findings highlight that the adverse consequences of an aversive event are not necessarily determined by the event itself but to a large extent by our interpretation of it. As William Shakespeare wrote more than 400 years ago, "there is nothing either good or bad but thinking makes it so" (Shakespeare 1906). We here provide behavioral and neural evidence supporting this claim, with important implications for therapeutic interventions in mental disorders in which feelings of helplessness are prominent.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

Funding

German Research Foundation (Deutsche Forschungsgemeinschaft) to L.S. (grant number SFB 936, project B10).

Notes

This work was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft) to Prof. L. Schwabe [grant number SFB 936, project B10]. The authors thank Dhana Bräuer, Daniel Kutzner, Christoph Schäde, Jan Sedlacik, Anne Tiefert, Anja Turlach, Laura Clausen, Kim Löwisch, Jennifer Maurer, and Lena Piel for the assistance during data collection, Christian Büchel for the helpful comments on the experimental design, and Claus Hilgetag for the helpful comments on network analyses. We further thank two anonymous reviewers for their very helpful and constructive comments. *Conflict of Interest*: None declared.

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