Supporting Information

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SI Methods

Subjects. Forty-five right-handed, healthy young adults enrolled in the study. Twenty-two of these were stress-exposed students preparing for a medical licensing examination. The remaining 23 were control subjects. Inclusion criteria for all subjects were right-handedness, age 21–35, no history of psychiatric or neurological disease, and no contraindications for MRI. Stress-exposed subjects who reported low PSS scores ($n = 2$), defined as 1 standard deviation below the normative population mean, were excluded. Conversely, control subjects who reported high PSS scores ($n = 3$), defined as 1 standard deviation above the normative population mean, were also excluded.

The remaining 40 subjects (20 stressed and 20 matched controls; see supporting information (*SI*) Table S1 for demographic data) participated in an initial scanning session that included three components: (1) the Cohen perceived stress scale, (2) attentional control task training, and (3) fMRI scan while being tested on the same task. These are described below. Subjects were also asked to quantify their sleep in hours for the night preceding the experiment. There was no significant difference between the two groups (stressed, 7.4 h; controls, 7.7 h; $t = 0.86$, $P = 0.40$). All subjects were asked to return for a second session, ≈1 month after the first. The experimental procedure was approved by the Weill Cornell Medical College IRB, and written informed consent was obtained from all subjects before scanning.

Thirty subjects were retested in a second session, ≈1 month after the first. The procedure for the second session was identical to the first. Inclusion criteria are described below in *Reversibility Analysis*.

Perceived Stress Scale. Stress was quantified by self-report at the start of each session using the Cohen perceived stress scale (PSS), a standardized and reliable measure of an individual's perception of chronic psychosocial stress (1). This widely used, 10-item questionnaire measures the degree to which situations in a subject's life are perceived as stressful, yielding a single measurement for each subject on a 40-point scale. The perceived stress scale is a reliable tool for tracking changes in psychosocial stress over time. It has been validated extensively both in healthy subjects (1, 2) and as a correlate of physiological measures of disease in studies of diverse clinical populations, including major depression (3), wound healing (4), diabetes mellitus (5), coronary artery disease (6), prostate cancer screening (7), and the common cold (8), among others. Additional information on the perceived stress scale, including a more extensive list of studies validating it in various contexts, can be found online.

Diurnal measurement of salivary cortisol is another tool that has been used successfully to confirm a response to an acute stressor, and disrupted cortisol rhythms have been associated with chronically stressful experiences, like unemployment (9), "burnout" at work (10), depressed mood (11), and poverty (12). However, these studies also show that diurnal cortisol is a complex end point for gauging chronic stress: some report relatively higher morning cortisol levels (9–11), while others indicate that the morning surge may instead be blunted (12) and that associations between cortisol rhythms on the one hand and stress, brain structure, and cognition on the other may vary significantly with age (13) and gender (14). Likewise, experiments in rats indicate that the glucocorticoid response to repeated stress may attenuate over time in a manner that may be difficult to predict, that depends on the nature of the stressor, and that does not correlate well with observed effects on dendritic profiles (15). In short, these studies show that no single measure of diurnal cortisol rhythms is suitable in and of itself as a hard-and-fast assessment of chronic stress exposure.

Instead, we identified subjects who were exposed to a specific and identifiable chronic stressor and confirmed stress exposure using the perceived stress scale, precisely because cortical processing of perceived stress is believed to be the initiator of the response to a psychosocial trigger, and the PSS scale has been thoroughly validated as a reliable measure of this factor (2, 16–18). Indeed, variability in subjects' perception of a stressor may account in part for discrepancies between studies showing robust effects of stress on PFC function acutely (19, 20) and others showing more modest effects (21, 22) or no effects at all. The downside to our approach is that it does not directly address the role of cortisol in linking chronic stress exposure and disrupted PFC function. The bulk of the data from animal models strongly implicate glucocorticoid actions, although it is likely that they play a permissive role in a complex response that also involves excitatory amino acids, neurotrophins, adhesion molecules, altered glucocorticoid receptor expression patterns, and neuromodulators like serotonin (23).

Attentional Control Task. This task is described in more detail elsewhere (24). On each trial, subjects were presented with two circular square-wave gratings, one red and one green, each subtending 4.6° of visual space at an eccentricity of 4.6° from fixation, for 1500 ms. Each grating moved either up or down. A centrally located cue ("M" or "C") instructed the subject to attend to either the motion or the color of the stimuli. If the cue was an M, the subject responded manually by pressing a button corresponding to the side with the upward-moving grating, regardless of color. If the cue was a C, the subject responded by choosing the side with the red grating, regardless of motion (see Fig. 1*A*). Repeat trials were defined as those preceded by 2–5 trials of the same dimension. Shift trials were those preceded by 2–5 trials of the opposite dimension. Attention-shifting performance was quantified by comparing shift and repeat trial reaction time in milliseconds.

On some shift trials ("reversals"), the target response for the color dimension (red) was paired with the nontarget for the motion dimension (down), so the subject was required to override the response learned in the previous block of repeats. On others, the target response was the same in both dimensions. Response reversals were assessed by contrasting shift trials that required a reversal of the prepotent response learned in the previous block of repeats with those that did not (Fig. 1*B*). Previous work showed that response reversals are comparably difficult but are mediated by a network independent of the prefrontal areas that mediate attention shifts (24), in analogy to the task paradigm used in the rodent model (25).

Each trial ended with a centrally located white fixation cross, subtending 1.2° of visual space, with a variable duration (500–12,500 ms). Reaction times and accuracies were recorded for all trials using the E-Prime and IFIS software packages (Psychology Software Tools). Color and motion trials were presented in a pseudorandomized order such that the task cue could not be predicted, and shift and repeat trials were counterbalanced for dimension and side of target presentation.

Before each scanning session, subjects were trained on 3 blocks of 36 trials consisting of color discriminations, motion discriminations, and alternating color/motion discriminations,

respectively. In the scanner, subjects completed 6 blocks of 72 trials, which were presented in a jittered task design.

MRI Parameters. Images were acquired on a GE 3T MRI scanner using a quadrature head coil. Functional scans were acquired using a spiral in-and-out sequence (26) with the following parameters: repetition time (TR) = 2000, echo time (TE) = 30, field of view (FOV) = 200 mm, 64 × 64 matrix, and 29 5-mm axial slices. Anatomical data sets included 3D high-resolution spoiled gradient echo (SPGR) images (TR = 25, TE = 5, 124 1.5-mm coronal slices) and a T1-weighted in-plane scan (TR = 500, TE = min, FOV = 200 mm, 256 × 256 matrix, 29 5-mm axial slices).

MRI Preprocessing Procedures. MR images were preprocessed and analyzed using the freely available AFNI software package (http://afni.nimh.nih.gov). Preprocessing of fMRI data included slice scan time correction, temporal filtering, spatial smoothing (Gaussian filter with FWHM = 5.0 mm), linear trend removal, 3D motion correction, and normalization to a percentage of change from run-average baseline. Functional data sets were automatically coregistered to the 3D SPGR anatomical volume. Both functional and anatomical data sets were then transformed into Talairach space.

Behavioral Data Analysis. Reaction time (RT) and accuracy were recorded for all trials, and only correct trials were included in reaction time analyses. Attention-shifting performance was quantified by comparing shift and repeat trial reaction time in milliseconds. Response reversal performance was quantified by contrasting shift trials that required a reversal of the prepotent response learned in the previous block of repeats with those that did not. Previous work indicated that reaction time was a more sensitive measure than accuracy (24).

To assess how psychosocial stress modulates attention-shifting performance, we calculated a mean shift cost (in milliseconds) for each of the 40 subjects who participated in the first scanning session by subtracting mean repeat trial RT from mean shift RT. We then compared shift costs in stressed subjects vs. controls (Student's *t*-test) and regressed shift costs on PSS scores. To assess whether psychosocial stress effects on behavior were specific to attention shifting or reflected a more generalized impairment of cognition and task performance, we performed similar analyses for response reversals and mean repeat trial reaction time and accuracy. For each regression analysis, boxplots were visually inspected for outliers, which were defined as data points that differed from the group mean by 2 standard deviations in either direction on either dimension. Three outliers were excluded from the behavioral analysis on this basis. The results are depicted in Fig. 1.

Functional MRI Data Analysis: Effects of Stress on PFC Function. The aim of the experiments reported here was to examine how psychosocial stress modulates shift-related activity in dorsolateral prefrontal cortex. This involved (1) identifying areas of dorsolateral prefrontal cortex (DLPFC) that contributed to attention shifting and then (2) examining how functional connectivity in this area varied with stress:

1. We used a general linear model and mixed-effects ANOVA to delineate the neural circuitry involved in attention shifting. After preprocessing, functional time courses for all subjects were analyzed together on the basis of the least mean squares solution to a general linear model in which trial type (shift vs. repeat) was the primary predictor. Only correct trials were included in the analysis. The general linear model yielded voxelwise beta weights for the shift and repeat conditions for each subject. A 2-factor (trial type, subject) mixed-effects ANOVA was used to identify areas showing a main effect of trial type, and voxelwise *t*-tests of shift vs. repeat beta weights were used to determine the directionality of these effects. For this contrast, we used a threshold of $P < 0.001$ with a minimum cluster size of 11 voxels (transformed) to correct for multiple comparisons as confirmed by Monte Carlo simulation (27). Attention shifting engaged a largely frontoparietal network including bilateral DLPFC and other areas described in Table S2. The particular contributions of these regions to attention shifting are the subject of another article (24).
2. Next, we sought to assess how chronic stress affects functional properties of this network. In rats, chronic stress selectively impairs extradimensional attentional set-shifting (25) and reduces apical dendritic arborization and spine density in the medial prefrontal cortex, which is known to mediate this function in rodents (28). These dendrites are the target of long-range corticocortical projections and are assumed to play an important computational role in cognitive functions mediated by a distributed network of structures (29). Accordingly, we reasoned that if chronic stress reduces long-range corticocortical axospinous input to the PFC by reducing dendritic arborization, then it may also disrupt fMRI measures of long-range functional connectivity.

We used functional connectivity analysis to test this hypothesis (for a similar approach, see refs. 30 and 31). Functional connectivity analysis assesses the degree to which the voxelwise BOLD signal covaries with activity in a particular region of interest, termed the seed volume. We focused our analysis on lateral prefrontal cortex, which is known to mediate attentional shifts in analogous tasks in primates (24, 32). The median BOLD signal time courses in 3 × 3 × 3 voxel cubes surrounding the coordinates of peak activation in left and right DLPFC (see Table S2) served as seed points for the analysis, in which we (1) identified regions that were significantly coupled with the seed points and then (2) examined how this coupling varied with stress.

First, the BOLD signal time series for each voxel across the brain was regressed on the median activity time series for the seed volume for each subject, using mean whole-brain signal and the predicted hemodynamic response for shift trials as covariates to control for baseline drift and variance attributable to shift-related activity, respectively. This generated whole-brain voxelwise maps of functional connectivity (R^2) for each subject. Whole-brain voxelwise 1-sample *t*-tests of these maps vs. 0 defined functional connectivity maps for left and right DLPFC. The threshold for this analysis was $P < 0.001$ with a minimum cluster size of 11 voxels, as above.

Second, we examined how these voxelwise maps of functional connectivity varied with stress, using 2-factor (stress, high vs. low; subject), mixed-effects ANOVA and voxelwise *t*-tests of connectivity (R^2) in stressed vs. control subjects, with brain regions showing significant connectivity in the analysis above serving as a mask. The results of the analyses for left and right DLPFC are depicted in Fig. 3*A* and Table S3. We also assessed whether attention-shifting performance depends on the integrity of the network delineated in Fig. 2*B*, using a multivariate linear regression of shift cost on measures of prefrontal connectivity (R^2), while controlling for stress (PSS scores) as a covariate, using the same mask (Fig. 2*C*, Table S4). These masked analyses used a threshold of $P < 0.005$ with a minimum cluster size of 13 transformed voxels to correct for multiple comparisons. This correction was confirmed by Monte Carlo analysis with more details below.

Reversibility Analysis. To control for confounding variables unrelated to stress and to assess the reversibility of stress effects on PFC function, stressed subjects were retested ≈1 month later, after 1 month of reduced stress, confirmed by reassessment on

the PSS. Eighteen of 20 stressed subjects and 17 of 20 control subjects returned for a second session. Stress-exposed subjects who reported persistently elevated PSS scores in session 2, defined as 1 standard deviation above the normative population mean, were excluded ($n = 3$). To control for practice effects, we retested an equal number of control subjects, excluding those whose PSS scores on retest exceeded the normative population mean by 1 standard deviation ($n = 2$). The second testing session was identical to the first.

Three-factor (stress, high vs. low; session, one vs. two; subject), mixed-effects ANOVA was used to assess reversibility. Post hoc *t*-tests (session 1, high vs. low stress; session 2, high vs. low stress) of PSS scores, shift costs, and functional connectivity were used to confirm that stress effects on these measures were absent in session 2. Stress-by-session interactions were used to confirm the significance of the reversal. The search volume for this analysis included all areas showing a main effect of stress, averaged over the first and second sessions, defined by a threshold of $P < 0.005$ with a minimum cluster size of 12 transformed voxels. This ensured that the analysis region was independent of the tested interaction. As noted in the main text, significant interactions confirmed the reversal in all regions showing an effect in session 1 that met search volume inclusion criteria. In regions showing a weaker session 1 effect—cingulate, posterior parietal, and higher-order visual areas—post hoc *t*-tests revealed the same trend, although the significance of this interaction could not be confirmed. These results are depicted in Fig. 3*C* and Table S5.

Monte Carlo Analysis of Thresholding Criteria. As described above, thresholding criteria for each analysis above incorporated a minimum cluster size to maximize power and minimize the likelihood of false positives. A procedure for selecting optimal criteria and estimating the corresponding probability of a type I error (α) is described in detail elsewhere (27). Briefly, we used the AlphaSim component of the AFNI software package to quantify α for a given per-voxel significance level (p) and minimum cluster size (n) through Monte Carlo simulation of 1000 randomly generated data sets with dimensions and inter-voxel spatial correlations specified to approximate the data set for a given analysis.

Whole-brain analyses were performed at a threshold of $P < 0.001$ with a minimum cluster size of 11 transformed voxels (≈6 untransformed voxels). Monte Carlo simulation predicted an overall significance of $P = 0.040$ given these criteria. The masked analyses were limited to areas showing significant functional connectivity with DLPFC (≈17% of the whole-brain data set). These analyses were performed at a threshold of $P < 0.005$ with a minimum cluster size of 13 transformed voxels (≈7 untransformed voxels). Monte Carlo simulation predicted an overall significance of $P = 0.033$ given these criteria.

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Table S1. Demographic details by group

Group	*N*	Age (years)	Gender		Sleep (h)	PSS
			Male	Female		
Overall	40	25.8	19	21	7.5	14.4
Session 1						
Stressed	20	26.1	9	11	7.4	17.7
Control	20	25.5	10	10	7.7	11.1
Session 2						
Stressed	15	25.2	8	7	8.1	10.1
Control	15	25.1	9	6	7.8	10.9

PSS, perceived stress scale.

Table S2. Attention shifts engaged DLPFC bilaterally and other frontoparietal areas

	BA	*X*	*Y*	*Z*	Peak *t*	d.f.
Dorsolateral prefrontal						
L DLPFC	9/8	41	35	27	4.73	38
R DLPFC	9/8	−37	38	32	4.41	38
Other areas						
ACC	32	−1	8	43	4.40	38
R insula	44/47	−56	14	2	4.31	38
L premotor	6	25	−6	63	4.95	38
R premotor	6	−22	−1	63	4.39	38
L PPC	40	38	−46	41	4.38	38
	7	10	−67	57	5.75	38
R PPC	40	−46	−36	47	4.04	38
	7	−8	−77	44	5.93	38
L fusiform	37	50	−65	−12	4.27	38
R fusiform	37	−49	−61	−12	4.21	38

Attention shifts engaged DLPFC bilaterally, among other areas in a frontoparietal network. The dorsolateral prefrontal areas served as seed points for the functional connectivity analysis. BA, Brodmann area; *X*, *Y*, *Z* refer to coordinates in Talairach space; *t*-statistics are for the contrast of shift vs. repeat beta weights for all subjects; d.f., degrees of freedom; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; PPC, posterior parietal cortex.

Table S3. Stress-disrupted functional connectivity between left and right DLPFC and other areas of a shift-related frontoparietal network

	BA	*X*	*Y*	*Z*	Peak *t*	d.f.
Effects on L DLPFC coupling						
R DLPFC	9/46	−41	35	29	−5.11	38
L STG/MTG	38/21	43	11	−28	4.63	38
L insula	13	34	23	2	−4.32	38
R insula	13	−35	23	14	−3.84	38
L premotor	6	19	−7	62	−4.15	38
L MTG	20/28	49	−13	−10	3.49	38
R dPPC	7	−29	−52	53	−3.48	38
Effects on R DLPFC coupling						
L DLPFC	46/9	34	47	17	−4.57	38
ACC	32	−2	26	38	−3.41	38
R insula/VLPFC	45/44	−53	14	17	−4.19	38
R premotor	6	−41	14	41	−3.81	38
R putamen	—	−17	8	5	−4.39	38
R PCC	31	−2	−37	38	−3.83	38
R vPPC	40	−50	−40	26	−3.44	38
L fusiform cortex	20/37	46	−43	−13	−3.48	38
L cerebellum	—	28	−49	−46	−4.57	38

BA, Brodmann area; *X*, *Y*, *Z* refer to coordinates in Talairach space; *t*-statistics are for the contrast of R^2 in stressed vs. control subjects; d.f., degrees of freedom; DLPFC, dorsolateral prefrontal cortex; STG, superior temporal gyrus; MTG, middle temporal gyrus; PPC, posterior parietal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex.

Table S4. Functional connectivity between DLPFC and areas of posterior parietal and premotor cortex predicted attention-shift costs independent of stress effects

	BA	*X*	*Y*	*Z*	Peak R^2	*F*
L DLPFC coupling and shift cost						
L premotor	6	61	−1	11	0.26	13.74
L ventral PPC	40	46	−31	38	0.30	5.43
L dorsal PPC	7	25	−55	44	0.25	6.68
R DLPFC coupling and shift cost						
R premotor	6	−50	2	32	0.29	8.06
R ventral PPC	40	−38	−31	41	0.30	11.40
R dorsal PPC	7	−23	−49	59	0.38	14.73

BA, Brodmann area; *X*, *Y*, *Z* refer to coordinates in Talairach space; R^2 coefficients represent the correlation between functional coupling in the given voxel and shift cost; *F*-statistics represent the significance of the regression of shift cost on functional connectivity and PSS vs. PSS alone; DLPFC, dorsolateral prefrontal cortex; STG, superior temporal gyrus; MTG, middle temporal gyrus; PPC, posterior parietal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex.

Table S5. Stress effects on DLPFC functional coupling were reversible

	BA	*X*	*Y*	*Z*	Session 1	Session 2	Mean effect	Interaction
L DLPFC coupling								
L premotor	6	22	−1	59	−3.38***	−1.59	−2.85**	**9.62***
Not included in search volume								
R DLPFC	9/46	−41	35	29	−4.03***	−1.25	−3.02**	*6.88*
L STG/MTG	38/21	43	11	−28	4.94***	−0.19	1.95	*4.03*
L MTG	20/28	49	−13	−10	3.86***	−0.80	1.61	*5.93*
R dPPC	7	−31	−52	53	−2.16*	−0.02	−1.62	*3.62*
R DLPFC coupling								
L DLPFC	46/9	37	44	20	−4.00***	−1.31	−3.32***	**15.4***
R premotor	6	−41	17	41	−4.70***	0.01	−3.21***	**16.1***
R putamen	—	−20	8	7	−4.99***	−1.24	−3.48***	**8.58***
L cerebellum	—	28	−55	−46	−3.51***	−0.70	−2.79**	**6.91***
Not included in search volume								
ACC	32	−2	26	38	−2.58*	0.08	−1.61	*4.28*
R PCC	31	−2	−37	38	−2.95**	−1.31	−2.85**	*4.61*
R vPPC	40	−59	−40	35	−2.66*	−0.22	−1.94	*5.18*
L fusiform	20/37	55	−49	−10	−2.48*	1.05	−1.17	*6.04*

BA, Brodmann area; *X*, *Y*, *Z* refer to the coordinates in Talairach space of the peak interaction. Data in ″Session 1″ and ″Session 2″ columns are *t*-statistics with d.f. = 28 and represent the results of post hoc contrasts confirming effects in session 1 but not in session 2. Data in the ″Interaction″ column are *F*-statistics with d.f. = 1, 28 and represent the significance of the interaction between session and stress grouping and confirm that stress effects on connectivity were reversible in a second session 1 month later, independent of task experience. The search volume for this ANOVA included all areas showing a significant main effect of stress as described above. Interaction statistics for areas within this search volume are significant (boldface type). Areas showing a weaker effect in session 1 or 2 occurring over a smaller volume did not meet cluster threshold criteria for inclusion in the search volume. Accordingly, the significance of the reversal interaction could not be verified in these areas (italics), but *t*-tests of connectivity for peak voxels show a comparable trend. d.f., degrees of freedom; DLPFC, dorsolateral prefrontal cortex; STG, superior temporal gyrus; MTG, middle temporal gyrus; (d/v)PPC, (dorsal/ventral) posterior parietal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.005$.