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Prolonged hemodynamic response during incidental facial emotion processing in inter-episode bipolar I disorder

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Abstract

This fMRI study examined whether hemodynamic responses to affectively-salient stimuli were abnormally prolonged in remitted bipolar disorder, possibly representing a novel illness biomarker. A group of 18 DSM-IV bipolar I-diagnosed adults in remission and a demographically-matched control group performed an event-related fMRI gender-discrimination task in which face stimuli had task-irrelevant neutral, happy or angry expressions designed to elicit incidental emotional processing. Participants' brain activation was modeled using a "fully informed" SPM5 basis set. Mixed-model ANOVA tested for diagnostic group differences in BOLD response amplitude and shape within brain regions-of-interest selected from ALE meta-analysis of previous comparable fMRI studies. Bipolar-diagnosed patients had a generally longer duration and/or later-peaking hemodynamic response in amygdala and numerous prefrontal cortex brain regions. Data are consistent with existing models of bipolar limbic hyperactivity, but the prolonged frontolimbic response more precisely details abnormalities recognized in previous studies. Prolonged hemodynamic responses were unrelated to stimulus type, task performance, or degree of residual mood symptoms, suggesting an important novel trait vulnerability brain dysfunction in bipolar disorder. Bipolar patients also failed to engage pregenual cingulate and left orbitofrontal cortex – regions important to models of automatic emotion regulation – while engaging a delayed dorsolateral prefrontal cortex response not seen in controls. These results raise questions about whether there are meaningful relationships between bipolar dysfunction of specific ventromedial prefrontal cortex regions believed to automatically regulate emotional reactions and the prolonged responses in more lateral aspects of prefrontal cortex.

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Keywords

Bipolar; emotion; hemodynamic shape; fMRI; facial

A central feature of bipolar disorder is an inability to regulate mood (American Psychiatric Association 2000). Numerous studies report neural dysfunction within limbic and prefrontal brain regions and evidence for behavioral impairments when bipolar disorder-diagnosed patients (BP) perform emotional tasks (Wessa and Linke 2009). Collective evidence from this body of research supports theories emphasizing bipolar hyper-function of limbic regions that identify emotional information in conjunction with hypo-function of prefrontal brain regions thought to regulate inappropriate or task-irrelevant affective responses (Cerullo et al. 2009; Phillips et al. 2008a; Strakowski et al. 2005; Wessa and Linke 2009; Ochsner and Gross 2005; Womer et al. 2009; Blumberg et al. 2002; Green et al. 2007). However, no studies have yet examined whether mood dysregulation in bipolars might also involve impairment in the ability to disengage emotion-related neural processing (which could be equally important as exaggerated emotion-induced neural response in explaining vulnerability for BP), or clarified the latter's state versus trait-like status.

Failure to disengage a brain region normally would manifest in fMRI as prolonged hemodynamic response to a briefly presented emotional stimulus. This can be measured through simple extensions of conventional GLM-based fMRI timeseries analysis techniques that quantify voxelwise variability to peak latency or duration, then test whether this variability is systematically greater in one group compared to another using standard group comparison statistics (Lindquist et al. 2009). Such prolonged hemodynamic responses have been found in previous research. For instance, emotional stimulation resulted in a longer-duration amygdala hemodynamic response in regions normally active during self-referential cognition (Vaughn et al. 2010), in unipolar depression (Siegle et al. 2002), and in BP adolescents (Wegbreit et al. 2012). In the latter study, acutely symptomatic BP showed a prolonged response to fearful faces relative to controls in right dorsolateral prefrontal cortex. Prior studies also have shown that BP affective disturbances are not constrained to acutely manic or depressed episodes. Emotional reactivity – heightened sensitivity to affectively-valenced stimuli when BP are not acutely symptomatic – has emerged as a possible BP endophenotype (Henry et al. 2008b). For example, compared to non-patient controls, remitted BP show greater emotional arousal and stronger startle reflex (M'Bailara et al. 2009), greater appraisal of stress to minor disturbances (Myin-Germeys et al. 2003), and greater subjective emotional intensity (Henry et al. 2008b). Prolonged emotion-related neural processing seems to be a viable neural correlate that might underlie such heightened emotional reactivity, even when patients are in a euthymic state.

For that reason, we sought to determine whether or not prolonged emotional response represented a vulnerability to BP. In this study we focused on studying bipolar patients currently in remission so that any findings could not easily be attributed to abnormal variability in mood state. We were specifically interested in detecting any prolonged neural response to incidental emotional processing; that is, non-directed, often non-conscious processing of affective information present in the environment during the performance of other tasks. Although numerous studies of symptomatic BP have employed affective facial stimuli, relatively few have used fMRI methods to study incidentally-elicited emotion (Lawrence et al. 2004; Pavuluri et al. 2008; Pavuluri et al. 2009; Wessa et al. 2007), and only two reports describe incidental affective brain function in remitted BP. In one such report, remitted BP showed greater hemodynamic responses to emotional facial expressions in left amygdala, dorsomedial prefrontal cortex, and left putamen (Surguladze et al. 2010), similar to findings in symptomatic BP patients (Pavuluri et al. 2009; Lawrence et al. 2004;

Wessa et al. 2007; Pavuluri et al. 2007; Chen et al. 2006; Blumberg et al. 2005). Another study reported greater striatal activation to positively-valenced stimuli in remitted BP, along with decreased dorsolateral prefrontal response to neutral and emotional stimuli (Hassel et al. 2008). Importantly, similar findings in unaffected bipolar relatives (Surguladze et al. 2010) reinforce the likelihood that limbic over-activity to incidental affective facial expressions represents a neurobiological trait of emotion system dysfunction.

Therefore, the primary objective of this exploratory study was to extend these previous studies of remitted BP by examining whether fMRI-measured amygdala response would be prolonged in remitted BP relative to controls. We hypothesized we would find evidence for prolonged limbic response indicative of a novel brain functional biomarker, likely related to abnormal BP emotional reactivity. We also wished to specifically characterize any hemodynamic response shape differences in proposed prefrontal cortex regions for insights into abnormal frontolimbic emotion regulation (Ochsner and Gross 2005; Phillips et al. 2008a) during BP remission. Finally, we predicted that we would find prolonged hemodynamic response in these regions, and planned to examine any such results within the context of emotion regulation theories that might suggest ways in which abnormally prolonged prefrontal activation could relate to inefficient or abnormal control over limbic reactivity.

Methods

Participants

We recruited 24 bipolar I-diagnosed adults and 22 non-psychiatric control participants from the Institute of Living/Hartford Hospital adult psychiatric services programs and the local community using written informed consent procedures approved by Hartford Hospital and Yale Institutional Review Boards. Illness phase and possible etiological heterogeneity due to psychosis (Potash 2006; Bora et al. 2010) were controlled by sampling a non-psychotic BP sample in early remission from an acute illness phase. Therefore, the study was designed to be sensitive to trait-like abnormalities involved in the incidental processing of emotional information that might represent a vulnerability to bipolar I disorder. All BPs were clinically stable and receiving outpatient care (i.e., no hospitalizations within 1 month of study enrollment). Six BP participants ultimately were excluded – 4 had excessive head motion during fMRI, and 2 were found upon psychiatric interview to meet current mood episode criteria at the time of scanning – leaving 18 patient datasets.

Axis I diagnoses were evaluated for all participants using the Structured Clinical Interview for DSM-IV Disorders (SCID-I/P) (First et al. 2002) performed by experienced interviewers. All 18 bipolar participants retained in the study reported no lifetime history of psychotic features associated with mood episodes. Remission was defined as not meeting any current DSM IV criteria for bipolar disorder. In addition, participants' residual mood-related problems at the time of fMRI assessment were measured on the day of scanning using the Young Mania Rating Scale (YMRS) (29) and Montgomery-Åsberg Depression Rating Scale (MADRS) (30). Using commonly suggested cutoffs, 11 BP were fully euthymic (YMRS = 7 and MADRS = 10), 2 reported non-acute residual manic symptoms (YMRS = 12), 2 residual depressive symptoms (MADRS = 19), 2 mixed residual symptoms, and one BP qualified as mildly hypomanic (YMRS=14). Nine patients were most recently depressed before stabilization, 7 manic and 2 mixed. Nearly all (16 of 18) bipolar participants were taking psychotropic medications (Table 1). Three bipolar participants had anxiety disorder symptoms (panic disorder=2, GAD=1) within one month of evaluation, but none met full disorder criteria (Table 1). Fourteen bipolar participants reported lifetime alcohol/substance abuse or dependence, but none reported abuse within the previous three months, and all tested negative on a urine drug screen the day of fMRI.

Control participants had neither personal history of DSM-IV psychiatric illness, nor any history of psychiatric illness in first-degree relatives. The non-BP, healthy control comparison group was not significantly different in age, gender and race/ethnicity (Table 1). All participants were right handed. Although groups differed in years of education, previous studies have found this more likely is due to the disorder's disruption of educational attainment (Vonk et al. 2011) rather than a reflection of limited intelligence. Exclusion criteria for all participants included lifetime history of head injury, CNS disease, focal lesions, documented mental retardation or dementia, ECT in the last six months, any current major medical disease, positive urine screens for common drugs of abuse and current pregnancy.

fMRI Paradigm

The event-related fMRI paradigm examined neural activity elicited by incidental emotional processing, similar to that used in previous studies of symptomatic and remitted bipolar disorder (Lawrence et al. 2004; Chen et al. 2006; Hassel et al. 2008; Surguladze et al. 2010) that engages emotional systems to a greater degree than comparable explicit emotional processing tasks (Chen et al. 2006), activates prefrontal and limbic structures implicated in BP, and did not demand overt cognitive processing of emotional information. Forty-two single-face pictures (with 14 task-irrelevant angry, 14 happy, or 14 neutral expressions; (Lundquist et al. 1998)) were presented in pseudorandom order for 3 seconds with a 9-second inter-stimulus interval during which a fixation cross served as a baseline measure. Participants were instructed to identify via button press whether the face was male (index finger) or female (middle finger). Stimuli were projected onto a screen behind participants' heads viewed using a head coil-attached mirror. Participants completed a single task session lasting 8:48 min. Stimuli were presented and accuracy/reaction time collected using E-Prime (Psychology Software Tools, Inc.). Because Kolmogorov-Smirnov tests of normality and Levene's tests of variance homogeneity indicated performance data did not meet parametric statistic assumptions, Mann-Whitney *U*-tests compared proportion of trials completed, accuracy, and reaction time between groups.

Functional MRI Image Acquisition

All fMRI data were collected using a 3.0 Tesla Siemens Allegra MRI scanner at the Olin Neuropsychiatry Research Center, Institute of Living at Hartford Hospital. Functional MRI data for this task was acquired using a gradient-echo echo-planar imaging (EPI) pulse sequence: repetition time (TR)=1500 msec, echo time (TE)=28 msec, flip angle=65°, field of view=24×24 cm, acquisition matrix=64×64, voxel size=3.4×3.4 mm, slice thickness=5 mm, number of slices=29 (acquired sequentially).

fMRI Data Pre-Processing

Data analysis used Statistical Parametric Mapping software (SPM5; <http://www.fil.ion.ucl.ac.uk/spm>). After correcting for slice timing differences, data were spatially realigned and movement-corrected using INRIAalign (Freire et al. 2002) before normalization into Montreal Neurological Institute stereotactic space (EPI.mnc). Images were spatially smoothed using a Gaussian 8 mm full-width-at-half-maximum kernel.

Individual Participant fMRI Modeling

Individual fMRI analysis involved regressing single subject BOLD image time-series on stimuli onsets for angry, happy or neutral stimuli convolved with a "fully informed" basis set (Friston et al. 1998; R. Henson and Friston 2007). This basis set consisted of synthetic canonical hemodynamic response functions that not only evaluated the main effect of activation amplitude as is typically done in most fMRI analyses, but also the temporal (TD)

and dispersion derivatives (DD) of estimated hemodynamic response (R. Henson 2003). The latter two terms quantified early versus late hemodynamic peak and prolonged versus truncated response, respectively. Thus, each stimulus class was represented by three regressors in the first-level general linear model (GLM). By including derivative terms into the model, it not only is possible to improve overall model fit (e.g., (R. N. Henson et al. 2002)), but also the information from the TD and DD terms can be used either to provide more accurate estimates of task-related activation (e.g., (Calhoun et al. 2004)) or for hypothesis testing about differences in the shape of hemodynamic response. SPM5 autoregressive model (AR1) corrected for temporal autocorrelations. Six translation and rotation movement parameters from image realignment were entered as covariates of no interest. A 128 sec high pass filter was applied. Nine SPM contrast images were generated for each participant, representing main effect, TD, and DD estimates of hemodynamic response for neutral, angry or happy stimuli (collapsed across stimuli male/female gender) relative to the un-modeled implicit fixation baseline.

Region of Interest Analysis of Group fMRI Data

The study hypothesis was tested using an ROI approach. ROIs were selected following activation likelihood estimation (ALE) meta-analysis (Laird et al. 2005) performed on published studies using similar fMRI tasks of non-directed facial emotion processing (Supplement 1, Supplemental Tables 1–2, Supplemental Figure 1) along with two ROIs chosen for their proposed role in emotion regulation (Ochsner and Gross 2005; Phillips et al. 2008a). Study ROIs represented bilateral dorsolateral, ventrolateral, and orbitofrontal prefrontal cortices, bilateral amygdala and ventral putamen, and midline ventromedial and dorsomedial prefrontal regions (Table 3). Spheres with 5 mm radii were constructed around ROI centers. The ROI size was chosen to be large enough to have multiple voxels to average signal across for a stable estimate of signal change, but also narrow enough to ensure focus on the intended brain region. For each participant, average ROI values within this space were extracted from contrast images corresponding to the nine *valence* $\times$ *basis set* conditions.

ROI values were used in a series of PASW Statistics 18.0 2 $\times$ 3 $\times$ 3 mixed-model ANOVAs (*group* $\times$ *valence* $\times$ *basis set*), performed independently for each ROI. For ROIs showing significant *group* effects, the primary study hypothesis for prolonged response was evaluated by significant *group* $\times$ *basis set* effects to confirm that the shape of the hemodynamic response significantly differed between study groups. *Group* $\times$ *valence* effects tested to see whether BP versus control differences depended on stimulus valence, while three-way interactions further examined these results in the context of stimulus valence. False Discovery Rate was used to correct for multiple comparisons for all primary ROI analyses (Genovese et al. 2002). When sphericity assumptions were violated for repeated measurements (e.g., for basis set or valence), Greenhouse-Geiser corrections evaluated significance. *Post hoc* tests on main effect, TD, and DD average ROI coefficient values characterized the exact nature of hemodynamic response shape differences. Two-sample post hoc *t* tests on TD and DD measurements determined how groups differed in peak latency or response duration (TD – early versus late peak; DD – narrow versus prolonged response window). Peristimulus time histograms of fMRI-measured signal change averaged within ROIs illustrated hemodynamic shape differences. This approach uses a Finite Impulse Response model (R. Henson and Friston 2007; Ollinger et al. 2001) to provide a timepoint by timepoint estimate of activation that followed stimulus onsets. To bolster confidence in our findings using the “fully informed” basis set approach, we performed supplemental mixed-model ANOVAs (*group* $\times$ *valence* $\times$ *FIR timepoint*) for the first 18 seconds of this response window (i.e., 12 timepoints), with Greenhouse-Geiser corrections

for sphericity violations in each ROI. This *post hoc* analysis helped to ensure that our findings were not due to the methodological approach chosen as the primary analysis.

Other Supplemental Analyses

Because previous research has linked event-related fMRI activation profile and reaction time in many of the brain regions examined (Yarkoni et al. 2009), ROI analyses were re-run using participant mean reaction time as a covariate to confirm findings were robust to subject-wise decision-making or motor response time differences. Other *post hoc* analyses examined the linear association of YMRS or MADRS scores in the BP sample to ROI values to determine if any effects were related to residual manic and depressive symptoms. Importantly, we also examined group differences using only the canonical HRF term to be able to discuss our TD and DD results in the context of what a conventional analysis approach would detect in the data. One-sample *t* test against zero for canonical model fit estimates collapsed across fMRI task conditions effectively characterized whether ROIs in each group were “activated” or not, while two-sample *t* tests examined group response amplitude differences.

Finally, a 2×3×3 mixed-model voxelwise SPM5 factorial ANOVA evaluated *group*, *valence* and *basis set* effects and all statistical interactions to identify any effects falling outside study ROIs. We conservatively only reported such results that survive whole brain corrections for multiple comparisons ($q < .05$ FDR).

Results

Behavioral Data

Mann-Whitney *U*-tests revealed no significant group differences between BP and controls (Table 2) in trial completion percentage ($U=134.5$, $p=0.28$). There was a trend towards longer median response times in patients ($U=233$, $p=0.055$) that was present during viewing of neutral, angry, and happy pictures equivalently. Study groups differed in overall gender labeling accuracy ($U=97$, $p=0.021$) due to more frequent BP errors on angry ($U=109$, $p=.041$) and happy ($U=88$, $p=.003$) stimuli. However, the discrepancy was marginal (overall accuracy 97.7% for controls vs. 94.7% for BP). No significant correlations existed between participant accuracy and reaction time in either group, suggesting there was no speed/accuracy tradeoff when errors were made.

fMRI Results

To visualize fMRI task activation, the main effect of BOLD signal change (collapsed across valences, groups, and ME, TD, and DD terms) were projected onto a rendered brain using a $q < .05$ FDR threshold (Figure 1), using whole brain FDR $q < .05$ thresholds. This figure depicts “activation” to task irrespective of specific experimental factors.

Group Differences

Peri-stimulus time histograms showing both groups’ estimated hemodynamic response for each ROI are shown in Figure 2. Nearly every *a priori* ROI showed a significant hemodynamic response to stimuli in either control or bipolar samples, but the groups differed as to whether a response was detected in each region. Activity in bilateral dorsolateral, right mid-insula, and the cognitive division of the caudal anterior cingulate ROI were only detected in BP (Table 3). BP showed no evidence for left orbitofrontal or pregenual cingulate hemodynamic response to stimuli. Figure 2 inspection reveals that dorsomedial prefrontal ROI did engage for bipolar patients, but its peak was shifted much later than could be captured by the canonical HRF term.

Most ROIs (13 of 16) showed significant differences between bipolar and control groups, all of which survived multiple comparisons correction (Table 3). The remaining left orbitofrontal cortex ($p<.056$), right amygdala ($p<.092$), and left putamen ($p<.054$) ROIs showed statistical trends towards a main effect group difference. Such group differences represented BP abnormality in activation to stimuli, regardless of emotional valence or hemodynamic shape. Partial η^2 effect sizes ranged from 0.07 to 0.31 (average 0.18) for all ROIs, which were medium-to-large effects (Cohen 1990). Although many regions seemingly had greater amplitude response in BP upon visual inspection, *post hoc t* tests confirmed statistically significant greater BP amplitude only in right mid-insula ($p<.018$) and the cognitive division of the caudal anterior cingulate ($p<.046$). Motor cingulate had a trend-level *group* effect ($p<.062$). When tested by conventional analyses (Supplemental Table 3), the majority of ROI group differences represented medium partial η^2 effect sizes where BP had greater magnitude responses than controls. This suggests that a larger sample might have provided greater statistical power to detect more significant amplitude effects.

Differences in Hemodynamic Response Shape

The ANOVA testing the primary study hypothesis for altered hemodynamic response shape revealed significant *group* $\times$ *basis set* interactions in 10 of 16 ROIs, all of which survived corrections for multiple comparisons (Table 3). This indicates that the majority of brain regions whose activity differed between BP and controls also differed in the contribution of latency or duration GLM terms to group differences. Dorsomedial prefrontal ($p<.055$; partial $\eta^2=0.080$) and left amygdala ($p<.061$; partial $\eta^2=0.071$) had trend *group* $\times$ *basis set* effects. Because these are comparable effect sizes and their group difference main effects were strongly significant, these ROIs were considered valid for *post hoc* derivative term testing.

Table 4 lists the results of *post hoc* tests for these ROIs, with values describing the latency and duration of hemodynamic response in each study group, as well as *t* test comparisons of between-group differences. Results of latency and duration group comparisons are expressed using a difference score to easily describe whether BP had later-peaking or prolonged responses relative to controls in each ROI. The primary study hypothesis for prolonged BP hemodynamic responses was supported for left amygdala, dorsomedial prefrontal, right dorsolateral prefrontal, bilateral ventrolateral prefrontal/anterior insula, bilateral mid-insular cortex, and both cognitive and motor divisions of caudal anterior cingulate cortex ROIs through statistically significant prolonged response duration effects. Figure 2 depicts prolonged hemodynamic rise-and-fall in BP for these regions. In addition, left dorsolateral prefrontal and right putamen ROIs had a significantly later-peaking response.

Right amygdala ($F=2.676$, $p=.034$) and left mid-insula ($F=3.427$, $p=.013$) ROIs had significant three-way *group* $\times$ *valence* $\times$ *basis set* interaction effects, indicating that hemodynamic response shape differed depending on the incidental emotional content of the stimuli (Figure 3). *Post hoc t* tests on valence-specific main effect, TD and DD values showed that right amygdala generally had a later peak than the canonical model only for happy-valenced stimuli in BP. The interaction in left mid-insula ROI was driven by a greater, later-peaking and prolonged response to neutral stimuli and later-peaking response to angry stimuli.

The only region where BP exhibited either earlier latency or shorter duration of hemodynamic response was the pregenual cingulate. This simply reflected blunted engagement of the negative-going BOLD response in BP.

In supplemental analyses, only the left dorsolateral prefrontal cortex ROI group difference effect failed to be replicated when analyses were re-done covarying for individual mean reaction time; however, importantly the significant *group* $\times$ *basis set* interaction for this ROI

was confirmed. No correlations between YMRS or MADRS scores and ROI values for amplitude, latency or duration survived corrections for multiple comparisons. At uncorrected significance levels, BP YMRS scores were linked only to prolonged right amygdala ($p < .004$). YMRS was also correlated with later-peaking dorsomedial ($p < .013$) and right putamen ($p < .025$), while MADRS-measured depression severity was associated with amplitude ($p < .038$) and latency ($p < .033$) of ventrolateral/anterior insula response. These correlation results indicate that any residual symptoms of mania or depression were largely unrelated to the main study findings.

Our supplemental analysis of the data using a Finite Impulse Response model confirmed that findings of differently shaped hemodynamic responses between groups was not due to the analytic approach chosen. As detailed in Supplemental Table 4, *group* $\times$ *FIR Timepoint* effects were found in 8 of 10 ROI findings with p values $< .05$ and that survived multiple comparisons. This effect for right putamen ($p = .028$) failed to survive corrections. The effect for the right ventrolateral prefrontal/anterior insula ROI was $p = .060$, or nearly significant. However the three-way interactions of *group* $\times$ *valence* $\times$ *FIR timepoint* found for left mid-insula and right amygdala using the “fully informed” basis set approach were not replicated.

Effects of Emotional Valence

Because emotional effects on brain activation are not central to the study aim, these are detailed in Supplement 2 and Supplemental Figure 2.

Supplemental Whole-Brain Results

Additional significant effects from whole-brain analysis were observed only in the *group* $\times$ *basis set* contrast. These included left (BA18; $q = 0.002$, $F_{342} = 17.19$) and right mid-occipital gyrus (BA18/19; $q = 0.011$, $F_{342} = 12.42$), right cuneus (BA 18; $q = 0.015$, $F_{342} = 11.71$), right inferior occipital gyrus (BA 18; $q = 0.026$, $F_{342} = 10.68$), and right cerebellum ($q = 0.007$, $F_{342} = 13.20$). Inspection of group time-course plots revealed that BP had lesser hemodynamic response than controls in all these regions (Supplemental Figure 3).

Discussion

This was the first fMRI study to examine whether a prolonged neural response to affectively-valenced stimuli might be found in emotion-processing brain regions in remitted bipolar I disorder. As hypothesized, BP had a prolonged response in left amygdala and several prefrontal cortex brain regions, confirming that disengagement of emotion processing neural substrates is abnormal in bipolar disorder. By statistically parsing apart different aspects of the hemodynamic response, we were able to show that group differences in latency and duration outweighed those of simple amplitude in many regions tested and were not clearly related to residual symptoms of mania or depression. Importantly, we also showed that conventional fMRI analysis approaches would have indicated only greater amplitude response in BP, raising the possibility that failure to disengage neural processing likely would have been found in numerous previous fMRI studies if methods to examine the shape of the hemodynamic response had been used. Greater amygdala activity is a well-replicated finding in both remitted and symptomatic BP when processing both emotional and non-emotional material (Savitz and Drevets 2009; Wessa and Linke 2009) and has been proposed as a trait that interferes with proper function of frontolimbic-striatal networks responsible for emotional homeostasis (Cerullo et al. 2009). The longer duration limbic response found in this study could represent a novel aspect of this putative vulnerability trait, as the effect on activation duration was detected in patients who no longer met any criteria for bipolar I disorder, and was independent of task performance or residual BP mood symptoms. Interpretation of this finding should be greatly influenced by the fact that

prolonged hemodynamic response was not specific to emotional stimuli, as only right amygdala had an emotion-specific longer-duration response (to happy stimuli). Instead, there was a lengthening of BP hemodynamic response for most frontolimbic regions examined, regardless of stimulus valence. The generality might be related to previously-described BP difficulties in discriminating emotional expressions (Bozidakis et al. 2006; Getz et al. 2003; Lembke and Ketter 2002) and tendency to imbue neutral stimuli with affective meaning (McClure et al. 2003).

The second study finding was that remitted BP did not engage pregenual cingulate and left orbitofrontal cortex to all stimuli, believed to be key components of an automatic emotion regulation system (Phillips et al. 2008a). Left-lateralized ventral prefrontal cortex dysfunction has been found in previous bipolar disorder automatic emotion regulation studies (Lagopoulos and Malhi 2007; Malhi et al. 2007) and is thought to be a mood-independent trait (Blumberg et al. 2003). If considered within the context of a feed-forward model, the current results suggest that neural representations of emotional salience in the amygdala are not effectively appraised by the strongly inter-connected (Rolls 2000; Yu et al. 2011; Salzman and Fusi 2010) ventral prefrontal brain regions. This might be a specific failure point for BP within the larger automatic regulation system, where rostral cingulate is unable to redirect attention away from emotionally-salient stimuli (Phillips et al. 2008a) and orbitofrontal dysfunction impairs outcome-based appraisal of emotionally-salient stimuli (Ochsner and Gross 2005). Such possibilities can be tested directly with effective connectivity analyses in future studies (e.g., Dynamic Causal Modeling techniques, etc.).

The co-occurrence of these two findings prompts speculation that the prolonged response observed in dorsomedial, bilateral mid-insula, bilateral ventrolateral prefrontal/anterior insula, and anterior cingulate ROIs might reflect other automatic regulation system regions attempting ineffectively to regulate amygdala response without assistance from dysfunctional medial frontal cortex areas. This might represent a form of neural “compensation” in the presence of a primary BP neural deficit, where other neural systems are engaged to accomplish needed emotional regulation. The insula is highly interconnected with both primary association and sensory areas (Fusar-Poli et al. 2009), amygdala and anterior cingulate (Morris et al. 1996; Phillips et al. 2003) and is involved in the evaluative and experiential aspects of emotional states (Phan et al. 2002; Dolan 2002). Dorsomedial prefrontal cortex is important for emotional processing (Murphy et al. 2003), particularly integrating both exteroceptive and interoceptive cues in appraising emotional salience (Phan et al. 2002). Collectively, these regions seem optimized to elaborate on neural processing of affective significance. Nearly all these regions either comprise the automatic emotion regulation system proposed by Phillips et al., or serve as components of within both proposed voluntary and involuntary regulation systems (Phillips et al. 2008a). The abnormal engagement of dorsolateral prefrontal cortex in BP that was not seen in controls might also represent a form of compensation. This region is linked to voluntary forms of emotional control (e.g., suppression, reappraisal, regulation or volitional attentional control) (Ochsner and Gross 2005; Phillips et al. 2008a). Abnormal BP dorsolateral prefrontal engagement is interesting in part because the fMRI task did not call for explicit recognition of, or reaction to, the stimuli emotional content. Engagement of voluntary emotion regulation system resources in a compensatory manner when automatic systems fail might initiate through signaling from cingulate or dorsomedial prefrontal regions shared by both proposed systems (Phillips et al. 2008a) to the dorsolateral regions. Even if ultimately these prolonged prefrontal responses are not best explained by compensatory emotion regulation system function, they might reflect physiological reactions elicited when the amygdala signals (either accurately or inaccurately) the presence of affective content. Alternatively, this experiment cannot rule out greater conscious awareness of emotional content in BP engaging dorsolateral prefrontal cortex.

Study strengths include its analytic novelty, consistency of BP activation abnormality findings with previous reports, and the absence of psychosis in the BP sample. Although the inferences that can be drawn about duration of neuronal activity are necessarily limited given the nature and sluggishness of the hemodynamic response, regional differences in the persistence of hemodynamic activation found to be characteristic of BP in remission likely reflect abnormal ongoing or elaborative processing in key neural systems. The relationship between BOLD response shape and underlying physiological parameters (e.g., neuronal/glial activity) is not fully understood, suggesting that metabolic explanations, rather than factors that abnormally prevent the disengagement of certain brain regions in BP, also should not be ruled out. However, the regional specificity of prolonged BP response (as well as BP activation deficits in visual cortex found in the whole brain supplemental analyses) argues against systemic effects on BOLD signal measurement in BP. Another issue is that analytic recovery of true amplitude, latency and duration characteristics of the BOLD response is complex (Handwerker et al. 2012). Not only can hemodynamic variability be simply due to cerebral blood flow changes secondary to vascular volume or elasticity, but also different hemodynamic shape analysis methods have strengths and weaknesses. For instance, comparison of various latency-sensitive techniques shows that peak deviations >3 sec are poorly captured by the approach used in this study (Lindquist et al. 2009). Also, most latency/duration modeling approaches can under-estimate amplitude, latency or duration in ways affecting both statistical power and Type-I error (Lindquist et al. 2009). Therefore, replication of these results using relatively less-biased Finite Impulse Response or nonlinear shape modeling would bolster the findings. The noise properties of the BOLD timeseries signals also might play a role in the accuracy of hemodynamic shape estimation. If future studies can further validate the hemodynamic shape differences seen here and better understand the specific factors that influence them, it should be possible to design future fMRI experiments that make use of purpose-constructed basis sets that optimize the detection of BOLD signal changes at different delays or heights for different parts of the hemodynamic response function curve (e.g., FMRIB's Linear Optimal Basis Sets (FLOBS); (Woolrich et al. 2004)). The main clinical limitation was the absence of trait emotional reactivity behavioral measures (Nock et al. 2008; Henry et al. 2008a; Pompili et al. 2008; Orsillo et al. 2007) to link brain activity abnormalities to clinical measurement methods. It also is unclear to what extent the altered BP hemodynamic response function in these regions might be treatment-related; dorsolateral prefrontal activation in particular has been shown to be modulated by BP medications (Phillips et al. 2008b). However, our previous study of medication-naïve BP adolescents also found evidence for prolonged prefrontal hemodynamic response in dorsolateral prefrontal cortex when processing emotional stimuli (Wegbreit et al. 2012). At least one other study has found relatively greater limbic over-activity in unmedicated BP (Blumberg et al. 2005), suggesting that medications might attenuate this finding. Therefore, future examination of unmedicated remitted patients might reveal even greater prolongation of hemodynamic response. Regardless, because nearly all our bipolar participants were receiving one or more psychotropic medications (including a wide variety of mood stabilizers, anxiolytics, antidepressants and antipsychotics at different doses), we were unable to conduct an informative statistical analysis to link the effects of a specific medication to brain function abnormality. A much larger sample would be needed to yield meaningful medication subgroup results.

In conclusion, this study indicates that adult BP patients in early remission have abnormalities not simply in how strongly certain frontolimbic brain regions respond when confronted with affectively-laden facial stimuli, but also that this response is of a longer duration. Additional evidence for aberrant persistent neural activity within brain systems already implicated as abnormal in BP would further support new lines of inquiry into cellular mechanisms and genetic factors that might underlie such abnormalities, validating a use for fMRI in understanding BP pathophysiology beyond that of simply identifying which

brain regions have abnormal response amplitude. Future research also can help to determine whether this abnormality is merely part of the BP phenotype, or alternatively represents an endophenotypic marker of the illness. We believe it is more likely that the findings will ultimately be found to represent a novel endophenotype given the bipolar patients' lack of acute mood disturbance, the general absence of association between the patients' hemodynamic abnormalities and the group's few residual mood symptoms, and the correspondence of implicated brain regions to those identified in a previous study of bipolar patient family members (Surguladze et al. 2010). If future studies indeed validate prolonged frontolimbic neural responses as a BP endophenotype, investigators should begin to examine the diagnostic specificity of the findings. It would be interesting to study the underlying role of serotonergic function as a mediator of prefrontal-amygdala connectivity, as SSRI antidepressants sometimes exacerbate bipolar mood disorder (Tondo et al.), but reduce limbic hyper-activity to negative facial stimuli in unipolar depression (Ruhe et al. 2011). It also should be determined whether prolonged emotional system brain function might lessen with longer symptom remission, and if any effects of illness duration are related to abnormal persistence of BP frontolimbic activation. Though again, the detection of prolonged neural response to emotional stimuli in adolescent BP (Wegbreit et al. 2012) provides initial evidence for early life emergence of this abnormality, consistent with our interpretation of it as a trait vulnerability. It also would be interesting to determine how such longer duration activation abnormalities relate to well-described neuropsychological impairments in remitted BP (Glahn et al. 2004). Future study of hemodynamic shape also might help to clarify inconsistent findings regarding mood-congruent versus -incongruent attentional biases towards emotional stimuli (Wessa et al. 2007) as a vulnerability for the disorder. Perhaps most importantly, future studies should more fully describe how the various nodes of proposed emotion regulation circuits interact to effectively modulate emotional reactions, and describe abnormal neural system function in BP. Although our statistical approach did not allow for inferences to be drawn regarding temporal sequence of neural activity, our interpretation of the results in the context of emotion regulation neurocognitive theory raises questions that could be addressed using techniques such as Dynamic Causal Modeling used in future studies. Such results would likely inform model-building for both theories of emotion regulation and BP pathophysiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Brain rendering depiction of significant signal change to facial stimuli in the gender-identification fMRI task in the combined bipolar and control study groups. This map was constructed considering all main effect, temporal derivative, and dispersion derivative voxelwise data simultaneously for the best possible estimate of “activation” to task. Statistical results are thresholded at $q < .05$ False Discovery Rate corrections for searching the whole brain. Areas in red-yellow represent activation to all stimuli classes, whereas blue-turquoise represent negative BOLD signal change.

Figure 2. Peristimulus time histograms showing average study group hemodynamic response time-courses based around the voxel-centers of regions-of-interest showing significant ($p < 0.05$ Holm-Bonferroni corrected) ANOVA $group \times basis\ set$ effects.

Figure 3. Peristimulus time histograms showing hemodynamic response to neutral, positive, and negative facial affective stimuli in bipolar and non-bipolar control groups in regions-of-interest showing a significant interaction of *group* $\times$ *valence* $\times$ *basis set* conditions in the mixed-effect ANOVA.

Table 1

Summary of Participant Demographic and Clinical Characteristics

	Bipolar (n=18)	Controls (n=22)
Age	33.9 (+/-11.0)	35.9 (+/-11.7)
Gender	11 male (61.1%)	11 male (50.0%)
Ethnicity (% non-white)	11.1%	9.1%
Right-handedness	100%	100%
Education (in years) ^a	14.1 (+/-2.3)	16.4 (+/-1.7)
Parental Education (in years)	14.1 (+/-3.0)	13.5 (+/-3.3)
Young Mania Rating Scale ^b	4.8 (+/-4.8)	-
Montgomery-Åsberg Depression Rating Scale ^c	4.9 (+/-6.0)	-
<i>Current DSM-IV Diagnoses</i>		
Bipolar I Disorder w/o Psychotic Features	n = 18	n = 0
Most Recent Depressed	n = 9	-
Most Recent Manic	n = 7	-
Most Recent Mixed	n = 2	-
Anxiety Disorders	n = 3	n = 0
<i>Current Psychotropic Medications</i>		
Lithium	n = 3	n = 0
Atypical Antipsychotics	n = 7	n = 0
Antidepressants	n = 8	n = 0
SSRI	n = 6	-
SNRI	n = 1	-
Atypical	n = 7	-
Anxiolytics/Anticonvulsants	n = 12	n = 0
No medication	n = 2	n = 22
<i>Average Medications Taken</i>	2.3 (+/-1.2)	-

^aSignificant group difference in proband education ($t=3.60$, $df=29.7$, $p=0.001$ two-tailed)

^bYMRS: data missing for 2 bipolar subjects

^cMADRS: data missing for 1 bipolar subject

Table 2

Summary of Participant fMRI Behavioral Performance

	Bipolar^a	Controls^b	<i>U</i>	<i>p</i>
Accuracy (% correct)				
Neutral	98.3 (+/-4.02)	96.8 (+/-5.90)	186	.497
Angry	93.3 (+/-6.90)	97.5 (+/-3.50)	109	.041
Happy	92.4 (+/-8.55)	98.9 (+/-2.62)	88	.003
<i>Total</i>	94.7 (+/-4.95)	97.7 (+/-2.94)	97	.021
Response Time (msec)				
Neutral	1094.6 (+/-332.0)	950.0 (+/-209.8)	227	.082
Angry	1129.8 (+/-285.6)	990.6 (+/-213.9)	224	.100
Happy	1016.3 (+/-231.5)	923.0 (+/-174.3)	224	.100
<i>Total</i>	1080.2 (+/-272.7)	954.5 (+/-190.9)	233	.055
Trials responded (%)				
<i>Total</i>	98.2 (+/-3.3)	99.3 (+/-2.2)	134.5	0.28

^aBehavioral data is missing for 1 bipolar participant

^bBehavioral data is missing for 2 control participants

Table 3

fMRI Region of Interest (ROI) analysis results showing Non-Bipolar Control and Bipolar group activation in each ROI and mixed-effect ANOVA results for *Group* main effect and *Group* $\times$ *Basis Set* interaction effects

Anatomical Description	ROI Center Coordinates			Controls ROI "Activation"			Bipolar ROI "Activation"			Group Main Effect			Group $\times$ Basis Set Interaction		
		<i>t</i>	<i>p</i>	<i>t</i>	<i>p</i>	<i>t</i>	<i>t</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>p</i>
L Dorsolateral Prefrontal (BA 9/46)	-42 30 27	1.635	-			3.491	.003*	.028*	5.227	.028*	5.136	.012**†			
R Dorsolateral Prefrontal (BA 9)	42 36 30	1.722	.100			2.161	.045	.0003	15.576	.0003	6.493	.004**†			
R Dorsomedial Prefrontal (BA 9)	3 54 33	1.458	-			1.544	-	.0004	14.801	.0004**†	3.285	.055			
L Ventrolateral Prefrontal/Anterior Insula	-36 21 -6	6.200	.000004*			6.270	.000008*	.009**†	7.603	.009**†	5.112	.008**†			
R Ventrolateral Prefrontal/Anterior Insula	36 21 -3	8.283	.00000005*			5.872	.00002*	.005**†	8.781	.005**†	4.442	.027**†			
L Mid-Insula (BA 13)	-42 6 3	5.276	.00005*			5.742	.00002*	.002**†	10.774	.002**†	9.149	.0006**†			
R Mid-Insula (BA 13)	45 -3 0	0.547	-			3.355	.004*	.0002**†	16.877	.0002**†	9.427	.0005**†			
L Orbitofrontal	-33 30 -15	2.230	.037			1.142	-	.056	3.885	.056	2.487	.100			
R Orbitofrontal	27 24 -15	5.089	.00005*			5.161	.00008*	.017**†	6.245	.017**†	1.081	-			
Anterior Cingulate (motor)	0 15 39	3.096	.005*			5.201	.00007*	.005**†	8.815	.005**†	7.884	.003**†			
Anterior Cingulate (cognitive)	0 24 27	0.537	-			3.029	.008*	.001**†	12.468	.001**†	10.749	.0003**†			
Pregenual Anterior Cingulate	-3 36 0	-4.011	.0006*			-1.250	-	.022**†	5.731	.022**†	6.156	.003**†			
L Amygdala	-24 3 -24	2.645	.015*			4.205	.0006*	.014**†	6.578	.014**†	2.898	.061			
R Amygdala	21 0 -21	3.559	.002*			3.132	.006*	.092	2.985	.092	0.454	-			
L Putamen	-18 15 -3	5.727	.00001*			2.569	.020*	.054	3.945	.054	2.293	-			
R Putamen	21 15 -6	2.661	.015*			3.391	.003*	.029*	5.172	.029*	4.672	.012**†			

* Survives False Discovery Rate correction for multiple comparisons.

† Significant at $p < .05$ uncorrected for multiple comparisons after analyses were re-run controlling for individual differences in reaction time.

Table 4

Post-hoc *t* test results comparing mean study group ROI derivative term values between groups

Region	Mean ROI coefficient for each basis function term				One sample <i>t</i> tests determining significant TD or DD effects				Group TD and DD comparison results			
	Basis Function	Controls Mean (SD)	Bipolar Mean (SD)	<i>t</i>	Controls		Bipolar		<i>t</i>	<i>p</i>	Difference	<i>p</i>
					<i>t</i>	<i>p</i>	<i>t</i>	<i>p</i>				
L Dorsolateral Prefrontal (BA 9/46) *	TD	1.45 (3.22)	-1.90 (4.42)	2.118	.046		-1.828	.085	2.778	0.011	-3.36	
	DD	0.84 (2.67)	-0.79 (3.61)	1.483	.153		-.924	.368	1.642	-	-1.63	
R Dorsolateral Prefrontal (BA 9) *	TD	2.17 (3.56)	-3.35 (5.47)	2.857	.009		-2.593	.019	3.841	0.001	-5.51	
	DD	1.53 (2.62)	-0.93 (4.26)	2.745	.012		-.922	.369	2.243	0.041	-2.46	
R Dorsomedial Prefrontal (BA 9)	TD	0.04 (3.11)	-4.04 (5.47)	.055	.957		-3.137	.006	2.966	0.009	-4.08	
	DD	-0.22 (2.78)	-2.88 (4.73)	-.366	.718		-2.582	.019	2.215	0.045	-2.66	
L Ventrolateral Prefrontal/ Anterior Insula *	TD	1.96 (3.53)	-2.87 (7.11)	2.597	.017		-1.710	.105	2.793	0.015	-4.82	
	DD	3.03 (3.18)	0.46 (5.01)	4.480	.0002		.390	.702	1.977	0.069	-2.57	
R Ventrolateral Prefrontal/ Anterior Insula *	TD	3.19 (4.89)	-2.41 (7.97)	3.057	.006		-1.282	.217	2.728	0.015	-5.60	
	DD	2.54 (3.43)	0.13 (4.00)	3.471	.002		.141	.890	2.049	0.052	-2.41	
L Mid-Insula (BA 13) *	TD	0.66 (3.27)	-3.79 (4.03)	.945	.355		-3.987	.001	3.854	0.0006	-4.45	
	DD	1.24 (2.69)	-0.55 (2.71)	2.162	.042		-.864	.399	2.089	0.044	-1.79	
R Mid-Insula (BA 13) *	TD	0.62 (3.50)	-3.95 (4.01)	.833	.414		-4.179	.0006	3.850	0.0006	-4.57	
	DD	0.52 (3.00)	-3.19 (4.63)	.814	.425		-2.921	.010	3.057	0.007	-3.71	
L Orbitofrontal	TD	1.32 (2.93)	-0.91 (2.19)	2.114	.047		-1.764	.096	2.674	0.009	-2.23	
	DD	-0.08 (2.36)	0.59 (2.8)	-.168	.868		.898	.381	-0.831	-	0.68	
R Orbitofrontal	TD	0.40 (3.04)	-1.70 (3.36)	.617	.544		-2.154	.046	2.078	0.047	-2.10	
	DD	1.21 (3.45)	-0.12 (3.17)	1.651	.114		-.160	.875	1.261	-	-1.33	
Anterior Cingulate (motor) *	TD	4.53 (8.11)	-4.11 (9.18)	2.618	.016		-1.902	.074	3.160	0.004	-8.64	
	DD	5.20 (4.72)	0.63 (6.57)	5.171	.00004		.405	.691	2.559	0.019	-4.57	

Region	Mean ROI coefficient for each basis function term				One sample t tests determining significant TD or DD effects				Group TD and DD comparison results			
	Basis Function	Controls Mean (SD)	Bipolar Mean (SD)	t	Controls		Bipolar		t	p	p	Difference
					t	p	t	p				
Anterior Cingulate (cognitive) *	TD	4.32 (6.50)	-3.23 (5.36)	3.120	.005	.020	-2.560	.020	3.953	0.0003		-7.55
	DD	3.86 (4.67)	-0.45 (4.92)	3.872	.0009		-.386	.705	2.831	0.008		-4.31
Pregenuar Anterior Cingulate *	TD	5.05 (6.07)	-0.37 (4.02)	3.898	.0008		-.390	.701	3.243	0.002		5.42
	DD	0.27 (3.50)	-0.6 (4.38)	.362	.721		-.582	.569	0.699	-		0.87
L Amygdala	TD	-1.57 (5.02)	-4.84 (5.04)	-1.463	.158		-4.075	.0008	2.048	0.048		-3.27
	DD	1.70 (3.74)	-1.31 (3.97)	2.135	.045		-1.401	.179	2.466	0.019		-3.01
R Amygdala	TD	-4.45 (7.37)	-6.68 (5.87)	-2.829	.010		-4.829	.0002	1.043	-		-2.24
	DD	0.90 (4.91)	-1.52 (7.00)	.861	.399		-.921	.370	1.283	-		-2.42
L Putamen	TD	-0.77 (3.88)	-3.29 (3.6)	-.935	.361		-3.887	.001	2.112	0.040		-2.52
	DD	-0.61 (1.8)	-0.36 (3.53)	-1.594	.126		-.434	.670	-0.289	-		0.25
R Putamen *	TD	-0.46 (3.90)	-4.00 (3.99)	-.552	.587		-4.258	.0005	2.829	0.008		-3.54
	DD	0.59 (2.55)	-0.23 (3.36)	1.086	.290		-.295	.772	0.881	-		-0.82

* For regions-of-interest with a significant $group \times basis$ set interaction effect, TD – Temporal Derivative; (+) earlier peak, (-) later peak in Bipolar versus Controls. DD – Dispersion Derivative; (+) shorter duration, (-) longer duration in Bipolar versus Controls