Fronto-limbic neural variability as a transdiagnostic correlate of emotion dysregulation

Valeria Kebets1,2,5, Pauline Favre2,5, Josselin Houenou4,5, Mircea Polosan6, Nader Perroud1, Jean-Michel Aubry1, Dimitri Van De Ville2,7 and Camille Piguet1,5

INTRODUCTION

Emotion regulation allows individuals to modulate, manage or organize emotions in order to help them meet the demands of the environment and achieve their goals [1–3], implicating various processes and systems (e.g., cognitive, behavioral, social, biological). In contrast, emotion dysregulation has been described as “a pattern of emotional experience and/or expression that interferes with appropriate goal-directed behavior” [4]. Emotion dysregulation is a central feature of psychopathology, and is key to both the development and maintenance of mood, personality and anxiety disorders, among others [5–7]. Because it is both a risk factor for psychopathology in the general population, and is common across many forms of psychiatric disorders, a better understanding of the neurobiological underpinnings of emotion dysregulation may have important clinical applications, for instance in predicting or measuring the efficacy of a therapeutic intervention [8, 9] in a transdiagnostic setting.

Emotion regulation is thought to rely on a fronto-limbic network, whereby the prefrontal cortex (PFC) exerts cognitive control over the amygdala, a subcortical structure that is central to emotion processing and salience perception [10–12]. Unsurprisingly, alterations in this network are central to the pathophysiology of bipolar disorder (BD), borderline personality disorder (BPD), and attention deficit/hyperactivity disorder (ADHD), which are all characterized by emotion dysregulation [13–18]. Notably, the three disorders also share risk factors, such as childhood trauma and genetic overlap [19–22]. This suggests that emotion dysregulation might have underlying neurobiological mechanisms that are shared across these disorders.

A measure that has received increasing attention in the past few years is neural variability, obtained by computing within-subject BOLD signal variability over the timecourse. First considered as neural “noise”, it has since been proposed as an index of local system dynamics [23]. Indeed, a certain level of instability is thought to be required for the brain to flexibly explore different functional network configurations and adapt to various environmental demands [24–26]. Neural variability has been shown to vary with age [27–32], task performance...
[28, 30, 33, 34], but also symptom severity [35–38]. However, these relationships are often not linear (e.g., inverted U-shape in development and aging), and are task-, difficulty-, and circuit-dependent [33, 39, 40]. Nevertheless, this body of work demonstrates the functional relevance of neural variability, and it can provide meaningful information that is complementary to mean-based measures.

Studies investigating neural variability in clinical populations have implicated neural circuits that are relevant for psychopathology. Indeed, brain signal variability in the medial PFC during rest was shown to correlate positively with increased ADHD symptoms and inattention in children with and without ADHD [38]. Furthermore, brain signal variability has been shown to vary with mood shifts. In patients with BD, opposing patterns of neural variability were found in the default and sensorimotor networks (SMN) between patients in the depressed and manic phases [37]. This pattern mirrored the psychomotor behavior (i.e., acceleration/slowing), as well as the affective state (i.e., external/internal focus) that characterize the manic and depressive phases, respectively. Similarly, higher brain signal variability in the SMN was shown in individuals with a cyclothymic temperament compared to those with a depressive temperament in the general population [35]. Interestingly, it was suggested that increased neural variability in specific circuits might facilitate local neuronal responses to incoming stimuli, and lead to over-excitation of specific behaviors/symptoms, e.g., psychomotor behavior, ruminations [35, 37]. However, to date, most studies looking at neural variability have relied on case-control comparisons, and few have tested for transnostic, dimensional relationships.

In contrast to traditional case-control reports, a recent movement in psychiatry has advocated for a dimensional approach in the search for neurobiological markers of psychiatric symptoms. The NIMH’s Research Domain Criteria (RDoC) framework is one of the initiatives working towards developing a neurobiologically-based classification of mental disorders that integrates findings from behavioral science, neuroscience, and genetics [41, 42]. Consequently, we favored a transdiagnostic approach in the present work by leveraging a multi-site cohort of healthy individuals and individuals suffering from conditions strongly associated with emotion dysregulation (ADHD, BD, and BPD). We aimed to identify an emotion dysregulation dimension with associated patterns of blood-oxygen level-dependent (BOLD) variability, present in varying degrees among all individuals from our transdiagnostic cohort, which would suggest fundamental neurobiological mechanisms that transcend diagnostic boundaries. We relied on partial least squares, a multivariate data-driven technique that extracts latent components by maximizing covariance between spatial patterns of neural variability and behavior (here, emotion dysregulation, as expressed by a combination of affective lability, depression and mania assessments). More specifically, we hypothesized that neural variability in the fronto-limbic circuit would be related to individual variation in emotion dysregulation.

**MATERIALS AND METHODS**

**Participants**

Data for this study were collected from three sites (Geneva, Paris, Grenoble; see Fig. S1 for participants’ inclusion and exclusion criteria). All participants gave their written informed consent. The research was conducted according to the principles of the Declaration of Helsinki and was approved by the University of Geneva research Ethics Committee (CER 13–081), the Paris CPP Ile de France IX Ethics Committee, and the Grenoble University Hospital Ethics Committee (n° 2011-A00425–36). Inclusion criteria for all participants were age between 18 and 55, no history of alcohol or drug abuse/dependence, no current or past cardiac or neurological disease. Exclusion criteria for all participants were a history of neurological disease or head trauma with loss of consciousness, any significant cerebral anatomical abnormality, and contraindications for MRI.

Individuals with BD were recruited from the outpatient Mood Disorder Program of the Geneva University Hospital, from two university-affiliated participating centers (AP-HP, Henri Mondor Hospitals Créteil and Fernand Widal-Lariboisières Hospitals, Paris, France), and from the expert center for BD of Grenoble University Hospital. The clinical diagnosis was established using the DSM-IV-TR criteria by specialized psychiatrists and confirmed by the Mini-International Neuropsychiatric Interview [43], the Structured Clinical Interview for the DSM-IV [44], or the Diagnostic Interview for Genetic Studies (DIGS) [45]. Individuals were under stable medication for four weeks. Patients in Grenoble and Geneva were included in the study if they reported having been euthymic for at least 1 month prior to scanning and if they had a MADRS score <15 and a YMRS score <7. Patients in Paris were not in the acute phase of BD at the time of scanning.

Individuals with BPD and ADHD were recruited from the outpatient Emotional Dysregulation Unit for BPD and ADHD of the Geneva University Hospital. BPD diagnosis was established with the SCID for DSM-IV Axis II Personality Disorders [46], and ADHD diagnosis with the Diagnostic Interview for ADHD in Adults (DIVA 2.0), by trained clinicians as part of the standard procedure of these specialized programs. Some patients were under psychotropic medication for comorbidities, as reported in Table 1. Participants were instructed not to take psychostimulants on the day of the study data acquisition.

Control participants were recruited via local databases as well as through advertisement and were matched with patients in terms of age, sex, education, and handedness. Exclusion criteria were past or present neurological or psychiatric disorders (Geneva, Grenoble), personal or family history of Axis I mood disorder, schizophrenia, or schizoaffective disorder (Paris), use of psychotropic medication, and contraindication for MRI. All participants underwent clinical assessment by trained raters using the DIGS [45].

In total, 122 individuals with BD were recruited on all three sites, 93 healthy controls (HC) were recruited on two sites (i.e., Geneva and Paris), while 24 individuals with BPD and 21 individuals with ADHD were only recruited on one site (i.e., Geneva). We excluded ten participants (8 BD, 1 BPD, and 1 HC) for excessive in-scanner motion; 69 participants (39 BD, 2 BPD, 1 ADHD, and 27 HC) because they had not completed the clinical measures of interest; nine participants because they scored above 15 on the MADRS (7 BD, 2 BPD) and 6 because they scored above 7 on the YMRS (5 BD, 1 HC). The final sample thus comprised 166 participants, including 63 euthymic BD, 20 ADHD, 19 BPD, and 64 HC. The demographic, imaging, and clinical data of the final sample are shown in Table 1.

**Clinical assessment**

We used the Affective Lability Scales (ALS [47]), the Montgomery-Åsberg Depression Rating Scale (MADRS [48]), and the Young Mania Rating Scale (YMRS [49]) to measure different facets of emotion dysregulation. The ALS quantifies measures of affective lability, which refers to the frequency, speed, and range of changes in affective states [50]. The ALS is a 54-item self-reported questionnaire on which participants rate the tendency of their mood to shift between a “normal state” and different affects (depression, anger, anxiety, and elation), as well as their tendency to experience shifts between elation and depression, and between anxiety and depression. The total score was obtained by averaging across the six subscales, i.e., anger, anxiety, anxiety/depression, depression, depression/elation, elation. The MADRS and YMRS are both clinician-rated scales that evaluate depressive and manic symptoms, respectively. The total score (sum across all items) was used for both scales.

**Magnetic resonance imaging acquisition**

Briefly, participants were scanned on 3T MRI scanners (see detailed MRI acquisition parameters in the Supplementary Methods). A resting state (RS) functional magnetic resonance imaging (fMRI) sequence, as well as an anatomical scan were acquired in all participants.

**Resting state fMRI preprocessing**

The first ten RS functional images were discarded to ensure signal equilibration, and the remaining images were preprocessed using SPM12 tools (https://fil.ion.ucl.ac.uk/spm/software/spm12). Functional images were first realigned, followed by co-registration of the mean functional image with the anatomical scan. Functional images were normalized to the MNI space with SPM12 “segment”, resampled to 3 mm isotropic voxels, and then spatially smoothed with a 6 mm full-width-at-half-maximum (FWHM) Gaussian filter. The average signal within a mask of white matter (WM) and cerebrospinal fluid (CSF) were extracted using the Data Processing Program of the Geneva University Hospital, from two university-affiliated participating centers (AP-HP, Henri Mondor Hospitals Créteil and Fernand Widal-Lariboisières Hospitals, Paris, France), and from the expert center for BD of Grenoble University Hospital. The clinical diagnosis was established using the DSM-IV-TR criteria by specialized psychiatrists and confirmed by the Mini-International Neuropsychiatric Interview [43], the Structured Clinical Interview for the DSM-IV [44], or the Diagnostic Interview for Genetic Studies (DIGS) [45]. Individuals were under stable medication for four weeks. Patients in Grenoble and Geneva were included in the study if they reported having been euthymic for at least 1 month prior to scanning and if they had a MADRS score <15 and a YMRS score <7. Patients in Paris were not in the acute phase of BD at the time of scanning.

Individuals with BPD and ADHD were recruited from the outpatient Emotional Dysregulation Unit for BPD and ADHD of the Geneva University Hospital. BPD diagnosis was established with the SCID for DSM-IV Axis II Personality Disorders [46], and ADHD diagnosis with the Diagnostic Interview for ADHD in Adults (DIVA 2.0), by trained clinicians as part of the standard procedure of these specialized programs. Some patients were under psychotropic medication for comorbidities, as reported in Table 1. Participants were instructed not to take psychostimulants on the day of the study data acquisition.

Control participants were recruited via local databases as well as through advertisement and were matched with patients in terms of age, sex, level of education, and handedness. Exclusion criteria were past or present neurological or psychiatric disorders (Geneva, Grenoble), personal or family history of Axis I mood disorder, schizophrenia, or schizoaffective disorder (Paris), use of psychotropic medication, and contraindication for MRI. All participants underwent clinical assessment by trained raters using the DIGS [45].

In total, 122 individuals with BD were recruited on all three sites, 93 healthy controls (HC) were recruited on two sites (i.e., Geneva and Paris), while 24 individuals with BPD and 21 individuals with ADHD were only recruited on one site (i.e., Geneva). We excluded ten participants (8 BD, 1 BPD, and 1 HC) for excessive in-scanner motion; 69 participants (39 BD, 2 BPD, 1 ADHD, and 27 HC) because they had not completed the clinical measures of interest; nine participants because they scored above 15 on the MADRS (7 BD, 2 BPD) and 6 because they scored above 7 on the YMRS (5 BD, 1 HC). The final sample thus comprised 166 participants, including 63 euthymic BD, 20 ADHD, 19 BPD, and 64 HC. The demographic, imaging, and clinical data of the final sample are shown in Table 1.

**Clinical assessment**

We used the Affective Lability Scales (ALS [47]), the Montgomery-Åsberg Depression Rating Scale (MADRS [48]), and the Young Mania Rating Scale (YMRS [49]) to measure different facets of emotion dysregulation. The ALS quantifies measures of affective lability, which refers to the frequency, speed, and range of changes in affective states [50]. The ALS is a 54-item self-reported questionnaire on which participants rate the tendency of their mood to shift between a “normal state” and different affects (depression, anger, anxiety, and elation), as well as their tendency to experience shifts between elation and depression, and between anxiety and depression. The total score was obtained by averaging across the six subscales, i.e., anger, anxiety, anxiety/depression, depression, depression/elation, elation. The MADRS and YMRS are both clinician-rated scales that evaluate depressive and manic symptoms, respectively. The total score (sum across all items) was used for both scales.
Table 1. Demographic, imaging, and clinical profile of the sample used in the analyses (N = 166).

|                          | Bipolar (N = 75) | ADHD (N = 20) | Borderline (N = 21) | Controls (N = 65) | F/chi² | p val |
|--------------------------|------------------|---------------|---------------------|-------------------|--------|-------|
| **Demographics**         |                  |               |                     |                   |        |       |
| Age, mean (SD)           | 37.22 (11.61)    | 24.00 (3.45)  | 27.05 (4.67)        | 35.06 (12.01)     | 10.82  | 1.61E-06 |
| Sex (F/M)                | 30/33            | 7/13          | 19/0                | 37/27             | 20.39  | 1.41E-04 |
| Education, mean (SD)     | 13.22 (2.70)     | 16.00 (2.81)  | 14.84 (3.18)        | 12.67 (2.86)      | 8.34   | 3.97E-05 |
| **Imaging**              |                  |               |                     |                   |        |       |
| Scanner (1/2/3/4)        | 16/21/10/16      | 20/0/0/0      | 19/0/0/0            | 16/48/0/0         | 68.21  | 1.03E-14 |
| Framewise displacement, mean (SD) | 0.17 (0.09) | 0.14 (0.05)  | 0.13 (0.04)         | 0.17 (0.07)       | 7.59   | 8.83E-05 |
| **Clinical**             |                  |               |                     |                   |        |       |
| ALS, mean (SD)           | 1.04 (0.64)      | 1.12 (0.48)   | 1.80 (0.46)         | 0.42 (0.40)       | 39.44  | 3.44E-19 |
| MADRS, mean (SD)         | 4.84 (4.51)      | 3.55 (3.44)   | 7.68 (3.45)         | 1.23 (2.17)       | 20.90  | 1.69E-11 |
| YMRS, mean (SD)          | 1.68 (1.87)      | 0.00 (0.00)   | 1.47 (1.39)         | 0.66 (1.39)       | 8.77   | 2.00E-05 |
| **Disease severity**     |                  |               |                     |                   |        |       |
| Disease duration, mean (SD) | 14.59 (9.34) | 6.80 (5.31)  | 9.23 (5.39)         | –                 | –      | –     |
| # Hospitalizations, mean (SD) | 3.95 (3.24) | 0.05 (0.22)  | 1.94 (2.54)         | –                 | –      | –     |
| **Medication (by target)** |            |               |                     |                   |        |       |
| Dopaminergic, No. (%)    | 44 (70%)         | 15 (75%)      | 1 (5%)              | 0 (0%)            | –      | –     |
| Serotonergic, No. (%)    | 46 (73%)         | 1 (5%)        | 2 (11%)             | 0 (0%)            | –      | –     |
| Glutamatergic, No. (%)   | 42 (67%)         | 0 (0%)        | 0 (0%)              | 0 (0%)            | –      | –     |
| GABAergic, No. (%)       | 36 (57%)         | 0 (0%)        | 0 (0%)              | 0 (0%)            | –      | –     |
| Norepinephrinergic, No. (%) | 30 (48%) | 15 (75%)      | 0 (0%)              | 0 (0%)            | –      | –     |
| Lithium, No. (%)         | 38 (60%)         | 0 (0%)        | 0 (0%)              | 0 (0%)            | –      | –     |
| No medication, No. (%)   | 30 (48%)         | 5 (25%)       | 17 (89%)            | 46 (72%)          | –      | –     |
| Medication load, mean (SD) | 2.14 (1.51) | 0.85 (0.59)  | 0.16 (0.50)         | 0.31 (0.53)       | –      | –     |

Groups were compared with either ANOVAs (for continuous measures) or chi-squared tests (for categorical measures). All p-values that survived false discovery rate (FDR) correction (q < 0.05) are indicated in bold. Disease severity and medication use are only shown for informative purposes, but were not compared between groups.

aBased on 138 participants.
bBased on 82 patients.
cBased on 55 patients.
dMedication was sorted by the neurotransmitter system(s) affected by the medication used by participants, based on the Neuroscience-based Nomenclature (NbN-2 [91, 92], http://nbn2r.com/). The list of medications and their categorization can be found in Table S5. Note that percentages may add up to more than 100% because some individuals take more than one medication.

Assistant for Resting-State fMRI toolbox [51]. The effects of WM, CSF, and six motion parameters were regressed out from the time-course, and a bandpass filter (0.01–0.10 Hz) was applied. Motion scrubbing [52] was applied to correct for motion artefacts; i.e., framewise displacement (FD) was calculated as the sum of the absolute values of the six realignment parameters, and scans with a FD higher than 0.5 mm, as well as one scan before and two scans after, were excluded from the analysis. Participants with a time-course containing less than 4 min of scanning were excluded (8 BD, 1 BPD, and 1 HC).

**DARTEL group template**

A group template was generated with the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL [53]) from the gray matter and white matter tissue segments of all the participants comprising the entire original sample (N = 250, see Fig S1). Participants’ T1 images were first segmented using the Computational Anatomy Toolbox (CAT12; http://www.neuro.uni-jena.de/cat/) “Segment Data” and the tissue segments were normalized to the tissue probability maps by means of an affine transformation. The group template was then normalized to the MNI space, and additional registration to the ICBM template was applied. Finally, the template was downsampled in order to match the dimensions of the functional images, and then binarized to include only voxels with a ≥50% gray matter probability.

Because of incomplete cerebellar coverage in 33 participants, we decided to exclude the cerebellum from the DARTEL template. To do so, we used a bilateral mask of the cerebellum as defined in Hammers atlas [54, 55], a probabilistic anatomical atlas based on 83 manually-delineated regions drawn on MR images of 30 healthy adult subjects. In order to encompass the whole cerebellum, we first smoothed the mask with a 25 mm FWHM Gaussian filter, then downscaled the mask to match the dimensions of the DARTEL template, and excluded the cerebellum mask from the DARTEL template.

**BOLD signal variability**

Voxel-wise BOLD signal variability was obtained for each participant by computing the standard deviation of each preprocessed time-course. This approach is equivalent to the frequency-domain computation of the amplitude of low-frequency fluctuations (ALFF) between 0.01 and 0.1 Hz [56, 57], and is strongly correlated with mean-square successive differences (MSSD) [28, 58]. BOLD signal variability maps were constrained to the binarized DARTEL template (excluding the cerebellum), and were z-scored across all voxels included in the template within each participant [57]. Age, sex, scanner, and head motion (i.e., mean FD) were linearly regressed out from the imaging data prior to the PLS analysis using a general linear model on MATLAB.

**Partial least squares (PLS) analysis**

We used PLS analysis to identify BOLD signal variability spatial patterns related to emotion dysregulation across all participants. PLS is a multivariate data-driven statistical technique that aims to maximize covariance between two matrices [59, 60]. The optimal relationship between the two data matrices is represented as latent components (LCs), which are weighted linear combinations of the original data that maximally covary with each other. A LC is characterized by a spatial pattern of neural variability and a behavioral pattern of affective lability.

Translational Psychiatry (2021) 11:545
depression, and mania (imaging and behavioral saliences, respectively). By linearly projecting the imaging and behavioral measures of each participant onto their respective saliences, we obtain individual-specific brain and behavior scores, which reflect the participants’ imaging and behavioral contribution to each LC. Importantly, the PLS analysis was agnostic on the diagnostic group, so that transdiagnostic brain-behavior associations could be extracted.

The statistical significance of the LCs was assessed by constructing a null distribution of the singular values using permutation testing (1000 permutations), whereby the behavioral data was permuted within each diagnostic group, so that latent components would not be driven by group differences. To determine which behavioral measures and voxels were driving the significant LC, we computed Pearson’s correlations between the original imaging data and brain scores, as well as between the original behavioral measures and behavioral scores [61, 62]. A higher positive (or negative) correlation for a particular behavioral measure for a given LC indicates greater importance of the behavioral measure for the LC, while a higher positive (or negative) correlation for a particular imaging measure for a given LC indicates greater importance of that imaging value for the LC. We estimated confidence intervals for these correlations with a bootstrapping procedure that generated 1000 samples with replacement from participants’ imaging and behavioral data, while accounting for diagnostic groups (i.e., bootstrap resampling was performed within each diagnostic group) in order to avoid spatial and behavioral patterns being driven by group differences, since our aim was to find transdiagnostic patterns of emotion dysregulation. Z-scores were computed by dividing each correlation coefficient by its bootstrap-estimated standard deviation, and were considered as strong contributors to LCs at absolute values >3, corresponding to a robustness at a confidence interval of approximately 99% [60]. See Supplementary Methods for more details.

Posthoc analyses
Two-sample $t$-tests were performed to test whether brain and behavioral scores were different between participants from different diagnostic groups. Group differences in demographic, head motion, and clinical measures were tested using one-way analysis of variance (ANOVA; for continuous measures) or chi-squared tests (for categorical measures). We also tested if there were any significant associations between PLS brain (or behavioral) scores and disease severity, as well as medication use, using either Pearson’s correlations (for continuous measures), or $t$-tests (for binary measures). All posthoc analyses were corrected for multiple comparisons at a false discovery rate (FDR) of $q < 0.05$.

Control analyses
A number of control analyses were computed to assess the robustness of our results (detailed in the Supplementary Methods). Briefly, we used BOLD signal variability maps that included the cerebellum; we accounted for education level or early life trauma; we considered patients only; and we considered only participants from the one site, all yielding saliences that were similar to the original brain and behavior saliences (see Table S4), all showing the reliability of our findings. Detailed results are reported in the Supplementary Results, Tables S5–S7, and Figs. S2–S4.

DISCUSSION
In this work, we aimed to identify spatial patterns of neural variability related to emotion dysregulation in a multi-site transdiagnostic cohort, using a multivariate data-driven approach. We found that emotion dysregulation was associated with a pattern of increased BOLD signal variability in the ventromedial PFC, dorsomedial and dorsolateral PFC, amygdala, hippocampus, insula and motor cortex, and decreased BOLD signal variability in occipital regions. Our findings are in line with emotion dysregulation being a dimensional construct that spans across individuals with affective disorders such as ADHD, BD, and BPD, rather than being specific to any of these disorders. Importantly, the spatial pattern of brain signal variability associated with this dimension bears a compelling resemblance to the fronto-limbic circuit that is thought to subserve emotion regulation, and is impaired in ADHD, BD, and BPD. Our findings therefore add evidence to brain signal variability being a relevant proxy of neural efficiency, and support emotion dysregulation as a transdiagnostic dimension with neurobiological underpinnings that transcend diagnostic boundaries.

The patterns of brain signal variability associated with greater emotion dysregulation were mainly located in the fronto-limbic system, which plays a key role in emotional control/regulation [12, 63]. Critically, abnormalities in the fronto-limbic network are thought to underpin emotion dysregulation in pathophysiological models of BD and BPD [13–16, 18]. The suggested mechanism involves hyper-activation of limbic regions responsible for emotion generation—in particular, the amygdala, hippocampus, and ventral striatum—coupled with hypo-activation of the PFC, which is responsible for cognitive control. This circuit has shown structural abnormalities in individuals with BD [14, 64–66], BPD [15, 16], but also ADHD [67], e.g., altered volumes of the amygdala and hippocampus, and cortical thinning of the PFC. In BPD patients, abnormal patterns of activity in the amygdala, hippocampus, ventrolateral PFC, and dorsolateral PFC were shown during emotion processing [15, 16, 68], but also at rest, where the ACC, medial PFC and dorsolateral PFC were found to be hyper-
activated during resting state in BPD patients compared to control participants [69]. Furthermore, neural activation and connectivity of fronto-limbic regions, especially the ACC, amygdala, insula, and ventrolateral PFC, showed changes following psychotherapy aimed at improving emotion regulation in BPD patients [70]. Abnormal patterns of activity and connectivity of fronto-limbic regions have been reported in euthymic BD patients, especially involving the amygdala and the medial PFC at rest [71, 72], and during emotion regulation tasks [73, 74]. Moreover, psychosocial intervention in individuals with BD or at risk for BD may induce functional and structural changes in these regions [75–77]. Emotion dysregulation is also prevalent in ADHD, and fronto-limbic alterations involving the amygdala, orbitofrontal cortex, ventral striatum, and PFC have also been reported in this population [17]. We note however, that in addition to fronto-limbic regions, spatial patterns of neural variability maps associated with LC1 also featured brain regions whose role in emotion dysregulation is not clear (e.g., occipital regions; see Table S3 for a list of the BOLD signal variability clusters that reliably contributed to LC1).

Previous studies of neural variability in ADHD [38, 78–80], BD [37, 81–86], and BPD patients [87, 88] have failed to show any consistent pattern, although some have reported alterations in regions of the fronto-limbic network (mostly the PFC). In ADHD patients, increased BOLD signal variability in the dorsolateral PFC, inferior frontal and orbitofrontal cortex were found during a Stroop task [78], as well as increased brain signal variability in the ventromedial PFC during a vigilance task in adolescents with ADHD compared to controls [80]. Moreover, greater MSSD in the dorsolateral PFC during rest was related to greater ADHD symptom severity, while greater MSSD in the ventromedial PFC was positively correlated with inattention across children with ADHD and typically developing children [38]. In BPD patients, increased ALFF was shown in the hippocampus [88], while increased ALFF in the ventral PFC, dorsolateral PFC, and insula were found in euthymic BD patients [85], compared to controls. The fronto-limbic circuit also overlaps with the DMN, in particular the ventromedial PFC and hippocampus. We found increased neural variability of the ventromedial PFC to be associated with LC1, which was mostly driven by greater levels of depression. This partly corroborates a previous study contrasting neural variability patterns in the DMN and SMN, i.e., higher DMN/SMN ratio in the depressive phase of BD and the inverse pattern during mania, which were positively correlated with depression and mania scores, respectively [37]. Therefore, our findings somewhat corroborate previous reports of altered neural variability in these clinical populations, but for the first time in a network directly associated with emotion regulation.

Our findings may be in apparent contrast to the prevailing view that brain signal variability facilitates neural flexibility by allowing fluid transitions between brain states via a stochastic resonance effect [24, 25]. However, while it appears to be beneficial to task performance, heightened neural variability was also shown to correlate with worse clinical symptoms in various conditions [36–38]. As neural variability is thought to increase sensitivity to incoming stimuli, it is possible that heightened neural variability might lead to over-reactivity of specific neural circuits, as a maladaptive strategy to prepare for potentially relevant events,
which instead supports the maintenance of emotion dysregulation in affective disorders. Consequently, our findings support the use of neural variability as a relevant proxy for dysfunctional processing, which might be useful in tracking symptom severity and treatment efficacy [89].

The present study has several strengths including the use of a multivariate data-driven approach and the relatively large transdiagnostic cohort. Moreover, our approach aligns with recent initiatives such as the RDoC [41, 42], that promote transdiagnostic cohort. Moreover, our approach aligns with recent multivariate data-driven approach and the relatively large severity and treatment effects, which might be useful in tracking symptom variability correlates of emotion dysregulation in the fronto-limbic system, further improving our understanding of the pathogenesis of affective disorders. Importantly, emotion dysregulation is a transdiagnostic construct that has shown clinical utility as a therapeutic target, as demonstrated by a decrease in maladaptive emotion regulation strategy use and symptom severity (e.g., depression, anxiety, substance use, etc.), regardless of the treatment protocol, the construct of emotion regulation that was examined, and the targeted disorder [9]. Indeed, transdiagnostic protocols aimed at improving emotion regulation have been shown to provide rapid and significant improvement in individuals with various forms of severe mental illness [8]. In this context, our approach might also provide a robust way of tracking therapeutic effects of interventions aimed at enhancing emotion regulation.

**CODE AVAILABILITY**

The code for the MRI preprocessing, BOLD signal variability extraction, as well as the PLS outputs can be found on [https://github.com/ValKebets/BOLDsd_ED](https://github.com/ValKebets/BOLDsd_ED), while the code for the PLS analysis is publicly available at [https://github.com/danzioelle/myPLS](https://github.com/danzioelle/myPLS).

**REFERENCES**

1. Campos JJ, Campos RG, Barrett KC. Emergent themes in the study of emotional development and emotion regulation. Dev Psychol. 1989;25:394–402.

2. Gross JJ. The emerging field of emotion regulation: an integrative review. Rev Gen Psychol. 1998;2:271–99.

3. Hilt LM, Hanson JL, Pollack SD. Encyclopedia of adolescence. Amsterdam: Elsevier; 2011. p. 160–9.

4. Beauchaine TP. Future directions in emotion dysregulation and youth psychopathology. J Clin Child Adolesc Psychol. 2015;44:875–96.

5. Aida A, Nolen-Hoeksema S, Schweizer S. Emotion-regulation strategies across psychopathology: a meta-analytic review. Clin Psychol Rev. 2010;30:217–37.

6. Sheppes G, Suri G, Gross JJ. Emotion regulation and psychopathology. Ann Rev Clin Psychol. 2015;11:379–405.

7. Weissman DG, et al. Difficulties with emotion regulation as a transdiagnostic mechanism linking child maltreatment with the emergence of psychopathology. Dev Psychopathol. 2019;31:899–915.

8. Fowler JC, et al. Emotion dysregulation as a cross-cutting target for inpatient psychiatric intervention. J Affect Disord. 2016;206:224–31.

9. Sloan E, et al. Emotion regulation as a transdiagnostic treatment construct across anxiety, depression, substance, eating and borderline personality disorders: a systematic review. Clin Psychol Rev. 2017;57:141–63.

10. Adolphs R. Neural systems for recognizing emotion. Curr Opin Neurobiol. 2002;12:169–77.

11. LeDoux JE. The emotional brain: the mysterious underpinnings of emotional life. New York: Simon and Schuster; 1996.

12. Ochsner KN, Silvers JA, Buhle JT. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Ann N Y Acad Sci. 2012;1251:E1–E24.

13. Chase HW, Phillips ML. Elucidating neural network functional connectivity abnormalities in bipolar disorder: toward a harmonized methodological approach. Biol Psychiatry Cogn Neurosci Neuroimaging. 2016;1:288–98.

14. Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. Am J Psychiatry. 2014;171:829–43.

15. Ruocco AC, Carbone D. A neurobiological model of borderline personality disorder: systematic and integrative review. Harv Rev Psychiatry. 2016;24:311–29.

16. Schulze L, Schmahl C, Niedtfeld I. Neural correlates of disturbed emotion processing in borderline personality disorder: a multimodal meta-analysis. Biol Psychiatry. 2016;79:97–106.

17. Shaw P, Stringaris A, Nigg J, Leibenluft E. Emotion dysregulation in attention deficit hyperactivity disorder. Am J Psychiatry. 2014;171:276–93.

---

**Table 2.** Post-hoc associations between participants’ brain (or behavioral) scores, disease severity, and medication use (categorized by the neurotransmitter target).

| Brain scores | Behavior scores |
|--------------|-----------------|
| **Disease severity** |      |
| Disease duration | 0.11 | 0.334 | 0.01 | 0.958 |
| # Hospitalizations | −0.16 | 0.253 | 0.16 | 0.244 |
| **Medication use (by target)** |      |
| Dopaminergic | 2.40 | 0.018 | 2.10 | 0.037 |
| Serotonergic | −0.10 | 0.924 | 2.61 | 0.010 |
| Glutamatergic | −0.18 | 0.860 | −0.04 | 0.969 |
| GABAergic | −0.81 | 0.417 | 1.46 | 0.146 |
| Norepinephrinergic | 2.25 | 0.026 | 0.89 | 0.376 |
| Lithium | −1.87 | 0.064 | 0.73 | 0.467 |
| No medication | 0.99 | 0.325 | −0.74 | 0.458 |
| # Meds | −0.12 | 0.153 | 0.14 | 0.090 |

Pearson correlations (for continuous measures) or t-tests (for categorical measures) were computed across all participants. A higher r value indicates a stronger association between brain (or behavioral) scores and disease severity, while a higher t value indicates higher brain (or behavioral) scores in participants taking the specific medication. Significant correlations or t-tests that survived FDR correction (q > 0.05) are indicated in bold. The same analysis was performed after classifying medication by medication class (see Table S3).
34. Raja Beharelle A, Kova
42. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research
32. Samanez-Larkin GR, Kuhnen CM, Yoo DJ, Knutson B. Variability in nucleus
39. Garrett DD, McIntosh AR, Grady CL. Brain signal variability is parametrically
38. Nomi JS, et al. Resting-state brain signal variability in prefrontal cortex is asso-
20. Perroud N, et al. Comorbidity between attention de
29. Garrett DD, Kovacevic N, McIntosh AR, Grady CL. Blood oxygen level-dependent
24. Deco G, Jirsa V, McIntosh AR, Sporns O, Kötter R. Key role of coupling, delay, and
27. Andrews-Hanna JR, et al. Disruption of large-scale brain systems in advanced
22. Witt SH, et al. Genome-wide association study of borderline personality disorder
23. McIntosh AR, et al. The development of a noisy brain. Arch Ital Biol. 2016;113:4824
sorimotor networks balance in bipolar depression and mania. Proc Natl Acad Sci. 2019;40:1344
neuronal transmission and cognitive aging. Cereb Cortex. 2016;26:2074–83.
Nomi JS, Bolt TS, Ezie CEC, Uddin LQ, Hefler AS. Moment-to-moment BOLD signal
reflects regional changes in neural flexibility across the lifespan. J Neurosci. 2017;37:5539–48.
Samanez-Larkin GR, Kuhnen CM, Yoo DJ, Knutson B. Blood oxygen level-dependent
variance mediates cyclothymic and depressive temperaments. Hum Brain Mapp. 2019;40:1344
Armbruster-Genc DJN, Ueltzhöffer K, Fiebach CJ. Brain signal variability differ-
entially affects cognitive flexibility and cognitive stability. J Neurosci. 2016;36:9378–87.
Raja Beharelle A, Kovacevic N, McIntosh AR, Levine B. Brain signal variability
relates to stability of behavior after recovery from diffuse brain injury. Neuro-
Image. 2012;60:528–37.
Conio B, et al. Opposing patterns of neuronal variability in the sensorimotor
network mediate cyclothymic and depressive temperaments. Hum Brain Mapp. 2019;40:1344–52.
Easson AK, McIntosh AR. BOLD signal variability and complexity in children and
adolescents with and without autism spectrum disorder. Dev Cogn Neurosci. 2019;31:1009–20.
Martino M, et al. Contrasting variability patterns in the default mode and sen-
orimotor networks balance in bipolar depression and mania. Proc Natl Acad Sci. 2016;113:4824–9.
Nomi JS, et al. Resting-state brain signal variability in prefrontal cortex is asso-
cted with ADHD symptom severity in children. Front Hum Neurosci. 2018;12:90.
Garrett DD, McIntosh AR, Grady CL. Brain signal variability is parametrically
modifiable. Cereb Cortex. 2014;24:2931–40.
Mišić B, Mills T, Taylor MJ, McIntosh AR. Brain noise signal variability is task-dependent and region
specific. J Neuropsychol. 2010;14:2667–76.
Cutlbert BN. The RDoC framework: facilitating transition from ICD/DSM to
dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry. 2014;13:28–35.
Insel T, Cutlbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research
domain criteria (RDoC): toward a new classification framework for research on
mental disorders. Am J Psychiatry. 2010;167:748–51.
Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The
Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and
validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10.
J Clin Psychiatry. 1998;59:22–33.
First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for
DSM-IV-TR axis I disorders, research version, patient edition (SCID-I/P). New
York: Biometrics Research, New York State Psychiatric Institute; 2002.
Numerator J, et al. Diagnostic interview for genetic studies. Rationale, unique
features, and training. NIHMH Genetics Initiative. Arch Gen Psychiatry. 1994;51:849–59.
disorder: preliminary findings from a follow-up state-based fMRI study. Psychiatry Res Neuroimaging. 2014;223:84–93.
75. Favre P, Houenou J, Baciu M, Pichat C, Poupon C, Bougerol T, et al. White matter plasticity induced by Psychoeducation in bipolar patients: a controlled diffusion tensor imaging study. Psychother Psychosom. 2016;85:56–60.
76. Favre P, Baciu M, Pichat C, De Pourtalès MA, Fredembach B, Garçon S, et al. Modulation of fronto-limbic activity by the psychoeducation in euthymic bipolar patients. A functional MRI study. Psychiatry Res Neuroimaging. 2013;21:4285–95.
77. Garrett AS, Miklózít D, Howe ME, Singh MK, Acquaye TK, Hawkey CG, et al. Changes in brain activation following psychotherapy for youth with mood dysregulation at familial risk for bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2015;56:215–20.
78. Depue BE, Burgess GC, Hillcutt EG, Bidwell LC, Ruzic L, Banich MT. Symptom-correlated brain regions in young adults with combined-type ADHD: their organization, variability, and relation to behavioral performance. Psychiatry Res Neuroimaging. 2010;182:96–102.
79. Mowinckel AM, Alnæs D, Pedersen ML, Ziegler S, Fredriksen M, Kaufmann T, et al. Increased default-mode variability is related to reduced task-performance and is evident in adults with ADHD. Neuralimage Clin. 2017;16:369–82.
80. Sørensen L, Eichele T, van Wageningen H, Plessen KJ, Stevens MC. Amplitude variability over trials in hemodynamic responses in adolescents with ADHD: the role of the anterior default mode network and the non-specific role of the striatum. Neuralimage Clin. 2016;12:397–404.
81. Liu C-H, Ma X, Wu X, Li F, Zhang Y, Zhou FC, et al. Resting-state abnormal baseline brain activity in unipolar and bipolar depression. Neurosci Lett. 2012;515:202–6.
82. Lu D, Jiao Q, Zhong Y, Gao W, Xiao Q, Liu X, et al. Altered baseline brain activity in children with bipolar disorder during mania state: a resting-state study. Neuropsychiatr Dis Treat. 2014;10:317–23.
83. Lui S, Yao L, Xiao Y, Keedy SK, Reilly JL, Keefe RS, et al. Resting-state brain function in schizophrenia and psychotic bipolar probands and their first-degree relatives. Psychol Med. 2015;45:97–108.
84. Meda SA, Wang Z, Ivelja E, Pouydal G, Keshavan MS, Tamminga CA, et al. Frequency-specific neural signatures of spontaneous low-frequency resting state fluctuations in psychosis: evidence from bipolar-schizophrenia network on intermediate phenotypes (B-SNIP) consortium. Schizophr Bull. 2015;41:1336–48.
85. Xu K, Liu H, Li H, Tang Y, Womer F, Jiang X, et al. Amplitude of low-frequency fluctuations in bipolar disorder: a resting state fMRI study. J Affect Disord. 2014;152–154:237–42.
86. Zhang Z, Bo Q, Li F, Zhao L, Wang Y, Liu R, et al. Increased ALFF and functional connectivity of the right striatum in bipolar disorder patients. Prog Neuropsychopharmacol Biol Psychiatry. 2020. https://doi.org/10.1016/j.pnpbp.2020.110140.
87. Lei X, Zhong M, Liu Y, Jin X, Zhou Q, Xi C, et al. A resting-state fMRI study in borderline personality disorder combining amplitude of low frequency fluctuation, regional homogeneity and seed based functional connectivity: J Affect Disord. 2017;218:299–305.
88. Salvador R, Vega D, Pascual JC, Marco J, Canales-Rodríguez EJ, Aguilar S, et al. Converging medial frontal resting state and diffusion-based abnormalities in borderline personality disorder. Biol Psychiatry. 2016;79:107–16.
89. Dinsteen I, Heeger DJ, Behrmann M. Neural variability: friend or foe? Trends Cogn Sci. 2015;19:322–8.
90. Pereira-Sanchez V, Franco AR, Vieira D, de Castro-Manglano P, Soutullo C, Millham MP, et al. Systematic review: medication effects on brain intrinsic functional connectivity in patients with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2020. https://doi.org/10.1016/j.jaac.2020.10.013.
91. Zohar J, Stahl S, Moller HJ, Blier P, Kupfer D, Yamawaki S, et al. A review of the current nomenclature for psychotropic agents and an introduction to the neuroscientific nomenclature: Eur Neuropsychopharmacol. 2015;25:2318–25.
92. Zohar J, Nutt DJ, Kupfer DJ, Moller HJ, Yamawaki S, Speeding M, et al. A proposal for an updated neuropsychopharmacological nomenclature. Eur Neuropsychopharmacol. 2014;24:1005–14.

ACKNOWLEDGEMENTS
We wish to thank Gwladys Rey for her initial help in gathering a multi-site database, Anne-Elisabeth Dumoulin and Eleonore Pham for their help in the recruitment of participants, and Alexandre Dayer for his inspirational guidance and enthusiasm for this project. He will stay in our hearts.

AUTHOR CONTRIBUTIONS
CP and JMA formulated the research question. VK, PF, JH, JP, JMA, DVDV, and CP conceptualized the project, and designed the study and methods. PF, JH, MP, NP, and CP collected the neuroimaging data, and performed the clinical assessment of participants. JMA provided institutional support. VK analyzed the data and wrote the manuscript. All the authors reviewed the manuscript and provided critical input.

FUNDING
This work was supported by the Swiss National Center of Competence in Research; “Synapsy: the Synaptic Basis of Mental Diseases”, financed by the Swiss National Science Foundation (grant number 51NF40-158776), a grant of the Swiss National Science Foundation to JMA (grant number 32003B-156914) and the Fondamental Suisse Foundation. VK was partly supported by the Singapore National Research Foundation (NRF) Fellowship (Class of 2017) and the Singapore Ministry of Defense (Project CURATE). Her work utilized resources provided by the Center for Functional Neuroimaging Technologies, NIH P41EB015896 and instruments supported by NIH 1S10RR023401, NIH 1S10RR019307, and NIH 1S10RR023043 from the Athinoula A. Martinos Center for Biomedical Imaging at the Massachusetts General Hospital. The computational work was partially performed on resources of the National Super-computing Centre, Singapore (https://www.nxcc.sg). This work was supported by the French ANR under the “VIP” (MNP 2008) Project; the Investissements d’Avenir programs managed by the ANR under references ANR-11-IDEX-002 (Labex BioPey) and ANR-10-COHO-10-01; and the Fondation pour la Recherche Médicale (“Biomodérmatique pour la biologie 2014”). This work was also supported by research grants from Grenoble University Hospital (http://www.chu-grenoble.fr/). The Grenoble MRI facility IRMAGE was partly funded by the French program “Investissement d’avenir” run by the “Agence Nationale pour la Recherche” (http://www.agence-nationale-recherche.fr/); Grant “Infrastructure d’Avenir en Biologie Santé” (grant number ANR-11-INBS-0006).

COMPETING INTERESTS
The authors declare no competing interests.

ADDITIONAL INFORMATION
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41398-021-01666-3.

Correspondence and requests for materials should be addressed to Valeria Kebets. 

Reprints and permission information is available at http://www.nature.com/reprints 

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2021