Neurobiological and behavioural studies of affective instability in clinical populations: a systematic review

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ABSTRACT

Objectives: To evaluate the neurobiological, psychophysical and behavioural measures of affective instability in clinical populations.

Data sources: A range of medical and psychological science electronic databases were searched (including MEDLINE, EMBASE, and PsycINFO). Hand searching and reference checking are also included.

Review methods: Reviews, systematic reviews, experimental and cross-sectional studies, providing affective instability in neurobiological and behavioural measurements in clinical populations. Studies were selected, data was extracted and quality was appraised.

Results: Twenty-nine studies were included, 6 of which were review studies (one a meta-analysis) and 23 of which were primary studies, across a wide variety of disorders including ADHD, bipolar affective disorder, schizophrenia, severe mood dysregulation, major depression, and borderline personality disorder.

Conclusions: The bulk of the studies converge on the role of the amygdala, particularly in borderline personality disorders, and how it connects with other areas of the brain. Future research needs to extend these findings across diagnoses and development.

Indexing terms: mood, affective, instability, dysregulation, lability, emotion, bipolar, borderline, RDoC

1. INTRODUCTION

Affective instability (AI) is widely described in the psychiatric literature but there is a lack of agreement and consistency in how it is assessed, measured and defined. Conceptions of AI include ideas that it incorporates frequent affective category shifts, disturbances in affect intensity, excessively rapid emotion rise-times, delayed return to emotion baseline, excessive reactivity to psychosocial cues, endogenously driven, random, chaotic or rapid-cycling changes and overdramatic affective expression (Koenigsberg, 2010). The term is used interchangeably with mood instability, affective lability, affective and emotional dysregulation and mood swings, by researchers and clinicians alike, and as a result all these terms have been used in studies.

The variability of how the term is used makes it difficult to know how common it is. AI as described in the Diagnostic and Statistical Manual –IV (DSM-IV) has been estimated to have a general population prevalence of around 14% (Black et al., 2006, Marwaha, 2012). Despite the problems of definition there is general agreement that AI is clinically important. AI described as "due to a marked reactivity of mood" (pg. 663) is a diagnostic criterion in borderline personality disorder (BPD), and is defined in DSM-5 as: '… being due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days) […] These episodes may reflect the individual's extreme reactivity to interpersonal stresses' (pg. 664) (APA, 2013). In people with BPD, prospective studies show that it is the strongest factor in the diagnostic criteria for that disorder that predicts suicidal behaviour and more so than a negative mood state overall (Yen et al., 2004). Neuroticism (Korten et al., 2012) and having more interpersonal difficulties with partners are both linked to AI as well as future depression (Miller and Pilkonis, 2006, Thompson et al., 2011). Linehan (Linehan, 1993) considers emotional dysregulation as not just a symptom of BPD but potentially the cause of the disorder (Crowell et al., 2009). What is clear, however, is that in addition to the substantial prevalence of mood instability in the general population, and its importance in the contemporary conceptualisation of borderline personality disorder, it is also a feature of several psychiatric disorders. Fluctuation of mood has been known to be a key feature of bipolar affective

disorder (BP), yet clinicians may see affective instability in disorders other than BPD or BP such as ADHD, depression, PTSD (Broome and Marwaha, in submission) and it may be an important feature in the onset of psychosis (Marwaha et al., 2013a,b and Marwaha et al., 2014).

In previous work, we have systematically reviewed psychometric measures and definitions of Affective Instability (AI), transdiagnostically, in adults (Marwaha et al., 2014) affective instability is an important psychopathological construct, linked to distress and impairment (Marwaha et al., 2013a, Marwaha et al., 2013b) and can be a feature of many childhood and adult-onset psychiatric illnesses. There is little research studying neurobiological and behavioural measurements of affective instability in clinical populations. The current systematic review aims to collate evidence on the neurobiological and behavioural measurement for affective instability in clinical populations, across the diagnostic spectrum, with a goal to consider whether AI meets the ideal expressed in the Research Domain Criteria (RDoC) of a clinical phenotype that is of importance and can be studied neuroscientifically through experimental designs (Cuthbert and Insel, 2013). RDoC supports research that studies biobehavioural dimensions, which cut across existing diagnostic categories, with the key idea being that advances in genetics, systems neuroscience and behavioural science are not whlly consistent with the existing categories of mental disorder as defined in both the ICD and DSM. Hence, traditional psychiatric taxonomies may be an impediment to translational research in mental health. Given that AI manifests developmentally, utilizing neuroscientific and behavioural approaches, in addition to psychometric strategies, may allow mechanisms underpinning AI to be detected prior to the problems associated with it developing, and hence offer a window for early detection, intervention and prevention of harms.

2. METHODS

We used the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) for guidance regarding reporting of search, extraction and synthesis of results in this review (Moher et al., 2009).

2.1 Eligibility criteria

Studies were included if they met the following criteria:

a) Study design: for primary studies, experimental studies (randomized controlled trials, nonrandomized controlled trials, controlled before-and-after studies, and cross-sectional studies); as well as reviews.

b) Participants: we defined clinical population as subjects meeting the diagnostic criteria of DSM-IV or ICD-10.

c) Neurobiological and behavioural measurements: we defined neurobiological measurements as including any affective neuroscience paradigm, for example, fMRI, EEG and PET; behavioural measurements as any format of cognitive and behavioural test/task, for example: the Attention Network Test (ANT).

d) Comparison: we did not have restrictions for the comparator characteristics.

e) Outcomes: we included studies that reported outcomes relating to neurobiological and behavioural measurements for affective instability.

2.2 Information sources

The following bibliographic databases were searched MEDLINE, Embase, PsycINFO, PsycArticles and Web of Science. The main search was from the date of inception of each database to February 2012, and was then updated till January 2014. Five journals (Journal of Affective Disorders, Journal of Abnormal Psychology, The American Journal of Psychiatry, Journal of American Academy of Child and Adolescent Psychiatry, and Psychological Medicine) were hand searched from June 2007 to January 2014. These journals were considered most likely to include relevant papers after running of our search strategy. Reference lists of included studies were also searched for relevant citations.

2.3 Search

We discussed and developed our search strategy by using 5 groups of search terms as below;

Group 1 (Affective)	**Group 2 (Mood)**	**Group 3 (Emotion)**	**Group 4 (Disorder)**	**Group 5 (Established Measures)**
Affective	Mood	Emotion instability	Borderline	Mood Disorder

instability	instability		Personality Disorder (BPD)	Questionnaire
Affective dysregulation	Mood dysregulation	Emotion dysregulation	Bipolar disorders (BP)	Short Mood and Feelings Questionnaire
Affective lability	Mood lability	Emotion lability	Post-Traumatic Stress Disorder (PTSD)	Affective Liability Scale
	Mood swings		Attention deficit hyperactivity disorder (ADHD)	Affect Intensity Measure
			Unstable personality traits	Strengths and Difficulties Questionnaire
				Child Behavior Checklist

Search was based on terms from Group 1, 2, or 3 being present with a term from Group 4 or a term from 1, 2 or 3 being present with a term from 5. The above search included all reviews and primary studies. If a previous overview or systematic review was found, the reference lists of these reviews were searched in order to identify and retrieve the primary studies.

2.4 Study selection

Two researchers (ZH and JE) independently scanned titles and abstracts of articles, to identify relevant articles to retrieve in full. One researcher (ZH) scanned all titles and abstracts of articles, and another researcher (JE) scanned half of them. The results of included studies were compared between the two researchers, and more than 80% of the included studies overlapped. If articles appeared potentially eligible but no abstract was available, the full article was retrieved. We restricted language in English. Any disagreements between researchers were referred to a third researcher (SM or MB). Hand-search was carried out by ZH and MI, and results scanned by JE, and referred to MB.

2.5 Data collection process

Based on full articles, data were extracted on study design, participants, measurements and outcomes using a standardised data extraction form by one researcher (ZH). Any uncertainties were referred to other researchers (SM/MB).

2.6 Risk of bias in individual studies

The risk of bias in individual studies were assessed including: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias as indicated in the Cochrane guidelines (Higgins and Green, 2011).

2.7 Summary measures

The principal summary measures used in each study were reported.

2.8 Synthesis of results

The included studies were heterogeneous in terms of design, measurements and outcomes, hence findings have been synthesised narratively. The findings have been presented and grouped by study design.

2.9 Risk of bias across studies

Any risk of bias that may affect the cumulative evidence (e.g., selective reporting of outcomes within studies) was assessed as described above for assessing risk of bias in individual studies.

3. RESULTS

3.1 Study selection

Figure 1 shows the process of identification and selection. Six reviews/meta-analyses and 23 primary studies were included in the current paper.

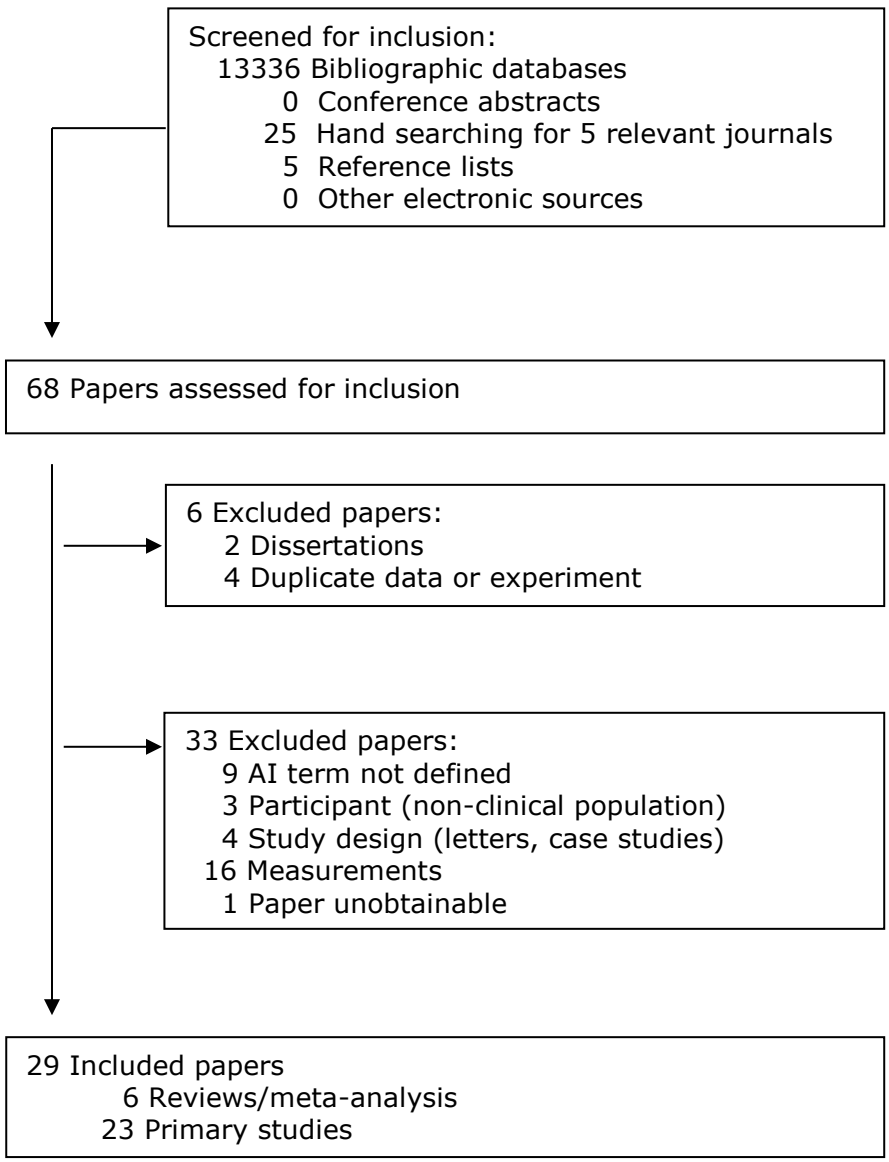


Figure 1 PRISMA flow chart

3.2 Study characteristics

Six reviews (21%) focused solely on neurobiological measurement of AI in BPD, BP and PTSD. Nine (31%) primary studies reported neurobiological measurement of AI, 5 (17%) primary studies reported behavioural measurement of AI, and 9 (31%) primary studies conducted both neurobiological and behavioural measurements. The characteristics of included primary studies are shown in Table 1. Interestingly, none of the primary studies found examined AI in PTSD, yet Lang et al., (2012) did study the effect of trauma on BP. Reviews and the meta-analysis are summarised in Table 2.

3.3 Risk of bias within primary studies

A risk of bias assessment was carried out for each included primary study. All studies were non-RCT designed, which were judged to be at high risk of selection biases. The performance bias and detection bias were judged to be at high risk high as participants could not be blinded to group allocation. The risk of attrition bias and outcome reporting bias was judged to be low in all studies.

3.4 Results of individual studies

The findings of primary studies are shown in Table 1, including neurobiological and behavioural methodology and measure of AI used, with the Review papers and the meta-analysis summarised in Table 2.

Table 1: Study characteristics and main findings

First author (date)	Country	Sample (age)	Measure of affective instability	Main finding in affective instability
Neuroimaging				
Almeida (2009)	USA	21 with BP (31.9 years) 25 control group (29 years)	Event related fMRI paradigm Viewing of happy/neutral faces	Abnormally increased right parahippocampal gyrus and subgenual cingulate gyrus effective connectivity and reduced activation of the parahippocampal gyrus, in response to emotional stimuli, in participants with BP
Brotman (2010)	USA	43 with BP (8-17 years) 18 with ADHD 29 with SMD 37 control group	Event related fMRI paradigm Attending to emotional and non-emotional aspects of neutral faces	Children/adolescents with BP and SMD rated neutral faces as more fearful. When rating fear, participants with ADHD demonstrated hyperactivity of the left amygdala; participants with SMD demonstrated hypoactivity
Doll (2013)	Germany	14 with BPD (30.4 years) 16 control group (34 years)	Resting state fMRI	Aberrant intra intrinsic functional connectivity (iFC) was found within the three networks (salience, default mode, central executive) in patients with BPD. Inter iFC of the central executive network decreased and inter iFC of the salience network increased
Frick (2012)	Germany	21 with BPD (27.1 years) 20 control group (24.8 years)	Behavioural and neurophysiological (fMRI) responses of participants during 'Reading the mind in the eyes' test	Participants with BPD had faster mental state discrimination for affective eye gazes: stronger activation of the amygdala, more activity of the medial frontal gyrus, left temporal pole and middle temporal gyrus. Healthy control participants showed greater insula and superior temporal gyri activation
Holtmann (2013)	Germany	16 with BPD (25.6 years) 24 control group (26.8 years)	fMRI with modified version of the Eriksen flanker task	Patients with BPD showed atypical response pattern with increased activation of the right amygdala during emotional interference in the incongruent flanker condition but emotion-related amygdala deactivation in the congruent condition. In the incongruent condition, trait anxiety was negatively correlated with both dorsal and rostral anterior cingulate cortex

First author (date)	Country	Sample (age)	Measure of affective instability	Main finding in affective instability
				fMRI responses (during emotional interference), in patients with BPD
Kamphausen (2013)	Germany	13 with BPD (29.3 years) 15 control group (32 years)	Instructed fear task combined with fMRI and skin conductance response	Patients with BPD did not show fMRI signal decrease of amygdala activity or relative ventromedial PFC (vmPFC) activity increase over time, but showed increased amygdala, vmPFC connectivity and decreased subgenual anterior cingulate cortex and dorsal anterior cingulate cortex connectivity
Kanske (2013)	Germany	22 with BP (39.4 years) 22 control group (40.5 years)	fMRI to localise the neural network specific to mental arithmetic cognitive task and test the effect of emotional distractors on the neural network	No group difference on task performance and neural network activation. Significantly slower behavioural response times with introduction of emotional distractors correlating with increased right parietal lobe activation in patients with BP
Korgaonkar (2013)	Australia	30 with MDD (41.2 years) 30 control group (35.7 years)	fMRI-cognitive tasks assessing function of selective attention, sustained attention, working memory, impulsivity, inhibition fMRI-emotional processing tasks assessing explicit conscious and implicit nonconscious awareness	Patients with MDD displayed hypoactivation of the dorsolateral prefrontal cortex (with working memory updating, conscious emotion processing), hyperactivation of the dorsomedial PFC (working memory, response inhibition) and hypoactivation of the dorsomedial PFC (conscious processing of positive emotion)
Krause-Utz (2012)	Germany	22 with BPD (28.2 years) 22 control group (27.4 years)	fMRI with adapted Sternberg working memory task whilst distracted by emotional (negatively arousing) and neutral pictures from the International affective picture system	Longer reaction times, higher activation of the amygdala and insula and dampened activation of the dorsolateral PFC, during emotional distraction, in patients with BPD. Negative correlation between activation in limbic brain regions and self-reports of current dissociative states

First author (date)	Country	Sample (age)	Measure of affective instability	Main finding in affective instability
Lang (2012)	Germany	14 with BPD (27.2 years) 15 with nonPTSD (29.3 years) 15 control group (24.7 years)	fMRI examining subjective ratings of negative emotional experience and brain activity following up and down regulation of emotional responses to standardised negative scripts	All groups used cognitive reappraisal to up-and-down-regulate negative emotions. Participants with BPD and non-PTSD showed early deactivation in the PFC; healthy controls showed early increased activation of the PFC and amygdala. Anterior cingulate cortex was more activated in healthy controls than BPD or non-PTSD
Maier (2013)	Germany	Experiment 1 17 with ADHD (33.6 years) 17 control group (31.1 years) Experiment 2 13 with ADHD (36.5 years) 17 control group (34.8 years)	Skin conductance response and fMRI in two different fear learning paradigms with unpleasant electrodermal stimulation used as the unconditioned stimulus	Participants with ADHD showed reduced activation of the dorsal anterior cingulate cortex to a neutral conditioned stimulus and increased activation of the amygdala to a controlled stimulus
Nusslock (2012)	USA	21 with BP (31.5 years) 20 control (31.6 years)	fMRI during a card-guessing paradigm to examine reward-related brain function to anticipation and receipt of monetary reward and loss	Greater ventral striatal and right-sided orbitofrontal activity displayed in participants with BP during anticipation (but not outcome) of monetary rewards and elevated left-lateral orbitofrontal cortex activity during reward anticipation
Perez-Rodriguez (2012)	USA	38 with BPD (30.5 years) 36 control group (28.4 years)	Fluro-deoxyglucose positron emission tomography used in point subtraction aggression paradigm	Lower striatal relative glucose metabolism (within caudate and putamen) in male patients with BPD-IED. No differences observed between male and female groups in clinical or behavioural measures
Perlman	USA	20 with PBSD (13.5	fMRI during task-irrelevant emotional face	Decreased activation of the fusiform gyrus of patients with PBSD, in processing facial emotions, in particular when

First author (date)	Country	Sample (age)	Measure of affective instability	Main finding in affective instability
(2012)		years) 20 non BP (13.7 years) 20 control group (13.5 years)	processing	processing angry faces
Radulescu (2012)	USA	9 with schizophrenia (36.1 years) 26 control group (25.1 years)	fMRI whilst subjects viewed affect-valent stimuli	Distinct power spectrum scale invariance was observed in two clusters localised to the orbitofrontal/medial PFC: β close to white noise in schizophrenia patients and pink noise in controls
Physiological				
Ebner-Priemer (2005)	Germany	21 with BPD (28.5 years) 21 control group (29.7 years)	Left orbicularis oculi electromyogram, skin conductance, heart rate, startle response task	Higher startle response (of the orbicularis oculi) in participants with BPD influenced by present-state dissociative experiences: Enhanced startle response in patients with low dissociative experiences and reduced response in those with high dissociation
Hallquist (2010)	USA	74 with BPD (46 years) 40% psychiatric sample 60% community sample	Attention network task (ANT) and pupil size	Negative correlation between affective instability (subscale of the personality assessment inventory-borderline scale) and pupil size when viewing negative faces. Pupil dilation on congruent trials of the ANT was associated with the affective instability subscale
Rich (2007)	USA	21 with SMD (7-17 years) 35 with narrow-phenotype BP 26 control group	The Affect Posner task (to manipulate emotional demands and induce frustration) Measurement of mood response, behaviour (reaction time and accuracy), brain activity	Children with SMD and BP reported more arousal than controls during frustration. Children with BP had lower P3 amplitude than children with SMD or comparison children, when frustrated. Children with SMD had lower N1 event-related potential amplitude than the other groups, in all three tasks

First author (date)	Country	Sample (age)	Measure of affective instability	Main finding in affective instability
			(event-related potentials)	
Struve (1976)	USA	190 with schizophrenia (age unclear)	Electroencephalogram (EEG) to investigate the B-Mitten EEG pattern	The B-Mitten reactive schizophrenia association is not considered to be primary: The differential process-reactive schizophrenia mitten incidence might be a secondary epiphenomenon of a fundamental underlying process. A relationship is suggested between mitten dysrhythmia and dysphoric affective dysregulation
Behavioural Tasks				
Bornovalova (2008)	USA	76 with BPD (18-62 years)	Paced auditory serial addition task (PASAT) Computerised PASAT-C Computerised mirror-tracing persistence task	Substance abuse patients with BPD scored higher on self-report measures of emotion dysregulation and lower on willingness to tolerate emotional distress. Self-report and behavioural measures accounted for unique variance in BPD status
Gratz (2006)	USA	17 with BPD (34.1 years) 18 control (37.3 years)	Modified version of Paced auditory serial addition task	Participants with BPD were less willing to experience distress in the pursuit of a goal: They were more likely to terminate a task and terminate quicker. Participants with BPD did not have greater difficulty engaging in goal-directed behaviour when distressed
Herpetz (1997)	Germany	75 with PD (27.3 years) 25 control group (32.1 years)	Affect-stimulation designed short story, analysis of responses to quality, intensity and alterations over time	Higher intensity of affective responses and rapid affect alterations in participants with impulsive personalities. Those with a history of self-harm demonstrated evidence of desperation, anxiety, strain and loneliness
Cognitive Tasks				
Lundervold (2011)	Norway	58 with ADHD (33.6 years) 56 control group (29.2 years)	Attention network task (ANT)	Adults with ADHD were less accurate on the ANT. Those reporting affective fluctuations appeared more alert but slower and more distracted by conflicting stimuli than ADHD without affective fluctuations

Notes: ADHD = attention deficit hyperactivity disorder, BP = bipolar disorder; BPD = borderline personality disorder, fMRI = functional magnetic resonance imaging, IED = intermittent explosive disorder, MDD = major depressive disorder, non-PTSD = trauma exposed healthy subjects without post traumatic stress disorder, PBSD = paediatric

First author (date)	Country	Sample (age)	Measure of affective instability	Main finding in affective instability

bipolar spectrum disorder, PD = personality disorder, PFC = prefrontal cortex, PTSD = post traumatic stress disorder, SMD = severe mood dysregulation

Table 2: Review study characteristics and main findings

First Author (date)	Type of review	Clinical group	Review aims	Main findings
Daros (2013)	Meta analysis	BPD	To understand the underlying mechanisms of emotion dysregulation by exploring the relationship between emotion recognition deficits and emotion accuracy	Patients with BPD were less accurate at emotion recognition especially anger and disgust. Patients misperceived emotions considered neutral by control group more often seeing them as negative
Lanius (2010)	Narrative review	PTSD	To explore the neural manifestations of the dissociative subtype in PTSD, comparing to those underlying the reexperiencing/ hyperarousal subtype. Describes a model of emotion dysregulation in PTSD	Reexperiencing/hyperarousal is seen as emotional dysregulation that involves emotional undermodulation, mediated by failure of prefrontal inhibition of the same limbic regions. Dissociative subtype of PTSD is viewed as emotional dysregulation that involves overmodulation, mediated by midline prefrontal inhibition of the same limbic regions. Both modulation types dynamically interplay, leading to alternating symptom profiles
Lanius (2011)	Narrative review	PTSD	To examine the relevance of the SCAN paradigm for an understanding of the psychology and neurobiology of PTSD and its treatment	SCAN offers a paradigm for understanding psychological trauma and the clinical outcomes (i.e. emotional/self awareness, emotion regulation; social emotional processing and self-referential processing). These collective psychological functions are mediated by: cortical midline structures, amygdala, insula, posterior parietal cortex and temporal poles. Chronic trauma related experiences reflect impairments in multiple social cognitive and affective functions
Mauchnik	Narrative	BPD	To understand the biological correlates	The HPA axis is affected in patients with BPD; hippocampal and amygdala atrophy is observed. The correlates of affective dysregulation

(2005)	review		of BPD	include EEG slowing, evoked potentials abnormalities, elevated rapid eye movement sleep density, higher acoustic startle response, prolonged habituation in electromyogram and increased amygdala activation
Phillips (2008)	Narrative review	BP	To develop a neural model of emotion regulation (including the neural systems implicated in voluntary and automatic emotion regulatory sub-processes) To use the model as a theoretical framework to examine functional neural abnormalities in these neural systems, which may predispose to development of severe emotion dysregulation BP	Structural and functional neuroimaging studies show left-sided abnormalities in prefrontal cortical regions are implicated in automatic rather than voluntary emotion regulation, in adult BP. In children/adolescents with or at risk of BP studies show functional and structural abnormalities in the prefrontal cortex, limbic and paralimbic regions implicated in emotion regulation
Townsend (2012)	Narrative review	BP	To review the fMRI literature on adult BP using emotion processing or regulation paradigms	Specific abnormalities found in the frontal-limbic regions. Using a variety of paradigms, these studies show that amygdala activation varies as a function of mood state and the prefrontal cortex remains persistently hypoactivated across mood states

Notes: BP = bipolar disorder; BPD = borderline personality disorder; fMRI = functional magnetic resonance imaging; PTSD = post traumatic stress disorder; SCAN = social cognitive and affective neuroscience;

4. DISCUSSION

4.1 Précis of primary papers and of the meta-analysis

The primary studies listed above utilize a variety of methods to examine AI, including functional neuroimaging, electrophysiology, measures of physiology, mood induction, and attention tasks and therefore we have grouped the narrative précis by methodology.

4.1.1Neuroimaging

Almeida and colleagues (Almeida et al., 2009) utilized event-related fMRI to study patients with type 1 bipolar affective disorder in remission and hence the presence of emotional dysregulation was deemed to be present based upon the diagnosis of the participants, rather than a state measure of mood dysregulation at the time of data collection. Both effective connectivity and activation were determined in the clinical group with reference to healthy controls. On response to the emotionally salient stimuli (happy and neutral faces), the bipolar participants demonstrated greater connectivity between the right parahippocampal gyrus and the subgenual cingulate gyrus, as well as decreased activation of the parahippocampal gyrus. The authors suggest that such changes may reflect impairment of the ventromedial system that in turn is responsible for involuntary regulation of the behavioural response to emotional stimuli, and the appraisal and encoding of emotional stimuli.

Brotman et al., (Brotman et al., 2010) studied four groups of participants: those with bipolar, with ADHD, with severe mood dysregulation (as determined by the Leibenluft criteria), and healthy controls. All participants were exposed to neutral faces during fMRI. Interestingly, both the bipolar and severe mood dysregulation groups rated the faces as more fearful than the ADHD and control groups, but on rating their levels of fear, those with ADHD demonstrated hyperactivity of the left amygdala, whereas those with severe mood dysregulation showed hypoactivity. There was no difference in the control or bipolar participants. The authors note that the amygdala has a role in emotional processing and valence, and particularly facial affect and hence hypoactivity here may relate to the clinical and interpersonal difficulties of this group.

Doll et al. (Doll et al., 2013) analysed intrinsic functional connectivity within (intra-iFC) and between (inter-iFC) three networks (salience -SN; default mode -DMN; central executive - CEN) known for their involvement in emotion and behaviour regulation, in patients with BPD. They investigated the presence of aberrant functional connectivity in these networks, which they hypothesised to correspond with emotional instability. The group acquired resting-state fMRI data in these patients and, using high-model-order independent component analysis and found aberrant intra-IFC in all three networks in patients compared to healthy controls, confirming previous findings. Their inter-iFC results demonstrated increased inter-iFC between CEN and DMN, both these networks usually being anti-correlated, and most importantly they found an overall decrease in inter-iFC for CEN and an increase for SN. Given the dominant role of the CEN in cognitive control and the SN in emotion regulation, the authors interpreted the shift of inter-iFC from CEN to SN to underlie persistent emotion instability in BPD.

Frick and colleagues (Frick et al., 2012) included interpersonal relationship instability in their interpretation of emotional instability in BPD and investigated changes in mentalizing ability which may underpin interpersonal and emotional dysfunction in these patients. The group compared mental state discrimination ability and fMRI responses between patients and controls during RMET (Reading of the Mind in the Eyes' Test), where subjects must infer a mental state from images of the eye region of the face. Results were in line with previous findings and showed hypersensitive mental state discrimination in the BPD group, which attributed a mental state to images of affective eye gazes with greater accuracy and speed compared to the control group. The RMET also corresponded to comparatively increased activation of the amygdala, medial frontal gyrus, the left temporal pole and the middle temporal gyrus in BPD patients and increased activation of the insula and the superior temporal gyri in controls. The authors suggest this hypersensitive mentalizing ability, reflected by an exaggerated amygdala response, causes BPD patients to be hypervigilant to social stimuli.

Holtmann et al. (Holtmann et al., 2013) examined the effects of short-term emotional distress on cognitive performance in patients with BPD. Using fMRI, the group analysed changes in fronto-limbic activity in response to distracter fearful faces, during the Eriksen Flanker task, where subjects must respond to the direction of a central arrowhead stimulus flanked by arrowheads pointing in the same (congruent condition) or opposite (incongruent condition). They expected increased amygdala activity in response to fearful faces and reduced DLPFC and ACC activity, specifically during the most difficult

incongruent condition with emotional distracter stimuli, compared to controls. They found an increase in right amygdala activation during emotional interference (fearful vs. neutral faces) in the incongruent condition in patients, but amygdala deactivation in the congruent condition, and this was accompanied by increased neural activation of the dACC and rACC when exposed to emotional relative to neutral faces and in the incongruent relative to the congruent condition. Specifically in the incongruent condition, these dACC/rACC responses negatively correlated with trait anxiety in patients but not in controls. The increased right amygdala activation is interpreted by the authors as an increased implicit processing of task irrelevant negative emotional stimuli and behavioural compensation was potentially achieved by increased recruitment of dACC and rACC. They also suggested that the impact of trait anxiety on ACC activation in the incongruent condition may form a mechanism for the vulnerability of cognitive processing to emotional interference in BPD.

Kamphausen et al., (Kamphausen et al., 2013) explored the role of aberrant fronto-limbic circuitry in affective dysregulation in BPD, using a fear-learning paradigm. Patients with BPD and controls underwent fMRI scanning of emotion regulation networks and skin conductance response recording while presented with two coloured stimuli: one which they were instructed represented a succeeding aversive event (conditioned stimulus - unpleasant electrodermal stimulation) and the other as representing safety. The aversive event was only experienced once during instruction, and never during scanning. As previously hypothesised, the group observed that the increased amygdala activation for the BPD group did not decline over time - with increase in right amygdala activity correlating with disease severity, compared to the control group which habituated eventually. BPD patients also displayed a decrease in vmPFC activity over the course of presenting stimuli, in contrast to controls where activity in this region increased. Compared to controls, increased connectivity between the amygdala and vmPFC and decreased connectivity between sgACC with dACC was also found in the BPD group. These aberrations in connectivity and a prolonged amygdala response are suggested by the authors to form part of the pathological neural response underlying affective dysregulation in BPD.

Kanske et al., (Kanske et al., 2013) questioned whether increased emotional distractibility in BP is a vulnerability marker or develops consequent to disease onset, by considering the impact of emotion distraction on cognitive function in these patients. The group used fMRI scanning on three groups: BP patients, first-degree relatives and individuals with hypomanic personality traits, as well as a control group, to ascertain the effects of emotional distracter images on neural networks found to be implicit in

the cognitive (numerical) tasks each group performed. The group found no difference between task performance and activation of the neural networks in all three groups, but introduction of emotional distracters led to a slower behavioural response time in BP patients, who also exhibited increased activation of the neural networks under distractor conditions, particularly right parietal lobe activation which correlated with a slower response time. No such neuropsychological deficits were found in the two high-risk population groups. The authors suggested that while emotional dysregulation underpins these cognitive deficits, as evidenced by their appearance under emotion distracter conditions, they manifest post disease onset.

Korgaonkar and colleagues (Korgaonkar et al., 2013) described patterns of prefrontal dysregulation thought to underlie cognitive and emotional dysregulation in MDD. Drawing upon MDD participants from the International Study to Predict Optimized Treatment in Depression (iSPOT-D), the group used fMRI to determine the direction of activity in prefrontal regions of interest (hypo or hyperactivity) in these patients during a comprehensive series of 5 cognitive and emotional processing tasks. In contrast to controls, MDD patients distinctly displayed hypoactivation of the dlPFC during working memory updating tasks and conscious negative emotion processing; hyperactivation of the dmPFC during working memory and response inhibition cognitive tasks and hypoactivation of the dmPFC during conscious positive emotion processing. The authors argued that use of the tasks in a standardised fashion across the cohort removed the impact of variations in task protocol, and relates differences in circuit activation to cognitive and emotional dysregulation in MDD. The authors suggest that standardised use of this battery of tasks to identify this "bio-signature" of neural activation in MDD could be used to predict treatment response and identify treatment targets.

Krause-Utz et al., (Krause-Utz et al., 2012) explored the effect of emotional dysregulation and self-reported dissociation on cognitive function in BPD, and aberrant activity in the neural circuitry involved. Using fMRI techniques in a working memory performance paradigm, the group assessed the impact of negative emotion distraction, using emotional and control neutral images during task performance, on reaction times and neural activity on BPD patients. Unlike control participants, Patients with BPD demonstrated significantly longer reaction times during emotion distraction, compared to being confronted with neutral images during task performance. This delay in reaction was also accompanied by significantly increased activation of the amygdala and insula and dampened activation of dlPFC during emotion distraction in BPD patients versus controls. Self-reported dissociation scores also

negatively correlated with response time and neural activity. The authors suggest that increased reactivity of limbic regions to emotionally distracting images disrupts working memory performance, as evidenced by slower reaction times in BPD, and dissociative states dampen the effects of emotion distraction on working memory, thus providing a link between emotional arousal and cognitive impairment in BPD.

Lang et al., (Lang et al., 2012) explored cognitive reappraisal and neural mechanisms underlying trauma-history in trauma-exposed individuals with BPD. The group assessed neural activity with fMRI, alongside emotional experience with subjective rating scales, during a cognitive reappraisal paradigm where individuals were instructed to up or down-regulate emotional responses to standardised negative scripts. Three cohorts were examined: 1) trauma- exposed BPD patients (teBPD); 2) trauma-exposed healthy subjects (teHC); 3) non-traumatised healthy controls (HC), in order to distinguish the effects of trauma exposure from a BPD diagnosis. All cohorts could successfully cognitively reappraise. The HC cohort increased activation of PFC during emotional up-regulation, in contrast with the teBPD and teHC cohorts, which demonstrated significant early deactivation. ACC activation was also significantly increased in the HC cohort during up and down-regulation conditions compared to the teBPD and teHC cohorts. As there was no significant difference between teBPD and teHC cohorts, the group considered the deactivation of cognitive control regions, during the up regulation condition, in trauma-exposed individuals to indicate compensatory changes associated with trauma exposure, for dealing with distress.

Maier et al. (Maier et al., 2014) explored the role of emotional dysregulation in ADHD by examining alterations in fear learning in this group. Using fMRI, neural responses in patients with ADHD and healthy controls were recorded in two different fear learning paradigms: firstly in uninstructed fear learning (UF) involving a Pavlovian conditioning format where an unconditioned stimulus (UCS) - unpleasant electrodermal stimulation- was paired with a neutral conditioned stimulus (CS+) but never with a control stimulus (CS-); and secondly in verbally instructed fear learning (IF) where participants were informed that UCS (previously experienced) may be paired with CS+ but never with CS-. In the IF paradigm, ADHD patients demonstrated a significant decrease in BOLD signal in the dorsal anterior cingulate cortex (dACC) in response to the CS+, and an enhanced response in the amygdala to the CS-, compared to controls. The dACC and amygdala both being components of the fear conditioning neural network defined by the authors, they interpreted these activation differences as an abnormal processing of verbally transmitted threat and safe cues, a potential mechanism for emotional dysregulation in this

clinical group. The authors also noted that their findings in ADHD were unique compared to similar studies in ASPD and BPD, indicating some disease specificity of emotional dysregulation in ADHD.

Nusslock et al., (Nusslock et al., 2012) investigated hyper-responsive reward processing circuitry underlying emotional dysregulation in BP by examining brain activity with fMRI scanning in patients with BP during reward anticipation and reward receipt in a card-guessing paradigm. The group found elevated activation of ventral striatal and OFC regions during reward anticipation but not receipt, compared to controls. The group posits the hyper-responsiveness of reward processing regions as a neural mechanism underpinning hypo/mania in BP,that could be a potential biomarker for the disease.

Perez-Rodriguez et al., (Perez-Rodriguez et al., 2012) discovered sex differences in abnormal striatal function underlying intermittent explosive disorder in BPD (BPD-IED). Using 18Fluoro-deoxyglucose-PET scanning, the group assessed striatal activity (measured as relative glucose metabolism) in patients with BPD-IED compared to controls, during aggression-provoking and none-provoking versions of a Point Substraction Aggression Paradigm. The group found that, despite no significant difference in clinical or behavioural assessments, male BPD-IED patients demonstrated significantly lower striatal activity in both conditions compared to female BPD-IED patients and controls of both sexes, with there being no significant difference between all latter groups. The authors suggest that differential frontal-striatal circuitry frames emotional dysregulation in IED, between the sexes.

Perlman et al., (Perlman et al., 2013) identified aberrations in face processing circuitry in Paediatric Bipolar Spectrum Disorder (PBSD), which may underpin poor performance in emotional face judgement tasks in these patients. Using fMRI scanning, the group analysed three cohorts: 1) PBSD patients; 2) a non-bipolar clinical population matched in terms of demographics and comorbidities; 3) healthy controls, when unconsciously processing emotional faces presented during performance of tasks to which they were irrelevant. The group found significantly decreased activation of the fusiform gyrus in the PBSD cohort compared to the clinical and healthy control cohorts, which was most marked during angry face processing compared to all other emotions. The authors suggest that dysfunctional emotional processing is not limited to emotional regions of the brain in PBSD and hypoactivation of the fusiform

gyrus may be linked to impairment in social function, which relies upon emotional face processing, in this population.

Radulescu et al., (Radulescu et al., 2012) investigated the dynamic features of patterns of neural regulation in response to emotional stimuli, that may underlie emotional dysregulation in schizophrenia. Using fMRI scanning across the whole brain, they used Power Spectrum Scale Invariance (PSSI) to measure patterns of neural activity during the passive viewing of affect-valent faces, in schizophrenic patients and controls. By calculating the power spectral density for each subject, the group could derive a β value – a measure of whether data has underlying trends, for comparison between the two cohorts. The group found a significant difference in PSSI between patients and controls in Brodmann Area 10 (orbitofrontal/medial prefrontal cortex) – a result consistent with previous findings, where the β value resembled white noise in patients and pink noise in controls. The group posits that finding patterns underlying neural dysregulation in Brodmann Area 10 is compatible with impairments in emotional regulation in this clinical population, a function that inheres to this brain region.

4.1.2 Physiological measures including electrophysiology

Ebner-Priemer at al. (Ebner-Priemer et al., 2005) used the autonomic startle response (ASR) paradigm as a way to assess affective dysregulation in those with borderline personality disorder (BPD). Those with BPD demonstrated an increased startle response, as measured by electromyogram of the orbicularis oculi, but this startle response was attenuated by those who scored high on measures on dissociation. Hence, startle response in those with BPD may be differentially affected by two criteria for the diagnosis: namely, affective dysregulation or dissociation. The authors suggest that the enhanced startle response in BPD may be mediated by enhanced amygdala activation.

Hallquist et al., (Hallquist et al., 2010) sought to explore information processing in BPD using pupil reactivity as a physiologic index of cognitive emotional processing. The participants completed the Personality Assessment Inventory-Borderline Features Scale (PAI-BOR) prior to completing a social cognition task, viewing emotional faces. There was a negative correlation between the affective instability subscale of the PAI-BOR and pupil dilatation on viewing negative faces. The authors suggest that individuals with intense interpersonal relationships characteristic of BPD experience a blunted

emotional response or difficulties with emotion regulation when faced with negative social cues. However, greater dilation was linked with BPD features on a cognitive task.

Rich et al., (Rich et al., 2007) studied children with severe mood dysregulation, defined as nonepisodic irritability and hyperarousal without episodes of euphoric mood and those with 'narrow phenotype' bipolar disorder (a history of one episode of mania or hypomania), as well as healthy controls. Participants completed the completed the affective Posner task, an attentional task that manipulated emotional demands and induced frustration. As well as mood and behavioural response, event-related potential were measured using EEG. Children with severe mood dysregulation had lower N1 event-related potential (50-150 ms after stimulus presentation) amplitude than comparison subjects or children with narrow-phenotype bipolar disorder, reflecting impairments in the initial stages of attention. The psychophysiological data showed a double dissociation. Specifically, patients with narrow-phenotype bipolar disorder had decreased P3 amplitude when frustrated (suggesting executive attention deficits), but exhibited no N1 amplitude deficit. In contrast, subjects with severe mood dysregulation were unimpaired on P3 amplitude but had decreased N1 amplitude on all three tasks. Thus, the psychophysiological correlates of frustration differed between these two patient groups: comparable perturbations in subjective reports of affect (e.g., increased frustration, relative to comparison subjects) were associated with different physiology.
Struve and Klein, (Struve and Klein, 1976) examined a group of patients with schizophrenia, mood and anxiety disorders, and 'character' disorder with EEG to look for the B-mitten complex, an age-related deep sleep EEG abnormality, and argued that such a finding indicated the degree of dysphoric affective dysregulation that was transdiagnositic in nature, rather than indicating the pattern of onset and course of schizophrenia as had been previously thought.

4.1.3 Behavioural tasks inducing emotional distress

Bornovalova et al., (Bornovalova et al., 2008) examined the relationship between diagnosis, scores on the DERS measure and performance on behavioural tests of willingness to tolerate emotional frustration (The Computerized Mirror-tracing Persistence Task (MTPT-C)) in a group accessing services for alcohol and substance misuse disorders, but with additional psychiatric comorbidity. Those with borderline personality disorder had both higher scores on the self-report measure of emotion dysregulation and

less willingness to tolerate emotional distress on the behavioural measures of emotion dysregulation. When both the DERS and behavioural responses were used in a logistic regression to predict BPD as the dependent variable, together they accounted for for 59% of the variance in BPD status, and correctly classifying 92% of participants without BPD and 67% of participants with BPD (with an overall correct prediction rate of 84%).

Gratz and colleagues (Gratz et al., 2006) offer a definition of emotion dysregulation that includes an unwillingness to experience emotional distress as part of pursuing desired goals; and the inability to engage in goal-directed behaviours when experiencing distress (Gratz et al., 2006, pg. 850). Participants with and without borderline personality disorder carried out the Paced Auditory Serial Addition Task – Computerised (PAST-C), an experimental measure of distress tolerance shown to induce emotional distress in the form of anxiety, anger, frustration, and irritability. Those with BPD were both more likely to terminate the task than controls, and to terminate quicker. However, despite the investigators' prediction, their performance on the task was no different to controls. Participants were also scored on the the Difficulties in Emotion Regulation Scale (DERS). This is a 36-item measure that assesses individuals' typical levels of emotion dysregulation across six domains: non-acceptance of negative emotions, inability to engage in goal- directed behaviours when distressed, difficulties controlling impulsive behaviours when distressed, limited access to emotion regulation strategies perceived as effective, lack of emotional awareness, and lack of emotional clarity. Scores on this measure related to termination of the task.

Herpertz et al., (Herpertz et al., 1997) used a mood induction experiment, based upon reading a story, to determine whether those with personality disorder would show higher intensity and altered emotional response compared to controls. The study confirmed its hypothesis and additionally demonstrated that those with a history of self-harm demonstrated greater evidence of affective qualities such as desperation, anxiety, loneliness and strain. The affective measure was based upon the sub-divisions of the story itself and a Likert scale relating to the intensity of the prominent affect in each subdivision of the story.

4.1.4 Cognitive tasks

Lundervold et al., (Lundervold et al., 2011) examined the effect of affective fluctuations in a group with ADHD. Fluctuations were assessed by use of the Mood Disorder Questionnaire (MDQ), a measure designed for bipolar affective disorder, and the groups performed the Attention Network Task (ANT). Adults with ADHD were characterized by impairment on accuracy and variability measures calculated from the ANT. Within the ADHD group, adults reporting affective fluctuations seemed to be more alert (i.e., less impacted by alerting cues), but slower and more distracted by conflicting stimuli than the subgroup without such fluctuations. The authors suggest that the cognitive heterogeneity in ADHD may in part be explained by such affective fluctuations.

Daros et al. (Daros et al., 2013) conducted a meta-analysis of 10 studies examining deficits in emotion perception, the hypothesised basis of emotional dysregulation, in BPD. The authors quantitatively synthesised data from these studies pertaining to the accuracy with which patients with BPD performed in facial emotion recognition tasks, when compared with non-psychiatric controls. Specifically, they explored the relationship between certain types of emotion recognition deficits, such as negative emotion recognition (i.e. sadness, anger, fear, etc.) with emotion accuracy, to elicit the underlying mechanisms of emotion dysregulation in these patients. They found patients with BPD to be statistically significantly less accurate at facial emotion recognition (collapsed across all emotions) than controls, particularly in recognition of anger and disgust, though not when considering all negative emotions or all happy emotions as a group. Patients also significantly misperceived emotions (specifically negative emotion) in faces considered neutral by controls. The authors suggest that increased attention in patients with BPD to highly salient stimuli, such as the highly intensely angry or disgusted faces in the studies, may interfere with the cognitive processes underlying the accurate identification of these emotions. Data on the misattribution of negative emotions to neutral faces was limited and the authors conceded that mood state-related biases (rarely reported) could be responsible.

5. Conclusion

The papers found above cover a wide range of affective psychopathology including within disorders such as ADHD, bipolar affective disorder, schizophrenia, severe mood dysregulation, major depression, and borderline personality disorder. No primary studies were found in this systematic search which examined affective instability in PTSD. Measures to determine affective instability and mood

dysregulation in the studies differ: some studies assume that such dysregulation exists due a given diagnosis being present, others assess mood dysregulation with a specific measure such as the MDQ, DERS, and PAI-BOR as well as bespoke measures. Techniques employed to study mood dysregulation have used emotionally salient stimuli (faces) in fMRI, and those that induce certain emotional states – in this review we found use of both narrative-based mood induction (via reading a story) as well as a task-evoked frustration based upon performance of a task, such as the PAST-C. An important wider point relates to this in that many of the primary studies do not employ a variety of methods in studying affective instability; that is, behavioural, physiological, cognitive neuropsychological, and imaging variables are typically studied in isolation in the main, with only 9 studies (31%) included here examining both behavioural and neuroscientific variables. This is, unfortunately, a feature of psychiatric research more generally, with two-thirds of studies examining aetiology of disorders (for example) working within one explanatory level (Kendler, 2014) and hence the studies included in this review are likely to reflect the wider research field. We would, with Kendler, advocate a pluralistic view of psychiatry that, to work transdiagnositically and within the RDoC framework, seeks to examine important variables at different levels and how they inter-relate.

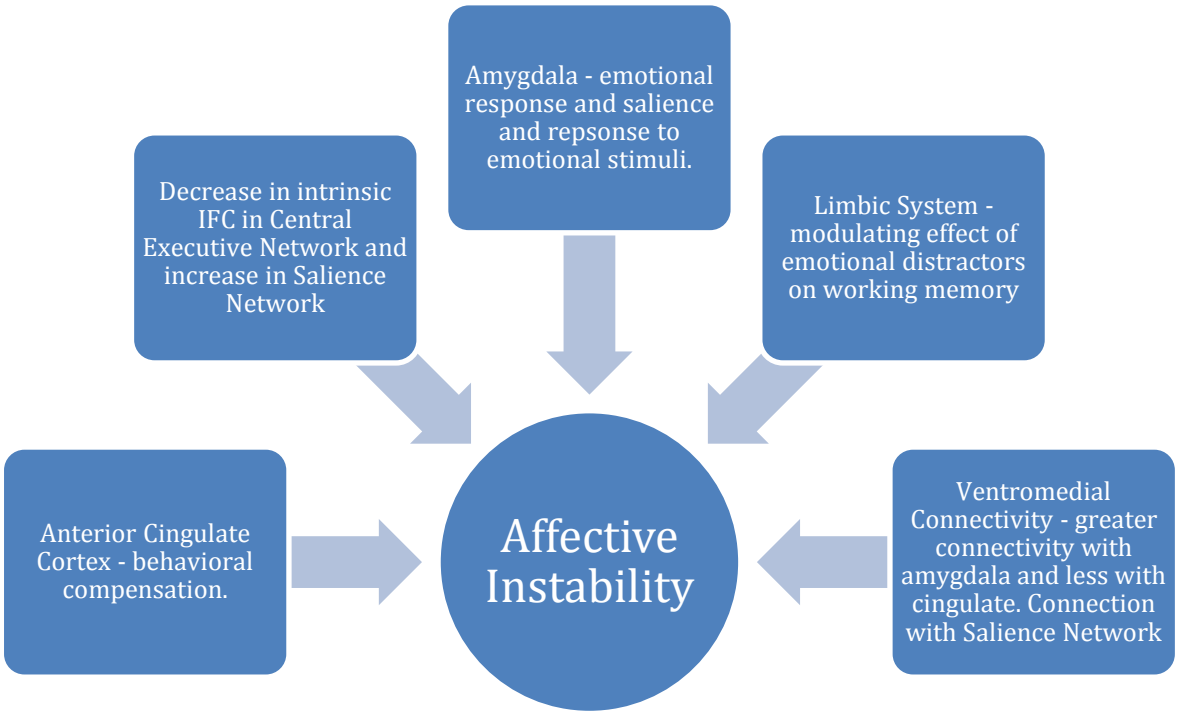
Only tentative conclusions are possible in terms of describing neurobehavioral correlates of affective instability given the heterogeneity of diagnoses, measures, and methodologies employed. As can be seen, the majority of the functional neuroimaging studies found examined affective instability within borderline personality disorder. Despite a variety of different tasks, there seems some convergence in that alterations in amygdala activation are found and interpreted to reflect problems in emotional processing, salience to emotional stimuli, and the individual's behavioural response to such stimuli. Functional connectivity analysis suggests a change in connectivity between regions such that the salience network may become more connected than the central executive network, and increased connectivity between the ventromedial prefrontal cortex and the amygdala, and decreased between areas of the anterior cingulate. In addition, the anterior cingulate cortex may have a role in behavioural compensation in mood instability in BPD (Holtmann et al., 2013), and the limbic system (specifically, amygdala, insula, and DLPFC) in modulating the impact of emotional distraction on working memory in those with BPD (Krause-Utz et al., 2012). Studies on other disorders are less clear but it is of interest that in studies of bipolar disorder, connectivity in ventromedial regions is also implicated (Almeida et al., 2009). In work not included in the review (Das et al., 2014) (in press at the

time of the search), resting state connectivity can distinguish between borderline and bipolar participants. This study again emphasises the role of the salience network – with connectivity between this area and the right fronto-parietal cortex increased in those with BPD, and its connection with the ventromedial PFC decreased in those with BP. For schizophrenia, BA 10 (orbitofrontal and prefrontal cortex) may have a role in the emotional dysregulation seen in the disorder (Radulescu et al., 2012) and the amydala and anterior cingulate cortex in processing threat and safety cues in ADHD (Maier et al., 2014). Please see Figure 2.

The importance of the amygdala is further emphasised by its implication in mediating the startle response, measured by electromyography. In terms of behavioural and cognitive tasks, there seems to be some consistency in that those with BPD are less able to tolerate emotional distress, and make errors on identifying facial emotions.

Based on these studies, the amygdala is a key area to understand affective instability in those with BPD, with connectivity between the salience network and other regions possibly being relevant transdiagnostically. The precise nature and location of this changed connectivity appears to be more diagnostically specific. It is clear that the amygdala has a role in the identification of stimuli with affective value (Armony, 2013) as well as subserving Pavlovian conditioning (Moscarello and LeDoux, 2013), and facilitates the synaptic plasticity of other structures (such as the basal ganglia and hippocampus) responsible for the storage of emotional memories (Paz and Pare, 2013).

Figure 2. Schematic of anatomical areas linked to Affective Instability,



Moving forward, we suggest that affective instability be measured accurately at the point of any study – both using detailed measures as described in our previous systematic review (Marwaha et al., 2014), but also perhaps by a behavioural task, such as a serial addition task as a way to elicit inability to tolerate emotional distress. Further imaging studies should examine the role of the amygdala in affective instability transdiagnostically to determine whether the findings for BPD are present in other disorders, and whether any other changes are present that may be disorder specific, such as the connectivity of the salience network. In addition to thinking across diagnoses, AI can be studied developmentally as to whether the subtle changes observed in adults with disorder may be present as markers or precursors, signifying the later development of disorders.

To conclude we would suggest that AI would meet the requirements of RDoC – it is likely to reflect problems in a core behavioural function of the brain, seems likely to be related to a dysfunction in neural circuits, and is dimensional (or rather, may have a few dimensions (Marwaha et al., 2014)). Indeed, based upon our prior systematic review (ibid), the unitary construct of affective instability may be able to be dissected out into more precise dimensions, for example: 'rapid oscillations of intense affect, with a difficulty in regulating these oscillations or their behavioral consequences' (Marwaha et al., 2014; pg. 1793). The translational approach of RDoC sees the traditional psychiatric illnesses as arising out of combinations, across systems, of these basic processes (Fulford et al., 2014), and hence

endorses a transdiagnostic and developmental conception of psychopathology, grounded in solid characterisation both of the behavioural function and its neural causes, and relates psychopathology to a biobehavioural dimension occurring in the general population. More long-term, the goal would be that not only would these RDoC constructs themselves be iteratively re-defined and superseded, based pragmatically on their success as objects amenable to a translational scientific approach, but that the traditional psychiatric categories could be 're-built' based upon these constructs, and hence in turn our patients may be able to benefit more easily from advances in aetiology being able to be translated to treatment interventions.

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